The Role of Diagnostic Imaging in Identifying Appropriate Strategies for Heart Failure Management

Doctorate of Philosophy

Thesis

Submitted by:

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Charles Sturt University
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Certificate of Authorship

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Abstract

Purpose: The aim of this study was to determine whether regional sympathetic activity is independently predictive of adverse cardiac events (CE) in heart failure (HF) patients, and whether 123I-mIBG SPECT imaging can perform this role.

Methods: Twenty-two clinically diagnosed HF patients were recruited into this study. The subjects underwent myocardial perfusion SPECT and cardiac sympathetic imaging with 123I-mIBG. Early (at 15 min post-injection) and delayed (four hours post-injection) planar and SPECT scintigraphy was performed. Visual and semi-quantitative analysis was conducted on these images, and global (from planar imaging) and regional (from SPECT imaging) uptake and washout indices obtained. The patients were clinically followed up for up to two years and the CEs in these patients were recorded. The occurrence of CE was then correlated with the various demographic, clinical, scintigraphic and biochemical parameters.

Results: The occurrence of CE in HF was independent of the patients’ demographics or the cause of HF. Left ventricular ejection fraction (LVEF) had no concordance with CE, however a decrease of 5% or more in LVEF was a significant predictor of CE ($p = 0.011$). Genetic biomarkers were also unable to predict CE. Global or regional uptake had limited ability to predict CE, where as regional washout from inferior ($p = 0.005$) and lateral ($p = 0.085$) walls were statistically significant predictors of CE. A high washout of 40% or more from
the peri-infarcted and non-infarcted segments on MPS was also a significant predictor of CE ($p = 0.035$).

**Conclusion:** HF is a complex, multi-factorial progressive disease that appears to be regional to begin with, but then progressively involves the whole heart. The role of the autonomic nervous system, especially the sympathetic nervous system, is central to the clinical course of the disease, especially the incidence of sudden cardiac death (SCD). 123I-mIBG provides a valuable tool in not just imaging the global sympathetic innervation of the heart, but also in assessing the regional distribution. This allows earlier diagnosis and stratifications of patients at risk of cardiac events, in particular SCD. While previous reports indicate that delayed washout offers identification of risk, the key marker is regional washout of 123I-mIBG from non-infarcted myocardium.
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Figure 6.5 A plot demonstrating no statistically significant difference in the age of the patients based on the difference in the aetiology of HF (p = 0.412). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.6 A plot demonstrating no statistically significant difference in the age between patients who had a CE to those who did not (p = 0.198). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.7 A plot demonstrating no statistically significant difference in the LVEF early of the patients based on the difference in the cause of HF (p = 0.593). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.8  A plot demonstrating no statistically significant difference in the LVEF early of the patients based on CE (p = 0.620). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.9  A plot demonstrating no statistically significant difference in the LVEF early based on CE (p = 0.061). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.10  Age versus SDNN early. No statistically significant correlation was noted (R2 = 0.05, p = 0.442).

Figure 6.11  Age versus %RR>50 early. No statistically significant correlation was noted (R2 < 0.01, p = 0.840).

Figure 6.12  Age versus rms-SD early. No statistically significant correlation was noted (R2 < 0.01, p = 0.952).

Figure 6.13  Plot of SDNN early versus LVEF early. No statistically significant correlation was noted (R2 = 0.12, p = 0.210).

Figure 6.14  %RR>50 early versus LVEF early. No statistically significant correlation was noted (R2 = 0.11, p = 0.219).

Figure 6.15  rms-SD early versus LVEF early. No statistically significant correlation was noted (R2 = 0.17, p = 0.122).

Figure 6.16  SDNN early versus ΔLVEF. A statistically significant correlation was noted (R2 = 0.27, p = 0.048) indicating a decrease in LVEF with an increase in SDNN early.

Figure 6.17  %RR>50 early versus ΔLVEF. No statistically significant correlation was noted (R2 = 0.08, p = 0.298).

Figure 6.18  rms-SD early versus ΔLVEF. No statistically significant correlation was noted (R2 = 0.26, p = 0.055).

Figure 6.19  A plot demonstrating statistically significant difference in the SDNN early based on ΔLVEF-5% (p = 0.020). This observation is however not supported by the tiny overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.20 A plot demonstrating no statistically significant difference in %RR>50 early based on CE (p = 0.442). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.21 A plot demonstrating statistically significant difference in rms-SD early based on CE (p = 0.039). This observation is however not supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.22 A plot demonstrating statistically significant difference in SDNN early based on CE (p = 0.012). Note the absence overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.23 A plot demonstrating no statistically significant difference in %RR>50 early based on CE (p = 0.136). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.24 A plot demonstrating a statistically significant difference in rms-SD early based on CE (p = 0.033). This observation is however not supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.25 A plot demonstrating no statistically significant difference in age based on ACE genotype (p = 0.552). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.26 A plot demonstrating no statistically significant difference in LVEF early based on ACE genotype (p = 0.132). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.27 A plot demonstrating no statistically significant difference in ∆LVEF based on ACE genotype (p = 0.783). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.28 A plot demonstrating no statistically significant difference in age based on UCP SNP rs1800849 (p = 0.297). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.29  A plot demonstrating no statistically significant difference in age based on UCP SNP rs660339 (p = 0.251). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.30  A plot demonstrating no statistically significant difference in age based on UCP SNP rs659366 (p = 0.729). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.31  A plot demonstrating no statistically significant difference in LVEF early based on UCP SNP rs1800849 (p = 0.177). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.32  A plot demonstrating no statistically significant difference in LVEF early based on UCP SNP rs660339 (p = 0.411). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.33  A plot demonstrating no statistically significant difference in LVEF early based on UCP SNP rs659366 (p = 0.052). This observation is supported by the overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.34  A plot demonstrating a statistically significant difference in ΔLVEF based on UCP SNP rs1800849 (p = 0.035). This observation is not supported by the overlap of the 95% CIs represented by the top and bottom portion of the diamonds, and is due to the outlier AA genotype.

Figure 6.35  A plot demonstrating no statistically significant difference in ΔLVEF based on UCP SNP rs660339 (p = 0.067). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.36  A plot demonstrating no statistically significant difference in ΔLVEF based on UCP SNP rs659366 (p = 0.106). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.37  Plot of age versus TL. No statistically significant correlation was noted (R2 = 0.15, p = 0.094).

Figure 6.38  Age versus T/S. No statistically significant correlation was noted (R2 = 0.05, p = 0.331).
Figure 6.39  Plot of age versus T/S_mean. No statistically significant correlation was noted (R2 = 0.04, p = 0.404).

Figure 6.40 TL versus LVEF early. No statistically significant correlation was noted (R2 = 0.15, p = 0.094).

Figure 6.41 T/S versus LVEF early. No statistically significant correlation was noted (R2 = 0.02, p = 0.555).

Figure 6.42 T/S_mean versus LVEF early. No statistically significant correlation was noted (R2 = 0.01, p = 0.611).

Figure 6.43 TL versus ΔLVEF. No statistically significant correlation was noted (R2 < 0.01, p = 0.689).

Figure 6.44 T/S versus ΔLVEF. No statistically significant correlation was noted (R2 = 0.12, p = 0.128).

Figure 6.45 T/S_mean versus ΔLVEF. No statistically significant correlation was noted (R2 = 0.06, p = 0.282).

Figure 6.46 A plot demonstrating no statistically significant difference in TL based on ΔLVEF-5% (p = 0.508). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.47 A plot demonstrating no statistically significant difference in T/S based on ΔLVEF-5% (p = 0.068). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.48 A plot demonstrating no statistically significant difference in T/S_mean based on ΔLVEF-5% (p = 0.168). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.49 A plot demonstrating no statistically significant difference in TL based on CE (p = 0.264). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.50 A plot demonstrating no statistically significant difference in T/S based on CE (p = 0.558). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.51 A plot demonstrating no statistically significant difference in T/S_mean based on CE (p = 0.497). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.52 Age versus global early H:M and. No statistically significant correlation was noted (R² = 0.07, p = 0.234).

Figure 6.53 Age versus global delayed H:M. No statistically significant correlation was noted (R² = 0.11, p = 0.137).

Figure 6.54 Age versus global washout. No statistically significant correlation was noted (R² = 0.11, p = 0.127).

Figure 6.55 LVEF early versus global early H:M. No statistically significant correlation was noted (R² < 0.01, p = 0.804).

Figure 6.56 LVEF early versus global delayed H:M. No statistically significant correlation was noted (R² = 0.04, p = 0.403).

Figure 6.57 LVEF early versus global washout. No statistically significant correlation was noted (R² = 0.04, p = 0.360).

Figure 6.58 ΔLVEF versus global early H:M and. No statistically significant correlation was noted (R² < 0.01, p = 0.804).

Figure 6.59 ΔLVEF versus global delayed H:M and. No statistically significant correlation was noted (R² < 0.01, p = 0.858).

Figure 6.60 ΔLVEF versus global washout and. No statistically significant correlation was noted (R² = 0.02, p = 0.560).

Figure 6.61 EDV versus global early H:M. No statistically significant correlation was noted (R² = 0.01, p = 0.614).

Figure 6.62 EDV versus global delayed H:M. No statistically significant correlation was noted (R² = 0.02, p = 0.540).

Figure 6.63 EDV versus global washout. No statistically significant correlation was noted (R² < 0.01, p = 0.904).

Figure 6.64 SDNN early versus global early H:M. No statistically significant correlation was noted (R² = 0.03, p = 0.540).

Figure 6.65 SDNN early versus global delayed H:M. No statistically significant correlation was noted (R² = 0.02, p = 0.628).

Figure 6.66 SDNN early versus global washout. No statistically significant correlation was noted (R² = 0.19, p = 0.109).
Figure 6.67 %RR>50 versus global early H:M. No statistically significant correlation was noted (R^2 = 0.04, p = 0.458).

Figure 6.68 %RR>50 versus global delayed H:M. No statistically significant correlation was noted (R^2 < 0.01, p = 0.931).

Figure 6.69 %RR>50 versus global washout. A non-statistically significant correlation was noted (R^2 < 0.01, p = 0.753).

Figure 6.70 rms-SD versus global early H:M. No statistically significant correlation was noted (R^2 = 0.01, p = 0.715).

Figure 6.71 rms-SD versus global delayed H:M. No statistically significant correlation was noted (R^2 < 0.01, p = 0.780).

Figure 6.72 rms-SD versus global washout. No statistically significant correlation was noted (R^2 = 0.01, p = 0.687).

Figure 6.73 A plot demonstrating no statistically significant difference in $\Delta$LVEF-5% based on global planar early H:M (p = 0.780). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.74 A plot demonstrating no statistically significant difference in $\Delta$LVEF-5% based on global delayed H:M (p = 0.950). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.75 A plot demonstrating no statistically significant difference in global planar washout based on $\Delta$LVEF-5% (p = 0.101). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.76 A plot demonstrating no statistically significant difference in early H:H based on CE (p = 0.072). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.77 A plot demonstrating no statistically significant difference in delayed H:M based on CE (p = 0.142). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.78  A plot demonstrating a statistically significant difference in global washout based on CE (p = 0.004). This observation is supported by no overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.79  A plot demonstrating no statistically significant difference in planar early H:M based on ACE genotype (p = 0.183). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.80  A plot demonstrating no statistically significant difference in planar delayed H:M based on ACE genotype (p = 0.062). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.81  A plot demonstrating no statistically significant difference in planar washout based on ACE genotype (p = 0.913). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.82  A plot demonstrating no statistically significant difference in planar early H:M based on UCP SNP rs1800849 (p = 0.980). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.83  A plot demonstrating no statistically significant difference in planar delayed H:M based on UCP SNP rs1800849 (p = 0.905). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.84  A plot demonstrating no statistically significant difference in planar washout based on UCP SNP rs1800849 (p = 0.814). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.85  A plot demonstrating no statistically significant difference in planar early H:M based on UCP SNP rs660339 (p = 0.980). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.86 A plot demonstrating no statistically significant
difference in planar early H:M based on UCP SNP
rs660339 (p = 0.905). This observation is supported
by the considerable overlap of the 95% CIs
represented by the top and bottom portion of the
diamonds.

Figure 6.87 A plot demonstrating no statistically significant
difference in planar washout based on UCP SNP
rs660339 (p = 0.814). This observation is supported
by the considerable overlap of the 95% CIs
represented by the top and bottom portion of the
diamonds.

Figure 6.88 A plot demonstrating no statistically significant
difference in planar early H:M based on UCP SNP
rs659366 (p = 0.490). This observation is supported
by the considerable overlap of the 95% CIs
represented by the top and bottom portion of the
diamonds.

Figure 6.89 A plot demonstrating no statistically significant
difference in planar delayed H:M based on UCP
SNP rs659366 (p = 0.280). This observation is
supported by the considerable overlap of the 95%
CIs represented by the top and bottom portion of the
diamonds.

Figure 6.90 A plot demonstrating no statistically significant
difference in planar washout based on UCP SNP
rs659366 (p = 0.255). This observation is supported
by the considerable overlap of the 95% CIs
represented by the top and bottom portion of the
diamonds.

Figure 6.91 TL versus early H:M. No statistically significant
correlation was observed (R2 = 0.02, p = 0.533).

Figure 6.92 TL versus delayed H:M. No statistically significant
correlation was observed (R2 = 0.01, p = 0.68).

Figure 6.93 TL versus global washout. No statistically significant
correlation was observed (R2 < 0.00, p = 0.782).

Figure 6.94 T/S versus early H:M. No statistically significant
correlation was observed (R2 = 0.02, p = 0.571).

Figure 6.95 T/S versus delayed H:M. No statistically significant
correlation was observed (R2 = 0.01, p = 0.732).

Figure 6.96 T/S versus global planar washout. No statistically
significant correlation was observed (R2 = 0.02, p =
0.586).

Figure 6.97 T/S_mean versus early H:M. A statistically
significant correlation was observed (R2 = 0.23, p =
0.033)
Figure 6.98  T/S_mean versus delayed H:M. No statistically significant correlation was observed (R^2 = 0.12, p = 0.147).

Figure 6.99  T/S_mean versus global washout and T/S. No statistically significant correlation was observed (R^2 = 0.02, p = 0.609).

Figure 6.100  A plot demonstrating no statistically significant difference in TL based on CE (p = 0.264). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.101  A plot demonstrating no statistically significant difference in T/S based on CE (p = 0.558). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.102  A plot demonstrating no statistically significant difference in T/S_mean based on CE (p = 0.497). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.103  Kaplan–Meier survival curves of cardiac event rates in patients with CHF divided into 2 groups according to global delayed H:M. Patients with H:M ≤ 1.6 had more CE than those with H:M > 1.6 (p = 0.248).

Figure 6.104  Kaplan–Meier survival curves of cardiac event rates in patients with CHF divided into 2 groups according to global delayed H:M. Patients with H:M ≤ 1.5 had more CE than those with H:M > 1.5 (p = 0.046).

Figure 6.105  Kaplan–Meier survival curves of cardiac event rates in patients with CHF divided into 2 groups according to global washout. Patients with washout > 27% had more CE than those with washout ≤ 27% (p = 0.003).

Figure 6.106  Age versus early whole SPECT MUP. No statistically significant correlation observed (R^2 = 0.04, p = 0.378).

Figure 6.107  Age versus delayed whole SPECT MUP. No statistically significant correlation observed (R^2 = 0.02, p = 0.511).

Figure 6.108  Age versus whole SPECT washout. No statistically significant correlation observed (R^2 = 0.04, p = 0.382).

Figure 6.109  LVEF early versus early whole SPECT MUP. Statistically significant correlation was observed (R^2 = 0.25, p = 0.017).
Figure 6.110  LVEF early versus delayed whole SPECT MUP. Statistically significant correlation was observed (R^2 = 0.18, p = 0.048).

Figure 6.111  LVEF early versus whole SPECT washout. No statistically significant correlation observed (R^2 = 0.15, p = 0.079).

Figure 6.112  ΔLVEF versus early whole SPECT MUP. No statistically significant correlation was observed (R^2 = 0.07, p = 0.221).

Figure 6.113  ΔLVEF versus delayed whole SPECT MUP. No statistically significant correlation was observed (R^2 < 0.01, p = 0.870).

Figure 6.114  ΔLVEF versus whole SPECT washout. No statistically significant correlation observed (R^2 = 0.07, p = 0.220).

Figure 6.115  Early H:M versus whole SPECT early MUP. Statistically significant correlation was noted (R^2 = 0.44, p < 0.001).

Figure 6.116  Delayed H:M versus whole SPECT delayed MUP. Statistically significant correlation was observed (R^2 = 0.45, p < 0.001).

Figure 6.117  EDV versus whole SPECT early MUP. No statistically significant correlation was observed (R^2 < 0.01, p = 0.829).

Figure 6.118  EDV versus whole SPECT delayed MUP. No statistically significant correlation between was observed (R^2 < 0.01, p = 0.668).

Figure 6.119  Planar washout versus whole SPECT washout. Statistically significant correlation was observed (R^2 = 0.27, p = 0.013).

Figure 6.120  A plot demonstrating no statistically significant difference in early whole SPECT MUP based on ΔLVEF-5% (p = 0.339). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.121  A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on ΔLVEF-5% (p = 0.858). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.122 A plot demonstrating no statistically significant difference in whole SPECT washout based on ΔLVEF-5% (p = 0.671). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.123 A plot demonstrating no statistically significant difference in early whole SPECT MUP based on CE (p = 0.998). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.124 A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on CE (p = 0.814). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.125 A plot demonstrating no statistically significant difference in whole SPECT washout based on CE (p = 0.509). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.126 A plot demonstrating no statistically significant difference in early whole SPECT MUP based on ACE genotype (p = 0.088). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.127 A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on ACE genotype (p = 0.206). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.128 A plot demonstrating no statistically significant difference in whole SPECT washout based on ACE genotype (p = 0.255). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.129 A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs1800849 (p = 0.890). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.130 A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on UCP SNP rs1800849 (p = 0.414). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.131 A plot demonstrating no statistically significant difference in whole SPECT washout based on UCP SNP rs1800849 (p = 0.742). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.132 A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs660339 (p = 0.085). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.133 A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on UCP SNP rs660339 (p = 0.501). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.134 A plot demonstrating no statistically significant difference in whole SPECT washout based on UCP SNP rs660339 (p = 0.648). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.135 A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs659366 (p = 0.014). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.136 A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs659366 (p = 0.109). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.137 A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs659366 (p = 0.242). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.138 TL versus whole SPECT early MUP. No statistically significant correlation was observed (R² = 0.02, p = 0.581).

Figure 6.139 TL versus whole SPECT delayed MUP. No statistically significant correlation was observed (R² = 0.13, p = 0.113).

Figure 6.140 TL versus whole SPECT washout. No statistically significant correlation observed (R² = 0.02, p = 0.563).

Figure 6.141 T/S versus whole SPECT early MUP and T/S. No statistically significant correlation was observed (R² = 0.05, p = 0.345).

Figure 6.142 T/S versus whole SPECT delayed MUP. No statistically significant correlation was observed (R² = 0.01, p = 0.669).

Figure 6.143 T/S versus whole SPECT washout. No statistically significant change correlation was noted (R² < 0.00, p = 0.693).

Figure 6.144 T/S_mean versus whole SPECT early MUP. Statistically significant correlation seen (R² = 0.23, p = 0.031).

Figure 6.145 T/S_mean versus whole SPECT delayed MUP. No statistically significant correlation observed (R² = 0.06, p = 0.306).

Figure 6.146 T/S_mean versus whole SPECT washout. Non-statistically significant correlation was noted (R² = 0.04, p = 0.391).

Figure 6.147 Graph of planar early H:M versus 123I-mIBG early TDS. Non-statistically significant correlation was noted (R² = 0.01, p = 0.608).

Figure 6.148 Planar delayed H:M versus 123I-mIBG delayed TDS. No statistically significant correlation was noted (R² = 0.05, p = 0.338).

Figure 6.149 123I-mIBG early TDS versus early whole SPECT MUP. Non-statistically significant correlation was noted (R² = 0.17, p = 0.060).

Figure 6.150 123I-mIBG delayed TDS versus delayed whole SPECT MUP. No statistically significant correlation was noted (R² = 0.07, p = 0.234).

Figure 6.151 123I-mIBG early TDS versus early anterior MUP. No statistically significant correlation was noted (R² = 0.13, p = 0.101).

Figure 6.152 123I-mIBG early TDS versus early lateral MUP. No statistically significant correlation was noted (R² = 0.10, p = 0.146).
Figure 6.153 123I-mIBG early TDS versus early lateral MUP. Statistically significant correlation was observed ($R^2 = 0.21$, $p = 0.033$).

Figure 6.154 123I-mIBG early TDS versus early lateral MUP. Statistically significant correlation was observed ($R^2 = 0.19$, $p = 0.044$).

Figure 6.155 123I-mIBG early TDS versus early luminal MUP. Statistically significant correlation was observed ($R^2 = 0.44$, $p < 0.001$).

Figure 6.156 123I-mIBG early TDS versus early luminal MUP. Non-statistically significant correlation was noted ($R^2 = 0.16$, $p = 0.068$).

Figure 6.157 123I-mIBG late TDS versus delayed anterior MUP. No statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.316$).

Figure 6.158 123I-mIBG late TDS versus delayed lateral MUP. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.379$).

Figure 6.159 123I-mIBG late TDS versus delayed inferior MUP. Statistically significant correlation was noted ($R^2 = 0.18$, $p = 0.050$).

Figure 6.160 123I-mIBG late TDS versus delayed septal MUP. Statistically significant correlation was noted ($R^2 = 0.19$, $p = 0.041$).

Figure 6.161 123I-mIBG late TDS versus delayed apical MUP. Statistically significant correlation was noted ($R^2 = 0.28$, $p = 0.011$).

Figure 6.162 123I-mIBG late TDS versus delayed luminal MUP. Non-statistically significant correlation was noted ($R^2 = 0.11$, $p = 0.132$).

Figure 6.163 123I-mIBG early TDS versus anterior RW%. Non-statistically significant correlation was noted ($R^2 = 0.06$, $p = 0.278$).

Figure 6.164 123I-mIBG early TDS versus lateral RW%. Non-statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.923$).

Figure 6.165 123I-mIBG early TDS versus lateral RW%. Non-statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.322$).

Figure 6.166 123I-mIBG early TDS versus septal RW%. Statistically significant correlation was noted ($R^2 = 0.41$, $p = 0.001$).

Figure 6.167 123I-mIBG early TDS versus apical RW%. Statistically significant correlation was noted ($R^2 = 0.21$, $p = 0.034$).
Figure 6.168 123I-mIBG early TDS versus luminal RW%. Non-statistically significant correlation was noted (R² = 0.41, p = 0.001).

Figure 6.169 123I-mIBG early TDS versus whole SPECT RW%. Statistically significant correlation was noted (R² = 0.31, p = 0.008).

Figure 6.170 123I-mIBG delayed TDS versus anterior RW%. Statistically significant correlation was noted (R² = 0.19, p = 0.042).

Figure 6.171 123I-mIBG delayed TDS versus lateral RW%. Non-statistically significant correlation was noted (R² = 0.01, p = 0.623).

Figure 6.172 123I-mIBG delayed TDS versus inferior RW%. Non-statistically significant correlation was noted (R² = 0.04, p = 0.360).

Figure 6.173 123I-mIBG delayed TDS versus septal RW%. Statistically significant correlation was noted (R² = 0.69, p < 0.001).

Figure 6.174 123I-mIBG delayed TDS versus apical RW%. Statistically significant correlation was noted (R² = 0.32, p = 0.007).

Figure 6.175 123I-mIBG delayed TDS versus luminal RW%. Statistically significant correlation was noted (R² = 0.28, p = 0.012).

Figure 6.176 Statistically significant correlation between delayed 123I-mIBG TDS and mean whole SPECT washout was observed (R² = 0.39, p = 0.002).

Figure 6.177 ∆TDS versus early anterior MUP. Statistically significant correlation was noted (R² = 0.25, p = 0.022).

Figure 6.178 ∆TDS versus early lateral MUP. Statistically significant correlation was noted (R² = 0.32, p = 0.007).

Figure 6.179 ∆TDS versus early inferior MUP. Statistically significant correlation was noted (R² = 0.39, p = 0.002).

Figure 6.180 ∆TDS versus early septal MUP. Non-statistically significant correlation was noted (R² = 0.12, p = 0.117).

Figure 6.181 ∆TDS versus early apical MUP. Statistically significant correlation was noted (R² = 0.35, p = 0.005).

Figure 6.182 ∆TDS versus early whole SPECT MUP. Statistically significant correlation was noted (R² = 0.23, p = 0.026).

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Figure 6.183  \( \Delta TDS \) versus delayed anterior MUP. Non-statistically significant correlation was noted (\( R^2 = 0.11, p = 0.151 \)).

Figure 6.184  \( \Delta TDS \) versus delayed lateral MUP. Non-statistically significant correlation was noted (\( R^2 = 0.17, p = 0.065 \)).

Figure 6.185  \( \Delta TDS \) versus delayed inferior MUP. Statistically significant correlation was noted (\( R^2 = 0.25, p = 0.021 \)).

Figure 6.186  \( \Delta TDS \) versus delayed septal MUP. Statistically significant correlation was noted (\( R^2 = 0.21, p = 0.036 \)).

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Figure 6.201 TL versus early lateral MUP. No statistically significant correlation was noted (R² = 0.02, p = 0.506).

Figure 6.202 TL versus early inferior MUP. No statistically significant correlation was noted (R² = 0.07, p = 0.243).

Figure 6.203 TL versus early septal MUP. No statistically significant correlation was noted (R² = 0.13, p = 0.117).

Figure 6.204 TL versus early apical MUP. No statistically significant correlation was noted (R² = 0.01, p = 0.615).

Figure 6.205 TL versus early luminal MUP. Statistically significant correlation between early luminal MUP and TL (R² = 0.21, p = 0.041).

Figure 6.206 TL versus delayed anterior MUP. No statistically significant correlation was noted (R² = 0.01, p = 0.704).

Figure 6.207 TL versus delayed lateral MUP. No statistically significant correlation was noted (R² = 0.11, p = 0.158).

Figure 6.208 TL versus delayed inferior MUP. No statistically significant correlation was noted (R² = 0.13, p = 0.116).

Figure 6.209 TL versus delayed septal MUP. Statistically significant correlation was noted (R² = 0.22, p = 0.037).

Figure 6.210 TL versus delayed apical MUP. No statistically significant correlation was noted (R² = 0.07, p = 0.261).

Figure 6.211 TL versus delayed lumen MUP. Statistically significant correlation observed between delayed lumen MUP and TL (R² = 0.25, p = 0.026).
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Figure 6.228 T/S versus delayed apical MUP. No statistically significant correlation was noted (R² = 0.03, p = 0.441).

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Figure 6.230 T/S versus anterior RW%. No statistically significant correlation was noted (R² = 0.01, p = 0.710).

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Figure 6.232 T/S versus inferior RW%. No statistically significant correlation was noted (R² = 0.01, p = 0.764).

Figure 6.233 T/S versus septal RW%. No statistically significant correlation was noted (R² = 0.04, p = 0.376).

Figure 6.234 T/S versus apical RW%. No statistically significant correlation was noted (R² = 0.02, p = 0.518).

Figure 6.235 T/S versus luminal RW%. No statistically significant correlation was noted (R² = 0.01, p = 0.640).

Figure 6.236 T/S_mean versus early anterior MUP. No statistically significant correlation was noted (R² = 0.18, p = 0.060).

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Figure 6.251  T/S_mean versus septal RW%. No statistically significant correlation was noted (R^2 < 0.01, p = 0.909).

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Figure 6.254  A plot demonstrating no statistically significant difference in early anterior MUP based on CE. (p = 0.170). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

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Figure 6.277 Kaplan–Meier survival curves for instances of CE based on RW% from inferior wall. RW% of 45% from the inferior wall was a statistically significant threshold for predicting CE (p = 0.005).

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Figure 6.279 Kaplan–Meier survival curves of study patients divided into 2 groups according to lateral RW%. RW% of 25% from the lateral wall was not statistically significant in predicting CE (p = 0.085).

Figure 6.280 Kaplan–Meier survival curves of study patients divided into 2 groups according to luminal RW%. RW% of 25% from the lateral wall was not statistically significant in predicting CE (p = 0.150).

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Figure 7.1 Early (left) and delayed (right) planar 123I-mIBG scans using MEAP showing less septal penetration (background).

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Figure 7.3 Base-line early (left) and delayed (right) 123I-mIBG scan and resting perfusion (middle) of the case study patient showing poor 123I-mIBG uptake and washout is matched with the perfusion defect.

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**List of Abbreviations and Acronyms**

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<th>Abbreviation</th>
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<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACEI</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>Ach</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AHF</td>
<td>Acute heart failure</td>
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<tr>
<td>ANP</td>
<td>Atrial natriuretic peptide</td>
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<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<tr>
<td>BNP</td>
<td>Brain natriuretic peptide</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CAN</td>
<td>Cardiac autonomic neuropathy</td>
</tr>
<tr>
<td>CE</td>
<td>Cardiac events</td>
</tr>
<tr>
<td>CHF</td>
<td>Chronic heart failure</td>
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<tr>
<td>CITP</td>
<td>C-terminal telopeptide of collagen I</td>
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<tr>
<td>cMRI</td>
<td>Cardiac MRI</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>DCM</td>
<td>Dilated cardiomyopathy</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DOPA</td>
<td>Dihydroxyphenylalanine</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ECM</td>
<td>Extracellular matrix</td>
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<tr>
<td>EMT</td>
<td>Extraneuronal monoamine transporters</td>
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<tr>
<td>ETT</td>
<td>Exercise tolerance testing</td>
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<tr>
<td>g-SPECT</td>
<td>gated-SPECT</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>HFP EF</td>
<td>Heart failure with preserved EF</td>
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<tr>
<td>HFREF</td>
<td>Heart failure with reduced ejection fraction</td>
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<td>HLA</td>
<td>Horizontal long axis</td>
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<tr>
<td>HRV</td>
<td>Heart rate variability</td>
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<tr>
<td>HTN</td>
<td>Hypertension</td>
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<tr>
<td>ICD</td>
<td>Implantable cardioverter/defibrillator</td>
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<tr>
<td>IHD</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>IL-4</td>
<td>Interleukin-4</td>
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<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>iv</td>
<td>Intra venous</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left bundle branch block</td>
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<tr>
<td>LEHR</td>
<td>Low energy high resolution collimator</td>
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<tr>
<td>LVEDV</td>
<td>LV end-diastolic</td>
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<tr>
<td>LV EF</td>
<td>Left ventricular ejection fraction</td>
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<td>LVESV</td>
<td>LV end-systolic volume</td>
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LVH  Left ventricular hypertrophy
mAchRs  muscarinic Ach receptors
MDCT  Multi-detector computed tomography
MEGP  Medium energy general purpose
mIBG  meta-iodobenzyl guanididne
miRNA  Small non-coding RNA
MPO  Myeloperoxidase
MPS  Myocardial perfusion scintigraphy
MUPI  Early and delayed uptake index
nAchRs  nicotinic Ach receptors
NE  norepinephrine
NSF-HF  Normal systolic function HF
NTproBNP  N-terminal prohormone BNP
NYHA  New York Heart Association
OR  Odds-ratio
oxLDL  oxidised low density lipoprotein
PIIIINP  Procollagen III
PINP  Procollagen I
PNS  Parasympathetic nervous system
RAAS  Renin-angiotensin-aldosterone system
RBBB  Right bundle branch block
RGHPS  Rest gated heart pool scan
rms-SD  Squared differences between successive RR intervals
SA  Short axis
SCD  Sudden cardiac death
SDNN  Standard deviation of RR intervals
SNP  Single nucleotide polymorphism
SNS  Sympathetic nervous system
SPECT  Single Photon Emission Computed Tomography
SVT  Supraventricular tachycardia
TC  Takotsubo cardiomyopathy
TDS  Total defect score
TNF-α  Tumour necrosis factor-α
UCP  Uncoupling protein
VLA  Vertical long axis
VT  Ventricular tachycardia
ΔTDS  Change in total defect score
Chapter 1

Introduction
Heart failure (HF) is a major and escalating global public health problem that has reached epidemic proportions (Roger, 2013). Twenty-three million people worldwide are estimated to have HF (Bleumink et al., 2004; Roger, 2013; Tendera, 2004). Its prevalence is increasing due to ageing of the population with stable incidence rates (Bleumink et al., 2004; Fauci et al., 2008; McMurray & Stewart, 2000; Remme & Swedberg, 2001; Roger, 2013; Tendera, 2004). More than 550,000 new cases occur each year in the United States (Roger, 2013; Thom et al., 2006), making it the most common chronic medical disorder in US (Bisognano, 2009). In Australia 325,000 people are estimated to suffer from chronic heart failure (CHF) with a prevalence of 1.5% - 2.0% of the general population, leading to an estimated cost of $1 billion (Krum et al., 2006).

The incidence of HF has not declined significantly with the American Heart Association (AHA) reporting a 22% increase in incidence over the 2005 - 2012 period in the over 45 year population (Go et al., 2013; Rosamond et al., 2007; Thom et al., 2006). Despite advances in medical therapy, HF carries a high annual mortality of about 20% with a high proportion of these deaths being sudden cardiac death (SCD) (Jessup & Brozena, 2003; Salukhe, Francis, & Sutton, 2003). The HF burden has been increasing due to ageing of the population, increasing levels of obesity, metabolic syndromes in the population and increased survival of patients suffering from acute coronary diseases (Krum et al., 2006). The cost burden worldwide has also been steadily increasing as HF patients require increasing and multiple hospitalisations (Bleumink et al., 2004; Go et al., 2013; Jessup & Brozena, 2003)
Dr. Eckardt’s description of HF as being a label for a cardiovascular syndrome that is lacking a uniform criteria for definition, highlights the problem when studying HF (Coronel, de Groot, & van Lieshout, 2001). A universally acceptable definition of HF is hampered by the variability of the clinical symptoms and signs, and of their aetiologies (Coronel et al., 2001). HF is said to occur when the heart is unable to pump blood adequately to meet the metabolic needs of the body (R. A. Clark, McLennan, Dawson, Wilkinson, & Stewart, 2004; Lenfant, 1994). The Heart Failure Society of America 2010 practice guidelines (Lindenfeld et al., 2010) describe HF as a syndrome caused by cardiac dysfunction due to either myocardial loss or dysfunction and characterised by LV dilatation, hypertrophy or both. This dysfunction leads to neurohormonal and circulatory abnormalities.

HF is a syndrome with symptoms and signs caused by cardiac dysfunction, resulting in reduced longevity (Mosterd & Hoes, 2007; Tchou et al., 1988). HF may be viewed as a progressive disorder that is initiated after an “index event” either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or alternatively disrupts the ability of the myocardium to generate force, preventing the heart from contracting normally (Libby, Bonow, Mann, & Zipes, 2007). In the face of injury to the heart, compensatory mechanisms are triggered to maintain adequate systemic perfusion and restore cardiac output. In the short term, these mechanisms can be effective in maintaining appropriate cardiac function, however if sustained chronically these compensatory processes result in global myocardial remodelling, and may cause secondary injury to the heart, perpetuating a spiral of structural and functional decline. CHF involves both mechanical failure and cardiac autonomic neuropathy with a much
reduced level of the cardiac autonomic nervous system (Francis, Goldsmith, Levine, Olivari, & Cohn, 1984).

HF diagnosis is a complex and multistep procedure. Initial presentation of the patient is usually non-specific symptoms like dyspnoea, fatigue and/or oedema. Further evaluation for the cause of these symptoms may lead to the presence of an acute or chronic heart disease, which upon further clinical, lab and imaging – primarily echocardiographic – assessment leads to the eventual diagnosis of HF (Hunt et al., 2005; Krum, Jelinek, Stewart, Sindone, & Atherton, 2011).

HF classification has been confounded by a multiplicity of terms such as acute and chronic, left and right, high and low-output, congestive and undulating. This is due to the fact that HF is diagnosed predominantly on patient presentation, with no single objective measureable imaging or biochemical parameter. The most common criterion for diagnosis is the one used in the Framingham study which employs a system of major and minor criteria and is based on signs and symptoms, whereas the prognosis and management is based on the New York Heart Association (NYHA) classification system, which again is patient symptom based (Ho, Anderson, Kannel, Grossman, & Levy, 1993). Definitive diagnosis is complicated by the fact that these signs and symptoms may be caused by non-cardiac diseases.

The existing system for classification of HF patients is the NYHA functional classification (McMurray et al., 2012). This system being symptom based and subjective may be misleading as changes in the symptoms and thus NYHA class may change without any change in the underlying cardiac status (Jessup
& Brozena, 2003; Packer & Cohn, 1999; Wieczorek et al., 2002). The main issue with NYHA is that it is bidirectional with the patients moving from one class to the other in both directions with change in patient medication or some concomitant illness (Bennett, Riegel, Bittner, & Nichols, 2002; Currie et al., 2011). Dependence on NYHA for guiding implantable cardioverter-defibrillator (ICD) implantation leads to a significant device failure rate (Gerson, Abdallah, Muth, & Costea, 2010). Alternative classification system, based on cardiac structural abnormality has been proposed by the American College of Cardiology (ACC) and AHA. The ACC/AHA HF classification in unidirectional, thus once patients’ progress from one class to the next, there is no regression as it is based on underlying cardiac status, thus if ICD implantation is based on this system, there is likely to be lower rate of device failure (Hunt et al., 2005; McMurray et al., 2012).

Management of HF is also quite complicated. Multiple pharmaceutical and non-pharmaceutical interventions are required to maintain optimal patient health. Counterproductive activation of the renin-angiotensin-aldosterone axis (RAAS) needs to be disrupted, fluid overload needs to be managed and myocardial contractile support provided in cases where required. In patients where there is a risk of SCD, ICD implantation may be needed. It requires treatment to be individualised depending on the presenting symptoms. Death in HF patients usually occurs due to one of two mechanisms, progressive HF or SCD (Bradley et al., 2003). Prevention of mortality due to progression of HF or SCD is the main aim of treatment. Progressive HF is primarily managed by medical therapy and may ultimately require cardiac transplant, however device therapy is
needed for prevention of electrical disturbances leading to SCD (Currie et al., 2011).

Treatment of the underlying cause may lead to a slowing or stoppage of the progression of disease, while symptomatic treatment may reduce the morbidity. Fluid and sodium retention require reduction in the sodium intake and the use of diuretics in case it does not suffice, along with angiotensin converting enzyme inhibitor (ACEI), and a β-blocker (Hunt et al., 2005). Rhythm disturbances require use of digoxin, however its inability to control ventricular response during exercise requires further measures such as ICD implantation (Hunt et al., 2005; Krum et al., 2011; O’Brien et al., 2001; Sanders, Hlatky, & Owens, 2005). ICD implantation is a costly affair with a number of ICDs not discharging during the patients' lifetime, with as many as one-third of the patients who suffer SCD are ineligible for ICDs under the existing criteria (Allen LaPointe et al., 2011; Currie et al., 2011; O’Brien et al., 2001).

The existing system of SCD management in HF imposes a large and sometimes unnecessary burden on the health care systems and brings into question the rationale for continuing to use the existing management strategies (O’Brien et al., 2001). This problem can be mitigated by the use of molecular imaging. The agent that has to date provided evidence of efficacy in this regard is meta-iodobenzyl guanididne (mIBG). It can be labelled with Iodine-123 making it a practical imaging agent. The existing approach for use of 123I-mIBG imaging has been a global one, which fails to take in account the initial regional nature of the disease (Currie et al., 2011).
Chapter 2

Background
2.1 INTRODUCTION

Our understanding of the aetiology and progression of HF has changed from a simple cardiac injury and overload to a complex interplay of genetic, neurohormonal, inflammatory, and biochemical changes acting on the cardiac myocytes and/or the interstitium (Braunwald, 2008; Choudhary et al., 2013; Emdin, Vittorini, Passino, & Clerico, 2009). There is a sustained sympathetic overdrive in patients with HF, with concomitant autonomic nervous system failure which can lead to SCD (Carrio, Cowie, Yamazaki, Udelson, & Camici, 2010; Currie et al., 2011). An understanding of the nature of the cardiac autonomic neuropathy (CAN) is needed to understand the likelihood of a patient suffering SCD. Molecular imaging has the ability to visualise and quantify the sympathetic nervous system (SNS) of the heart and make it a valuable tool for diagnosis and prognosis of HF.

2.2 AUTONOMIC NERVOUS SYSTEM

The autonomic nervous control system (ANS) is the primary neural mediator of the responses to external and internal stimuli and operates predominantly without conscious control (Teff, 2008). Its role is to respond to visceral sensations and excite or inhibit smooth muscles, cardiac muscles and glands (Tortora & Derrickson, 2008). It has two divisions, sympathetic and the parasympathetic which are tonically active and compose of both sensory and motor neurons (McCorry, 2007; Tortora & Derrickson, 2008). The main input is from the sensory neurons and the visceral activity is regulated via exciting or inhibiting the level of the activity (Tortora & Derrickson, 2008). The higher centre control over the ANS is exerted via the limbic system of the brain (Kardon, 2005).
Afferent nerves convey information from organs, muscles, the limbic system, the circulatory system and sensory organs to the central part of the ANS. The efferent pathways consist of the parasympathetic and the sympathetic nervous system, which have mostly opposite effects on organs (Hamill, Shapiro, & Vizzard, 2012). The functions of the parasympathetic and the sympathetic nervous system are illustrated in Figure 2.1. The sympathetic nervous system is predominant in active situations, ranging from small actions such as posture changes to “flight-fight-or-fright” actions. The parasympathetic nervous system is predominant during periods of lower activity, in most individuals this is the larger part of the day. The sympathetic output originates from the ventrolateral medulla in the brain stem and is effectuated through sympathetic preganglionic neurons located in the spinal cord at the T1-L2 segments. The parasympathetic output also originates from the brainstem (nucleus ambiguus) and is effectuated through cranial nerves (CN3, CN7, CN9, CN10) and the spinal cord at the S2-4 segments (Hamill et al., 2012). The most important neurotransmitters in the efferent part of the ANS are norepinephrine (NE) for sympathetic transmission and acetylcholine for parasympathetic transmission (Hamill et al., 2012). The first motor neuron in the autonomic motor pathway is called the preganglionic neuron. Its cell body lies in the brain or spinal cord, and its axon exits the CNS as part of the cranial or spinal nerve (Barrett, 2010; Guyton & Hall, 2006; Tortora & Derrickson, 2008). The axon of a preganglionic neuron is a small-diameter, myelinated type B fibre that usually extends to an autonomic ganglion, where it synapses with a postganglionic neuron, the second neuron in the autonomic motor pathway (Barrett, 2010; Guyton & Hall, 2006). The postganglionic neuron lies outside the CNS. Its cell body and dendrites are located in an autonomic ganglion, where it forms synapses with one or more
preganglionic axons. The axon of a postganglionic neuron is a small-diameter, unmyelinated type C fibres that terminates in the viscera (Barrett, 2010; Guyton & Hall, 2006; Tortora & Derrickson, 2008). The preganglionic neurons convey nerve impulses from the CNS to the autonomic ganglia, and postganglionic neurons relay the impulses from the autonomic ganglia to the organ (Barrett, 2010).

Figure 2.1: Functions of the parasympathetic and the sympathetic nervous system (http://medicalterms.info/anatomy/Autonomic-Nervous-System/).

The sympathetic and parasympathetic nerve fibres mainly secrete a neurotransmitter which is either acetylcholine or NE (Barrett, 2010). Those fibres that secrete acetylcholine are said to be cholinergic, while those that secrete NE are said to be adrenergic (Tortora & Derrickson, 2008). All preganglionic neurons are cholinergic in both the sympathetic and the parasympathetic nervous systems (Barrett, 2010). Almost all of the postganglionic neurons of the parasympathetic system are cholinergic (Barrett, 2010; Tortora & Derrickson, 2008). Conversely, most of the postganglionic
sympathetic neurons are adrenergic (Barrett, 2010; Tortora & Derrickson, 2008).

Autonomic postganglionic neurons do not have discrete axon terminals (Guyton & Hall, 2006). Neurotransmitters are released from numerous swellings located at intervals along the axons of these neurons, called varicosities (Guyton & Hall, 2006). Within these varicosities, neurotransmitters are synthesised and then stored in along with a rich supply of mitochondria that produce adenosine triphosphate (Guyton & Hall, 2006). The membrane of the axon contains voltage-gated sodium and potassium channels that support propagation of action potentials (Guyton & Hall, 2006). Additionally the membrane in the region of each varicosity contains voltage-gated calcium channels that open when action potential reaches them (Guyton & Hall, 2006). These calcium channels allow entry of calcium into the cytosol stimulating the release of neurotransmitter by exocytosis (Guyton & Hall, 2006). The neurotransmitter binds with specific receptors on the effector cells (Guyton & Hall, 2006). The receptor causes a conformational change in the structure of the protein molecule to which it is bound. In turn, the altered protein molecule excites or inhibits the cell either by:

- causing a change in cell membrane permeability to one or more ions or
- activating or inactivating an enzyme attached to the other end of the receptor protein (Guyton & Hall, 2006).

For a substance to serve effectively as a neurotransmitter, it must be rapidly inactivated or removed from the neuroeffector junction in order to let new signals to get through and influence effector tissue function (McCorry, 2007).
The SNS and the parasympathetic nervous system (PNS) employ different mechanism to achieve this.

### 2.2.1 Parasympathetic nervous system

The PNS is primarily concerned with the conservation of energy and maintenance of organ function during time of minimal activity (Stern, Koch, & Muth, 2000). Further, it promotes restoration of health following threats or challenges (Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996). The parasympathetic division is sometimes called the ‘rest and digest’ system (McCorry, 2007). The PNS is organised mainly for discrete and localised discharge and is rapid and reflexive in nature (Stern et al., 2000). The parasympathetic system slows the heart rate (HR) and also lowers the blood pressure (BP).

The craniosacral outflow is the source of central neuronal pathways providing the efferent innervation of peripheral ganglia of the PNS. The cranial nerves involved include cranial nerves III, VII, IX, and X, and the sacral outflow is primarily via levels S2 - S4 (Barrett, 2010; Kardon, 2005). The vagus nerve (cranial nerve X) is the most important anatomic structure by which the PNS exerts its influence, hence the term vagal is frequently used synonymously with parasympathetic (Guyton & Hall, 2006). Via the two vagus nerves, parasympathetic fibres reach the heart, lungs, stomach, gallbladder, liver, pancreas and the intestines (Tortora & Derrickson, 2008). PNS also has pre- and postganglionic neurons, but some of the preganglionic neurons travel uninterrupted into the wall of the target organ, where the postganglionic neurons are located (Figure 2.2) (Robertson, Biaggioni, Burnstock, Low, & Paton, 2012;
Thus, some of the postganglionic neurons are very short. The neurotransmitter in the parasympathetic nerve endings is acetylcholine (Ach) (Guyton & Hall, 2006).

Figure 2.2: Organisation of the parasympathetic nervous system from the spinal cord to the organs (Tortora & Derrickson, 2008).

Ach is synthesised in the terminal endings and varicosities of the cholinergic nerve fibres where it is stored in vesicles in a highly concentrated form (Mathias & Bannister, 2013). Once Ach is secreted into a tissue by a cholinergic nerve ending, it persists in the tissue for a short while it performs its nerve signal transmitter function. Then it is hydrolysed into choline and acetate by the enzyme acetylcholinesterase. The choline is then transported back into the terminal nerve ending, where it is reused for synthesis of more acetylcholine.

Two major classes of cholinergic receptors, nicotinic receptors and muscarinic receptors, are distinguished based on the findings from pharmacological studies using two acetylcholine agonists; nicotine and muscarine (Tortora & Derrickson, 2008). At least four subclasses of nicotinic receptors and five subclasses of muscarinic receptors (M1-M5) exist (Genzen, Van Cleve, & McGehee, 2001; Mathias & Bannister, 2013). Nicotinic cholinergic receptors are located on the cell bodies and dendrites of sympathetic and parasympathetic postganglionic neurons (Mathias & Bannister, 2013). ACh causes excitation of the ganglionic neuron by opening chemically gated channels in the postsynaptic membrane (Stanfield, 2013). Muscarinic receptors occur at cholinergic neuromuscular or
neuro-glandular junctions in the parasympathetic division. They also occur at the few cholinergic junctions in the sympathetic division. Muscarinic receptors are G proteins (Mathias & Bannister, 2013). Their stimulation produces longer-lasting effects than does the stimulation of nicotinic receptors. The response can be excitatory or inhibitory, depending on the activation or inactivation of specific enzymes. M2 and M3 are the main subtypes found in autonomic target organs (Mathias & Bannister, 2013). M2 receptors are located in the heart; binding of an agonist to these receptors opens potassium channels and inhibits adenylyl cyclase (Mathias & Bannister, 2013).

2.2.2 Sympathetic nervous system

The SNS helps mediate vigilance, arousal, activation, and mobilisation, and prompts bodily resources to cope with increased metabolic needs during challenging situations (Sapolsky, 2004). The SNS normally is continuously active; the degree of activity varies from moment to moment (Stern et al., 2000). However, during emergencies or threat, activity of the sympathetic nervous system peaks. The sympathetic division is thus closely linked to the ‘fight-or-flight’ response, also called the acute stress response, which triggers rises in respiration, HR and BP. The sympathetic nervous system consists of two chains of ganglia, which lie parallel to the vertebral column, two prevertebral ganglia (the celiac ganglion and hypogastric plexus) and nerves, which extend from ganglia to the target organs, such as eye, heart, bronchi, pylorus, adrenal medulla and trigone. Consequently signals from the cord passes through preganglionic neurons, the ganglion and postganglionic neurons to the target organ (Figure 2.3). The neurotransmitter in preganglionic nerve endings is
acetylcholine, but most of the postganglionic neurons secrete NE (Guyton & Hall, 2006).

Figure 2.3: Organisation of the sympathetic nervous system from the spinal cord to the effected organ (Tortora & Derrickson, 2008).

NE is synthesised from synthesised from tyrosine in noradrenergic nerve terminals (Figure 2.4). Tyrosine is first converted to dihydroxyphenylalanine (DOPA), the rate-limiting step in catecholamine synthesis, by tyrosine hydroxylase and finally to dopamine (Barrett, 2010). A carrier, that can be blocked by reserpine, transports dopamine into the vesicle, where it is converted to NE by dopamine-β-hydroxylase (Guyton & Hall, 2006).
Figure 2.4: The adrenergic nervous system. Endogenous catecholamines are synthesised from tyrosine in sequential steps to L-DOPA by tyrosine hydroxylase, dopamine by aromatic amino acid decarboxylase, and NE by dopamine β-hydroxylase. After exocytosis, NE may be transported back into synaptic vesicles by the NE transporter (NET) and vesicular monoamine transporter (VMAT). Catecholamines are metabolised by monoamine oxidase (MAO) or catechol O-methyltransferase (COMT). Binding of NE to α2-adrenoceptors on the surface of sympathetic terminals causes pre-synaptic feedback inhibition of NE release (Hein, 2006).

The biological effects of catecholamines are mediated by adrenergic receptors on the surface of target tissue cells. Historically, adrenergic receptor subtypes were classified according to the particular response elicited after the administration of various sympathetic stimulating drugs: those that elicited an excitatory response were designated alpha (α), and those that elicited an inhibitory response were designated beta (β) (Ahlquist, 1966). Subsequent investigations uncovered that the excitatory or inhibitory responses were dependent on the identity of associated G protein subunits (Birnbaumer, 1990; Gilman, 1987). To date at least nine subtypes of adrenoceptors have been
cloned, including six α- (α1A, α1B, α1D, α2A, α2B and α2C) and three β-subtypes (β1, β2 and β3), which have been found in different proportions in numerous tissues throughout the body (Lymperopoulos, Rengo, & Koch, 2013). The physiological relevance of adrenergic receptor subtype diversity has been investigated using both pharmacological ligands and the targeted deletion of receptor genes in mice (Philipp & Hein, 2004). The β-adrenoceptor family is the primary receptor subtype found in cardiac and skeletal muscle (Kaumann & Molenaar, 1997; Lymperopoulos et al., 2013; Lynch & Ryall, 2008). However, a smaller population of α-adrenoceptors are also present, often associated with blood vessels and muscle spindle fibres (Bombardi et al., 2006), and are expressed in higher proportions in highly vascularised slow-twitch muscles (Rattigan et al., 1986).

Upon interaction with NE, α-1 receptors exert limited positive inotropic effects on the cardiac muscles, secretions from salivary glands and contraction of the prostate (Barrett, 2010; Strittmatter et al., 2012). α-2 receptors are located in the brain and peripheral nerves (Gilsbach & Hein, 2012; Lehto et al., 2015). α-2 receptors serve as autoceptors on sympathetic nerves and is a part of negative feedback loop, inhibiting the release of NE (Berthelsen & Pettinger, 1977; Gilsbach & Hein, 2012). Furthermore, these receptors also mediate metabolic and endocrine changes such as inhibition of lipolysis in adipose tissue and reduction of insulin release from the pancreas (Barrett, 2010). β-1 receptors cause a positive inotropic and chronotropic effects on the heart and release of renin from kidneys (Barrett, 2010). β-2 receptors relax smooth muscles of the bronchi, pelvic organs and the vascular structures of the gut and skeletal
muscle (Barrett, 2010). β-2 receptors located in liver and skeletal muscle elicit activation of glycogenolysis and gluconeogenesis (Guyton & Hall, 2006).

The action of NE is terminated by reuptake of free NE into the pre-synaptic nerve ending, or it is broken down and inactivated by two relatively slow-acting enzymes: catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) (Tortora & Derrickson, 2008). The NE that undergoes reuptake is retained, concentrated, and stored in the granules, or it is metabolised by intraneuronal MAO (Kardon, 2005). The reuptake of catecholamines from the synaptic cleft is mediated by high affinity, low capacity, sodium-chloride dependent, transporters present in the outer membrane of the presynaptic nerve endings (Robertson et al., 2012). This transport system is also known as the uptake-1 mechanism (Robertson et al., 2012). In addition to uptake-1, catecholamines are removed from the circulation by a second transport system. This second transport system consists of sodium-chloride independent, corticosterone-sensitive, high-capacity extraneuronal monoamine transporters (EMT), originally discovered as a transport mechanism in rat heart and designated as uptake-2 mechanism (Iversen, 1997).

### 2.3 CARDIAC AUTONOMIC SUPPLY

The heart is richly supplied by the sympathetic and parasympathetic nervous systems (Figure 2.5). The blood supply of the heart and the HR are controlled by the interaction of the sympathetic and the parasympathetic nerve supply (Table 2.1) (Carrió, 2001; Patel & Iskandrian, 2002). The heart is innervated by the parasympathetic nervous system via the vagal nerve and by the sympathetic nervous system via nerves arising from the upper thoracic region of
the spinal cord (Tortora & Derrickson, 2008). Baroreflexes buffer blood pressure, and thereby play a central role in the autonomic regulation of the cardiovascular system (Tortora & Derrickson, 2008). Baroreceptors are not directly sensitive to blood pressure, but rather to the mechanical deformation of the nerve endings during stretching of the vascular wall (Robertson et al., 2012). Two types of baroreceptors can be distinguished. Cardiopulmonary baroreceptors are localised in the heart, vena cava, and pulmonary vasculature and respond to changes in central venous pressure, whereas arterial baroreceptors in the aortic arch and carotid sinuses respond to changes in arterial pressure (Robertson et al., 2012; Tortora & Derrickson, 2008). When venous return and arterial blood pressure increase, the sympathetic outflow to the heart and peripheral vasculature is inhibited and the parasympathetic outflow is stimulated, resulting in a decreased peripheral resistance and decreased heart rate (Martini, Nath, & Bartholomew, 2011). A decrease in venous return and arterial blood pressure results in more sympathetic outflow, decreased parasympathetic outflow, an increase in peripheral resistance and an increase in heart rate (Martini et al., 2011).
Figure 2.5: Cardiac sympathetic and parasympathetic nerve supply (Martini et al., 2011, p. 698).
Table 2.1: Cardiac and vascular effects of stimulation of the SNS and PNS.

<table>
<thead>
<tr>
<th></th>
<th>SNS</th>
<th>PNS</th>
</tr>
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<tbody>
<tr>
<td><strong>Heart</strong></td>
<td>1. Positive chronotropic effect: increases heart rate</td>
<td>1. Negative chronotropic effect: decreases heart rate</td>
</tr>
<tr>
<td></td>
<td>3. Positive inotropic effect: increases cardiac (ventricle and atrium) contraction</td>
<td>3. Negative inotropic effect: decreases cardiac (atrium) contraction</td>
</tr>
<tr>
<td><strong>Blood vessels</strong></td>
<td>Coronaries: Constricts (α); dilates (β)</td>
<td>little effect in most organs and dilation in some organs</td>
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Physiologically, parasympathetic tonic activation or ‘vagal tone’ plays an important role in maintenance of this autonomic balance within the body and particularly in the heart (Malik et al., 1996; Yasuma & Hayano, 2004). Afferent activation of the vagus nerve can modulate efferent sympathetic and parasympathetic functions centrally (Olshansky, Sabbah, Hauptman, & Colucci, 2008). The parasympathetic nervous system can inhibit sympathetic nerve traffic pre-synaptically, while sympathetic activation can inhibit parasympathetic activation pre-synaptically (Olshansky et al., 2008).

The balance between the PNS and the SNS is especially evident in the heart. Maintenance of this balance is important for the control of heart rate, electrical conduction rates, and contractility. Cardiac neuron innervation of the heart employs a unique electrochemical system innervated by both branches of the autonomic nervous system. PNS control of the heart is accomplished through the vagal nerve and intra-cardiac ganglia, while SNS control is primarily...
accomplished through stellate (cervical and superior thoracic) ganglia (Barrett, 2010; Martini et al., 2011). A number of diseases have the effect of disturbing the delicate balance between excess stimulation or loss of either the sympathetic or the parasympathetic component of the autonomic nerve supply, leading to altered haemodynamic states (Braune, Reinhardt, Schnitzer, Riedel, & Lücking, 1999; Carrió, 2001; Courbon et al., 2003).

2.3.1 Parasympathetic cardiac nerve supply

The parasympathetic nervous system has a strong relationship with cardiac function and health. Resting heart rate is primarily under the influence of parasympathetic outflow and inhibition (Malik et al., 1996; Yasuma & Hayano, 2004). Vagal control of the heart occurs on a beat-by-beat control. It has been postulated that parasympathetic activation of the heart evokes its responses within only 50-100ms, mostly due to relatively short postganglionic neurons, and because of very immediate inactivation of the neurotransmitter (Koeppen & Stanton, 2010).

Reduced function of the parasympathetic nervous system, reflected by reduced heart rate variability (HRV), is associated with ageing and a number of disease states, including diabetes and hypertension (HTN), with reductions in normotensive patients with a family history of HTN also noted (Lindmark, Wiklund, Bjerle, & Eriksson, 2003; Maver, Štrucl, & Accetto, 2004; Pikkujämsä et al., 1998). Two primary cholinergic receptors are known to be involved in parasympathetic modulation of the heart; muscarinic Ach receptors (mAchRs) which are G-protein coupled receptors and nicotinic Ach receptors (nAchRs) (Olshansky et al., 2008). The mAchRs are located in both the atria and the
ventricles with the majority being in the ventricles. PNS effects on cardiac function appear to be mainly controlled by M_2, M_3, and M_4 receptors, with the different subtypes having different effects (Brodde & Leineweber, 2004). The M_2 receptor seems to play a primary role in reduction of heart rate and decreasing contractility by directly acting on the atria and indirectly acting on the ventricles (Brodde & Leineweber, 2004). ACh slows the pacemaker potential decay and hyperpolarises the membrane, resulting in slowing of heart rate (Levick, 2013).

2.3.2 Sympathetic cardiac nerve supply

SNS innervates the entire heart from the apex to base (Carrió, 2001). The postganglionic cardiac sympathetic fibres from the stellate ganglion approach the base of the heart along the adventitial surface of the great vessels (Janes et al., 1986). From the base of the heart, these fibres are distributed to the various chambers as an epicardial plexus (Robertson et al., 2012). The effects of sympathetic stimulation decay gradually after stimulation is stopped (Robertson et al., 2012). The reuptake system takes up to 70% of the NE released during sympathetic stimulation; much of the remainder is carried away by the bloodstream (Goldstein, Brush, Eisenhofer, Stull, & Esler, 1988; Kingwell et al., 1994). These processes are slow. The onset of the cardiac response to sympathetic stimulation begins slowly for two main reasons. First, NE appears to be released slowly from the sympathetic nerve terminals (Gonon, Msghina, & Stjärne, 1993; Robertson et al., 2012). Second, the cardiac effects of the neurally released NE are mediated mainly by a relatively slow second messenger system involving cAMP (Polson, Goldberg, & Shideman, 1977). Hence, sympathetic activity alters the heart rate and AV conduction much more slowly than vagal activity does (Warner & Russell, 1969).
Increased sympathetic stimulation increases discharge of the SA node and augments AV nodal conduction. In addition contractility is also enhanced, which is mediated by postsynaptic myocardial β-adrenergic receptors. These receptors are abundant in myocardium and exert chronotropich, dromotropic, and inotropic effects. Both β1 and β2 subtypes are present in a ratio of about 5:1 in the healthy human heart (Bengel & Schwaiger, 2004; Bristow & Pitt, 1993; Riemann, Schäfers, Law, Wichter, & Schober, 2003). α-adrenoreceptors are mainly present in the vascular wall but are also found in ventricular myocardium, where they account for approximately 15% of cardiac adrenergic receptors (Riemann et al., 2003).

### 2.4 CARDIAC AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

CAN is a common and serious type of neuropathy, that involves the damage to both the sympathetic and parasympathetic branches of autonomic nerves innervating the heart and blood vessels, causing abnormal regulation of HR and vascular dynamics (Vinik & Erbas, 2006). The pathogenesis of CAN is often unclear (Vinik, Maser, Mitchell, & Freeman, 2003). CAN is associated with increased risk of occurrence of cardiac CE including myocardial infarction, HF, ventricular tachycardia or fibrillation and is encountered in a number of disease processes (Vinik & Erbas, 2006; Vinik & Ziegler, 2007). The most typical clinical manifestations of CAN are (Kahn, Sisson, & Vinik, 1987; Robertson et al., 2012; Schönauer et al., 2008; Vinik & Ziegler, 2007):

- Orthostatic intolerance
- Resting tachycardia
- Exercise intolerance
- Prolongation of QT interval
- Cardiac dysrhythmias
- Painless myocardial ischaemia
- Sudden death

There are a number of disease entities where CAN occurs, and that is what the pathophysiology of CAN depends upon.

2.4.1 Cardiac autonomic neuropathy in diabetes mellitus

Diabetes is the most common cause of autonomic neuropathy. CAN, an extensively studied form of diabetic autonomic neuropathy, is defined as impairment of autonomic control of the cardiovascular system in the setting of diabetes and after exclusion of other possible causes. Diagnostic criteria and staging are still under debate. Diabetic CAN is one of the most overlooked of all serious complications of diabetes, and can cause abnormalities in the heart rate control as well as the central and peripheral vascular dynamics (Vinik & Erbas, 2006). According to a recent recommendation the presence of one abnormal cardio-vagal test identifies possible or early CAN; at least two abnormal heart rate-based tests are required for a definite or confirmed diagnosis of CAN; and orthostatic hypotension (asymptomatic or symptomatic), in addition to any heart rate-based test abnormalities, identifies a condition of severe or advanced CAN (Tesfaye et al., 2010). More advanced stages of CAN carry an increasingly worse prognosis (Vinik & Ziegler, 2007).

Damage to cardiac autonomic nerve supply is a frequent complication of diabetes that can result in exercise intolerance, resting tachycardia, postural hypotension, silent myocardial ischaemia or infarction, arrhythmias, an
increased risk of SCD, and potentially present in as many as 40% of the patients with DM (Hattori et al., 1996; Mahgoub & Abd-Elfattah, 1998; Scholte et al., 2010; Scott & Kench, 2004; Stevens et al., 1998; Vinik & Ziegler, 2007). In the initial stages it is essentially asymptomatic (Mäntysaari et al., 1992). The neuropathy starts mostly as regionally rather than being global (Arora, Bulgarelli, Ghosh-Dastidar, & Colombo, 2008; Scholte et al., 2010). The progression of this neuropathy can be halted and in view of some authors be even reversible, thereby necessitating the need for early detection (Schnell et al., 1997; Scott & Kench, 2004; Stevens, Raffel, Allman, Schwaiger, & Wieland, 1999).

2.4.2 Cardiac autonomic neuropathy in cardiomyopathies

The nexus between stress and cardiovascular disorders has been well established. It has been hypothesised that the ANS may play a role in the development of hypertrophic cardiomyopathy (HCM), with increased sympathetic activity in the heart. A down-regulation of myocardial beta adrenoreceptors has previously been observed in these patients, probably due to locally increased levels of NE, and was shown to be associated with a reduced catecholamine reuptake by myocardial sympathetic nerve terminals (Brush et al., 1989; Lefroy et al., 1993; Schäfers et al., 1998). Unlike patients with congestive heart failure, no significant increase in circulating catecholamines has been found in patients with HCM, which further supports the idea that locally increased neurotransmitter concentrations are important in the down-regulation of myocardial β-adrenoreceptors (Lefroy et al., 1993; Schäfers et al., 1998). These pathophysiological findings suggest the presence of an increased sympathetic drive in the myocardium of patients with HCM.
Whether this is a primary or secondary phenomenon is not fully understood. Schwartz et al. (Schwartz, Pagani, Lombardi, Malliani, & Brown, 1973) found that increased afferent sympathetic firing in anaesthetised cats was associated with reduced efferent vagal-cardiac firing, indicating that locally released catecholamines in HCM patients also could result in reduced efferent vagal-cardiac firing.

Contractile abnormalities have been known to follow acute emotional stress (Wittstein et al., 2005). Takotsubo cardiomyopathy (TC) is stress-related acute reversible ventricular apical dysfunction without any significant coronary artery lesions (Akashi et al., 2004; Buchholz & Rudan, 2007). It is theorised that the syndrome is due to autonomic imbalance with excessive sympathetic stimulation (Akashi, Barbaro, Sakurai, Nakazawa, & Miyake, 2007; Dorfman & Iskandrian, 2009). TC is associated with markedly elevated serum concentrations of catecholamines (Wittstein et al., 2005). Presentation of TC primarily involves the distal LV myocardium, which is likely explained by the distribution of sympathetic receptors, of which the greatest density is in the apex (Kume et al., 2005; Kurisu et al., 2003; Scholte et al., 2006; Ueyama et al., 2002).

2.4.3 Cardiac autonomic neuropathy in HF

There is sustained sympathetic overdrive in patients with HF, with concomitant cardiac mechanical and autonomic nervous system failure which can lead to SCD (Carrio et al., 2010; Currie et al., 2011). In HF patients inhibitory input from baroreceptors and mechanoreceptors decreases and excitatory input increases, with the net result that there is a generalised increase in SNS activity and
blunted PNS stimulation, with a resultant loss of heart rate variability and increased peripheral vascular resistance (Coats et al., 1992; Floras, 2003). Altered baroreceptor function may be due to a resetting of the reflex pathways or by the altered Na,K-ATPase activity in the baroreceptor cell (Ferguson, Abboud, & Mark, 1984). As a result of the increase in sympathetic tone, there is an increase in circulating levels of NE. The elevated levels of NE occur due to increased release from sympathetic nerve endings and spill over into the plasma, as well as reduced reuptake capacity of up to 30% (Böhm, La Rosée, Schwinger, & Erdmann, 1995; Floras, 2003; Münch et al., 2005). This determines the advance of disease, the severity of symptoms, and the mode of death (Floras & Pitt, 1993; Robertson et al., 2012). Loss of parasympathetic tone is also seen early in course of HF, which may provide conditions suitable for onset of ventricular arrhythmias (Nolan et al., 1992; Olshansky et al., 2008).

### 2.5 HEART FAILURE

A multitude of definitions of HF have been put forward (McDonagh, Gardner, Clark, & Dargie, 2011). They highlight one or several features of this complex syndrome such as haemodynamics, oxygen consumption, or exercise capacity (Dickstein et al., 2008). An unequivocal, universally acceptable definition of HF is hampered by the variability of the clinical symptoms and signs, and of their aetiologies (Coronel et al., 2001). HF is said to occur when the heart is unable to pump blood adequately to meet the metabolic needs of the body (R. A. Clark et al., 2004; Lenfant, 1994). HF is a progressive disease in which there is a discrepancy between the metabolic demands and the blood supply because of loss / dysfunction of heart muscle because of dilatation and/or hypertrophy leading to either loss of the ability to pump out enough blood or adequate filling
(Currie et al., 2011; Lindenfeld et al., 2010; Tendera, 2004). Table 2.2 enumerates the various signs and symptoms of HF.

Table 2.2: Clinical signs and symptoms of patient suffering from HF (Dickstein et al., 2008).

<table>
<thead>
<tr>
<th>HF is a clinical syndrome in which patients have the following features:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptoms typical of HF (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling) And</td>
</tr>
<tr>
<td>• Signs typical of HF (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly) And</td>
</tr>
<tr>
<td>• Objective evidence of a structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)</td>
</tr>
</tbody>
</table>

2.5.1 Epidemiology of HF

Data from the Framingham Heart Study has demonstrated major reduction in MI mortality rate over 40 years without a concomitant decline in HF incidence post-MI, indicating that although acute treatments have improved, longitudinal outcomes may not have changed despite improvements in therapy (Fox, Evans, Larson, Kannel, & Levy, 2004; Velagaleti et al., 2008). Rapid advancements in health care have led to a decline in the rates of death after onset of HF by approximately one third from the 1950s to the 1990s (Lloyd-Jones et al., 2010). It is the leading cause of hospitalisation in the geriatric population (Ford et al., 2007; Lloyd-Jones et al., 2002). That is due to an increase in the life span and better survival from acute coronary diseases (with the widespread administration of thrombolytic therapy), the increased use of platelet aggregation inhibitors, β-blockers, ACEIs and revascularisation (Ford et al., 2007; Lloyd-Jones et al., 2002; Valgimigli et al., 2005).
The global burden of HF is estimated at 26 million, which is approximately 2% – 3% of the global adult population (López-Sendón, 2011). In developed countries, expenditure on CHF is about 2% of the total healthcare budget (Berry, Murdoch, & McMurray, 2001; Zarrinkoub et al., 2013). The lifetime cost of HF per patient is nearly $110,000 per year, the majority of which represents expenses associated with hospitalisation (Dunlay et al., 2011). The cost of HF in the US and Europe is estimated to be US$ 100 billion (Wilson Tang et al., 2007). The disease burden is estimated to be 325,000 in Australia with the cost of AU$ 1 billion (Abhayaratna et al., 2006; R. A. Clark et al., 2004). The one year mortality is 20% while the estimated 4-year survival is only 50% (Lloyd-Jones et al., 2010; Wilson Tang et al., 2007). Median survival time in male patients has been estimated to be 1.7 years after initial diagnosis and 3.2 years in female patients (von Haehling, Schefold, Lainscak, Doehner, & Anker, 2009). Due to high and increasing levels of related morbidity, HF imposes a considerable burden on the health care system of nearly all developed countries because of the long term pharmacological treatment and frequent hospitalisations associated with the syndrome (J. Chen, Normand, Wang, & Krumholz, 2011; R. A. Clark et al., 2004). It is estimated to cost the national health care systems more than cancer (O’Connell, 2000; S. Stewart, MacIntyre, Hole, Capewell, & McMurray, 2001; von Haehling et al., 2009).

CHF is essentially an age related disease, with 1% of the 65+ year population and 12% of individuals over 80 years suffering from CHF, accounting for 80% of the hospitalisations due to HF in the geriatric population (Go et al., 2013; Hunt et al., 2005). The incidence has failed to decrease significantly and there is still a rather high 50% mortality at 2.3 years for males and 1.7 years for females.
(Jhund et al., 2009; Roger et al., 2004). Even with the therapy as per the national guidelines it carries a 8 – 10% annual mortality rate (Carrio et al., 2010).

In the western world, coronary artery disease, alone or in combination with hypertension, seems to be the most common cause of HF. Ischaemic heart disease (present in > 50% of new cases), HTN (about two-thirds of cases) and idiopathic dilated cardiomyopathy (around 5%–10% of cases) are most frequently observed as the underlying cause in patients with CHF (Grieve & Shah, 2003; Hunt et al., 2005; Krum et al., 2006; Lenfant, 1994). Other than IHD and HTN, valvular heart disease, arrhythmias and alcohol are other common causes of HF in developed countries (McDonagh et al., 2011).

2.5.2 Aetiology of HF

Clinically HF represents the final common ground in pathogenesis wherein various causes of heart damage converge, and in this sense, the culprit injury responsible for the initial insult to the heart has limited bearing on the pathophysiology of the resulting cardiac failure (A. J. Meredith & McManus, 2013). Many of the pathological and clinical features of HF are universal; however, the underlying aetiology of HF may impact the manifestation and speed of disease progression, and indicate specific therapeutic strategies (Libby et al., 2007).

HF can be subdivided based on the type of dysfunction present and its effect on LVEF, and also by the chronic or acute manifestation of symptoms. Damage to the myocardium can result from numerous causes: infarction, infection or
genetic causes, valvular disorders, chronic systemic HTN, pulmonary disease, aberrant ventricular filling, cardiomyopathy and drug toxicity. If the onset is rapid, requiring urgent treatment, then it is termed as acute heart failure (AHF) and if the symptoms appear gradually after a prolonged course, then it is termed as CHF.

2.5.2.1 Acute heart failure
AHF is defined as a rapid change in HF signs and symptoms due to decompensation, resulting in a need for urgent therapy or emergency admission to hospital (McDonagh et al., 2011; Swedberg et al., 2005). AHF may result from new-onset failure or an acute decompensation of existing HF, circulatory failure as a result of sepsis or cardiogenic shock, or acute myocarditis. The symptoms are primarily the result of severe pulmonary congestion due to elevated LV filling pressures (with or without low cardiac output) characterised by signs of pulmonary congestion and fluid retention (Gheorghiade et al., 2005; Hunt et al., 2005; Libby et al., 2007). Patients with AHF have a very poor prognosis. Mortality is particularly high in patients with AHF with 62.5% mortality at one year (Zannad et al., 2006). AHF syndromes represent almost 60% of the total direct costs of HF in the US and mortality ranges from 10 - 60% at 60 days post-discharge (Gheorghiade et al., 2005; Kozak, Owings, & Hall, 2005; Mebazaa, Gheorghiade, Zannad, & Parrillo, 2008).

2.5.2.2 Chronic heart failure
CHF is what affects patients with HF once they are taking appropriate therapy or have had HF for some time (McDonagh et al., 2011). A treated patient with symptoms and signs, which have remained generally unchanged for at least a
month, is said to be ‘stable’ (Dickstein et al., 2008; McMurray et al., 2012). HF with LV systolic dysfunction (LVEF<40%), is currently termed heart failure with reduced ejection fraction (HFREF) or more simply as systolic HF (Lim, Beadle, & Frenneaux, 2009; McMurray, 2010; Paulus et al., 2007). Growing recognition of the prevalence of HF signs and symptoms in the presence of maintained systolic function (LVEF>50%) has led to the newer classification of heart failure with preserved EF (HFPEF) or normal systolic function HF (NSF-HF) (Hogg & McMurray, 2005; Leong, De Pasquale, & Selvanayagam, 2010; Paulus et al., 2007). Roughly half of all HF patients have HFPEF (Hogg, Swedberg, & McMurray, 2004; Leong et al., 2010). Cardiac pump function is dependent on filling as well as ejection, and the HFPEF phenotype is often, but not always, associated with impaired diastolic function and aberrant ventricular filling. Patients with HFPEF tend to be older, female, and present with a history of HTN, diabetes or atrial fibrillation (Lam, Donal, Kraigher-Krainer, & Vasan, 2011; D. S. Lee et al., 2009).

The mechanisms underlying HFPEF continue to be elucidated, however fibrosis and abnormal ECM turnover, impaired active relaxation, and cytoskeletal structure of myocytes have been implicated in its pathogenesis (Wood, Piran, & Liu, 2011). HFREF pathophysiology is better understood, resulting from the hypertrophic and fibrotic compensatory mechanisms initiated in response to myocardial injury (A. M. Shah & Mann, 2011). Extensive scarring resulting from myocyte loss initiates a global remodelling process ultimately resulting in a globally dilated heart with reduced LVEF (McMurray, 2010). Observational studies have suggested similar mortality for both types of HF (D. S. Lee et al., 2009), however a meta analysis of outcome studies demonstrated HFPEF had
a mortality rate half that of those with HFREF (Somaratne et al., 2009). Treatment strategies remain similar for both HFPEF and HFREF, and research is continuing to better delineate their differences in pathophysiology and outcomes to develop better management strategies for these two clinically distinct HF entities.

2.5.3 Pathophysiology of CHF

The clinical syndrome of HF reflects a continuum spanning from structural and functional abnormalities with minimal clinical manifestations to emergent decline with classical clinical symptoms and signs of HF (Libby et al., 2007). The cardinal manifestations of HF are dyspnoea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral oedema (Hunt et al., 2005; Libby et al., 2007; Mosterd et al., 1999) (Table 2.3.) The majority of patients with HF have symptoms due to an impairment of LV myocardial function (Hunt et al., 2005; Libby et al., 2007).
<table>
<thead>
<tr>
<th>Dominant clinical feature</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral oedema / congestion</strong></td>
<td>Breathlessness</td>
<td>Peripheral oedema</td>
</tr>
<tr>
<td></td>
<td>Tiredness, fatigue</td>
<td>Raised jugular venous pressure</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatomegaly, ascites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluid overload (congestion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cachexia</td>
</tr>
<tr>
<td><strong>Pulmonary oedema</strong></td>
<td>Severe breathlessness at rest</td>
<td>Crackles or rales over lungs, effusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia, tachypnoea</td>
</tr>
<tr>
<td><strong>Cardiogenic shock (low output syndromes)</strong></td>
<td>Confusion</td>
<td>Poor peripheral perfusion</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
<td>SBP &lt; 90 mmHg</td>
</tr>
<tr>
<td></td>
<td>Cold periphery</td>
<td>Anuria or oliguria</td>
</tr>
<tr>
<td><strong>High blood pressure</strong> (hypertensive HF)</td>
<td>Breathlessness</td>
<td>Usually raised BP, LV hypertrophy, and preserved LVEF</td>
</tr>
<tr>
<td><strong>Right HF</strong></td>
<td>Breathlessness</td>
<td>Evidence of RV dysfunction</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Raised JVP, peripheral oedema, hepatomegaly, gut congestion</td>
</tr>
</tbody>
</table>
As a consequence of damage to the myocardium in HF, due to events such as CAD and HTN, DM, idiopathic causes such as alcohol toxicity and a variety of less common causes such as amyloidosis and inherited cardiomyopathies, myocardial remodelling can be observed at all levels, from gross structural changes, to biochemical disturbances underlying myocardial dysfunction (McDonagh et al., 2011). Remodelling represents the interplay of mechanical, neurohormonal, genetic and biochemical factors effecting changes in phenotype including function (Figure 2.6). Ultimately, decompensation occurs and clinical symptoms become evident (McDonagh et al., 2011).

Traditionally, HF was viewed in terms of haemodynamic consequences and fluid retention only resulting from depressed cardiac function (Packer, 1992). In the 1980's, the realisation that neuro-hormonal activation plays a key role in the onset and progression of HF (Packer, 1992). Meanwhile, a new paradigm for HF is emerging. Cardiomyopathy of overload and subsequent abnormalities of programmed myocardial cell death (apoptosis) is increasingly viewed as a major contributor to the transition to overt heart failure (Mann, 2010; Narula et al., 1996; Taki, Wakabayashi, Inaki, Matsunari, & Kinuya, 2011).

Molecular and cellular mechanisms are the main players orchestrating these changes, which encompass myocyte growth, myocyte death, alterations in extracellular matrix (ECM) deposition and fibroblast function, inflammation, alterations in myocyte energetics and changes in excitation-contraction coupling (Barry & Townsend, 2010; Kehat & Molkentin, 2010).
Most types of heart failure are preceded by global or regional myocardial hypertrophy (Braunwald & Bristow, 2000). LV hypertrophy (LVH) is an important and independent risk factor for development of heart failure and premature death (Ho, Pinsky, Kannel, Levy, & Pitt, 1993; Levy, Garrison, Savage, Kannel, & Castelli, 1990; Lloyd-Jones et al., 2002). LVH may have a concentric or eccentric morphology, causing either a thickening or an elongation of the cardiomyocytes and the ventricle as such, in response to pressure-overload and volume-overload, respectively (Barry & Townsend, 2010; Heineke & Molkentin, 2006; Kehat & Molkentin, 2010). Neuro-hormonal activation, in particular activation of the SNS and the RAAS, is a hallmark of cardiac hypertrophy and subsequent heart failure, in which NE and angiotensin II are the primary effectors mediating hypertrophic, apoptotic and fibrotic events in the heart (Adams, 2004).

Extracellular matrix remodelling includes fibrosis and activation of collagen dissolving enzymes leading to chamber dilatation and changes in myocardial circulation (A. M. Shah & Mann, 2011). Extracellular collagen matrix plays a major role in LV remodelling (Caulfield & Borg, 1979; Olivetti, Capasso, Sonnenblick, & Anversa, 1990). Decrease, disruption, and/or defective composition of the extracellular collagen matrix may lead to LV dilation and rupture (Caulfield & Borg, 1979; Factor, Robinson, Dominitz, & Cho, 1987; Jugdutt, 2003; Weber et al., 1992). In a healthy heart most cells are non-myocytes, of which 90-95% are fibroblasts (Eghbali et al., 1988; Eghbali, Tomek, Woods, & Bhambi, 1991; Zak, 1974). Fibroblasts and myofibroblasts produce collagen, the principal component of cardiac structure (Alberts et al., 1995; E. J. Miller & Gay, 1992; Zak, 1974).
Figure 2.6: Injury to the heart initiates compensatory mechanisms involving the myocardium, vasculature and systemic neuro-hormonal systems. Compensatory mechanisms over time result in progressive remodelling and ultimately can lead to HF. Abbreviations: ANP - atrial natriuretic peptide; BNP - brain natriuretic peptide; MMP - matrix metalloproteinase; RAAS - renin angiotensin aldosterone system; TIMP - tissue inhibitor of matrix metalloproteinases; SERCA2a - sarcoplasmic calcium ATPase 2; SNS - sympathetic nervous system.
Injury to the myocardium results in spatially and temporally heterogeneous repair processes. In the presence of disturbances in cardiac function, contractility, or excessive hemodynamic burden, the heart and circulatory system have remarkable adaptive mechanisms such as, including increases in cardiac contractility, maintenance of perfusion and/or pressure, increases in preload, augmentation of contractile elements and ECM remodelling (Dec, DiSalvo, Hajjar, & Semigran, 2005). On a myocyte level, mechanisms regulating apoptosis and hypertrophy are also modulated. But the heart has a finite capacity for compensation, and chronic maintenance of function in the face of disease is, in the end, maladaptive (Dec et al., 2005). The inexorable decline in cardiac function in heart failure is central to the progressive nature of this condition.

2.5.4 Diagnosis of Chronic HF

HF is the common endpoint of a wide range of cardiovascular and non-cardiovascular conditions. It is a clinical diagnosis where no one investigation can be considered the 'gold standard' for confirming the diagnosis. Scoring systems that combine several measures such as symptoms, signs and investigative findings that present in a patient with suspected HF are scored, and if the total score is greater than a predetermined number, the patient is classified as having HF (Cowie et al., 1997). HF is characterised by a series of compensatory responses designed to maintain perfusion pressure and redistributive flow (Francis & Cohn, 1986). The clinical signs of HF reflect the consequences more than the causes of HF. The symptoms and signs are important as they alert a clinician to the possibility that HF exists, the clinical
suspicion must be confirmed by more objective tests particularly aimed at assessing cardiac function (McMurray et al., 2012).

Diagnosis of HF requires suspicion of HF, which is why cardinal symptoms and signs of HF have an important place in the diagnostic algorithm (McDonagh et al., 2011). Patients with CHF tend to complain of dyspnoea on effort, however as the disease progresses, orthopnoea and paroxysmal nocturnal dyspnoea may ensue (Ho, Pinsky, et al., 1993; McMurray et al., 2012). Fluid retention leading to complaint of ankle swelling and tiredness is frequently a prominent symptom (Falk, Swedberg, Gaston-Johansson, & Ekman, 2007). Traditionally more weight is given to diagnosing HF if the jugular venous pressure (JVP) is elevated or there are signs of peripheral oedema (McDonagh et al., 2011). Laboratory investigations and imaging procedures are required to confirm the diagnosis of HF by demonstrating and characterising underlying cardiac disease, assist in choice of therapy and providing a reference point for measuring the effect of therapeutic interventions (McMurray, 1996).

2.5.4.1 Classification of CHF

CHF when resulting from systolic dysfunction is termed as systolic HF, while CHF without reduced LVEF is termed as diastolic failure, backward failure or HFPEF (Fukuta & Little, 2008; Kitzman et al., 2002; Redfield et al., 2003). The approach that is most commonly used to quantify the degree of functional limitation imposed by HF is the one developed by the New York Heart Association (Table 2.4). This system assigns patients to one of four functional classes, depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion
(class III), on ordinary exertion (class II), or only at levels of exertion that would limit normal individuals (class I) (Goldman, Hashimoto, Cook, & Loscalzo, 1981; Hunt et al., 2005). The NYHA suffers from poor reproducibility and validity, for researchers and practitioners to look for alternative classifications such as the Specific Activity Scale (Table 2.5) proposed by Goldman et al using the criterion described in Table 2.6 (Goldman et al., 1981; Raphael et al., 2007).

Table 2.4: NYHA Functional Classification (Goldman et al., 1981)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or angina pain.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina pain.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical causes fatigue, palpitation, dyspnoea, or angina pain.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

Table 2.5: Specific activity scale functional classification (Goldman et al., 1981)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patient can perform to completion any activity requiring ( \geq 7 ) metabolic equivalents</td>
</tr>
<tr>
<td>Class II</td>
<td>Patient can perform to completion any activity requiring ( \geq 5 ) metabolic equivalents but cannot or does not perform to completion activities requiring ( \geq 7 ) metabolic equivalents</td>
</tr>
<tr>
<td>Class III</td>
<td>Patient can perform to completion any activity requiring ( \geq 2 ) metabolic equivalents but cannot or does not perform to completion activities requiring ( \geq 5 ) metabolic equivalents</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patient cannot or does not perform to completion activities requiring ( \geq 2 ) metabolic equivalents.</td>
</tr>
</tbody>
</table>
Table 2.6: Criteria for determination of the specific activity scale functional class modified from Goldman et al (1981).

<table>
<thead>
<tr>
<th></th>
<th>Any</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Can you walk down a flight of steps without stopping? (4.5 – 5.2 mets)</td>
<td>Go to # 2</td>
<td>Go to # 4</td>
<td></td>
</tr>
<tr>
<td>2. Can you carry anything up a flight of 8 steps without stopping (5 – 5.5 mets) or can you:</td>
<td>Class III</td>
<td>Class II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. is able to have sexual intercourse (5 – 5.5 mets)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. garden, rake, weed (5.6 mets)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. roller stake, dance foxtrot (5 – 6 mets)</td>
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<tr>
<td></td>
<td></td>
<td>d. walk at a 6.4-km/h rate on level ground (5 – 6 mets)</td>
<td></td>
</tr>
<tr>
<td>3. Can you carry at least 11 kg up 8 steps (10 mets) or can you:</td>
<td>Class I</td>
<td>Class II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. carry objects that are at least 36 kg (8 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. do outdoor work - shovel snow, spade soil (7 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. do recreational activities such as skiing, basketball, touch football, squash, handball (7 – 10 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>d. jog / walk 7 km/h (9 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Can you shower without stopping (3.6 – 4.2 mets) or can you:</td>
<td>Class III</td>
<td>Go to # 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. strip and make bed (3.9 – 5 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. mop floors (4.2 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. hang washed clothes (4.4 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>d. clean windows (3.7 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>e. walk 3.7 km/h (3 – 3.5 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>f. bowl (3 – 4.4 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>g. play golf (walk and carry clubs) (4.5 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>h. push power lawn mower (4 mets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Can you dress without stopping because of symptoms? (2 – 2.3 mets)</td>
<td>Class III</td>
<td>Class IV</td>
<td></td>
</tr>
</tbody>
</table>
The staged ACC/AHA HF classification recognises that HF is quite preventable and is often preceded by asymptomatic structural and functional abnormalities. This is in contrast to the NYHA classification which is entirely functional / symptomatic, not taking into account the underlying cardiac disorder that inevitably progresses. NYHA functional classification reflects a physician’s subjective assessment, suffers from significant inter-observer variability, changes frequently over relatively brief periods of time the treatments tend not to differ appreciably across the classes (Hunt et al., 2001; Radford et al., 2005). The NYHA class may improve upon initiation or change of treatment. This ACC/AHA classification recognises that development of HF has asymptomatic and symptomatic phases and treatments at each stage may reduce the morbidity and mortality (Hunt et al., 2001). The relationship between NYHA and ACC/AHA is shown in Table 2.7.
Table 2.7: Comparison between the NYHA and ACC/AHA Classifications for HF (Currie et al., 2011).

<table>
<thead>
<tr>
<th>Description</th>
<th>NYHA classification</th>
<th>ACC/AHA classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>No limitation and no symptoms from ordinary activity</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Mild limitation with activity and comfortable at rest or with mild exertion</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td>Significant limitation with any activity and comfortable only at rest</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Discomfort with any physical activity and symptoms occurring at rest</td>
<td>IV</td>
<td>D</td>
</tr>
</tbody>
</table>

- A: High risk of developing HF but no functional or structural heart deficits
- B: Structural heart deficit but no symptoms
- C: HF symptoms due to underlying structural heart deficit with medical management
- D: Advanced disease requiring hospitalisation, transplant, or palliative care

Arrows indicate potential directions of stage progression. Horizontal alignment indicates corresponding stages between the 2 classifications.
2.5.5 Diagnosis

Early detection of CHF is the key to reduction of mortality, morbidity and cost of HF as modern therapeutic regimen has the potential to improve symptoms and quality of life, slow down the rate of disease progression, and improve survival. Unfortunately, the clinical diagnosis of CHF is known to be difficult, especially in mild cases, as many features of the condition are not organ specific, and there may be few clinical features in the early stages of the disease (R. Hobbs, 2000; Khunti, Baker, & Grimshaw, 2000). Therefore biochemical assays and imaging of the patient need to be conducted for early and accurate assessment of CHF.

2.5.5.1 Electrocardiogram

The diagnostic impact of the electrocardiogram (ECG) is rather low, however a normal ECG almost completely excludes the diagnosis of HF (Davie et al., 1996; Fauci et al., 2008; Libby et al., 2007; Remme & Swedberg, 2001). ECG changes are common in HF, such as pathological Q waves, left ventricular hypertrophy (LVH) with strain, right or left bundle branch block, atrio-ventricular (AV) block, or T wave changes (Fauci et al., 2008; Libby et al., 2007; Remme & Swedberg, 2001). Rhythm disorders such as supraventricular tachyarrhythmias (SVT) and atrial fibrillation (AF) may also be present (Libby et al., 2007; Remme & Swedberg, 2001). A French hospital study (Cohen-Solal, Desnos, Delahaye, Emeriau, & Hanania, 2000) recorded ECG abnormalities in 96% of the HF patients, in whom AF was present in 37%, conduction disturbances in 36%, LVH in 31%, while 12% had a cardiac pacemaker. Non-sustained runs of ventricular tachycardia (VT) are found in more than 40% of the patients (Podrid, Fogel, & Fuchs, 1992), (Figure 2.7). SCD in HF is hypothesised to be caused by
ventricular fibrillation as seen in Figure 2.8 (Tomaselli & Zipes, 2004). A number of HF cases are secondary to HTN, which frequently leads to strain pattern and LVH on ECG (Figure 2.9) (Gradman & Alfayoumi, 2006).

Figure 2.7: VT with uniform wide QRS complex, often associated with DCM.

Figure 2.8: Ventricular fibrillation often seen patients with DCM (http://en.wikipedia.org/wiki/Ventricular_fibrillation).
Prolonged QRS complex is presumed to occur in approximately 30% of HF patients, with left bundle branch block (LBBB) being more common than right bundle branch block (RBBB) (Kashani & Barold, 2005). HF patients with bundle branch block have a higher mortality (Baldasseroni et al., 2002; Garrigue et al., 2001). Examples of LBBB and RBBB are seen in Figure 2.10 and Figure 2.11.
Supraventricular arrhythmias i.e. SVT and AF may also be present in HF and be occasionally associated with development of HF (Figure 2.12 and Figure 2.13) (Houmsse, Tyler, & Kalbfleisch, 2011).
2.5.5.2 Biomarkers

Various criteria have been given to define and evaluate biomarkers (Braunwald, 2008; Morrow & de Lemos, 2007). The term biomarker refers is said to be a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention (Naylor, 2003). A biomarker may include clinical images, physiologic tests and tissue-based analyses (Braunwald, 2008). Contemporary biomarkers used in clinical practice, and putative novel markers, can be broadly divided into six primary biological categories which reflect various aspects of the pathophysiology of HF as it is currently understood: inflammation, oxidative stress, extracellular matrix remodelling, neurohormones, myocyte injury and myocyte strain (Braunwald, 2008; Rocchiccioli, McMurray, & Dominiczak, 2010).

CHF is characterised by an inflammatory response that correlates with HF disease severity and prognosis. Evolving cardiac injury occurs due to activation of the inflammatory system, with proinflammatory cytokines, complement
system, autoantibodies being produced and the over expression of major histocompatibility complex molecules, and adhesion molecules which perpetuate the state of inflammation (D. Chen, Assad-Kottner, Orrego, & Torre-Amione, 2008). ROS are formed in the heart during oxidative phosphorylation in the mitochondria and as a by product of normal cellular aerobic metabolism (Giordano, 2005; Grieve & Shah, 2003). An imbalance between the production of reactive oxygen species (including superoxide and hydrogen peroxide) and endogenous antioxidant defence mechanisms occurs in HF (Giordano, 2005; Grieve & Shah, 2003). The structural integrity of the myocardium is provided by fibroblasts and the ECM (Porter & Turner, 2009). The ECM contributes to the tensile strength and organization to the heart, permitting distribution of mechanical force throughout the myocardium (Baudino, Carver, Giles, & Borg, 2006). In normal hearts, fibroblast number and net collagen deposition remain low, but in the setting of injury, fibroblasts migrate and proliferate, playing a central role in tissue remodelling by increasing collagen deposition and altering the composition of the ECM (Camelliti, Borg, & Kohl, 2005). The impact of reduced cardiac output in HF stimulates the RAAS system resulting in elevated aldosterone, renin and endothelin-1 (D. J. Stewart, Cernacek, Costello, & Rouleau, 1992; van Kimmenade & Januzzi, 2012). Brain natriuretic peptide (BNP) is produced in cardiac myocytes, shares peripheral receptors with atrial natriuretic peptide, and is the most significant neurohormone in HF management the N-terminal prohormone BNP (NTproBNP) (Hall, 2004; Rocchiccioli et al., 2010). Circulating levels of the myofibrillar proteins, cardiac troponins T and I, are sensitive and specific markers for myocardial injury and have improved the diagnosis, management and risk stratification of patients with acute coronary syndromes (Braunwald, 2008). Studies have demonstrated
cardiac troponin T is a predictor of outcome in patients with CHF and elevated levels are associated with increased risk of death (Latini et al., 2007; Peacock et al., 2008). Creatine kinase MB fraction, myosin light chain 1 and fatty-acid binding protein also exist in detectable levels in the blood of CHF patients and are predictors of death (Goto et al., 2003).

Lately there has been evolution of HF biomarkers, with a rapid increase in basic, clinical and translational research, especially genetic approaches (Choudhary et al., 2013; Dec et al., 2005; van Kimmenade & Januzzi, 2012). Given the varied aetiology and the complex clinical course of the disease, certain blood tests are mandatory in all patients with HF to delineate the cause of the symptoms and to effectively manage the patient. Clinical tests need to be conducted so as:

1. to detect anaemia,
2. to identify electrolyte disorders (hypokalaemia and/or hyponatraemia),
3. to assess renal and liver function,
4. to measure brain natriuretic peptide (severity of hemodynamic impairment), and
5. to detect the status of immune system by measuring systemic inflammatory markers (Fauci et al., 2008; Libby et al., 2007; Remme & Swedberg, 2001).

2.5.5.2.1 Systemic inflammation markers

Survival of an organism is dependent upon its ability to fight off offending invaders and damaged or necrotic tissues (Kumar, Abbas, Fausto, & Aster, 2010). The immune system is the body’s natural defence mechanism against pathogens and other stresses. The host response for the accomplishment of
these is called inflammation. Inflammation is fundamentally a protective response, designed to handle both the initial cause of cell injury and the consequences of injury (Lawrence, 2007). Without inflammation infections would progress unhindered and wounds never heal (Herrington, 2014; Kumar et al., 2010). Inflammation can sometimes be inappropriately triggered or poorly controlled, and is itself the cause of tissue injury in many disorders (Herrington, 2014; Kumar et al., 2010).

An important characteristic of physiological inflammation is the ability to maintain a self-limiting phenotype (Kumar et al., 2010). Resolution of the inflammatory response is mediated by the release of specific anti-inflammatory agents coupled with the down regulation of pro-inflammatory agents and apoptosis of cell mediators of inflammation (Eming, Krieg, & Davidson, 2007; Lawrence, 2007). Resolution of inflammation also requires the apoptosis of leukocytes and phagocytic clearance by local macrophages (Lawrence, 2007). Pathological inflammation can arise when the resolution of the inflammatory response is inadequate leading to chronic inflammatory disorders (Porta et al., 2009). Chronic inflammation may occur as a progression of a prolonged acute inflammatory response due to inadequate clearance of the inflammatory stimulus by the immune system or following episodes of repeated exposure to the stimulus (Baniyash, 2006).

The link between inflammation and HF was recognised in 1990 (Levine, Kalman, Mayer, Fillit, & Packer, 1990) who noted that inflammatory cytokine level of tumour necrosis factor (TNF), were elevated in the setting of HF. Activation of neurohormones and pro-inflammatory cytokines maintains and
worsens CHF (Anker & von Haehling, 2004; Sharma, Coats, & Anker, 2000). Activation of the immune system in HF has been studied extensively, whose multiple components interact in a complex way (Anker & von Haehling, 2004). The components of the immune system that are thought to be associated with pathogenesis of HF are cytokines, adhesion molecules, autoantibodies, nitric oxide and endothelin-1 (Sharma et al., 2000). Sub-clinical systemic inflammation is associated with CHF, and their periodic monitoring is integral to proper patient management (Bozkurt, Mann, & Deswal, 2010; Mathur & Pedersen, 2008; Suleiman et al., 2006; White et al., 2006; Yndestad et al., 2006). Studies have indicated that levels of inflammatory markers correlate with the progression of HF (Bozkurt et al., 2010; Yndestad et al., 2006). Rising levels of inflammatory markers are deemed as a sign of progression of HF (Bozkurt et al., 2010; Oikonomou et al., 2011; Suleiman et al., 2006; Yndestad et al., 2006). In addition to signifying disease severity, elevated blood levels of pro-inflammatory cytokines also correlate with increased mortality in patients with HF (Bozkurt et al., 2010).

Cytokines are low molecular weight proteins with multiple immune and inflammatory actions (Bozkurt et al., 2010). Cytokines are considered to be the physical messengers of the inflammatory response (Luster, 1998). The pro-inflammatory cytokine response is controlled by a series of immunoregulatory molecules, called the "anti-inflammatory cytokines" which act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response (Bozkurt et al., 2010). Cytokines are propounded to be a contributing factor in both central and peripheral manifestation CHF (Sharma et al., 2000).
Levels of cytokines such as

1. tumour necrosis factor-α (TNF-α),
2. interleukin-6 (IL-6) and
3. interleukin-4 (IL-4),

have been observed to be raised in patients with HF (Bozkurt et al., 2010; Deswal et al., 2001; Sharma et al., 2000; Yndestad et al., 2006). Some studies have been published about elevated levels of interleukin-1, interleukin-2, interleukin-18, and interferon-γ in HF, however these studies have shown inconsistent results (Bozkurt et al., 2010). TNF-α has been established as being central to systemic inflammatory response and its elevation is directly correlated with the severity of the disease by contributing to ventricular remodelling, interstitial fibrosis, and cardiomyocyte apoptosis (Chung et al., 2003; Hamid et al., 2009; Kwon, Coté, Cuffe, Kramer, & Braun, 2003; Setsuta et al., 2004).

Elevated levels of circulating TNF-α are seen in cases with advanced HF due to stress on the heart wall (Levine et al., 1990; Torre-Amione, Vooletich, & Farmer, 2000). Increase in ventricular wall stress causes the failing heart to produce TNF-α which is likely to cause progression of HF (Baumgarten et al., 2002; Palmieri et al., 2002; Torre-Amione et al., 2000). Immuno-histochemical studies on failing myocardium demonstrated the presence of TNF-α on myocytes (Torre-Amione et al., 2000). Increase in TNF-α leads to LV remodelling, pulmonary oedema and cardiomyopathy, along with asserting a negative ionotropic effect (Hegewisch, Weh, & Hossfeld, 1990; Millar et al., 1989; Yokoyama et al., 1993).
IL-6 directly affects cell-to-cell communications between cardiac myocytes and fibroblasts (van Kimmenade & Januzzi, 2012). Increase in IL-6 concentrations are associated with cardiac dysfunction and alteration of the cardiac extracellular matrix, which provides the skeletal structure for the heart (van Kimmenade & Januzzi, 2012). IL-6 plays a pivotal role in the regulation of cardiac myocyte hypertrophy and apoptosis (Wollert & Drexler, 2001). Circulating levels of IL-6 are elevated in patients with asymptomatic left ventricular dysfunction and CHF, with a progressive increase in direct relation to functional deterioration (Wollert & Drexler, 2001). IL-6 related cytokines may act in an autocrine manner with the myocardium, with TNF-α stimulation of cardiomyocytes increasing IL-6 synthesis (Wollert & Drexler, 2001). IL-6 promoted cardiac hypertrophy characterised by chamber dilatation, increasing contractile dysfunction and impaired survival (Wollert & Drexler, 2001).

C-reactive protein (CRP) is a marker of inflammation that has been shown in epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and SCD (Ridker, 2003). CRP has been used as a biomarker in many diseases such as rheumatologic conditions, cancer, and IHD in which inflammation is an important part of pathogenesis or progression (Salazar et al., 2014). Inflammatory processes are significant in many aetiologies of HF, thus CRP has become a clinically useful marker in its evaluation in the setting of HF patients (Braunwald, 2008). Data from the Val-HeFT trial demonstrated that high levels were associated with more severe symptoms and poorer prognosis (Anand et al., 2005). CRP levels more than 25 mg/L had significant increase in short- and long-term mortality in patients with HF (Mueller, Laule-Kilian, Christ, Brunner–La Rocca, & Perruchoud, 2006).
Analyses have shown CRP to be an independent predictor of adverse outcome in both acute and chronic HF, however it might be less than ideal as a biomarker because of its non-specific nature and the lack of a therapeutic imperative associated with its increase (van Kimmenade & Januzzi, 2012; Wang et al., 2012).

An imbalance between reactive oxygen species and the endogenous antioxidant defence mechanisms can have profound deleterious effects on the pathogenesis and progression of HF (Kanani et al., 1999; Ungvári, Gupte, Recchia, Bátkai, & Pacher, 2005). This imbalance leads to increase apoptosis and necrosis of myocytes, and damage cellular proteins (Braunwald, 2008). Markers of oxidative stress such as oxidised low density lipoprotein (oxLDL), myeloperoxidase (MPO) and isoprostane have been studied in the context of HF, have been shown to correlate well with severity of HF, and are independent predictors of death in a variety of cardiovascular conditions (Cristina Polidori et al., 2004; Kameda et al., 2003; Tang et al., 2006).

The myocardium contains a collagen matrix that is a major determinant of its architecture, structural integrity and mechanical properties (Weber, 1989). Remodelling of the ECM is central in the progression of HF, and profiling of matrix biomarkers has shown promise in linking the pathophysiology of disease progression with clinical outcomes (Li, Liu, Villarreal, & Garcia, 2014). Work by several groups has indicated that circulating collagen metabolites may reflect myocardial remodelling processes and have utility in diagnosis and/or prognosis of HF (Cicoira et al., 2004; Querejeta et al., 2000; Spinale & Zile, 2013). The N-terminal peptides of procollagen I (PINP) and procollagen III (PIIINP) are
reflective of collagen synthesis, and their levels in the blood have been associated with mortality and hospitalisation in HF (Zannad et al., 2000). The C-terminal telopeptide of collagen I (CITP) is a marker of collagen degradation, and has also been linked to HF outcomes such as reduced LVEF due to stiffening of the LV (Klappacher et al., 1995). Biomarker panels incorporating MMPs, TIMPs and the collagen metabolites CITP, PINP and PIIINP may be reflective of disease pathogenesis and indicate management options in both chronic and acute HF (Biolo et al., 2009; Zile et al., 2011). Although collagen metabolites may play a role as biomarkers of HF, they are not cardiac specific and represent general collagen turnover rates in the body as a whole (Alla et al., 2006; Braunwald, 2008).

Circulating levels of the myofibrillar proteins, cardiac troponin-T and troponin-I, are sensitive and specific markers for myocardial injury and have improved the diagnosis, management and risk stratification of patients with acute coronary syndromes (Braunwald, 2008). The role of these markers in HF is increasing as more sensitive assays become available (Braunwald, 2008). Recent studies have demonstrated cardiac troponin T is a predictor of outcome in patients with acute decompensated HF and elevated levels are associated with increased risk of death in CHF patients due to progression of HF (Latini et al., 2007; Peacock et al., 2008). Creatine kinase MB fraction, myosin light chain 1 and heart fatty-acid binding protein also exist in detectable levels in the blood of HF patients and are predictors of death (Goto et al., 2003). Niessner et al (2009) have suggested role of apoptotic processes in HF, and demonstrated the value of the pro-apoptotic molecule sFAS as an independent risk factor predictor of progression of HF.
Volume overload, chamber dilatation and ventricular hypertrophy in HF increase wall tension and induce myocyte stretch with the consequent release of brain natriuretic peptide (BNP) (Hall, 2004; Pfister & Schneider, 2004). BNP acts to increase natriuresis, diuresis and arterial vasodilation, and is among the many compensatory mechanisms which occur in HF (Pfister & Schneider, 2004). As a marker of myocyte stress and neurohormonal activation, BNP, and NTproBNP, remain central in HF management with a sensitivity of 97% and specificity of 84% (Bettencourt, 2004). Novel circulating markers of myocyte stress have been identified which add to the prognostic value of BNP. Adrenomedullin (ADM) is a 52-amino acid peptide with structural homology to calcitonin gene-related peptide synthesised by many mammalian tissues including the adrenal medulla, endothelial and vascular smooth muscle cells, myocardium and central nervous system (Beltowski & Jamroz, 2004). Adrenomedullin inhibits migration and proliferation of vascular smooth muscle cells and attenuates myocardial remodelling by inhibiting protein synthesis in cardiomyocytes and proliferation of cardiac fibroblasts (Beltowski & Jamroz, 2004). Adrenomedullin, released in response to pressure and volume overload, has vasodilator, inotropic and natriuretic actions, and has been shown to be elevated in patients with HF (Khan et al., 2007). ST2 is an interleukin (IL)-1 receptor family member which has been identified as a biomarker for cardiac strain and is secreted by myocytes in response to stretch, whose elevated levels are predictive of mortality (Januzzi et al., 2007; Ky et al., 2011; Pascual-Figal et al., 2009).

Small non-coding RNAs (miRNAs) provide transcriptional and post-transcriptional regulation of gene expression by base-pairing with messenger
RNA and silencing their translation (Endo et al., 2013). miRNAs have become both a focus of HF biomarker discovery efforts, and novel therapeutic targets, due to their role in regulating clusters of genes involved in myocardial remodelling (Goren et al., 2012). A number of mouse models of cardiac injury have demonstrated mechanistic involvement of miRNAs in hypertrophic and fibrotic remodelling (Adachi et al., 2010). There are reports of circulating miRNAs demonstrating good diagnostic performance in discriminating HF from normal cases, including miR423-5p and miR-126 (Fukushima, Nakanishi, Nonogi, Goto, & Iwai, 2011; Tijsen et al., 2010). As more research on miRNA is carried out, the value of these novel markers is likely become more apparent.

2.5.5.3 Genetic markers

Age is closely related to the development and progression of cardiovascular disease, but genetic and environmental factors also play an important role. Genetic variation is differences in deoxyribonucleic acid (DNA) sequences between individuals and populations, and it can take on a variety of forms (Tajima, 1989). The most common form of genetic variation is the single nucleotide polymorphism (SNP), which occurs every 100 to 300 base-pairs along the three billion base-pair human genome (Kwok, 2003). Other common forms of genetic variation are insertion/deletions and copy number variations (Almal & Padh, 2012). Genetic variation can be common, i.e. occurring in greater than 5% of the general population (Farrall, 2004). Most genetic variation is believed to be random mutation and have neutral effect, but some genetic variation could have profound effect on phenotype, in which a single genetic variant is sufficient to cause disease (Farrall, 2004). The functional effect of genetic variation on phenotype can be easily seen for some human phenotypic
traits, but genetic variation also affects traits that are not readily visible, such as
the SNS and RAAS (Kennedy et al., 2005; P. D. Williams, Puddey, Beilin, &
Vandongen, 1993).

There is a large amount of variation within genes relevant to the SNS and RAAS, including receptors, enzymes, neurotransmitters, and hormones (Ueda,
Meredith, Morton, Connell, & Elliott, 1998). Genetic variation in the SNS and RAAS coding genes can have profound effects on protein function or
expression (M. P. Miller & Kumar, 2001). SNS and RAAS activation are integral
to HF development, progression, and pharmacotherapy, functional genetic
variants could affect the HF clinical phenotype at any or all of those stages
(Talameh, McLeod, Adams Jr, & Patterson, 2012). The relationship between
SNS and RAAS genetic variation and HF clinical outcomes, such as survival
and beta-blocker response, has not been fully characterised (Auslender, 2000;
Lymperopoulos, Rengo, & Koch, 2007).

With the better understanding of the complex interactions that underlie
development of HF, a number of genetic markers are being explored to better
understand and predict the course of the disease. Uncoupling proteins (UCPs)
are mitochondrial membrane proteins that control the membrane potential
(Laskowski & Russell, 2008). Published literature broadly agrees that there is
down-gradation of the UCP2 and UCP3 expression leading to increased levels
of reactive oxygen species, which is an important aetiological factor in cardiac
myocyte damage and increase risk of progression and SCD in CHF (Azzu,
Jastroch, Divakaruni, & Brand, 2010; Laskowski & Russell, 2008; Razeghi et al.,
2002; Salpea et al., 2010; Stephens, Bain, & Humphries, 2008).
ACEI role in the treatment of patients with HF has been well established (Díez et al., 2002; Group, 1987; Pitt et al., 2000). However, individual differences in therapy response to ACE are noted (Vegter et al., 2009). An important factor influencing ACEI efficacy is polymorphism in the ACE gene. This polymorphism was first described by Rigat et al (1990), and is based on the presence (insertion, I) or absence (deletion, D) of a 287 base pair element in intron 16 of the ACE gene. Patients with the ACE DD genotype have shown increased susceptibility for ACEI therapy in renal diseases (Perna et al., 2000; Ruggenenti et al., 2000).

Telomeres are repetitive non-coding DNA sequences, found at both ends of every chromosome, providing a protective cap (Serrano & Andrés, 2004; van der Harst et al., 2007). They prevent chromosomal ends from being recognised as double-strand breaks, inhibiting the activation of the DNA damage and repair response (Blackburn, Greider, & Szostak, 2006; Houben, Moonen, van Schooten, & Hageman, 2008). Telomere shortening, has been considered a driving force by which genetic and environmental factors jointly affect biological ageing, and possibly the risk for developing age-associated diseases. Telomeres are the extreme ends of chromosomes and shorten progressively during every cell cycle and therefore can be considered an indicator of biological age. Telomere length has been associated with cardiovascular disease and its risk factors with suggestions of association between short telomere length and atherosclerotic disease (Brouilette et al., 2007; van der Harst et al., 2007). Additionally short telomere length in the leucocytes has been
associated with systemic inflammation and oxidative stress (Bekaert et al., 2007; Houben et al., 2008).

Figure 2.14: Structure of telomeres (Houben et al., 2008).

CHF is characterised by increased myocyte apoptosis (Chimenti et al., 2003; Oh et al., 2003). Animal models have provided important pathophysiological insights into the role of telomeres and telomerase in cardiac failure and myocyte apoptosis (Leri et al., 2001; Leri et al., 2003; Oh et al., 2001; Oh et al., 2003). Telomere shortening in these mice is associated with attenuated myocyte proliferation, increased apoptosis and cardiac myocyte hypertrophy (Leri et al., 2003; Serrano & Andrés, 2004). Eventually, left ventricular failure and pathological cardiac remodelling, mimicking the end stage dilated cardiomyopathy of humans, develops in these mice with critically short telomeres (Leri et al., 2003). Endomyocardial biopsies from nineteen elderly patients with dilated cardiomyopathy when compared with biopsies from seven subjects without cardiomyopathy showed significant telomeric shortening, cellular senescence, and cell death (Chimenti et al., 2003). If short telomeres
and decreased telomerase activity has a role in pathogenesis of cardiovascular disease, telomere length in easily obtainable WBCs might provide a marker of increased cardiovascular risk and could be used to identify patients with early CHF (Brouilette et al., 2007; Fitzpatrick et al., 2007; Kajstura et al., 2000).

2.5.5.4 Exercise testing

Exercise tolerance testing (ETT) is a standard modality of integrative measurement of the haemodynamic, ventilatory and musculoskeletal systems (Albouaini, Egred, Alahmar, & Wright, 2007; Downing & Balady, 2011). During ETT, a gradually increasing physiological stress is induced. ETT testing is conducted with careful monitoring of the patients and both objective and subjective measurements (Wiklund, Comerford, & Dimenäs, 1991). CHF patients generally present with dyspnoea and/or fatigue which often limits their daily activities and, in worse cases, self-care (McDonagh et al., 2011). Hence, it is important to measure the functional capacity of CHF patients to assess the extent of their impairment. Patients with CHF may demonstrate normal cardiac performance at rest. Therefore, measures of left ventricular performance obtained at rest do not correlate well with functional capacity (Bittner, Weiner, Yusuf, & et al., 1993; Franciosa, Park, & Levine, 1981; Guyatt et al., 1985). Physiological stress, such as exercise, is usually needed to determine the extent of functional impairment (Bittner et al., 1993; Weber et al., 1992).

In clinical practice exercise testing is of limited value for the diagnosis of HF as it is often difficult to perform, may be a poor measure of limiting symptoms during daily activity, and have limited reproducibility unless patients are rigorously trained (Olsson, Swedberg, Clark, Witte, & Cleland, 2005). As a
diagnostic tool, its value only lies in excluding HF as a diagnosis in untreated patients with a normal exercise test (Libby et al., 2007; Remme & Swedberg, 2001). In patients who are elderly, frail or severely limited by HF another measure of exercise, namely the 6 minute walk test has been used as a form of exercise testing with some success (Guyatt et al., 1985; Lipkin, Scriven, Crake, & Poole-Wilson, 1986). The main role of exercise testing in CHF is more focused on functional and treatment assessment and on prognostic stratification (Fauci et al., 2008; Guyatt et al., 1985; Libby et al., 2007; Remme & Swedberg, 2001).

2.5.5.5 Chest X-ray

The chest x-ray has a long tradition in cardiology for assessing the size and shape of the heart, as well as for studying the structure and perfusion of the lung (Fauci et al., 2008; Libby et al., 2007; Remme & Swedberg, 2001). Research suggests that there is a poor relationship between heart size on a chest X-ray and CHF, as significant CHF may occur in the absence of cardiomegaly (A. L. Clark & Coats, 2000; Philbin, Garg, Danisa, & et al., 1998). The technique has lost much of its impact with the introduction of echocardiography, because the size and shape of the heart can be much better quantified by ultrasound. The presence and extent of pleural effusion are helpful information in the evaluation of HF patients and are still best determined with x-rays or CT scans (Libby et al., 2007).

2.5.5.6 Holter study

Patients with HF are known to experience a decrease in HR variability (HRV) due to ANS dysfunction (Koutelou et al., 2009; La Rovere et al., 2003). 24 hour
Holter studies can be utilised to the study the HRV and time domain indices. These indices such as the standard deviation of all the normal RR intervals (SDNN), the square root of the mean of the squared differences between successive RR intervals over 24 hours (rms-SD) and the percentage of the number of pairs of adjacent RR intervals differing by more than 50 ms in the entire Holter recording (%RR>50/pNN50), along with the frequency domain indices, can be utilised to detect the cardiac autonomic imbalance (Koutelou et al., 2009).

2.5.5.7 Echocardiography

Although the diagnosis of HF is based upon clinical findings, echocardiography is widely used and indeed advocated in patients with HF to determine aetiology, to document the degree of ventricular dysfunction and determine reversible or treatable causes of HF in a wide variety of hospital and community settings at moderate cost (Cheesman, Leech, Chambers, Monaghan, & Nihoyannopoulos, 1998; Hunt et al., 2005). Objective evidence of cardiac dysfunction, that is necessary for the diagnosis of HF, is best provided by echocardiography as enables the assessment of the anatomy and function of the heart, studying the myocardium and pericardium, and evaluating regional wall motion at rest and during pharmacological stress in HF (Fauci et al., 2008; Libby et al., 2007; Remme & Swedberg, 2001).

Although quantitative visual assessment has been shown to detect low left ventricular ejection fraction with good sensitivity and specificity, this procedure is only reliable with experienced observers and standardisation among different observers is difficult to obtain (Remme & Swedberg, 2001). The standard of
echocardiographic assessment of systolic LV function is currently the 2D biplane volume assessment (McGowan & Cleland, 2003; Thomas & Popović, 2006). Typically, this requires manual tracing of the blood-endocardial interface in diastole and systole in both the apical four and two chamber views. There are several adaptations of this method, based on different formulae but the Simpson's summation of discs is the most accurate in a wide range of clinical scenarios and is thus the recommended method (Esh-Broder, Ushakov, Imbar, & Yagel, 2004; McGowan & Cleland, 2003). In the setting of systolic impairment, the LV is likely to be dilated, spherical in shape and show impaired myocardial thickening, i.e. fibre shortening and depressed pump function (Figure 2.15). In patients with primarily diastolic abnormalities, the LV may be small, with hypertrophied walls and the LA is usually dilated (Figure 2.16).

Figure 2.15: Systolic HF. End-diastolic volume = 225 ml, end-systolic volume = 155 ml. LVEF = 31%.
Figure 2.16: NSF-HF. End-diastolic volume = 49 ml, end-systolic volume = 22 ml. LVEF = 55%.

Figure 2.17: Dilated LV with tenting of mitral valve on echocardiography
Figure 2.18: Spherical left ventricular with hypokinetic septum and dilated right ventricle on echocardiography.

Figure 2.19: Echocardiography in a patient with ischemic cardiomyopathy revealing thinned out and scarred interventricular septum (arrows).
The roles of exercise and dobutamine echo for identifying viable myocardium are clearly established (Pellikka, Nagueh, Elhendy, Kuehl, & Sawada, 2007). Recently, dobutamine echocardiography has been applied to patients with
coronary artery disease with severely depressed LV function. In patients with dilated cardiomyopathy, dobutamine echocardiography is useful in the differential diagnosis between idiopathic and ischaemic cardiomyopathy but its prognostic role remains controversial (Franchini, Traversi, Cannizzaro, Cobelli, & Pozzoli, 2000; Pinamonti, Perkan, Di Lenarda, Gregori, & Sinagra, 2002; Pratali et al., 2001; Ramahi et al., 2001; Scrutinio et al., 2000). Stress echo will continue to play an important role in patients with suspected IHD, however its routine application in all HF patients remains unproven.

The ACC/AHA guidelines for diagnosing NSF-HF, do not currently advocate a role for diagnostic echocardiography beyond assessment of systolic function (Hunt et al., 2005). The European guidelines recognise that echocardiography can assess diastolic function (Dickstein et al., 2008).

2.5.5.8 Computed Tomography

With the introduction of high resolution multi-detector computed tomography (MDCT), the role of CT has increased in cases of HF (Mangalat, Kalogeropoulos, Georgiopoulou, Stillman, & Butler, 2009). The 64-slice CT machines have enhanced spatial and temporal resolution, which allows non-invasive imaging of coronaries (Ghostine et al., 2008; Mangalat et al., 2009). MDCT also has the ability to provide reliable information on:

- LV structure and function
- Cardiac venous anatomy
- Pulmonary venous system
- RV function
Additionally it has the ability to provide information with regards to cardiac dyssynchrony evaluation, assessing cardiomyopathies, post-transplant annual follow-up, allowing it to act as alternative in patient who have contraindication to MRI (Mangalat et al., 2009). Evaluation of coronaries with MDCT is invaluable in (Ghostine et al., 2008):

- New onset HF
- Patients with known HF and previous revascularizations
- Recurrence of angina

LV structure and function, specifically LVEF, may also be determined by MDCT (Mangalat et al., 2009).

2.5.5.9 Cardiac magnetic resonance imaging

Cardiac MRI (cMRI) has a number of cardiac applications including evaluation of cardiac structure, assessment of ventricular function, and detection of myocardial infarction (Nekolla, Martinez-Moeller, & Saraste, 2009). cMRI is a unique imaging modality due to unsurpassed contrast between soft tissue structures. It is non-invasive, does not use ionising radiation and is able to provide high-resolution information about cardiac anatomy, function, flow, perfusion, viability and metabolism.

Recent advances in CMR technology have led to images of high spatial and temporal resolution (Cai et al., 2005). cMRI is the most accurate and reproducible method for the measurement of cardiac volumes, wall thicknesses and left ventricular mass. It also reliably detects thickened pericardium and quantitates myocardial necrosis, perfusion and function (Libby et al., 2007; Rajappan, Bellenger, Anderson, & Pennell, 2000; Remme & Swedberg, 2001).
However, the role of CMR in patients with HF has yet to be adequately defined (Libby et al., 2007; Paulus et al., 2007; Rajappan et al., 2000; Remme & Swedberg, 2001).

Figure 2.22: cMRI showing dilated cardiomyopathy: mid-wall late gadolinium enhancement in the septum revealing irreversibly injured myocardium (white arrows).

2.5.5.10 Rest gated heart pool scan

Measures of left ventricular function are consistently linked to end stage CE such as HF. Rest gated heart pool scan (RGHPS) provides most accurate measurements of left, and to a lesser extent, right ventricular ejection fraction and cardiac volumes (Libby et al., 2007; Remme & Swedberg, 2001; Shaw & Iskandrian, 2004). Tomographic assessment of RV and LV is most effectively carried out using SPECT RGHPS as the RV and LV are well separated (Zaret & Beller, 2010). RGHPS retains a role in HF management in assessment of
doxorubicin cardiotoxicity, and in serial assessment of patients with aortic insufficiency, congestive HF, and patients who have undergone cardiac transplantation (Zaret & Beller, 2010).

2.5.5.11 Myocardial perfusion imaging
Observational studies have suggested that as many as 70% of HF patients have IHD as the underlying aetiology. Myocardial perfusion SPECT (MPS) has a very high sensitivity and negative predictive value in predicting IHD as the underlying cause of chronic HF (Saltissi, Hockings, Croft, & Webb-Peploe, 1981; Soman et al., 2009; Tauberg, Orie, Bartlett, Cottington, & Flores, 1993). With the advent of gated-SPECT (g-SPECT) imaging, MPS has the ability to provide additional data such as regional wall motion abnormalities and LVEF, which is of significance in patients with HFREF.

Areas of myocardium which are perfused on MPS, but have reduced SNS innervation, are likely to be foci of irregular heart rhythm and be a source of fatal arrhythmias leading to SCD (Currie et al., 2011). Therefore MPS imaging is necessary in conjunction with SNS SPECT imaging for effective interpretation of regional sympathetic innervation loss (Calkins et al., 1993; Yukinaka, Nomura, Ito, & Nakaya, 1998).

2.5.5.12 Molecular imaging
Chronic sympathetic activation as a result of HF leads to a sequelae of conditions such as hypertrophy, ischemia, fibrosis, and arrhythmia. Molecular imaging techniques for cardiac SNS imaging can provide possible prognostic markers in patients with heart failure (Flotats & Carrió, 2004; Iqbal, Currie,
Greene, & Kiat, 2014; Knuuti & Sipola, 2005). The commonly used SPECT and PET imaging agents are 123I-mIBG and 11C-epinephrine (Iqbal et al., 2014).

2.6 MANAGEMENT OF CHF

The long-term goals of HF therapy are to delay or reverse disease progression, inhibit adverse cardiac remodelling, improve quality of life and symptoms, prevent hospitalisation and reduce mortality. A multi-disciplinary approach is often deployed with a primary emphasis on pharmacological therapy to achieve these goals. The majority of the evidence-based treatments that have been shown to successfully alter the natural history of HF, are based on antagonism of neurohormonal activation in HF. However, so far the success of neurohormonal antagonists is limited to the setting of HFREF. In contrast, neurohormonal antagonists have had limited or no efficacy in the setting of HFPEF, which may in part be related to a different pattern in neurohormonal activation (Benedict et al., 1993; Fonarow et al., 2007; Jessup & Brozena, 2003). Novel cell-based therapies for prevention of myocyte loss and regeneration of damaged myocardium are currently in clinical trials and show promise in stemming the cardiac damage that frequently leads to HF.

2.6.1 Pharmacological therapy

Pharmacological therapy is the mainstay of HF management and a number of different classes of medicines have been developed over the years to alleviate the symptoms and improve the quality of life and clinical status of the HF patients (McKelvie et al., 2013). Diuretics, predominantly loop diuretics are the mainstay of therapy for symptoms of hypervolaemia and/or pulmonary congestion in acute and chronic HF (Ellison, 2001). However, despite the pivotal role of diuretics in treating fluid overload and relieving symptoms of
congestion, there is no evidence that diuretics alone improve prognosis in the intermediate and longer term (Hunt et al., 2005). Mortality and morbidity benefits of beta-blockers are associated with significant heart rate reduction (Hunt et al., 2005).

2.6.1.1 Angiotensin-converting enzyme inhibitors
ACEIs are prescribed to all patients with left ventricular dysfunction regardless of symptoms as the first line therapy (Bisognano, 2009; Krum et al., 2006; Remme & Swedberg, 2001). After myocardial infarction treatment with ACEI can lead to a 28% reduction in death and hospital admission for HF in patients with left-ventricular dysfunction (Flather et al., 2000). ACEIs stabilise LV remodelling, alleviate symptoms, improve clinical status, and enhance the overall sense of well-being of patients with HF (Fauci et al., 2008; Hunt et al., 2005). RAAS suppression reduces vasoconstriction, protects against and may reverse left ventricular adverse remodelling and improves endothelial function (Collier & McDonald, 2012; Mehra, Uber, & Potluri, 2002). Mortality benefit from ACEIs was evident in SAVE, SOLVD and CONSENSUS trials (Francis et al., 1990; Pfeffer et al., 1992; Swedberg, Eneroth, Kjekshus, & Wilhelmsen, 1990). ACEI does not completely block angiotensin II generation due to alternative pathways in tissues, therefore angiotensin receptor blockers (ARBs) may be useful (Jorde et al., 2000). Treatment with ARBs also improves left ventricular remodelling and fibrosis (Díez et al., 2002). Thus, ARBs are a good alternative for those who are intolerant of ACEI in the long-term therapy of left ventricular dysfunction.
2.6.1.2 Diuretics

Many of the clinical manifestations of moderate to severe HF result from excessive salt and water retention that leads to an inappropriate volume expansion and resultant congestive symptoms. Diuretics, predominantly loop diuretics are the mainstay of therapy for symptoms of hypervolaemia and/or pulmonary congestion in acute and chronic HF. However, despite the pivotal role of diuretics in treating fluid overload and relieving symptoms of congestion, there is no evidence that diuretics alone improve prognosis in the intermediate and longer term. In stable HF patients, diuretic withdrawal has been shown to cause deterioration in haemodynamic and clinical status (Braunschweig, Linde, Eriksson, Hofman-Bang, & Rydén, 2002). On the other hand, there is also concern that diuretics can stimulate RAAS and SNS which in turn cause vasoconstriction and fluid retention and contribute to the cardiorenal syndrome (Gupta et al., 2010; Ikram, Chan, Espiner, & Nicholls, 1980). Diuretic use, especially administering in high doses, has been associated with increased adverse outcomes including worsening of HF, hospitalisation and death in both acute and chronic settings (Domanski et al., 2003; Eshaghian, Horwich, & Fonarow, 2006; Hasselblad et al., 2007; R. V. Shah et al., 2012). “Diuretic Optimization Strategies Evaluation” (DOSE) trial has settled many questions in relation to the optimal dosing strategies for loop diuretics in ADHF (Felker et al., 2011). The study showed similar efficacy in global assessment of symptoms with boluses or continuous infusion of frusemide but higher dose of frusemide (2.5 times previous oral dose equivalent) was associated with greater relief of symptoms, fluid loss, and fewer serious adverse events. Although there was transient worsening renal function, there was no sustained fall in estimated glomerular filtration rate (GFR). Diuretics can control fluid retention in HF, and
should be used to restore and maintain normal volume status in patients with congestive symptoms - dyspnoea, orthopnoea, oedema - or signs of elevated filling pressures - rales, jugular venous distension, or peripheral oedema (Ahmed, Husain, et al., 2006; Domanski et al., 2003; Fauci et al., 2008; Libby et al., 2007).

2.6.1.3 Digoxin
The digitalis glycosides exert their effects in HF patients by inhibition of sodium-potassium adenosine triphosphatase (ATPase) (Akera, Baskin, Tobin, & Brody, 1973). The benefit of digoxin therapy is thought to be due to its positive inotropic effect that increases cardiac output and decreases ventricular filling pressures. Digoxin improves cardiac function in patients with abnormal haemodynamics. In addition to its inotropic effects, digoxin may also attenuate, directly or indirectly, the neuroendocrine abnormalities in patients with HF (Ferguson et al., 1989). No significant effect on mortality or hospitalisations has been noted in ambulatory CHF patients (Ahmed, Rich, et al., 2006; Garg, Gorlin, Smith, & Yusuf, 1997).

2.6.1.4 Beta-blockers
Activation of the sympathetic nervous system is one of the cardinal pathophysiologic abnormalities in patients with CHF (Packer et al., 1996). Sympathetic nerve activity is elevated in HF, increases heart rate and work and is associated with a poor prognosis. Large scale trials have demonstrated a significant (32%) mortality benefit and reduced HF hospitalisations regardless of the aetiology of HF or functional class (Dargie & Lechat, 1999). The concomitant use of beta-blockers, ACEI/ARB and mineralocorticoid antagonist
are now incorporated into standard treatment for chronic HF, usually together with loop diuretics (Hunt et al., 2005).

All studies that show mortality and morbidity benefits of beta-blockers are associated with significant heart rate reduction even when target dose is not reached (Flannery, Gehrig-Mills, Billah, & Krum, 2008; McAlister, Wiebe, Ezekowitz, Leung, & Armstrong, 2009; Poole-Wilson et al., 2003). A post-hoc analysis from “Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure” (MERIT-HF) suggested it was the target heart rate achieved rather than the dose of beta-blocker that mattered (Wikstrand et al., 2002). The importance of heart rate reduction is further reinforced by the recent trials of Ivabradine (a selective I_f channel blocker that lowers heart rate without other cardiovascular actions) showing additional reductions in cardiovascular death and first HF hospitalisation when given to chronic HF patients with heart rate sustained at over 70bpm despite maximum tolerated doses of beta-blocker (Swedberg et al., 2010). Beta blocker therapy represents a major advance in the treatment of HF patients with a depressed EF. By reducing the harmful effects of excessive and continuous increased adrenergic drive on the myocardium, β-blockers cause time-dependent improvements in ventricular structure and function (Gheorghiade, Colucci, & Swedberg, 2003; Libby et al., 2007; Packer et al., 1996).

2.6.1.5 Limitations of pharmacotherapy

Traditional anti-arrhythmic drugs have failed to provide effective prophylaxis against SCD (Greene et al., 1993; Mason, 1993; Moyé, 2007). Although anti-arrhythmics are useful in terminating and lowering the recurrence rate of
arrhythmias, there is little evidence to suggest that they alter the outcome (Connolly et al., 2000; Kuck, Cappato, Siebels, & Rüppel, 2000; Mason, 1993). Besides the poor efficacy of anti-arrhythmic drugs, their use is further limited by a multitude of serious side effects and contraindications (Akiyama et al., 1992; L. Harris et al., 1983; Hohnloser, Kuck, & Lilienthal, 2000). Due to these reasons non-pharmacological forms of therapy were sought in order to overcome the limitations of anti-arrhythmic drugs.

2.7 IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Most patients with HF die suddenly or from progressive HF (Mehta et al., 2008). More patients with left ventricular systolic dysfunction will die suddenly before developing HF rather than dying subsequent to a diagnosis of HF (Yusuf, Pitt, Davis, Hood, & Cohn., 1992). The risk of dying from progressive HF is particularly high in the early period after diagnosis with over half of all progressive HF deaths in the first six months occurring within one month after diagnosis (Mehta et al., 2008). Large multi centre trials (MADIT, MUSTT and AVID) have shown that ICDs are beneficial in patients at high risk of SCD. SCD-HeFT study demonstrated a 7.2% absolute decrease in mortality after 5 years in heart failure patients who had ICD, when compared to those treated with amiodarone (Bardy et al., 2005).

HF patients with ventricular tachyarrhythmias or ventricular fibrillation, the ICD is highly effective in treating recurrences of these arrhythmias either by antitachycardia pacing or cardioversion–defibrillation, thereby reducing morbidity (Mushlin et al., 1998; Remme & Swedberg, 2001; Salukhe et al., 2003; Sanders et al., 2005; Tchou et al., 1988). The implantation of a defibrillator can lead to
ICDs now constitute the cornerstone in the management of ventricular arrhythmias as they have proved to reduce the absolute reduction in mortality by 1 – 3% (Currie et al., 2011). All patients who survive sudden cardiac arrest - not occurring within the context of acute MI and without an identifiable reversible precipitant - and those who are at a significantly increased risk of ventricular arrhythmias due to underlying structural, genetic or electrical cardiac disorders should be considered for ICD implantation (NICE, 2014). Implantation of an ICD is unlikely to save the average patient’s life (Stevenson & Desai, 2006). Fewer than 1 in 10 patients are likely to have their lives prolonged by the ICD placed for primary prevention of sudden death with HF (Stevenson & Desai, 2006).

The automatic ICD is a self-contained automatic system with extensive monitoring, diagnostic and therapeutic capabilities (Haqqani & Mond, 2009; Mirowski, 1985). The device consists of a pulse generator and three electrode leads (Figure 2.23.) The conductor is silver-cored tinsel wire and the insulator silicone rubber. Two trans-cardiac electrodes deliver the electrical counter shock directly to the heart: one catheter electrode is incorporated into an intravascular catheter positioned in the superior vena cava, while the second, a flexible rectangular patch, covers the apex of the heart; these defibrillating electrodes also sense the configuration of the cardiac electrogram. The third lead is an epicardial left ventricular cup or patch cathode and this together with
the transvenous coil delivers trans-cardiac electrogram morphology to the sensing circuit; it provides input signals for HR determination and R-wave synchronisation (Haqqani & Mond, 2009; Mirowski, 1985).

Figure 2.23: Original Mirowski automatic ICD (Haqqani & Mond, 2009)

ICD are typically implanted in the left pectoral region in a pocket fashioned by dissection between the pectoralis major and minor muscles and leads are placed transvenously with access either through the cephalic vein, axillary vein, or subclavian vein (Bisognano, 2009; Gradaus, Breithardt, & Bocker, 2003; Thakur et al., 1995).
As per the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, the indication for an ICD is patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV HF symptoms (Epstein et al., 2008). Additionally, patients with chronic HF and a low EF, who experience syncope of unclear origin, should also be considered for placement of an ICD (Epstein et al., 2008; Knight et al., 1999). Australian national guidelines for the management of CHF in Australia (Krum et al., 2011) state that biventricular pacing, or cardiac resynchronisation therapy (CRT), should be considered in patients who fulfil all the following criteria:

- NYHA Class III–IV symptoms despite optimal medical therapy
- Dilated HF with an ejection fraction ≤35%
- QRS duration ≥120 ms
- Sinus rhythm.

A suggested algorithm for the selection of patients who would benefit from an ICD is given in Figure 2.24.
Selecting Patients with Heart Failure for Discussion About ICD As Primary Prevention of Sudden Death

- Does patient have Class IV symptoms (most patients hospitalized with HF)?
  - Yes → No ICD now. Re-evaluate for stability and risk after 1 month
  - No →

- Does patient have risk profile for heart failure death during next year?
  - Yes → High risk HF profile
  - No →

- Is prognosis for more than one year survival with good overall functional status limited by non-cardiac conditions?
  - Yes → No ICD
  - No →

- Is patient within 40 days of myocardial infarction?
  - Yes → No ICD now. Re-evaluate after 3-6 mos of optimal Medical Rx
  - No →

- Are there reversible factors for which treatment may improve LVEF?
  - Yes → Less than 3-6 months optimal med Rx
  - No → Prolonged tachycardia
  - No → Excess alcohol consumption
  - No → Medications that can exacerbate HF

If all answers “No”: Discuss risks and benefits of ICD in outpatient setting

Figure 2.24: Algorithm for selecting patients with HF for discussion about ICD as primary prevention of SCD (Stevenson & Desai, 2006).
2.8 SUMMARY

HF is the common endpoint for a number of cardiac diseases resulting from decompensation leading to decline in cardiac function. It is a multi-factorial disease with the interplay of genetic, neurohormonal, inflammatory, and biochemical changes affecting the heart. SCD accounts for up to half of deaths in HF patients. There is loss of ANS supply to the heart in HF, which can lead to fatal arrhythmias and subsequent high risk of SCD. Pharmacotherapy for arrhythmias is ineffective, which led to the development of ICD therapy. The present criterion for ICD implantation is LVEF $\leq 35\%$, NYHA classification of III or IV and an ECG QRS duration $\geq 120$ ms. This criterion misses some 33% of HF patients who die of HF as they fail to meet the existing criteria, and many of ICDs that are implanted as a result of the existing criterion, never discharge during the lifetime of the patients as they tend of die of progressive HF. This has necessitated for modification of the existing criterion and the hunt for a test that will be better able to predict which HF patients may suffer SCD. Molecular imaging of the SNS has shown the most promise.
Chapter 3

Review of Literature
3.1 INTRODUCTION

The existing criterion of ICD implantation in HF patients is primarily based on LVEF and patient symptoms and has been described in literature as a suboptimal measure of mortality due to arrhythmia (Currie et al., 2011; Gerson et al., 2010; Ji & Travin, 2010). This has necessitated the search for a more effective test for stratification of HF patients who may suffer from SCD. This has led to the development and exploration of a number of molecular imaging agents. SNS is the main modulator of cardiac rhythm, therefore imaging of the SNS is a very effective target for molecular imaging with the ability for improved risk stratification of SCD in HF.

Radioiodinated mIBG (123I-mIBG) primarily localises in the medulla of the adrenal gland (Bombardieri et al., 2010). Its primary use is in the detection of pheochromocytoma (Wiseman et al., 2009). 123I-mIBG is used to localise the myocardial regions depleted of catecholamine stores due to infarction (Fagret, Wolf, & Comet, 1989). It is taken up by the LV in proportion to the SNS activity (Agostini, Carrio, & Verberne, 2009; Bombardieri et al., 2010; Hattori & Schwaiger, 2000; Saha, 2004). It has the ability to provide an insight into the SNS supply in HF (Baliga, Narula, & Dec, 2001).

3.2 RADIOPHARMACEUTICAL

3.2.1 Metaiodobenzylguanidine

Metaiodobenzylguanidine is a combination of an iodinated benzyl and a guanidine group (Bombardieri et al., 2010). Most of the injected mIBG is excreted unaltered in the urine (Wafelman, Hoefnagel, Maessen, Maes, & Beijnen, 1997). About 1% of the injected dose is eliminated in the faeces.
(Geatti, Shapiro, Shulkin, Hutchinson, & Sisson, 1988). In patients with normal renal function 40 to 55% of the administered activity is excreted via the urine in 24 hours and 70-90% in 96 hours (Flotats et al., 2010). It is a NE analogue and is taken up into vesicles within the pre-synaptic sympathetic nerve endings without undergoing metabolism or exerting any effect on the post-synaptic receptors thus allowing early and delayed imaging (Dilsizian, Chandrashekhar, & Narula, 2010). mIBG enters neuroendocrine cells by the same mechanism as that of reuptake of catecholamines from the synaptic cleft which is mediated by high affinity, low capacity, sodium-chloride dependent, transporters present in the outer membrane of the pre-synaptic nerve endings. This transport system is also known as the uptake-1 mechanism. In addition to uptake-1, catecholamines are removed from the circulation by a second transport system. This second transport system consists of sodium-chloride independent, corticosterone-sensitive, high-capacity extraneuronal monoamine transporters (EMT), originally discovered as a transport mechanism in rat heart and designated as uptake-2 mechanism (Iversen, 1997). Neuronal reuptake by uptake-1 is quantitatively most important for the clearance of released catecholamines, accounting for about 90% of their removal at the presynaptic nerve endings (Flotats & Carrió, 2004).
3.2.2 Iodine-123

Iodine belongs to the halogen group VIIA. Its atomic number is 53 and its only stable isotope is $^{127}$I. Of all the iodine isotopes, $^{123}$I is most suitable for in vivo diagnostic procedures because it has a convenient half-life (13.2 hr) and primary photon energy of 159 keV (89% abundance), and delivers a low radiation dose to the patient. $^{123}$I is a cyclotron-produced isotope. It transforms by electron capture and emission of 159 keV $\gamma$-rays into $^{123}$Te (Lieser, 1997). Besides the 159 keV gamma radiation, there are other high energy emissions which are in the range of 440 – 625 keV (2.4%) and 625 – 784 keV (0.15%), which tend to degrade the image because of their septal penetration (Dobbeleir, Hambýe, & Franken, 1999). Currently the best source of Iodine-123, having the least contamination with other radiiodides ($^{124}$I and $^{125}$I), is the proton bombardment of highly enriched Xenon-124, through which radionuclidian
impurities like $^{125}\text{I}$ and $^{121}\text{Te}$ are below 0.05%. (Figure 3.2) (Eersels, Travis, & Herscheid, 2005).

![Figure 3.2: Production of $^{123}\text{I}$ from enriched $^{124}\text{Xe}$ (Eersels et al., 2005).](image-url)

### 3.2.3 Radiolabelling

mIBG can be labelled with $^{123}\text{I}$ for diagnostic imaging. The $^{123}$I-mIBG structure is shown in Figure 3.3. For routine clinical studies, the production of $^{123}$I-mIBG involves isotopic exchange (Mangner, Wu, & Wieland, 1982).

![Figure 3.3: mIBG molecule labelled with I-123](image-url)
3.2.4 mIBG Imaging

3.2.4.1 Precautions

The standard precautions that are required prior to administration of radiotracer are followed. In pre-menopausal females ruling out of pregnancy is required, and in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of carrying out the procedure (Bombardieri et al., 2010). If the patients are breastfeeding, it should be discontinued at least 48 hours post-injection (Bombardieri et al., 2010). Similarly an evaluation of the effects of the necessary withdrawal of drugs interfering with 123I-mIBG scintigraphy and their replacement needs to be discussed with the referring physician (Bombardieri et al., 2010). Medicine such as opioids, tricyclic antidepressants, anti-hypertensives, symapathomimetic nasal decongestants, and antipsychotics interfere with mIBG uptake and should be stopped prior to mIBG studies (Saha, 2004; Solanki et al., 1992). Solanki et al (1992) have postulated the following mechanisms as being responsible for interference in mIBG uptake:

- Inhibition of sodium-dependent uptake system.
- Inhibition of uptake by active transport into vesicles.
- Competition for transport into vesicles.
- Depletion of content from storage vesicle.
- Calcium mediated.
- Other possible mechanisms.

A list of the medicines which interfere with mIBG uptake is given in Table 3.1.
<table>
<thead>
<tr>
<th>Amitriptyline</th>
<th>Loxapine</th>
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<tr>
<td>Amoxapine</td>
<td>Metaraminol</td>
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<td>Butriptyline</td>
<td>Methoserpidine</td>
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<td>Clomipramine</td>
<td>Methylephedrine</td>
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<td>Cocaine</td>
<td>Nicardipine</td>
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<td>Desipramine</td>
<td>Nifedipine</td>
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<td>Diltiazem</td>
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<td>Doxepin</td>
<td>Noradrenaline</td>
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<td>Dothiepin</td>
<td>Nortriptyline</td>
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<td>Ephedrine</td>
<td>Phenylephedrine</td>
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<td>Imipramine</td>
<td>Phenylpropalamine</td>
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<td>Iprindole</td>
<td>Protriptyline</td>
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<td>Isradipine</td>
<td>Pseudoephedrine</td>
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<td>Labetalol</td>
<td>Reserpine</td>
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<tr>
<td>Lidoflazine</td>
<td>Trimipramine</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>

Table 3.1: A list of medicines which reduces the uptake of mIBG (modified from Solanki et al., 1992).

3.2.4.2 Pre-examination

The patient is told to discontinue all foods and medicines that may interfere with the uptake of 123I-mIBG (Shulkin & Shapiro, 1998; Taïeb et al., 2012). It is possible that some foods containing vanillin and catecholamine-like compounds (such as chocolate and blue-veined cheeses) can interfere on the uptake of 123I-mIBG (depletion of granules) (Bombardieri et al., 2010; Stein & Black, 1991). Therefore it is necessary that a complete history be taken prior to injection to rule out the use of such foods.
3.2.4.3 Tracer injection, dosage and injected activity

$^{123}$I-mIBG is supplied as a single use 5 ml solution containing 74 MBq/ml of activity at calibration time. It is administered by slow intravenous injection (over 5 min) in a peripheral vein via a shielded syringe. The usual activity administered is 111 - 370 MBq (3 - 10 mCi) as per the published literature and EANM practice guidelines (Bombardieri et al., 2010; Carrio et al., 2010).

3.2.4.4 Instrumentation

A single (or multiple) head gamma camera with a large field of view and a low energy high resolution collimator (LEHR) is necessary to acquire planar and/or SPECT images. Some studies have utilised the medium energy general purpose (MEGP) collimator, mostly due to the higher energy gamma photons also emitted by $^{123}$I, but because of their low prevalence, and a lower sensitivity and spatial resolution of the MEGP as compared to the LEHR, its use has not been widely accepted (Agostini et al., 2009; Inoue et al., 2003; Verberne et al., 2005). Poor uptake of mIBG is noted in patients with HF as compared to normal controls, thus a higher sensitivity low energy collimator is preferred as compared to the medium or high energy collimators (Saha, 2004). Similarly post-SPECT processing involves slicing of the LV into small segments, thus a collimator that allows higher spatial resolution and thus smaller voxel volumes, is desired (Agostini et al., 2009). Fusion imaging with A SPECT/CT hybrid systems can improve diagnostic accuracy.
3.3 EFFICACY

HF patients tend to have a high prevalence of ventricular arrhythmias and a high incidence of SCD (I. T. Meredith, Broughton, Jennings, & Esler, 1991). The association between ventricular arrhythmias and SCD is well established, but the precise mechanisms involved still remain unclear (de Luna, Coumel, & Leclercq, 1989; Goldberger et al., 2008; Zipes et al., 2006). Cardiac SNS activity is an apparent link between impaired LV function and ventricular electrical instability (Schwartz, La Rovere, & Vanoli, 1992). Use of 123I-mIBG as a non-invasive cardiac SNS imaging agent to investigate its role in SCD has been investigated in a number of studies since the 1980s.

Cardiac uptake of 123I-mIBG was first noted in 1981 (Kline et al., 1981), and soon its role in HF was explored particularly in patients of idiopathic dilated cardiomyopathy (DCM) (Henderson et al., 1988; Schofer, Spielmann, Schuchert, Weber, & Schlüter, 1988). Schofer et al (1988) evaluated the uptake of 123I-mIBG in DCM by visual inspection and also calculated the heart to mediastinum (H:M) ratios, discovering that best images for visual analysis were those that were two hours post-injection. They also discovered that the two hours post-injection H:M ratios correlated with the LVEF (Schofer et al., 1988).

One of the first to explore the role of 123I-mIBG in the prognostic evaluation of patients with HF, and to suggest that the H:M ratio from the images at four hours after injection of 123I-mIBG have a clinical significance, were Merlet et al (1992). They also suggested that a weak correlation existed between H:M ratio and LVEF (r=0.50, p < 0.001) and concluded that HF patients with H:M of less than 1.2 had a dramatically reduced survival as compared to those who had
H:M ratio of more than 1.2 (Merlet et al., 1992). They calculated the survival prediction ability of the H:M of 1.2 (over a period of 25 months) to have a sensitivity of 95%, specificity of 93%, a positive predicted value of 84% and a negative predicted value of 98% (p < 0.001) (Merlet et al., 1992). A similar analysis by Nishioka et al (2007) over a period of 25 months suggested a delayed H:M cut-off of 1.36 with 75% sensitivity and 71% specificity, while the ADMIRE-HF (Jacobson et al., 2010) study concluded that a delayed H:M threshold more than 1.6 confers a good prognostic value and those patients have a 2-year cardiac death rate of 1.8% as compared to 11.2% for those with a delayed H:M less than 1.6, which Tanaka et al (2012) also agreed with. One study described a role of early (15 min) H:M cut-off of more than 1.536 as a threshold for event free survival in cardiac transplant patients with a sensitivity of 92% and specificity of 72% (Gerson, McGuire, & Wagoner, 2003).

Most early studies were conducted before SPECT gamma cameras became commonplace. Thus they predominantly evaluated parameters such as global early and delayed H:M and the tracer washout. Early H:M ratios in healthy controls were often much higher than those of patients with HF. In a study by Choi et al (2001) the 3 hours delayed H:M of healthy volunteers was 3.2 ± 1.4 whereas in a study by Agostini et al. (1998), four hours delayed H:M was 2.33 ± 1.8, 1.92 ± 0.42 in the study by Cohen-Solal et al (1999), 2.1 ± 0.3 by Cha et al (2008) and 2.7 ± 0.2 in the study by Atsumi et al (1998). In untreated HF patients early H:M was 2.1 ± 0.6 (Choi et al., 2001), 1.99 ± 0.38 (Soeki et al., 1998), 1.39 ± 0.21 (Cohen-Solal et al., 1999), 2.1 ± 0.3 (Atsumi et al., 1998), 1.64 ± 0.24 (Chizzola et al., 2006), 2.5 ± 0.7 (Cha et al., 2008), 1.83 ± 0.38 (Koutelou et al., 2009), 1.93 ± 0.3 (Katoh et al., 2010) whereas delayed H:M
were to the order of 2.0 ± 0.5 (Choi et al., 2001), 1.86 ± 0.44 (Soeki et al.,
1998), 1.35 ± 1.9 (Agostini et al., 1998), 1.6 ± 0.85 (Somsen et al., 1996), 1.9 ±
0.3 (Atsumi et al., 1998), 1.31 ± 0.2 (Cohen-Solal et al., 1999), 1.8 ± 0.7 (Cha et
al., 2008), 1.72 ± 0.32 (Koutelou et al., 2009), 1.42 ± 0.45 (Chizzola et al., 2006)
and 1.84 ± 0.4 (Katoh et al., 2010). WR in pre-treatment patients has been
found to be 45.9 ± 19.2% (Choi et al., 2001), 29.1 ± 9.1% (Soeki et al., 1998),
42 ± 14% (Atsumi et al., 1998), 34.8 ± 6.0% (Cohen-Solal et al., 1999), 55 ±
25% (Cha et al., 2008), 46.2 ± 12.9 (Koutelou et al., 2009), 29.1 ± 15.8 (Katoh
et al., 2010) and 38 ± 20% (Nishioka et al., 2007). A WR less than 26.9% has
been described as a good prognostic factor for a cardiac event-free survival rate
of 75.9% (Katoh et al., 2010), while Yamada et al (2003) defined it to be less
than or equal to 27%.

It can be observed that the studies fail to agree to early and delayed H:M values
or WR for either normal or HF patients. A study that found a significant role of
the cardiac WR and establish a clear difference in WR between patients with
HF and those without were conducted by Imamura et al (1995), which
demonstrated that changes in cardiac sympathetic activity is independent of the
underlying cause of HF. Ninety-six patients with HF and nine matched controls
were also included in the study. WR increased in proportion to the severity of
the disease in all HF patients (p < 0.01) (Imamura et al., 1995).

To establish statistically significant cut offs for early and delayed H:M ratios and
WR, Ehime MIBG Heart Failure study (Imamura, Fukuyama, Mochizuki,
Miyagawa, & Watanabe, 2001) was conducted. 171 patients with LVEF less
than 40% without any co-morbidities were recruited in the study and followed up
for 27 ± 8 months. The study population was divided into two groups according to events such as cardiac death or HF progression requiring hospitalisation plus cardiac death. Eleven patients suffered cardiac death and 16 required hospitalisation. Comparing the H:M from the early images, the event-free group had a H:M of 1.82 ± 0.27 as compared to the cardiac death group with a H:M of 1.59 ± 0.19 (p < 0.05) and 1.64 ± 0.24 (p < 0.01) for the hospitalisation group. The delayed H:M ratios were 1.68 ± 0.27 for the event-free cohort, 1.30 ± 0.18 (p < 0.01) for the cardiac death cohort and 1.44 ± 0.24 (p < 0.01) for the hospitalisation cohort. When comparing the WR, it was 44 ± 11% for the event-free group, 63 ± 10% (p < 0.01) (Figure 3.4) for the cardiac-death group and 53 ± 11% (p < 0.01) (Figure 3.5) for the hospitalisation group (Imamura et al., 2001).

Figure 3.4: Kaplan-Meier analysis of cumulative survival curves for patients in the ‘death from heart failure’ group divided into 2 subgroups based on their WR: more than 63% and less than 63% (Imamura et al., 2001).
Figure 3.5: Kaplan-Meier analysis of cumulative survival curves for patients in the ‘death or hospitalisation because of progressive heart failure’ group, divided into subgroups based on WR: >53% and less than 53% (Imamura et al., 2001).

All the above literature reveals the problems with the planar imaging, which is a lack of standardisation for early and delayed H:M and the washout indices. A whole range of delayed H:M cut-off values such as 1.2, 1.27, 1.35, 1.3, 1.4, 1.42, 1.44, 1.53, 1.75, 1.86, 1.9, 2.14, 2.21 have been described as those discriminating between patients who are at risk and those who are not (Agostini et al., 1998; Atsumi et al., 1998; Carrio et al., 2010; Cha et al., 2008; Chizzola et al., 2006; Choi et al., 2001; Gerson et al., 2002; Gerson et al., 2003; Gould et al., 2007; Imamura et al., 2001; Merlet et al., 1999; Ohkusu et al., 2002; Soeki et al., 1998; T. Yamada et al., 2003). Similarly washout values that are predictive of poorer prognosis have been various described in literature as being 27%, 29.1%, 42%, 45.9%, 49%, 55%, 66% etc (Atsumi et al., 1998; Cha et al., 2008; Choi et al., 2001; Imamura et al., 2001; Marini et al., 2005; Soeki et al., 1998; T. Yamada et al., 2003).
To overcome these issues a trial named AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) was conducted from July 2005 to February 2008 (Jacobson, Lombard, Banerjee, & Camici, 2009). This large multi-centre study was carried out in the US, Canada and Europe to evaluate the prognostic significance of 123I-mIBG quantitation of the cardiac sympathetic innervation in HF patients (Jacobson et al., 2010). 985 HF patients were recruited over the three years period (of whom 961 were included in the final analysis) with LVEF of less than or equal to 35%. Prior to the imaging all patients underwent clinical evaluation and a blood sample withdrawal for serum BNP and NE levels. The patients were injected with 370 MBq of 123I-mIBG and underwent planar and SPECT imaging after 15 min and 3 h 50 min post-injection. All patients also underwent myocardial perfusion imaging. All patients were followed up for a period of two years and the events recorded were HF progression as measured by the NYHA functional classification, spontaneous sustained VT of more than 30 s, cardiac resuscitation, appropriate ICD discharge or cardiac death. The patient population was then divided into two groups for analysis into as per the delayed (3 hour 50 min) 123I-mIBG H:M less than 1.6 and H:M more than or equal to 1.6. In patients with a H:M of more than or equal to 1.6 the two year event rate was 15% as compared to 38% for the ones with a H:M of less than 1.6 (p < 0.0001) (Figure 3.6). Cardiac death two-year probability in the cohort with H:M of ≥ 1.6 was 1.8% and in the H:M less than 1.6 cohort it was 11.2% (p = 0.001). An inverse correlation was found between delayed H:M ratio and the 2-year cardiac death rate (r = -0.83, p < 0.01) (Jacobson et al., 2010). Therefore even this trial failed to establish a cut-off for washout.
None of these trials have been able to conclusively provide a definitive answer to the sufficient discriminatory power to direct a definitive decision on management of HF patients or offer ICD in patients with a LVEF more than 35% or to decline it in those with an LVEF less than or equal to 35%, so that no HF patient suffers SCD and no implanted ICD goes unutilised. The discriminatory power is likely reduced by the global approach to calculations, where there is overlap between the counts from various walls of the heart, and the counts of anterior predominate those of lateral and inferior wall, where cardiac sympathetic dysfunction is thought to start (Currie et al., 2011). That is, CAN begins in the inferior wall of the heart and progresses through adjacent myocardial walls (lateral and septal) before eventually reaching the anterior wall (Scott & Kench, 2004). A normal value for planar uptake may reflect predominantly the anterior wall uptake and fail to highlight early CAN in the inferior wall (Currie et al., 2011). It is therefore necessary to look into literature which has explored into the role of 123I-mIBG regional SPECT imaging in HF patients.

Figure 3.6: Cumulative event curves comparing subjects With H/M less than 1.60 versus >1.60 (Jacobson et al., 2010).
Chapter 4

Critical Analysis of Key Literature
4.1 INTRODUCTION

Loss of cardiac SNS has been implicated in SCD in HF. All published literature regarding the role of mIBG in HF has suggested a role of global delayed H:M and washout as having prognostic significance. No definitive thresholds have been established for either of these parameters. Additionally, these parameters have no discriminatory power with regards to the biggest issue that cardiac SNS is supposed to address i.e. prediction of SCD in HF patients by mapping CAN. This is most likely due to the fact that global parameters are dominated by the anterior wall uptake of the radiotracer, whereas CAN is a regional process that often starts in the inferior wall. In order to diagnose CAN early in the process, when it is still a regional phenomenon, requires that SPECT rather than planar imaging be performed.

4.2 SEARCH METHODOLOGY

In order to conduct a comprehensive review of the key literature pertaining to the role of 123I-mIBG in HF, a search of the bibliographic databases was conducted. A search of PubMed for the search terms “mibg”, “SPECT” and “heart failure” and their related citations yielded 6,736 results in which the publication language was English. These results were searched and those that were not clinical trials were excluded from the list. The clinical trials were then further evaluated and ones with identifiable clinical end points and/or pre and post intervention 123I-mIBG scintigraphy data was available were included in this review. Those studies where there were co-morbidities or where the purpose was to compare the efficacy of one kind of medication over the other were also excluded. The algorithm for the selection of the studies included is in the figure below (Figure 4.1).
Figure 4.1: Algorithm for the identification of the key literature in the evaluation of HF patients with 123I-mIBG SPECT scintigraphy.

The studies were evaluated for their quality using the Jadad-Currie scale (appendix 1).
4.3 RESULTS

Sixteen studies met the inclusion criteria and were included in the study. All studies had a Jadad-Currie score of more than 10. With the exception of one study, all were carried out after 2000. All studies were prospective.

Table 4.1: Evaluation of papers included in the review using the Jadad-Currie scale.

<table>
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<tr>
<th>Reference</th>
<th>Year of Study</th>
<th>Type of Study</th>
<th>Jadad-Currie Score</th>
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<tr>
<td>Somsen et al</td>
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<td>Prospective</td>
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<tr>
<td>Zhao et al</td>
<td>2001</td>
<td>Prospective</td>
<td>12</td>
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<tr>
<td>de Milliano et al</td>
<td>2002</td>
<td>Prospective</td>
<td>19</td>
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<td>Kasama et al</td>
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<td>Marini et al</td>
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<td>Boogers et al</td>
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<td>Jacobson et al</td>
<td>2010</td>
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4.4 CRITICAL ANALYSIS

Somsen at al (1996) were the first the use of SPECT with 123I-mIBG and evaluated the effects of enalapril on cardiac sympathetic neuronal uptake in patients with CHF after a therapeutic trial of six weeks. SNS activity was measured before and after therapy in 23 patients with HF by injecting them with 185 MBq of 123I-mIBG and obtaining SPECT images four hours later. The SPECT images were reconstructed and short axis slices obtained. ROIs were drawn over the LV myocardium and the LV cavity. At the time of imaging venous blood sample was obtained to measure the $^{123}$I activity. mIBG uptake
was measured using the formula: \((M/C) \times A\), where \(M\) = myocardial activity, \(C\) = ventricular activity and \(A\) = venous blood sample \(^{123}\)I activity. The average mIBG activity increased from 16 ± 8.45 to 20 ± 9.67 (\(p = 0.013\)) (Somsen et al., 1996).

To evaluate the effect of metoprolol on the myocardial sympathetic nervous system in HF patients, a placebo-controlled trial was conducted in 54 CHF patients (de Milliano, de Groot, et al., 2002). The SNS was evaluated by 123I-mIBG scintigraphy before and six months after institution of therapy following a dose of 185 MBq and SPECT imaging 15 min and four hours post-injection. 11 patients were assigned to the placebo group and 43 to the treatment group. mIBG uptake was measured as mean counts/voxel from short-axis image. The uptake values were corrected for blood activity as compared to a venous blood sample and for radioactive decay. In the treated group an increase in uptake of 21.9% was noted over the six months period as compared to the placebo group, in which a fall of 7.8% was seen (\(p = 0.03\)). There was no difference in the improvement when the treated group was further divided based on the ischaemic or non-ischaemic aetiology of the CHF (de Milliano, de Groot, et al., 2002). In a separate paper, the authors stated that H:M ratio did not have any predictive power for the composite end points of heart transplant or cardiac death (de Milliano, Tijssen, van Eck-Smit, & Lie, 2002).

Zhao et al (2001) made an effort to explore the relationship between cardiac sympathetic innervation, LVEF and myocardial perfusion gated-SPECT using 99m-Tc tetrofosmin. They included 33 patients of either dilated or hypertrophic cardiomyopathy and five healthy controls in their study. All subjects underwent
gated-MPS and SNS imaging. The sympathetic imaging was carried out after 111 MBq of 123I-mIBG and planar and SPECT scintigraphy 15 min (early) and four hours (delayed) after injection. The static images were used for calculating early H:M ratio (H/Me) and delayed H:M ratio (H/Md) and global washout percentage (GW), while reconstructed gated-MPS images were used to generate 99mTc-tetrofosmin H:M ratio (H/M-TF). For regional analysis the short axis of the heart was divided into three parts from apex to base and then each of the three slices was divided into six segments. The apical and middle segments were then used for analysis, yielding 12 segments for each patient. Regional early and delayed uptake (MUP) and washout (RW) were calculated using the formulas:

\[
RW(\%) = \frac{[\text{mean early segment counts} - \text{mean delayed segment counts}]}{\text{mean early segment counts}} \times 100
\]

\[
\text{MUP} = \frac{\text{mean segment counts}}{\text{highest voxel counts in myocardial ROIs}} \times \frac{\text{H/M}}{\text{TF}}
\]

The regional g-MPS uptake was measured using the formula:

\[
\text{UPes} = \text{regional uptake in end – systole} \times \frac{\text{H/M}}{\text{TF}}
\]

In the DCM cohort, the H/Me was 1.85 ± 0.27 versus 2.17 ± 0.05 for the control group (p < 0.05). The H/Md was 2.66 ± 0.21 for the controls, 1.73 ± 0.39 for the DCM cohort and 2.28 ± 0.31 (p < 0.05). The global washout values were 11.88 ± 7.23% for the control group, 32.52 ± 9.75% for the DCM patients and 25.84 ± 7.61% in the HCM patients (p < 0.05). None of global parameters showed any
significant correlation with the LVEF. The only significant correlation between the 99mTc-tetrofosmin gated-SPECT and global 123I-mIBG parameters were in patients with HCM. The H/M-TF and H/Me, H/Md, GW correlation coefficients were 0.764 (p < 0.001), -0.612 (p < 0.05) and -0.365 (p > 0.1) respectively. Significant correlation was however found between UPes and regional 123I-mIBG parameters in both DCM and HCM patients. The correlation coefficients between UPes and MUPe, MUPd and RW were 0.3560 (p < 0.0001), -0.176 (p < 0.05) and -0.328 (p < 0.0001) in the DCM cohort. In the HCM cohort the UPes and MUPe, MUPd and RW correlation coefficients were 0.307 (p < 0.00001), -0.097 (p > 0.1) and 0.144 (p < 0.05). The authors also carried out correlation analysis between wall thickening (TH) and the 123I-mIBG regional parameters. The correlation coefficients between TH and RW was -0.412 (p < 0.001) in DCM patients and -0.350 (p < 0.001) in HCM patients (Zhao et al., 2001).

Although Zhao et al (2001) managed to establishing that regional parameters are much more sensitive than global ones, this effort was not followed by any other publication that utilised semi-quantitative methods in 123I-mIBG regional SPECT analysis. The group from the Gunma University School of Medicine, Maebashi, Japan conducting quite a few trials in which they employed 123I-mIBG imaging in HF prognostication and in evaluating a number of newer medicines for their role in management of HF using visual analysis of 123I-mIBG SPECT scans (Kasama et al., 2002; Kasama et al., 2003, 2005; Kasama et al., 2004; Kasama et al., 2008).

Kasama et al (2002) explored the role of addition of spironolactone in improving the cardiac sympathetic activity in patients with CHF. Thirty patients were
recruited in the study, with 15 patients additionally receiving spironolactone (group A) and 15 receiving standard treatment (group B). Cardiac SNS imaging was performed before initiation of therapy and after six months with iv injection of 111 MBq of 123I-mIBG and planar and SPECT imaging at 15 min and four hours post-injection. Delayed H:M ratios and WR was calculated from the planar images and the SPECT images were used to generate 20 segment polar maps and the uptake visually assessed using a four point scoring system (0 = normal uptake to 3 = severely reduced uptake). Total defect scores were obtained by adding the scores of all the 20 segments. The difference in the H:M for group A was 1.62 ± 0.20 in baseline images and 1.81 ± 0.23 in the 6 month images (p < 0.0001) and for patients in group B the values were 1.73 ± 0.20 and 1.67 ± 0.24 (p = NS). WR in group A reduced from 51 ± 9% (baseline) to 40 ± 10% at six months follow up (p < 0.001) and changed from 45 ± 7 and 51 ± 12 in group B (p = NS). TDS in group A was 37 ± 9 (baseline) and 25 ± 13 (six months follow up) (p = 0.0001) and 32 ± 8 and 33 ± 7 in group B (p = NS) (Kasama et al., 2002).

In another study they examined the role of addition of ARB in addition to the use of ACEI in patients with congestive HF (CHF) (Kasama et al., 2003). Thirty-two patients were recruited in the study, with 16 patients additionally receiving valsartan (group A) and 16 being treated with just ACEI and loop diuretic (group B). Cardiac SNS imaging was performed before and six months after initiation of therapy with intravenous (iv) injection of 111 MBq of 123I-mIBG and planar and SPECT imaging at 15 min and four hours post-injection. Delayed H:M ratios and WR was calculated from the planar images and the SPECT images were used to generate 20 segment polar maps and the uptake visually assessed.
using a four point scoring system (0 = normal uptake to 3 = severely reduced uptake). TDS was obtained by adding the scores of all the 20 segments. The difference in the H:M for group A was 1.66 ± 0.23 in baseline images and 1.81 ± 0.23 in the six month images (p < 0.001) and for patients in group B the values were 1.74 ± 0.20 and 1.69 ± 0.24 (p = NS). WR in group A reduced from 47 ± 9% (baseline) to 39 ± 10% at six months follow up (p < 0.01) and changed from 46 ± 7 and 50 ± 12 in group B (p = NS). TDS in group A was 37 ± 8 (baseline) and 31 ± 9 (six months follow up) (p < 0.001) and 46 ± 7 and 50 ± 12 in group B (p = NS) (Kasama et al., 2003).

Exploring the effects of atrial natriuretic peptide (ANP) infusion on the cardiac sympathetic nervous system of patients with HF, Kasama et al published another trial in 2004 (Kasama et al., 2004). Fifty-eight patients with decompensated HF, admitted to the ICU, and receiving low-dose dopamine and diuretics were divided into two group A and B. Group A contained 29 patents who were treated with ANP, while the remaining 29 patients did not receive ANP therapy. Three weeks post-treatment 123I-mIBG scintigraphy was carried using 111 MBq of the tracer and planar and SPECT imaging was performed 15 min and four hours post-injection. Delayed H:M ratios and WR was calculated from the planar images and the SPECT images were used to generate 20 segment polar maps and the uptake visually assessed using a four point scoring system (0 = normal uptake to 3 = severely reduced uptake). Total defect scores were obtained by adding the scores of all the 20 segments. The difference in the H:M between the groups was 1.86 ± 0.21 for group A and 1.62 ± 0.23 for group B (p = 0.0001). WR in group A was 42 ± 12% and 49 ± 12% in
group B (p < 0.05). TDS in group A was 30 ± 9 and 38 ± 9 in group B (p < 0.01) (Kasama et al., 2004).

In a clinical trial Kasama et al (2005) investigated the effects of ARBs on cardiac SNS activity in patients with HF who have preserved LVEF. They recruited 50 HF patients into their placebo-controlled study all of whom were NYHA functional class II or III with an LVEF more than 40%. The patients were evaluated just before and six months after institution of the ARB therapy. All patients underwent MPS with TI-201 and cardiac SNS evaluation with 111 MBq of 123I-mIBG and anterior planar and SPECT scanning 15 min and four hours post-injection. The planar image parameters recorded were H:M ratio from the delayed images and WR. The SPECT images were used to generate 20 segment polar maps and visual assessment was carried out using a four point scale (0 = normal to 3 = severely reduced uptake). The scores were added for each patient to determine the defect score (TDS). In the ARB treated cohort the H:M improved from 1.87 ± 0.24 to 2.00 ± 0.22 (p < 0.005) as compared to those on placebo in whom the change was from 1.84 ± 0.27 to 1.86 ± 0.27 (p = not provided). The WR in the ARB group decreased from 37 ± 11% to 32 ± 8 (p < 0.005) while in the placebo the group the change was from 30 ± 10% to 37 ± 13% (p = not provided). The TDS in the ARB group reduced from 28 ± 8 to 23 ± 8 (p < 0.0005) while the change in the placebo group was 28 ± 11 to 27 ± 12 (p = not provided) (Kasama et al., 2005).

In a five year-long study, published by Kasama et al (2008), the prognostic value of serial cardiac 123I-mIBG imaging was explored in patients with stabilised CHF and a reduced LVEF (less than 45%). 208 patients finished this
trial after a mean follow up period of 4.45 years. At the time of admission and six months after discharge from hospital, the patients’ SNS status was evaluated using 111 MBq of 123I-mIBG and planar and SPECT imaging 15 min and four hours after injection. H:M ratio was calculated from the planar images, while the SPECT imaging was used to calculate the WR (with no decay correction applied) and visual defect score (TDS) using a five point scale of 0 - 4 (0 = normal uptake and 4 = no uptake) and a 17-segment polar map. The TDS score was converted to the % denervation by the formula (TDS / 68) x 100, where 68 was the maximum possible visual score (4 x 17). Fifty-six patients died of progressive failure, SCD or MI. Patients with a change in WR of 5% or more over the six months period had a hazard ratio of 1.072 to suffer cardiac death (p < 0.001). A hazard ratio of 1.139 was calculated for patients to suffer SCD when the WR increased by 2% or more as compared to those with a change of less than 2% (p < 0.001). Baseline H:M ratio in patients who suffered cardiac death was 1.58 ± 0.22 as compared to 1.69 ± 1.9 for those who did not (p = 0.001). Baseline washout was 53 ± 10% versus 47 ± 10% respectively. Baseline %denervation was 60 ± 7% in cardiac death patients and 58 ± 11% in patients who did not have cardiac death (p = 0.239). When the second set of images were looked at, higher %denervation was recorded in patients with cardiac death 61 ± 13% compared to the non-cardiac death group 48 ± 11% (p < 0.001). Similarly the H:M ratio in the 6 month follow up images was 1.58 ± 0.23 in cardiac death group and 1.82 ± 0.22 in the non-cardiac death group (p < 0.001). WR also showed the same trend and was 57 ± 12% in the cardiac death group and 41 ± 11% in the non-cardiac death group (p < 0.001). Similar trends were noted when patients who suffered a SCD were compared to those who remained alive (Kasama et al., 2008).
Toyama et al (2009) investigated the effectiveness of the home oxygen therapy (HOT) in exercise capacity, SNS and cardiac function in HF patients with central sleep apnoea (CSA). They recruited 20 patients in the study who had signs and symptoms of HF and an LVEF of less than 45%. Besides the standard management strategy, 10 patients received HOT. Two weeks prior to and three months after institution of the therapy, the patients underwent 123I-mIBG and 99mTc-MIBI scintigraphy. The 123I-mIBG scan was carried out using 111 MBq of the radiotracer and planar and SPECT imaging was performed 15 min and four hours after injection. The planar images were analysed and H:M ratios from the delayed images and WR calculated. The SPECT images were utilised for semi-quantitative visual scoring using a four point scale of 0 - 3 (normal to severely reduced uptake) after generating a 20 segment polar map. TDS was calculated by adding all the visual scores. 99mTc-MIBI imaging was performed after injection of 720 MBq of the radio-pharmaceutical and gated SPECT acquisition 30 min later. The data was used to calculate TADS, LVEF and LV end-diastolic and LV end-systolic volumes (LVEDV and LVESV). A marked improvement in the 123I-mIBG TDS was seen in the patients in the HOT group from 31 ± 8 to 25 ± 9 (p < 0.05) while it changed from 36 ± 10 to 37 ± 8 in the non-HOT group (p = NS). The WR decreased from 49 ± 8% in the HOT group to 41 ± 5% (p < 0.05) with a slight increase in the non-HOT group from 50 ± 11% to 51 ± 11% (p = NS). The H:M ratio in the HOT group changed from 1.69 ± 0.22 to 1.82 ± 0.22 (p < 0.05) and in the non-HOT group it changed from 1.6 ± 0.23 to 1.63 0.36 (p = NS). Similar improvements in the exercise capacity and LVEF were seen in the HOT group as compared to the non-HOT group (Toyama et al., 2009).
The Gunma University School of Medicine group have consistently used the reconstructed SPECT images to obtain the washout and employed the visual scoring scheme to calculate the defect score. Various authors have used 3, 4 and 5 point scales and some have tried to quantify the scoring system by assigning percentage uptake values to these scores (Burgdorf, von Hof, Schunkert, & Kurowski, 2008; Courbon et al., 2003; Di Monaco, Bruno, et al., 2010; Di Monaco, Lanza, et al., 2010; Hatori et al., 2007; Hattori et al., 2003; Katsikis, Ekonomopoulos, Papaioannou, Kouzoumi, & Koutelou, 2012; Kurata et al., 2000; Marketou et al., 2002; Marshall, Cheetham, George, Mason, & Kelion, 2012; Miranda, Figueiredo, Maciel, Marin-Neto, & Simões, 2011; Momose et al., 2001; Schnell et al., 2002; Simantirakis et al., 2003; Spinelli et al., 2008; Watanabe et al., 2002). In the earlier studies a four point scale was used with a 20 segment polar map, while in the later ones a five point scale with a 17 segment polar map was employed. Although Gunma University School of Medicine group have not been the only ones to utilise the visual scoring system, in the author’s research they have the most number of publications which have utilised the same. However given the fact that visual scoring can be quite operator dependent and its reproducibility an issue, a more objective and operator independent system of SPECT image analysis needs to be developed, and nothing significant has yet been proposed in the literature.

Marini et al (2005) compared the loss of cardiac sympathetic innervation in patients with HF secondary to IHD as compared to the patients of dilated cardiomyopathy (DCM). They enrolled 20 patients in their study with NYHA class IIIb and LVEF less than 40%. Ten patients each had DCM and 10 IHD. All
patients underwent gated-SPECT myocardial perfusion scintigraphy. To evaluate the SNS status, all patients also underwent post-injection 5-min anterior planar and SPECT scintigraphy at 30 min and four hours after injection of 185 MBq of 123I-mIBG. H:M ratios were calculated from the delayed images and washout (WO) rates were also obtained from the mIBG images. The MPS and 123I-mIBG SPECT images were converted to 20 segment polar images and the counts in each of the segments was expressed as a percentage of the segment with the max counts in that polar map (referred to as the “reference segment”) along with the measurement of regional washout (WO) in each segment. The global H:M and WO characteristics were found to be similar in both groups of patients. When calculating regional uptake, in DCM patients the mean reference segment and damage segment uptake was 1.8 ± 0.96 and 1.39 ± 0.9 (p < 0.01) while in the IHD patients, it was 1.5 ± 0.89 and 1.06 ± 0.6 (p = 0.01). Comparing regional washout characteristics, the IHD group demonstrated 38 ± 21% washout in the reference segments and 46 ± 19% in the damaged segments (p < 0.05), while in the DCM group regional WO was 49 ± 18% in the reference segments and 35 ± 22% in the damaged segments (p < 0.05) (Marini et al., 2005).

Cohen-Solal et al (2005) extended the concept of visual scoring in SPECT by utilising two quantitative parameters. They calculated the extent and the severity of defect. The extent calculation was the number of segments with reduced uptake as a percentage of the total, while the severity score was the ratio of the average counts in a given segment to the segment with the maximum average counts.
In an effort to study the effects of carvedilol on various parameters in patients with chronic HF, Cohen-Solal et al (2005) conducted a randomised placebo-controlled trial. Sixty-four patients were recruited for the study, however only 43 finished the trial. In addition to other tests, the patients underwent cardiac SNS evaluation before and six months into the study with 111 - 148 MBq of 123I-mIBG and anterior chest planar (10 min view) and SPECT acquisitions 20 min and four hours after injection. The HM ratios and WR was calculated from the static images and the SPECT were used to generate a 17-segment polar map that was visually analysed for uptake on a scale of 0 - 4 with 0 being normal uptake and 4 being no uptake. The sum of the scores was designated as severity score index (SSI). Two more SPECT based parameters that were calculated were defect extent (DE) which was “number of pixels of defect/total number of pixels” and expressed as a percentage, and defect severity (DS) which was calculated using the formula “(mean counts/pixel in defect) / (mean counts/pixel in region with max counts)” again expressed as a percentage. The delayed H:M ratio for the pre-treatment scintigraphy was 1.49 ± 0.21 for the treated group and 1.46 ± 0.24 for the placebo group. It increased to 1.49 ± 0.21 for the treated group and reduced to 1.43 ± 0.24 for the placebo group (p = 0.003). WR did not change for either the placebo or the therapy group. The SSI in the initial imaging was 25.9 ± 19.9 for the carvedilol group and 23.6 ± 12.0 for the placebo group and decreased in the six month follow-up scanning to 21.6 ± 12.5 in the carvedilol group and no change was observed in the placebo group. DE decreased from 20.4 ± 11.2% to 15.0 ± 12.2% (p = 0.03) in the carvedilol group and changed from 21.8 ± 12.9% to 21.3 ± 10.6 (p = 0.8) in the placebo group. DS changed for the treated group from 52.6 ± 5.6% to 55.9 ± 6.0 (p =
0.014) versus 52.7 ± 4.2% to 52.6 ± 7.6 for the placebo group (p = 0.9) (Cohen-Solal et al., 2005).

Fujimoto et al (Fujimoto et al., 2004; Fujimoto et al., 2005) in their papers also employed a quantitation based SPECT scoring system. They established a small normal database from healthy volunteers undergoing 123I-mIBG cardiac SPECT and then calculated the extent and the severity of defects in the HF population as compared to the normal database. However the “normal” database was limited to a small number of subjects.

In a paper Fujimoto et al (2004) investigated the efficacy of 123I-mIBG myocardial scintigraphy in predicting adverse effects in HF patients with preserved LVEF. Seventy-four non-ischaemic cardiomyopathy patients with underwent cardiac sympathetic nervous function 60 days after stabilisation of symptoms following start of therapy. These patients were followed up for an average of 2.0 years and events such as death, hospitalisation for HF or arrhythmias. SNS scintigraphy was performed after i.v. administration of 111 MBq of 123I-mIBG and five min planar anterior chest (128x128 matrix) and SPECT images 20 min and four hours post-injection. From the planar images early and delayed H:M ratios (eH/M and dH/M) were calculated. For the SPECT image evaluation 17 normal healthy controls was imaged and polar maps generated. The patients SPECT images were compared to the healthy patients’ database and parameters derived were the extent of defect EXT and the severity of defect SEV. The extent of defect EXT% = (points at abnormal areas/total points) x 100 and the severity of defect SEV = total of difference in counts at abnormal areas/total points from the early and delayed images. From
the patients' early and delayed polar maps, the WR was also calculated. Fifteen patients suffered from CE in the follow up. Comparing the various parameters in the events positive population and the events negative population, it was found that that eH/M was 1.69 ± 0.27 in the event(+) group and 1.85 ± 0.28 in the event(-) group, while the dH/M was 1.52 ± 0.27 versus 1.74 ± 0.31 (p < 0.05). Similarly the early EXT (eEXT) score in the events(+) population was 50.3 ± 25.1 while that in the events(-) population was 33.1 ± 23.7 (p < 0.05). The delayed EXT (dEXT) score was 62.3 ± 38.2 in the events(+) patients and 40.9 ± 30.2 in the events(-) population (p < 0.01). Similarly eSEV in events(+) was 85.0 ± 79.1 and 45.8 ± 45.8 in the events(-) (p < 0.05). The WR in events(+) was 47.6 ± 12.6 and 40.7 ± 10.0 in the events(-) patients (p < 0.01). When Kaplan-Meier analysis for occurrence of CE, patients who had a WR of more than or equal to 48% suffered higher incidence of cardiac death than the patients with WR of less than 48% (p < 0.05), while the threshold for any cardiac event was 45% (p < 0.05) (Fujimoto et al., 2004).

A long term follow up study was conducted to study the efficacy of 123I-mIBG myocardial scintigraphy in predicting adverse effects in HF patients who had been on β-blocker therapy (Fujimoto et al., 2005). Fifty-three DCM patients underwent cardiac sympathetic nervous function before and within six months to one year of the initiation of the therapy. These patients were followed up for an average of 3.6 years and events such as death, hospitalisation for HF or arrhythmias. SNS scintigraphy was performed after i.v. administration of 111 MBq of 123I-mIBG and five min planar anterior chest (128x128 matrix) and SPECT images 20 min and four hours post-injection. From the patients' early and delayed polar maps, the WR was calculated. For further SPECT image
evaluation 19 normal healthy controls was imaged and polar maps generated. The patients SPECT images were compared to the healthy patients database and parameters derived were the extent of defect $\text{EXT}\% = \left(\frac{\text{points at abnormal areas}}{\text{total points}}\right) \times 100$ and the severity of defect $\text{SEV} = \text{total of difference in counts at abnormal areas/total points from the early and delayed images}$. Nine patients suffered from CE in the follow up. When comparing the various parameters in the events positive population and the events negative population, it was found that that the early EXT (eEXT) score in the events(+) population was $52.1 \pm 27.1$ while that in the events(-) population was $27.0 \pm 22.1$ ($p < 0.01$). The delayed EXT (dEXT) score was $68.1 \pm 26.4$ in the events(+) patients and $33.7 \pm 26.0$ in the events(-) population ($p < 0.01$). Similarly eSEV in events(+) was $86.0 \pm 99.3$ and $29.3 \pm 30.6$ in the events(-) ($p < 0.01$). The dSEV in events(+) was $106.0 \pm 67.7$ and $46.2 \pm 47.4$ in the events(-) patients. No significant difference was seen in the WR between the two populations. Additionally when comparing the pre and post therapy scans, a decrease in WR of 10 or more meant no CE. When Kaplan-Meier analysis for occurrence was carried out, patients who had a dEXT of less than 32.3 suffered far fewer CE than the patients with dEXT of 32.5 or more ($p < 0.01$) (Fujimoto et al., 2005).

Survival and event prediction studies were published based on various 123I-mIBG SPECT image parameters and a number of authors started to explore the role of implantable devices such as BiV and ICDs on the cardiac sympathetic nervous system and their impact on patients’ survival. In order to predict the long term efficacy of $\beta$-blocker / angiotensin-converting enzyme inhibitor (ACEI) therapy in patients with HF, two cohorts of patients, one with 88 patients treated
with ACEI / β-blockers (treated group) and another with 79 managed with other medicines (control group), were recruited for this study (Nakata et al., 2005). The follow up period was for 43 months during which there were 42 fatalities due to cardiac causes. Cardiac mIBG activity was assessed with planar and SPECT imaging at 30 min and four hours after injection of 111 MBq of 123I-mIBG. Analysis of the images was carried out by calculating the H:M ratios from early and delayed static images. WR was calculated from polar images generated from the early and delayed SPECT images without decay correction. Comparing the early H:M ratios in the patients who died, the treated group had H:M of 1.74 ± 0.32 while the control group had a H:M of 1.92 ± 0.43 (p = 0.185) while those who survived the ratios were 1.91 ± 0.32 versus 2.00 ± 0.37 respectively (p = 0.169). When looking at the delayed H:M in the patients who died, the treated group had H:M of 1.53 ± 0.28 and the control group H:M was 1.61 ± 0.30 (p = 0.420), while those who survived, treated group had H:M 1.70 ± 0.32 and control group H:M was 1.85 ± 0.45 (p = 0.038). Comparing the WR in the patients who suffered cardiac death, the treated and the control had WR of 38 (p = 1.0000), whereas in the surviving group the treated group had WR of 38 ± 10% and control 33 ± 17% (p = 0.047). When Kaplan-Meier analysis was carried out using a delayed H:M threshold of 1.53, those with H:M more than or equal to 1.53 had a reduction in mortality from 36% to 12%, as compared to those with H:M less than 1.53, whose reduction in mortality was 53% to 37% over 60 months (p < 0.05) (Nakata et al., 2005).

Boogers et al (2010) studied the role of cardiac sympathetic denervation with 123I-mIBG to predict the occurrence of ventricular arrhythmias in patients with ICD. They recruited 116 patients who underwent ICD implantation. The patients
were followed up every 3 - 6 months (for three years) for device check for appropriate discharge, along with that the secondary end point was cardiac death either by progressive HF or MI. All patients underwent cardiac sympathetic evaluation prior to ICD implantation with 185 MBq of 123I-mIBG and planar and SPECT imaging at 10 - 15 min (early) and 3 - four hours (delayed) imaging. Planar images were used to calculate early and delayed H:M ratios and the cardiac washout rate. The SPECT images were analysed using a 5-point visual scoring system of 0 - 4 (0 = normal uptake and 4 = no uptake) of a 17-segment polar map. The scores were collated for each of the 17 segments to calculate a defect score. All patients also underwent gated-MPS and the visual analysis of the MPS images also carried out in the same fashion. For the purpose of cumulative event rate analysis a mIBG SPECT defect score of more than 26 was regarded as large. In patients with a large defect in the delayed images, the rate if appropriate ICD discharge was 33% over the three year follow up period, where it was 5% in patients with a small defect (defect score ≤ 26). The rate of appropriate discharge or cardiac death in patients with a large defect was much higher than those with a small defect (HR = 8.29, p < 0.01) (Boogers et al., 2010).

ADMIRE-HF study is the largest study to date in which patients underwent planar and SPECT imaging after 15 min and 3 h 50 min post-injection. All patients also underwent myocardial perfusion imaging (Jacobson et al., 2010). However this study did not find any significance of 123I-mIBG SPECT data (Jacobson et al., 2010).
4.5 STATEMENT OF PROBLEM

Most existing studies utilise global planar imaging. The problem with this approach is that the heart size, which is quite variable between patients, has a substantial influence on the uptake values. Similarly the count statistics are influenced by the orientation of a patient’s heart. The anterior wall counts have a disproportionate influence on the total counts obtained from the heart obfuscating those from the other walls.

The critical review highlighted that regional visual uptake parameters have a high degree of predictability in HF. None of the studies since Somsen et al (1996) have carried out regional quantification parameters such as uptake and washout. With the suspicion that CAN is a regional phenomenon, which expands to include the whole of the heart, and that SCD is due to loss of cardiac SNS, it is important that a study be carried out that utilises 123I-mIBG SPECT to carry out semi-quantification and validate regional uptake and washout indices in search of a method to improve the criterion for implantation of ICD.

Existing SPECT studies have been unable to fulfil the desired role as they have predominantly used a global approach to imaging and quantification. These images included the lumen, which tends to affect the heart size with progressive disease, leading to change in the counts per pixel without any significant change in the actual uptake in the heart. Infarcted segments, which have no influence on CE in patients with HF, are also included in global SPECT imaging, thus confounding the uptake statistics, leading to poor sensitivity and specificity.
Additionally other issues that plague planar global imaging also affect this approach.
Chapter 5

Methodology
5.1 HYPOTHESIS
Regional cardiac sympathetic quantitation using 123I-mIBG SPECT provides better uptake and washout information and patient stratification for adverse events in patients with HF patients compared to planar or global SPECT imaging.

5.2 AIMS AND OBJECTIVES

5.2.1 Aims
The aim of this study was to determine whether regional sympathetic activity is an independently predictive of adverse CE in CHF patients.

5.2.2 Objectives
The objectives of this study were to assess whether regional cardiac sympathetic imaging using 123I-mIBG SPECT has any correlation with various clinical, biochemical, and imaging HF indicators.

5.3 PATIENT RECRUITMENT
Twenty-three HF patients with an LVEF less than 55% on echocardiography, diagnosed as suffering from HF, presenting at the Cardiac Health Institute, Sydney were recruited for this study. One patient was subsequently dropped as he had suffered from Takotsubo syndrome. Ethics approval for the study was obtained from the ethics committee of the Charles Sturt University. Informed written consent was taken for participation in the study.

The patient then underwent myocardial perfusion scintigraphy (MPS) with 99mTc-MIBI using the established standard protocol. Some patients who had
had their 99mTc-MIBI scans in the recent past (up to six months before the 123I-mIBG study) did not undergo a repeat MPS. Subsequently all the patients underwent cardiac sympathetic imaging with 123I-mIBG supplied by Australian Nuclear Science and Technology Organisation (ANSTO).

5.4 BIOCHEMICAL AND GENETIC ANALYSIS

A blood sample was obtained from each patient for evaluation of biochemical and genetic markers. The biochemical and genetic markers that the patients were being evaluated for were:

1. BNP
2. hsCRP
3. IL-6
4. TNF-α
5. ACE gene polymorphism
6. UCP 2 and UCP 3 SNP
7. Telomere length (using monochrome multiplex quantitative polymerase chain reaction technique)
5.5 IMAGING PROTOCOL

Patients were administered 185 – 200 MBq (5 – 7 mCi) of 123I-mIBG IV. The early phase imaging commenced 15 minutes post IV using 300 second anterior chest planar images. A 256x256 matrix on a Siemens variable angle eCam (Siemens Medical Solutions, Erlangen, Germany) gamma camera with a low energy high resolution (LEHR) collimator was employed. Planar imaging was followed by 180 degree SPECT (LPO45 to RAO45) using a 64x64 matrix, 60 projections at 25 seconds per projection. The patient was imaged supine with the arms extended above the head. Processing was carried out using a GE Xeleris workstation. The planar and SPECT acquisitions were repeated four hours post IV. Global myocardial, mediastinal, thyroid, lung and liver regions of interest were applied to the planar images.

5.6 PLANAR ANALYSIS

Normalised (counts per pixel) H:M were calculated for both the early phase (15 minutes after injection) and delayed phase (four hours after injection) using previously described methods (Bengel, Barthel, Matsunari, Schmidt, & Schwaiger, 1999; Matsuo et al., 2003; Zhao et al., 2001). Delayed image statistics were decay corrected. The global washout rate from early to delayed phases was calculated for myocardium, mediastinum, thyroid, lung and liver (Figure 5.1). Cardiac washout rate was determined by (Bengel et al., 1999; Matsuo et al., 2003; Zhao et al., 2001):

\[
\frac{[\text{early phase counts per pixel} - \text{delayed phase counts per pixel}]}{\text{early phase counts per pixel}} \times 100
\]
Regions were applied to the planar image as described by Verberne et al (2008) with the myocardium represented by a region that circumscribed the entire myocardium and the mediastinum region placed adjacent to the upper part of the lung on the midline of the chest. High lung uptake of 123I-mIBG is characteristic of HF and this represents a limitation of region of interest placement (Verberne, Somsen, Povinec, van Eck-Smit, & Jacobson, 2009). Regions of interest were also placed on the liver, thyroid and the right lung.
Figure 5.1: ROIs over the mediastinum, heart, liver, thyroid and right lung in the early and delayed 123I-mIBG static images.
5.7 REGIONAL ANALYSIS

Normalised regions of interest were drawn on 3 short axis (SA) slices i.e. mid, half way between apex and mid, and half way between mid and base slices, the mid vertical long axis (VLA) and mid horizontal long axis (HLA) SPECT slices (26). On the SA slices, regions included anterior, septal, lateral and inferior walls. One the VLA slice, the region included apex, anterior wall and inferior wall. On the HLA slice, the regions were apex, septum and lateral wall. Our approach was to use the SA slices and mid VLA and HLA slices to generate regions for each wall using larger regions that represented the entire territory (ie. anterior, lateral, septal, inferior and apex). The four hour data were decay corrected and regional washout rates (RW) and early and delayed uptake index (MUPe and MUPd) were determined using the method described by Zhao et al. (2001):

\[
RW\% = \left( \frac{\text{mean early segment counts} - \text{mean delayed segment counts}}{\text{mean early segment counts}} \right) \times 100
\]

\[
\text{MUP} = \frac{\text{mean segment counts}}{\text{maximum voxel counts in the myocardial region of interest}}
\]

Other parameters that were also calculated were the early and delayed regional uptake index (MUPI), early and delayed regional uptake normalised to the highest count voxel in the entire SPECT study and normalised to the liver. The formulas were:

\[
\text{MUPI} = \frac{\text{MUP}_{\text{early}}}{\text{MUP}_{\text{delayed}}}
\]
\[
\text{MUP}_{\text{max voxel counts}} = \frac{\text{mean segment counts} \times \text{counts of segment}_{\text{highest counts}}}{\text{maximum voxel counts in myocardial region of interest}}
\]

\[
\text{MUP}_{\text{liver}} = \frac{\text{mean segment counts}}{\text{maximum voxel counts in myocardial region of interest}} \times \text{mean liver counts}
\]

### 5.7.1 Perfusion gated-SPECT and 123I-mIBG SPECT analysis

The myocardial perfusion images were processed as per the established standard into short axis, vertical long axis and horizontal long axis images along with the generation of 20-segment polar maps. The perfusion polar maps were similarly analysed using the visual uptake scoring system (Table 5.1), and the total defect score (TDS) calculated. A \( \Delta \text{TDS} \) parameter was also calculated where:

\[
\Delta \text{TDS} = (\text{myocardial SPECT TDS}) - (\text{delayed 123I - mIBG TDS})
\]

A negative value represented areas that were perfused, but a sympathetic nerve supply defect and thus potentially at higher risk for arrhythmic events and SCD.

### 5.8 VISUAL QUANTITATATION

Twenty-segment polar maps were generated to demonstrate regional cardiac 123I-mIBG distribution at 15 minutes (left) and four hours (right) post IV administration. The polar maps were visually evaluated for uptake defects and scored using a five point scale (Table 5.1). The defect scores of the individual
segments were then added and TDS calculated for both the early and delayed SPECT polar maps.

Table 5.1: 5-point scale for visual scoring of uptake of 123I-mIJB and 99mTc-MIBI in the polar maps.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal uptake</td>
</tr>
<tr>
<td>1</td>
<td>Slightly reduced uptake</td>
</tr>
<tr>
<td>2</td>
<td>Moderately reduced uptake</td>
</tr>
<tr>
<td>3</td>
<td>Severely reduced uptake</td>
</tr>
<tr>
<td>4</td>
<td>No uptake</td>
</tr>
</tbody>
</table>

5.9 PATIENT FOLLOW UP

After the initial clinical evaluation at the time of the 123I-mIJBG study, the patients were clinically followed up regularly till the end of the study. Any CE that happened during the follow up phase were recorded, along with patients' medication and HF symptoms. The CEs were defined as:

1. Cardiac death due to HF progression or ventricular arrhythmia
2. Symptomatic cardiac arrhythmias requiring hospitalisation and/or defibrillation.
3. HF progression requiring increase in medication.
4. Myocardial infarction, cardiac bypass grafting or coronary artery by-pass surgery.
5. Need for ICD implantation
5.10 STATISTICAL ANALYSIS

Statistical analysis was carried out using JMP v10 software (SAS Institute Inc). Numeric results are expressed as mean (confidence interval). In all analyses, a p-value of less than 0.05 was considered as statistically significant. Correlation between continuous variables was evaluated using the one way ANOVA. The statistical significance was calculated using Chi-Square analysis for nominal data and Student’s t-test for continuous data. Pearson’s $\chi^2$ test was employed for categorical data with normal distribution and the Likelihood Ratio Chi-Square ($G^2$) test for categorical data without normal distribution. The F-test analysis of variances was used to determine statistically significant differences within grouped data. Ordinal data comparison with continuous data analysis was carried out using discriminant analysis. Odds ratio (OR) was calculated where contingency tables were used.

The differences between independent means and proportions were calculated with a 95% confidence interval (CI). Confidence intervals without an overlap and/or those which did not include zero were considered to support a statistically significant difference while CI with an overlap and/or those that included zero represented differences for which chance could not be excluded as the cause.

Various cut-off points of global and regional early and delayed H:M and washout percentage were selected to define a large patient group with a low or high risk of CE. Kaplan–Meier survival curves were used for survival comparisons between patient groups stratified according to these cut-off points and compared.
Chapter 6

Results
6.1 DEMOGRAPHIC DATA

Twenty-three patients agreed to participate in the study. One patient was excluded from the study as their signs and symptoms were consistent with Takotsubo syndrome. Consequently, the sampling frame included 22 patients who remained in the study to its completion. All patients were male with an average age of 72 years (range: 41 – 88 years). The aetiology of the HF in these patients included 12 (54%) with IHD, four (18%) suffering from DCM, three (13%) with HF secondary to chronic HTN, and one each had presented with hypertrophic cardiomyopathy (5%), myocarditis (5%) and valvular heart disease (5%) (Table 6.1 and Figure 6.1). The mean LVEF was 41.9% (95% CI: 38.2 – 45.6%), and the mean EDV was 157 ml (95% CI: 135 – 178 ml) (Table 6.2). The change in LVEF from recruitment to follow up (ΔLVEF) was calculated for all patients and, based on that data, patients were categorised into those with a significant drop in LVEF (decrease of 5% or more) and those with a ΔLVEF less than 5% (Table 6.2). Of the 22 patients, 10 (45%) patients suffered CE and 12 (55%) remained event free throughout follow up (Table 6.2). For those experiencing a CE, there was a mean of 303 days between 123I-mIBG scan date and the date of CE. Fifteen patients (68%) also underwent 24-hour Holter studies within a short period of the 123I-mIBG study (Table 6.4).
Table 6.1: Demographic data delineating relationship between age, aetiology of HF and CE.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Cause of HF</th>
<th>CE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>IHD</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>DCM</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>DCM</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>HTN</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>79</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>85</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>IHD</td>
<td>Y</td>
</tr>
<tr>
<td>13</td>
<td>65</td>
<td>IHD</td>
<td>Y</td>
</tr>
<tr>
<td>14</td>
<td>80</td>
<td>IHD</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>71</td>
<td>HTN</td>
<td>Y</td>
</tr>
<tr>
<td>16</td>
<td>41</td>
<td>HCM</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>72</td>
<td>HTN</td>
<td>N</td>
</tr>
<tr>
<td>18</td>
<td>77</td>
<td>IHD</td>
<td>Y</td>
</tr>
<tr>
<td>19</td>
<td>67</td>
<td>DCM</td>
<td>N</td>
</tr>
<tr>
<td>20</td>
<td>83</td>
<td>DCM</td>
<td>N</td>
</tr>
<tr>
<td>21</td>
<td>77</td>
<td>Valvular</td>
<td>Y</td>
</tr>
<tr>
<td>22</td>
<td>69</td>
<td>Myocarditis</td>
<td>N</td>
</tr>
</tbody>
</table>

Figure 6.1: Cause of HF in the study patients, showing the predominance of IHD as a cause of HF in the study cohort.
Table 6.2: A summary of the LVEF, ΔLVEF, ΔLVEF-5%, EDV, CE and the time to CE of the study cohort.

<table>
<thead>
<tr>
<th>No.</th>
<th>LVEF (%)</th>
<th>EDV (ml)</th>
<th>ΔLVEF</th>
<th>ΔLVEF-5%</th>
<th>CE</th>
<th>Time to event (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>103</td>
<td>15</td>
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</table>

In order to rule out the patients’ age and LVEF at the time of diagnosis as confounding factor, their correlation with each other and the cause of HF and CE was observed. It was observed that non-statistically significant correlation was noted between age and LVEF early ($R^2 = 0.06$, $p = 0.254$) (Figure 6.2), $\Delta$LVEF ($R^2 = 0.04$, $p = 0.354$) (Figure 6.3), $\Delta$LVEF-5% ($p = 0.418$) (Figure 6.4), cause of HF ($p = 0.412$) (Figure 6.5) and CE ($p = 0.198$) (Figure 6.6). The correlation between LVEF and cause of HF ($p = 0.593$) (Figure 6.7) and CE ($p = 0.620$) (Figure 6.8) also failed to reveal any statistically significance. No statistically significant correlation was noted between CE and LVEF ($p = 0.620$) (Figure 6.9).
Figure 6.2: No statistically significant correlation between age and LVEF early was observed (p = 0.254).

Figure 6.3: No statistically significant correlation between age and ΔLVEF was observed (p = 0.354).
Figure 6.4: A plot demonstrating no statistically significant difference in the age of the patients based on $\Delta$LVEF-5% ($p = 0.412$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.5: A plot demonstrating no statistically significant difference in the age of the patients based on the difference in the aetiology of HF ($p = 0.412$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.6: A plot demonstrating no statistically significant difference in the age between patients who had a CE to those who did not (p = 0.198). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.7: A plot demonstrating no statistically significant difference in the LVEF early of the patients based on the difference in the cause of HF (p = 0.593). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
A non-statistically significant correlation was observed between CE and ΔLVEF 
(p = 0.061), implying that ΔLVEF itself was not sufficiently able to predict CE in 
the study population (Figure 6.9). This limitation of LVEF was due to the fact 
that some patients had an improvement of LVEF due to optimal therapy.
Correlation of ΔLVEF-5% and CE was statistically significant (p = 0.011) (Table 
6.3). The OR of ΔLVEF-5% positive test subjects suffering a CE compared to 
ΔLVEF-5% negative patients was 11.67.
Figure 6.9: A plot demonstrating no statistically significant difference in the LVEF early based on CE (p = 0.061). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Table 6.3: Contingency table of ΔLVEF-5% and CE demonstrating a statistically significant relationship between ΔLVEF-5% and CE (p = 0.011). The OR was calculated to be 11.67.

<table>
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<tr>
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</tr>
</thead>
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Table 6.4 demonstrates the various time domain indices of the patients in the study at the time of recruitment and their relationship to ΔLVEF-5% and CE. Analysis of the time-domain parameters of the 24h Holter study SDNN early, %RR>50 early and rms-SD early was carried out and they were correlated with age, LVEF early and ΔLVEF, ΔLVEF-5% and CE. No statistically significant correlation was noted between age and SDNN early (R^2 = 0.05, p = 0.442) (Figure 6.10), %RR>50 early (R^2 < 0.01, p = 0.840) (Figure 6.11) and rms-SD
early ($R^2 < 0.01, p = 0.952$) (Figure 6.12). No statistically significant correlation was noted between LVEF early and SDNN early ($R^2 = 0.12, p = 0.210$) (Figure 6.13), %RR>50 early ($R^2 = 0.11, p = 0.219$) (Figure 6.14) and rms-SD early ($R^2 = 0.17, p = 0.122$) (Figure 6.15). Statistically significant correlation was noted between $\Delta$LVEF and SDNN early ($R^2 = 0.27, p = 0.048$) (Figure 6.16), while %RR>50 early ($R^2 = 0.08, p = 0.298$) (Figure 6.17) and rms-SD early ($R^2 = 0.26, p = 0.055$) (Figure 6.18) did not show any statistically significant correlation with $\Delta$LVEF. No statistically significant correlation was noted between $\Delta$LVEF and SDNN early ($p = 0.020$) (Figure 6.19), %RR>50 early ($p = 0.442$) (Figure 6.20) and rms-SD early ($p = 0.039$) (Figure 6.21). In correlating time domain 24h-Holter parameters with CE, it was noted that SDNN early ($p = 0.012$) (Figure 6.22) and rms-SD early ($p = 0.033$) (Figure 6.24) had statistically significant discriminatory power for predicting CE, while %RR>50 early did not ($p = 0.136$) (Figure 6.23). These imply that loss of parasympathetic innervation leads to increase in the likelihood of CE.

![Image](image_url)

**Figure 6.10:** Age versus SDNN early. No statistically significant correlation was noted ($R^2 = 0.05, p = 0.442$).
Figure 6.11: Age versus %RR>50 early. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.840$).

Figure 6.12: Age versus rms-SD early. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.952$).
Figure 6.13: Plot of SDNN early versus LVEF early. No statistically significant correlation was noted ($R^2 = 0.12$, $p = 0.210$).

Figure 6.14: %RR>50 early versus LVEF early. No statistically significant correlation was noted ($R^2 = 0.11$, $p = 0.219$).
Figure 6.15: rms-SD early versus LVEF early. No statistically significant correlation was noted ($R^2 = 0.17$, $p = 0.122$).

Figure 6.16: SDNN early versus $\Delta$LVEF. A statistically significant correlation was noted ($R^2 = 0.27$, $p = 0.048$) indicating a decrease in LVEF with an increase in SDNN early.
Figure 6.17: %RR>50 early versus ΔLVEF. No statistically significant correlation was noted ($R^2 = 0.08$, $p = 0.298$).

Figure 6.18: rms-SD early versus ΔLVEF. No statistically significant correlation was noted ($R^2 = 0.26$, $p = 0.055$).
Table 6.4: Summary of 24-hour Holter study data for a sub-set of the study population along with $\Delta$LVEF-5% and CE status.

<table>
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<th>rms-SD</th>
<th>$\Delta$LVEF-5%</th>
<th>CE</th>
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Figure 6.19: A plot demonstrating statistically significant difference in the SDNN early based on $\Delta$LVEF-5% ($p = 0.020$). This observation is however not supported by the tiny overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.20: A plot demonstrating no statistically significant difference in %RR>50 early based on CE (p = 0.442). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.21: A plot demonstrating statistically significant difference in rms-SD early based on CE (p = 0.039). This observation is however not supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.22: A plot demonstrating statistically significant difference in SDNN early based on CE ($p = 0.012$). Note the absence overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.23: A plot demonstrating no statistically significant difference in %RR>50 early based on CE ($p = 0.136$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.24: A plot demonstrating a statistically significant difference in rms-SD early based on CE (p = 0.033). This observation is however not supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

6.2 BIOMARKERS

ACE genotype of 13 study patients was correlated with patients’ age, LVEF early, ΔLVEF, ΔLVEF-5% and CE. Non-statistically significant correlation was noted between the ACE genotype and age (p = 0.552) (Figure 6.25), LVEF early (p = 0.132) (Figure 6.26) or ΔLVEF (p = 0.783) (Figure 6.27). It was further observed that there was no statistically significant relationship between the various ACE genotypes and ΔLVEF-5% (p = 0.800) (Table 6.5). ACE genotype also lacked the ability to predict CE in the study population (p = 0.709) (Table 6.6).
Figure 6.25: A plot demonstrating no statistically significant difference in age based on ACE genotype ($p = 0.552$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.26: A plot demonstrating no statistically significant difference in LVEF early based on ACE genotype ($p = 0.132$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.27: A plot demonstrating no statistically significant difference in $\Delta$LVEF based on ACE genotype ($p = 0.783$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Table 6.5: Contingency table of $\Delta$LVEF-5% versus ACE genotype. No statistically significant relationship between $\Delta$LVEF-5% and ACE genotype was noted ($p = 0.800$).

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Table 6.6: Contingency table of CE versus ACE genotype. No statistically significant relationship between CE and ACE genotype was noted ($p = 0.709$).

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<th>CE</th>
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Correlation of the UCP SNPs rs1800849, rs660339 and rs659366 was carried out with age, LVEF early, ΔLVEF, ΔLVEF-5% and instances of CE in a subset of the patient population (19 patients). The trend was similar to that of the ACE genotype, and no statistically significant correlation was observed. Correlation between age and UCP SNP rs1800849 (p = 0.297), rs660339 (p = 0.251) and rs659366 (p = 0.729) is shown in Figure 6.28, Figure 6.29 and Figure 6.30 respectively. Correlation between LVEF and UCP SNP rs1800849 (p = 0.177), rs660339 (p = 0.411) and rs659366 (p = 0.052) is shown in Figure 6.31, Figure 6.32 and Figure 6.33 respectively. Correlation between ΔLVEF and UCP SNP rs1800849 (p = 0.035), rs660339 (p = 0.067) and rs659366 (p = 0.106) is shown in Figure 6.34, Figure 6.35 and Figure 6.36 respectively. Correlation between ΔLVEF-5% and UCP SNP rs1800849 (p = 0.0.016), rs660339 (p = 0.098) and rs659366 (p = 0.235) is shown in Table 6.7,
Table 6.8 and Table 6.9 respectively. Correlation between UCP SNPs rs1800849 (p = 0.385), rs660339 (p = 0.122) and rs659366 (p = 0.240) and CE is shown in Table 6.10, Table 6.11 and Table 6.12 respectively.
Figure 6.28: A plot demonstrating no statistically significant difference in age based on UCP SNP rs1800849 (p = 0.297). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.29: A plot demonstrating no statistically significant difference in age based on UCP SNP rs660339 (p = 0.251). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.30: A plot demonstrating no statistically significant difference in age based on UCP SNP rs659366 ($p = 0.729$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.31: A plot demonstrating no statistically significant difference in LVEF early based on UCP SNP rs1800849 ($p = 0.177$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.32: A plot demonstrating no statistically significant difference in LVEF early based on UCP SNP rs660339 (p = 0.411). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.33: A plot demonstrating no statistically significant difference in LVEF early based on UCP SNP rs659366 (p = 0.052). This observation is supported by the overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.34: A plot demonstrating a statistically significant difference in \( \Delta \text{LVEF} \) based on UCP SNP rs1800849 (\( p = 0.035 \)). This observation is not supported by the overlap of the 95% CIs represented by the top and bottom portion of the diamonds, and is due to the outlier AA genotype.

Figure 6.35: A plot demonstrating no statistically significant difference in \( \Delta \text{LVEF} \) based on UCP SNP rs660339 (\( p = 0.067 \)). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.36: A plot demonstrating no statistically significant difference in ΔLVEF based on UCP SNP rs659366 (p = 0.106). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Table 6.7: Contingency table of ΔLVEF-5% and UCP SNP rs1800849. A statistically significant relationship between ΔLVEF-5% and UCP SNP rs1800849 was noted (p = 0.016) however the p value is unreliable due to low counts in a number of cells.

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Table 6.8: Contingency table of $\Delta$LVEF-5% and UCP SNP rs660339. No statistically significant relationship between $\Delta$LVEF-5% and UCP SNP rs660339 was noted ($p = 0.098$).

<table>
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Table 6.9: Contingency table of $\Delta$LVEF-5% and UCP SNP rs659366. No statistically significant relationship between $\Delta$LVEF-5% and UCP SNP rs659366 was noted ($p = 0.235$).

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Table 6.10: Contingency table of CE and UCP SNP rs1800849. No statistically significant relationship between CE and UCP SNP rs1800849 was noted ($p = 0.385$).

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</table>
Table 6.11: Contingency table of CE and UCP SNP rs660339. No statistically significant relationship between CE and UCP SNP rs660339 was noted (p = 0.122).

<table>
<thead>
<tr>
<th>UCP SNP rs660339</th>
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<td></td>
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<tr>
<td>TT</td>
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Table 6.12: Contingency table of CE and UCP SNP rs659366. No statistically significant relationship between CE and UCP SNP rs659366 was noted (p = 0.240).

<table>
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<th>UCP SNP rs659366</th>
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</tr>
</thead>
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<td></td>
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<tr>
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<tr>
<td>AG</td>
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<tr>
<td>GG</td>
<td>3</td>
</tr>
<tr>
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</table>

Telomere length markers TL, T/S and T/S_mean of the patients were studied. Correlation between age and TL ($R^2 = 0.15$, $p = 0.094$) (Figure 6.37), T/S ($R^2 = 0.05$, $p = 0.331$) (Figure 6.38) and T/S_mean ($R^2 = 0.04$, $p = 0.404$) (Figure 6.39) did not show any statistically significance. Correlation between LVEF early and TL ($R^2 = 0.03$, $p = 0.494$) (Figure 6.40), T/S ($R^2 = 0.02$, $p = 0.555$) (Figure 6.41) and T/S_mean ($R^2 = 0.01$, $p = 0.611$) (Figure 6.42) did not show any statistically significance. No statistically significant correlation was observed between $\Delta$LVEF and TL ($R^2 < 0.01$, $p = 0.689$) (Figure 6.43), T/S ($R^2 = 0.12$, $p = 0.128$) (Figure 6.44) or T/S_mean ($R^2 = 0.06$, $p = 0.282$) (Figure 6.45). No statistically significant correlation was observed between $\Delta$LVEF-5% and TL ($p$
= 0.508) (Figure 6.46), T/S (p = 0.068) (Figure 6.47) or T/S_mean (p = 0.168) (Figure 6.48). When the risk of CE was correlated with the TL, the reduction in CE was non-statistically significant (p = 0.264) (Figure 6.49). No statistically significant difference in CE in the study population were observed based on T/S (p = 0.558) (Figure 6.50) or T/S_mean (p = 0.497) (Figure 6.51). These results signify that telomere length parameters have no significant effect in predicting global HF parameters.

Figure 6.37: Plot of age versus TL. No statistically significant correlation was noted ($R^2 = 0.15$, p = 0.094).
Figure 6.38: Age versus T/S. No statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.331$).

Figure 6.39: Plot of age versus T/S_mean. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.404$).
Figure 6.40: TL versus LVEF early. No statistically significant correlation was noted ($R^2 = 0.15, p = 0.094$).

Figure 6.41: T/S versus LVEF early. No statistically significant correlation was noted ($R^2 = 0.02, p = 0.555$).
Figure 6.42: T/S\_mean versus LVEF early. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.611$).

Figure 6.43: TL versus $\Delta$LVEF. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.689$).
Figure 6.44: T/S versus ∆LVEF. No statistically significant correlation was noted ($R^2 = 0.12$, $p = 0.128$).

Figure 6.45: T/S_mean versus ∆LVEF. No statistically significant correlation was noted ($R^2 = 0.06$, $p = 0.282$).
Figure 6.46: A plot demonstrating no statistically significant difference in TL based on ∆LVEF-5% (p = 0.508). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.47: A plot demonstrating no statistically significant difference in T/S based on ∆LVEF-5% (p = 0.068). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.48: A plot demonstrating no statistically significant difference in T/S\_mean based on ΔLVEF-5% (p = 0.168). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.49: A plot demonstrating no statistically significant difference in TL based on CE (p = 0.264). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.50: A plot demonstrating no statistically significant difference in T/S based on CE (p = 0.558). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.51: A plot demonstrating no statistically significant difference in T/S_mean based on CE (p = 0.497). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

6.3 GLOBAL PLANAR 123I-MIBG ANALYSIS

The average early H:M ratio was 1.53 (95% CI: 1.43 – 1.63) and delayed H:M was 1.41 (95% CI: 1.32 – 1.49). Mean washout was 24.5% (95% CI: 21.7% – 27.4%). These parameters are detailed in Table 6.13. Correlation between
global uptake parameters, early and delayed H:M and washout, was carried out with age, LVEF early, $\Delta$LVEF, EDV, CE and the time domain 24h-Holter data. No statistically significant correlation was seen between early H:M ($R^2 = 0.07$, $p = 0.234$) (Figure 6.52), delayed H:M ($R^2 = 0.11$, $p = 0.137$) (Figure 6.53) and washout ($R^2 = 0.11$, $p = 0.127$) (Figure 6.54) and age. No statistically significant correlation was seen between early H:M ($R^2 < 0.01$, $p = 0.804$) (Figure 6.55), delayed H:M ($R^2 = 0.04$, $p = 0.403$) (Figure 6.56) and washout ($R^2 = 0.04$, $p = 0.360$) (Figure 6.57) and LVEF early. Correlation was carried out between $\Delta$LVEF and early ($R^2 < 0.01$, $p = 0.804$) (Figure 6.58) and delayed ($R^2 < 0.01$, $p = 0.858$) (Figure 6.59) H:M and washout ($R^2 = 0.02$, $p = 0.560$) (Figure 6.60) which did not show any statistically significant correlation. EDV and early ($R^2 = 0.01$, $p = 0.614$) (Figure 6.61) and delayed ($R^2 = 0.02$, $p = 0.540$) (Figure 6.62) H:M and washout ($R^2 < 0.01$, $p = 0.904$) (Figure 6.63) also revealed no statistically significant correlation.
Table 6.13: A summary of the global early and delayed H:M values and washout.

<table>
<thead>
<tr>
<th>No</th>
<th>Early H:M</th>
<th>Delayed H:M</th>
<th>Washout (%)</th>
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</thead>
<tbody>
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<td>1.46</td>
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<td>25.80</td>
</tr>
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Figure 6.52: Age versus global early H:M and. No statistically significant correlation was noted ($R^2 = 0.07, p = 0.234$).
Figure 6.53: Age versus global delayed H:M. No statistically significant correlation was noted ($R^2 = 0.11$, $p = 0.137$).

Figure 6.54: Age versus global washout. No statistically significant correlation was noted ($R^2 = 0.11$, $p = 0.127$).
Figure 6.55: LVEF early versus global early H:M. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.804$).

Figure 6.56: LVEF early versus global delayed H:M. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.403$).
Figure 6.57: LVEF early versus global washout and. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.360$).

Figure 6.58: $\Delta$LVEF versus global early H:M and. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.804$).
Figure 6.59: $\Delta$LVEF versus global delayed H:M and. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.858$).

Figure 6.60: $\Delta$LVEF versus global washout and. No statistically significant correlation was noted ($R^2 = 0.02$, $p = 0.560$).
Figure 6.61: EDV versus global early H:M. No statistically significant correlation was noted ($R^2 = 0.01, p = 0.614$).

Figure 6.62: EDV versus global delayed H:M. No statistically significant correlation was noted ($R^2 = 0.02, p = 0.540$).
Figure 6.63: EDV versus global washout. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.904$).

No statistically significant correlation was seen between SDNN and early ($R^2 = 0.03$, $p = 0.540$) (Figure 6.64) and delayed ($R^2 = 0.02$, $p = 0.628$) (Figure 6.65) H:M and washout ($R^2 = 0.19$, $p = 0.109$) (Figure 6.66). Correlation between %RR>50 and early ($R^2 = 0.04$, $p = 0.458$) (Figure 6.67) and delayed ($R^2 < 0.01$, $p = 0.931$) (Figure 6.68) H:M and washout ($R^2 < 0.01$, $p = 0.753$) (Figure 6.69) did not reveal any statistical significance. No statistically significant correlation was seen between rms-SD and early ($R^2 = 0.01$, $p = 0.715$) (Figure 6.70) and delayed ($R^2 < 0.01$, $p = 0.780$) (Figure 6.71) H:M and washout ($R^2 = 0.01$, $p = 0.687$) (Figure 6.72).
Figure 6.64: SDNN early versus global early H:M. No statistically significant correlation was noted ($R^2 = 0.03, p = 0.540$).

Figure 6.65: SDNN early versus global delayed H:M. No statistically significant correlation was noted ($R^2 = 0.02, p = 0.628$).
Figure 6.66: SDNN early versus global washout. No statistically significant correlation was noted ($R^2 = 0.19$, $p = 0.109$).

Figure 6.67: %RR>50 versus global early H:M. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.458$).
Figure 6.68: %RR>50 versus global delayed H:M. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.931$).

Figure 6.69: %RR>50 versus global washout. A non-statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.753$).
Figure 6.70: rms-SD versus global early H:M. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.715$).

Figure 6.71: rms-SD versus global delayed H:M. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.780$).
Figure 6.72: rms-SD versus global washout. No statistically significant correlation was noted ($R^2 = 0.01, p = 0.687$).

$\Delta$LVEF-5% and CE were also correlated with the global uptake and washout parameters. No statistically significant correlation was observed between $\Delta$LVEF-5% and early ($p = 0.780$) (Figure 6.73) and delayed H:M ($p = 0.950$) (Figure 6.74) and global washout ($p = 0.101$) (Figure 6.75). No statistically significant correlation was seen between CE and early ($p = 0.072$) (Figure 6.76) and delayed H:M ($p = 0.142$) (Figure 6.77), however a statistically significant correlation was observed between CE and washout ($p = 0.002$) (Figure 6.78).
Figure 6.73: A plot demonstrating no statistically significant difference in ∆LVEF-5% based on global planar early H:M (p = 0.780). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.74: A plot demonstrating no statistically significant difference in ∆LVEF-5% based on global delayed H:M (p = 0.950). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.75: A plot demonstrating no statistically significant difference in global planar washout based on $\Delta$LVEF-5% ($p = 0.101$). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.76: A plot demonstrating no statistically significant difference in early H;H based on CE ($p = 0.072$). This observation is supported by the small overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Trial subjects were grouped into presence or absence of global uptake or washout risk factors such as a delayed H:M of less than 1.6 (low delayed H:M) or a washout of more than 27% (high washout) or both. This data was then analysed against the presence of CE. Statistically significant correlation was
found between the presence of high washout rate \( (p < 0.001) \) (Table 6.15) and combined presence of low delayed H:M and high washout and CE \( (p < 0.001) \) (Table 6.16). The values are identical because the overarching factor in determining CE was presence of high washout rather than low global H:M. In our study population a delayed H:M of 1.6 proved to be statistically insignificant factor in predicting CE \( (p = 0.176) \) (Table 6.14). This makes the OR of suffering a CE when a patient has a high washout or a combination of low delayed H:M and high washout was 44.

Table 6.14: Contingency table of low delayed global H:M and CE \( (p = 0.176) \).

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</thead>
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</tr>
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</tr>
<tr>
<td></td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 6.15: Contingency table of high washout and CE \( (p < 0.001) \). The OR of CE in patients with a high washout in global 123I-mIBG was 44 times more than those with a low washout.

<table>
<thead>
<tr>
<th>High washout</th>
<th>CE</th>
<th></th>
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<tbody>
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</tr>
<tr>
<td></td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
</tbody>
</table>
Table 6.16: Contingency table of high washout and CE (p < 0.001). The OR of CE in patients with a low uptake and high washout in global 123I-mIBG was 44 times more than those with a high uptake and low washout.

![Contingency table](image)

Global imaging parameters were correlated with the various genetic markers that were obtained during the study. No statistically significant correlation was observed between ACE phenotypes and early (p = 0.183) (Figure 6.79) and delayed (p = 0.062) (Figure 6.80) H:M and washout (p = 0.913) (Figure 6.81). No statistically significant correlation was observed between UCP SNP rs1800849 and early (p = 0.980) (Figure 6.82) and delayed (p = 0.905) (Figure 6.83) H:M and washout (p = 0.814) (Figure 6.84). No statistically significant correlation was observed between UCP SNP rs660339 and early (p = 0.353) (Figure 6.85) and delayed (p = 0.512) (Figure 6.86) H:M and washout (p = 0.564) (Figure 6.87). No statistically significant correlation was observed between UCP SNP rs659366 and early (p = 0.490) (Figure 6.88) and delayed (p = 0.280) (Figure 6.89) H:M and washout (p = 0.255) (Figure 6.90). No statistically significant correlation was observed between TL and early (R² = 0.02, p = 0.533) (Figure 6.91) and delayed (R² = 0.01, p = 0.68) (Figure 6.92) H:M and washout (R² < 0.00, p = 0.782) (Figure 6.93).
Figure 6.79: A plot demonstrating no statistically significant difference in planar early H:M based on ACE genotype (p = 0.183). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.80: A plot demonstrating no statistically significant difference in planar delayed H:M based on ACE genotype (p = 0.062). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.81: A plot demonstrating no statistically significant difference in planar washout based on ACE genotype ($p = 0.913$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.82: A plot demonstrating no statistically significant difference in planar early H:M based on UCP SNP rs1800849 ($p = 0.980$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.83: A plot demonstrating no statistically significant difference in planar delayed H:M based on UCP SNP rs1800849 (p = 0.905). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.84: A plot demonstrating no statistically significant difference in planar washout based on UCP SNP rs1800849 (p = 0.814). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.85: A plot demonstrating no statistically significant difference in planar early H:M based on UCP SNP rs660339 ($p = 0.980$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.86: A plot demonstrating no statistically significant difference in planar early H:M based on UCP SNP rs660339 ($p = 0.905$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.87: A plot demonstrating no statistically significant difference in planar washout based on UCP SNP rs660339 ($p = 0.814$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.88: A plot demonstrating no statistically significant difference in planar early H:M based on UCP SNP rs659366 ($p = 0.490$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.89: A plot demonstrating no statistically significant difference in planar delayed H:M based on UCP SNP rs659366 (p = 0.280). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.90: A plot demonstrating no statistically significant difference in planar washout based on UCP SNP rs659366 (p = 0.255). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.91: TL versus early H:M. No statistically significant correlation was observed ($R^2 = 0.02, p = 0.533$).

Figure 6.92: TL versus delayed H:M. No statistically significant correlation was observed ($R^2 = 0.01, p = 0.68$).
Figure 6.93: TL versus global washout. No statistically significant correlation was observed ($R^2 < 0.00$, $p = 0.782$).

Correlation was carried out between T/S and global imaging parameters. No statistically significant correlation was observed between global early ($R^2 = 0.02$, $p = 0.571$) (Figure 6.94), and delayed ($R^2 = 0.01$, $p = 0.732$) (Figure 6.95) H:M, and washout ($R^2 = 0.02$, $p = 0.586$) (Figure 6.96).

Figure 6.94: T/S versus early H:M. No statistically significant correlation was observed ($R^2 = 0.02$, $p = 0.571$).
Figure 6.95: T/S versus delayed H:M. No statistically significant correlation was observed ($R^2 = 0.01$, $p = 0.732$).

Figure 6.96: T/S versus global planar washout. No statistically significant correlation was observed ($R^2 = 0.02$, $p = 0.586$).

Analysis was carried out between T/S_mean and other parameters. Global early ($R^2 = 0.23$, $p = 0.033$), but not global delayed ($R^2 = 0.12$, $p = 0.147$) H:M showed a statistically significant reduction with increasing T/S_mean (Figure
6.97, Figure 6.98). No statistically significant correlation with global washout was observed ($R^2 = 0.02, p = 0.609$) (Figure 6.99).

Figure 6.97: $T/S$ mean versus early H:M. A statistically significant correlation was observed ($R^2 = 0.23, p = 0.033$)

Figure 6.98: $T/S$ mean versus delayed H:M. No statistically significant correlation was observed ($R^2 = 0.12, p = 0.147$)
Instances of CE based on telomere parameters were carried out. It revealed that neither TL (p = 0.264) (Figure 6.100), nor T/S (p = 0.558) (Figure 6.101) or T/S_mean (p = 0.497) (Figure 6.102) had any statistically significant ability to predict CE.
Figure 6.100: A plot demonstrating no statistically significant difference in TL based on CE (p = 0.264). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.101: A plot demonstrating no statistically significant difference in T/S based on CE (p = 0.558). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Kaplan-Meier survival analysis was carried out using the global parameters of delayed H:M cut-offs of 1.6, 1.5 and a washout of 27% as the thresholds. It was noted that those with a delayed H:M less than or equal to 1.6 had a non-statistically significant higher rate of CE than those with a delayed H:M more than 1.6 \( (p = 0.248) \) (Figure 6.103). The delayed H:M cut-off or 1.5 \( (p = 0.046) \) (Figure 6.104) and a washout of 27% \( (p = 0.003) \) (Figure 6.105) is likely to be a statistically significant discriminator between patients who suffered a CE to those who did not.
Figure 6.103: Kaplan–Meier survival curves of cardiac event rates in patients with CHF divided into 2 groups according to global delayed H:M. Patients with H:M ≤ 1.6 had more CE than those with H:M > 1.6 (p = 0.248).

Figure 6.104: Kaplan–Meier survival curves of cardiac event rates in patients with CHF divided into 2 groups according to global delayed H:M. Patients with H:M ≤ 1.5 had more CE than those with H:M > 1.5 (p = 0.046).
Figure 6.105: Kaplan–Meier survival curves of cardiac event rates in patients with CHF divided into 2 groups according to global washout. Patients with washout > 27% had more CE than those with washout ≤ 27% (p = 0.003).

6.4 GLOBAL SPECT

Global SPECT uptake and washout parameters along with LVEF, ΔLVEF, EDV and CE are enumerated in Table 6.17. Correlation of global SPECT early (R² = 0.04, p = 0.378) (Figure 6.106) and delayed (R² = 0.02, p = 0.511) (Figure 6.107) MUP and washout (R² = 0.04, p = 0.382) (Figure 6.108) with age revealed no statistical significance. Correlation of global SPECT early (R² = 0.25, p = 0.017) (Figure 6.109) and delayed (R² = 0.18, p = 0.048) (Figure 6.110) MUP with LVEF early revealed statistical significance, while global SPECT washout (R² = 0.15, p = 0.079) (Figure 6.111) did not. Correlation of global SPECT early (R² = 0.07, p = 0.221) (Figure 6.112) and delayed (R² < 0.01, p = 0.870) (Figure 6.113) MUP and washout (R² = 0.07, p = 0.220) (Figure 6.114) with ΔLVEF revealed no statistically significance. Analysis was carried out between planar early and delayed H:M and washout and global SPECT early (R² = 0.44, p < 0.001) (Figure 6.115) and delayed (R² = 0.45, p < 0.001) (Figure 6.116) uptake and washout (R² = 0.27, p = 0.013) (Figure 6.119)
parameters which revealed good statistical correlation. Discriminant analysis between $\Delta$LVEF-5% and early ($p = 0.339$) and delayed ($p = 0.858$) whole SPECT MUP and washout ($p = 0.671$) did not reveal statistically significant difference. Discriminant analysis between CE and early ($p = 0.998$) and delayed ($p = 0.814$) whole SPECT MUP and washout ($p = 0.509$) did not reveal statistically significant difference in CE.
Table 6.17: Summary of early and delayed SPECT whole heart uptake and washout, LVEF, EDV, ΔLVEF and CE.

<table>
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<tr>
<th>No.</th>
<th>Early whole SPECT MUP</th>
<th>Delayed whole SPECT MUP</th>
<th>Whole SPECT washout</th>
<th>LVEF (%)</th>
<th>EDV (ml)</th>
<th>ΔLVEF</th>
<th>CE</th>
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Figure 6.106: Age versus early whole SPECT MUP. No statistically significant correlation observed ($R^2 = 0.04$, $p = 0.378$).

Figure 6.107: Age versus delayed whole SPECT MUP. No statistically significant correlation observed ($R^2 = 0.02$, $p = 0.511$).
Figure 6.108: Age versus whole SPECT washout. No statistically significant correlation observed ($R^2 = 0.04$, $p = 0.382$).

Figure 6.109: LVEF early versus early whole SPECT MUP. Statistically significant correlation was observed ($R^2 = 0.25$, $p = 0.017$).
Figure 6.110: LVEF early versus delayed whole SPECT MUP. Statistically significant correlation was observed ($R^2 = 0.18$, $p = 0.048$).

Figure 6.111: LVEF early versus whole SPECT washout. No statistically significant correlation observed ($R^2 = 0.15$, $p = 0.079$).
Figure 6.112: ΔLVEF versus early whole SPECT MUP. No statistically significant correlation was observed ($R^2 = 0.07$, $p = 0.221$).

Figure 6.113: ΔLVEF versus delayed whole SPECT MUP. No statistically significant correlation was observed ($R^2 < 0.01$, $p = 0.870$).
Figure 6.114: \( \Delta \text{LVEF} \) versus whole SPECT washout. No statistically significant correlation observed \( (R^2 = 0.07, \ p = 0.220) \).

Figure 6.115: Early H:M versus whole SPECT early MUP. Statistically significant correlation was noted \( (R^2 = 0.44, \ p < 0.001) \).
To study the effect of heart size on the global SPECT uptake, EDV volume was correlated with global SPECT early and delayed whole MUP. No statistically significant correlation was seen between EDV and early global SPECT whole MUP ($R^2 < 0.01$, $p = 0.829$), (Figure 6.117) and delayed global SPECT MUP ($R^2 < 0.01$, $p = 0.668$) (Figure 6.118). This implies that the cardiac size was not a confounding factor in whole heart SPECT uptake in our study population.
Figure 6.118: EDV versus whole SPECT delayed MUP. No statistically significant correlation between was observed ($R^2 < 0.01$, $p = 0.668$).

Figure 6.119: Planar washout versus whole SPECT washout. Statistically significant correlation was observed ($R^2 = 0.27$, $p = 0.013$).
Figure 6.120: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on ΔLVEF-5% (p = 0.339). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.121: A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on ΔLVEF-5% (p = 0.858). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.122: A plot demonstrating no statistically significant difference in whole SPECT washout based on $\Delta$LVEF-5% ($p = 0.671$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.123: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on CE ($p = 0.998$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Early (p = 0.088) and delayed (p = 0.206) SPECT whole heart MUP and washout (p = 0.255) did not reveal a statistically significant correlation with ACE genotype (Figure 6.126, Figure 6.127 and Figure 6.128). Early (p = 0.890) and delayed (p = 0.414) SPECT whole heart uptake and washout (p = 0.742)
did not revealed a statistically significant correlation with UCP SNP rs1800849 (Figure 6.129, Figure 6.130 and Figure 6.131). Early (p = 0.085) and delayed (p = 0.501) SPECT whole heart uptake and washout (p = 0.648) did not revealed a statistically significant correlation with UCP SNP rs660339 (Figure 6.132, Figure 6.133 and Figure 6.134). Early (p = 0.014) and delayed (p = 0.109) SPECT whole heart uptake and washout (p = 0.242) did not revealed a statistically significant correlation with UCP SNP rs659366 (Figure 6.135, Figure 6.136 and Figure 6.137).

Figure 6.126: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on ACE genotype (p = 0.088 This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.127: A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on ACE genotype (p = 0.206). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.128: A plot demonstrating no statistically significant difference in whole SPECT washout based on ACE genotype (p = 0.255). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.129: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs1800849 ($p = 0.890$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.130: A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on UCP SNP rs1800849 ($p = 0.414$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.131: A plot demonstrating no statistically significant difference in whole SPECT washout based on UCP SNP rs1800849 (p = 0.742). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.132: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs660339 (p = 0.085). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.133: A plot demonstrating no statistically significant difference in delayed whole SPECT MUP based on UCP SNP rs660339 (p = 0.501). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.134: A plot demonstrating no statistically significant difference in whole SPECT washout based on UCP SNP rs660339 (p = 0.648). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.135: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs659366 ($p = 0.014$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.136: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs659366 ($p = 0.109$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.137: A plot demonstrating no statistically significant difference in early whole SPECT MUP based on UCP SNP rs659366 (p = 0.242). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Early ($R^2 = 0.02$, $p = 0.581$) and delayed ($R^2 = 0.13$, $p = 0.113$) SPECT whole heart uptake and washout ($R^2 = 0.02$, $p = 0.563$) did not reveals a statistically significant correlation with TL (Figure 6.138, Figure 6.139 and Figure 6.140). T/S and early ($R^2 = 0.05$, $p = 0.345$) and delayed ($R^2 = 0.01$, $p = 0.669$) SPECT whole heart uptake and washout ($R^2 < 0.00$, $p = 0.693$) also did not reveal a statistically significant correlation (Figure 6.141, Figure 6.142 and Figure 6.143). Early global SPECT uptake revealed a statistically significant correlation with T/S_mean ($R^2 = 0.23$, $p = 0.031$) (Figure 6.144), while the delayed global SPECT ($R^2 = 0.06$, $p = 0.306$) and RW% ($R^2 = 0.04$, $p = 0.391$) did not (Figure 6.145, Figure 6.146).
Figure 6.138: TL versus whole SPECT early MUP. No statistically significant correlation was observed ($R^2 = 0.02, p = 0.581$).

Figure 6.139: TL versus whole SPECT delayed MUP. No statistically significant correlation was observed ($R^2 = 0.13, p = 0.113$).
Figure 6.140: TL versus whole SPECT washout. No statistically significant correlation observed ($R^2 = 0.02, p = 0.563$).

Figure 6.141: T/S versus whole SPECT early MUP and T/S. No statistically significant correlation was observed ($R^2 = 0.05, p = 0.345$).
Figure 6.142: T/S versus whole SPECT delayed MUP. No statistically significant correlation was observed ($R^2 = 0.01$, $p = 0.669$).

Figure 6.143: T/S versus whole SPECT washout. No statistically significant change correlation was noted ($R^2 < 0.00$, $p = 0.693$).
Figure 6.144: T/S_mean versus whole SPECT early MUP. Statistically significant correlation seen ($R^2 = 0.23$, $p = 0.031$).

Figure 6.145: T/S_mean versus whole SPECT delayed MUP. No statistically significant correlation observed ($R^2 = 0.06$, $p = 0.306$).
Figure 6.146: T/S_mean versus whole SPECT washout. Non-statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.391$).

6.5 SPECT REGIONAL ANALYSIS

SPECT regional analysis included visual scoring and regional uptake and washout quantification. Mean regional early and delayed uptake and washout of 123I-mIBG SPECT regions of the study patients is given in Table 6.18, Table 6.19 and Table 6.20. The total sample population values for mean regional early uptake, delayed uptake, mean uptake index and washout are given in Table 6.21.
Table 6.18: Mean early uptake in the different regions for each of the patients.

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<th>No.</th>
<th>Mean early ant MUP</th>
<th>Mean early lat MUP</th>
<th>Mean early inf MUP</th>
<th>Mean early sept MUP</th>
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Table 6.19: Mean delayed uptake in the different regions for each of the patients.

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Table 6.20: Mean WR from the different 123I-mIBG SPECT regions.

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Table 6.21: Mean regional uptake indices and washout.

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<th>Region</th>
<th>Mean early uptake (range)</th>
<th>Mean delayed uptake (range)</th>
<th>Mean uptake Index (range)</th>
<th>Washout % (range)</th>
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<tr>
<td>Anterior</td>
<td>1.31 (0.88-1.56)</td>
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<td>0.98 (0.28-1.63)</td>
<td>1.33 (0.88-2.99)</td>
<td>36.42 (4.42-76.91)</td>
</tr>
<tr>
<td>Inferior</td>
<td>0.95 (0.28-1.48)</td>
<td>0.75 (0.20-1.27)</td>
<td>1.34 (0.99-1.82)</td>
<td>39.32 (13.48-57.28)</td>
</tr>
<tr>
<td>Septum</td>
<td>1.08 (0.49-1.35)</td>
<td>1.00 (0.40-1.49)</td>
<td>1.10 (0.84-1.37)</td>
<td>27.21 (4.63 - 42.07)</td>
</tr>
<tr>
<td>Apex</td>
<td>1.01 (0.53-1.50)</td>
<td>0.86 (0.27-1.82)</td>
<td>1.54 (0.80-7.31)</td>
<td>35.87 (6.39-72.43)</td>
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<tr>
<td>Lumen</td>
<td>0.67 (0.27-1.02)</td>
<td>0.58 (0.18-1.07)</td>
<td>1.26 (0.87-2.91)</td>
<td>32.88 (4.13-70.45)</td>
</tr>
</tbody>
</table>
TDS from 20 segment polar maps of the resting MPS scans and the early and delayed 123I-mIBG scans are given in Table 6.22 along with the ΔTDS and CE. Early and delayed 123I-mIBG TDS were correlated against various global and regional parameters. Non-statistically significant correlation was seen between planar early H:M and 123I-mIBG early TDS ($R^2 = 0.01$, $p = 0.608$) (Figure 6.147), and planar delayed H:M and 123I-mIBG delayed TDS ($R^2 = 0.05$, $p = 0.338$) (Figure 6.148). No statistically significant correlation was observed between 123I-mIBG early TDS and early whole SPECT MUP ($R^2 = 0.17$, $p = 0.060$) (Figure 6.149), or between 123I-mIBG delayed TDS and delayed whole SPECT MUP ($R^2 = 0.07$, $p = 0.234$) (Figure 6.150). Non-statistically significant correlation between 123I-mIBG early TDS and early anterior MUP ($R^2 = 0.13$, $p = 0.101$) (Figure 6.151), early lateral MUP ($R^2 = 0.10$, $p = 0.146$) (Figure 6.152). Significant statistical correlation was noted between early 123I-mIBG TDS and early inferior wall ($R^2 = 0.21$, $p = 0.033$) (Figure 6.153), early septal ($R^2 = 0.19$, $p = 0.044$) (Figure 6.154), early apical ($R^2 = 0.44$, $p < 0.001$) MUP (Figure 6.155).
Table 6.22: Table of TDS for MIBI, early mIBG and delayed mIBG TDS, ∆TDS and CE.

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Figure 6.147: Graph of planar early H:M versus 123I-mIBG early TDS. Non-statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.608$).
Figure 6.148: Planar delayed H:M versus 123I-mIBG delayed TDS. No statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.338$).

Figure 6.149: 123I-mIBG early TDS versus early whole SPECT MUP. Non-statistically significant correlation was noted ($R^2 = 0.17$, $p = 0.060$).
Figure 6.150: $^{123}$I-mIBG delayed TDS versus delayed whole SPECT MUP. No statistically significant correlation was noted ($R^2 = 0.07$, $p = 0.234$).

Figure 6.151: $^{123}$I-mIBG early TDS versus early anterior MUP. No statistically significant correlation was noted ($R^2 = 0.13$, $p = 0.101$).
Figure 6.152: 123I-mIBG early TDS versus early lateral MUP. No statistically significant correlation was noted ($R^2 = 0.10$, $p = 0.146$).

Figure 6.153: 123I-mIBG early TDS versus early lateral MUP. Statistically significant correlation was observed ($R^2 = 0.21$, $p = 0.033$).
Figure 6.154: 123I-mIBG early TDS versus early lateral MUP. Statistically significant correlation was observed ($R^2 = 0.19$, $p = 0.044$).

Figure 6.155: 123I-mIBG early TDS versus early lateral MUP. Statistically significant correlation was observed ($R^2 = 0.44$, $p < 0.001$).
Figure 6.156: 123I-mIBG early TDS versus early luminal MUP. Non-statistically significant correlation was noted ($R^2 = 0.16, p = 0.068$).

Significant statistical correlation was also observed between delayed 123I-mIBG TDS and delayed inferior MUP ($R^2 = 0.18, p = 0.050$) (Figure 6.159), delayed septal MUP ($R^2 = 0.19, p = 0.041$) (Figure 6.160), delayed apical MUP ($R^2 = 0.28, p = 0.011$) (Figure 6.161). Other regional uptake parameters delayed anterior MUP ($R^2 = 0.05, p = 0.316$) (Figure 6.157), delayed lateral MUP ($R^2 = 0.04, p = 0.379$) (Figure 6.158) and delayed luminal MUP ($R^2 = 0.11, p = 0.132$) (Figure 6.162) did not reveal a statistically significant correlation with early or delayed 123I-mIBG TDS.
Figure 6.157: 123I-mIBG late TDS versus delayed anterior MUP. No statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.316$).

Figure 6.158: 123I-mIBG late TDS versus delayed lateral MUP. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.379$).
Figure 6.159: 123I-mIBG late TDS versus delayed inferior MUP. Statistically significant correlation was noted ($R^2 = 0.18$, $p = 0.050$).

Figure 6.160: 123I-mIBG late TDS versus delayed septal MUP. Statistically significant correlation was noted ($R^2 = 0.19$, $p = 0.041$).
Figure 6.161: 123I-mIBG late TDS versus delayed apical MUP. Statistically significant correlation was noted ($R^2 = 0.28$, $p = 0.011$).

Figure 6.162: 123I-mIBG late TDS versus delayed luminal MUP. Non-statistically significant correlation was noted ($R^2 = 0.11$, $p = 0.132$).

RW% of a number of regional cardiac segments were correlated with early and delayed 123I-mIBG TDS. Non-statistically significant correlation was noted between with early 123I-mIBG TDS and anterior ($R^2 = 0.06$, $p = 0.278$), lateral ($R^2 < 0.01$, $p = 0.923$) and inferior ($R^2 = 0.05$, $p = 0.322$) RW%. Septal ($R^2 = 0.41$, $p = 0.001$) (Figure 6.166), apical ($R^2 = 0.21$, $p = 0.034$) (Figure 6.167), luminal ($R^2 = 0.41$, $p = 0.001$) (Figure 6.168) and whole SPECT ($R^2 = 0.31$, $p =$ 238
0.008) (Figure 6.169) RW% correlated statistically significantly with early 123I-mIBG TDS. Delayed 123I-mIBG TDS correlated statistically significantly with anterior RW% ($R^2 = 0.19$, $p = 0.042$) (Figure 6.170), septal RW% ($R^2 = 0.69$, $p < 0.001$) (Figure 6.173), apical RW% ($R^2 = 0.32$, $p = 0.007$) (Figure 6.174), luminal RW% ($R^2 = 0.28$, $p = 0.012$) (Figure 6.175), while lateral RW% ($R^2 < 0.01$, $p = 0.923$) (Figure 6.171), inferior RW% ($R^2 = 0.05$, $p = 0.322$) (Figure 6.172) did not show any significant statistical correlation.

![Graph](image)

Figure 6.163: 123I-mIBG early TDS versus anterior RW%. Non-statistically significant correlation was noted ($R^2 = 0.06$, $p = 0.278$).
Figure 6.164: 123I-mIBG early TDS versus lateral RW%. Non-statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.923$).

Figure 6.165: 123I-mIBG early TDS versus lateral RW%. Non-statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.322$).
Figure 6.166: $^{123}$I-mIBG early TDS versus septal RW%. Statistically significant correlation was noted ($R^2 = 0.41$, $p = 0.001$).

Figure 6.167: $^{123}$I-mIBG early TDS versus apical RW%. Statistically significant correlation was noted ($R^2 = 0.21$, $p = 0.034$).
Figure 6.168: 123I-mIBG early TDS versus luminal RW%. Non-statistically significant correlation was noted ($R^2 = 0.41$, $p = 0.001$).

Figure 6.169: 123I-mIBG early TDS versus whole SPECT RW%. Statistically significant correlation was noted ($R^2 = 0.31$, $p = 0.008$).
Figure 6.170: 123I-mIBG delayed TDS versus anterior RW%. Statistically significant correlation was noted ($R^2 = 0.19$, $p = 0.042$).

Figure 6.171: 123I-mIBG delayed TDS versus lateral RW%. Non-statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.623$).
Figure 6.172: $^{123}$I-mIBG delayed TDS versus inferior RW%. Non-statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.360$).

Figure 6.173: $^{123}$I-mIBG delayed TDS versus septal RW%. Statistically significant correlation was noted ($R^2 = 0.69$, $p < 0.001$).
Figure 6.174: 123I-mIBG delayed TDS versus apical RW%. Statistically significant correlation was noted ($R^2 = 0.32, p = 0.007$).

Figure 6.175: 123I-mIBG delayed TDS versus luminal RW%. Statistically significant correlation was noted ($R^2 = 0.28, p = 0.012$).
Statistically significant correlation between delayed 123I-mIBG TDS and mean whole SPECT washout was observed ($R^2 = 0.39$, $p = 0.002$).

$\Delta$TDS was also correlated with early and delayed regional uptake. Mean early uptake in anterior segment ($R^2 = 0.25$, $p = 0.022$) (Figure 6.177), lateral segment ($R^2 = 0.32$, $p = 0.007$) (Figure 6.178), inferior segment ($R^2 = 0.39$, $p = 0.002$) (Figure 6.179), apical segment ($R^2 = 0.35$, $p = 0.005$) (Figure 6.181) and whole SPECT ($R^2 = 0.23$, $p = 0.026$) (Figure 6.182) correlated statistically significantly with $\Delta$TDS. Mean delayed uptake in inferior segment ($R^2 = 0.25$, $p = 0.021$) (Figure 6.185), septum ($R^2 = 0.21$, $p = 0.036$) (Figure 6.186) and apex ($R^2 = 0.20$, $p = 0.041$) (Figure 6.187) correlated significantly with $\Delta$TDS. No statistically significant correlation was observed between $\Delta$TDS and delayed anterior MUP ($R^2 = 0.11$, $p = 0.151$) Figure 6.183, luminal MUP ($R^2 = 0.10$, $p = 0.164$) (Figure 6.188) and whole SPECT MUP ($R^2 = 0.10$, $p = 0.166$) (Figure 6.189).
Figure 6.177: ΔTDS versus early anterior MUP. Statistically significant correlation was noted ($R^2 = 0.25, p = 0.022$).

Figure 6.178: ΔTDS versus early lateral MUP. Statistically significant correlation was noted ($R^2 = 0.32, p = 0.007$).
Figure 6.179: $\Delta$TDS versus early inferior MUP. Statistically significant correlation was noted ($R^2 = 0.39, p = 0.002$).

Figure 6.180: $\Delta$TDS versus early septal MUP. Non-statistically significant correlation was noted ($R^2 = 0.12, p = 0.117$).
Figure 6.181: $\Delta$TDS versus early apical MUP. Statistically significant correlation was noted ($R^2 = 0.35$, $p = 0.005$).

Figure 6.182: $\Delta$TDS versus early whole SPECT MUP. Statistically significant correlation was noted ($R^2 = 0.23$, $p = 0.026$).
Figure 6.183: ΔTDS versus delayed anterior MUP. Non-statistically significant correlation was noted ($R^2 = 0.11, p = 0.151$).

Figure 6.184: ΔTDS versus delayed lateral MUP. Non-statistically significant correlation was noted ($R^2 = 0.17, p = 0.065$).
Figure 6.185: ΔTDS versus delayed inferior MUP. Statistically significant correlation was noted ($R^2 = 0.25$, $p = 0.021$).

Figure 6.186: ΔTDS versus delayed septal MUP. Statistically significant correlation was noted ($R^2 = 0.21$, $p = 0.036$).
Figure 6.187: ΔTDS versus delayed apical MUP. Statistically significant correlation was noted ($R^2 = 0.20, p = 0.041$).

Figure 6.188: ΔTDS versus delayed luminal MUP. Non-statistically significant correlation was noted ($R^2 = 0.10, p = 0.164$).
Figure 6.189: ΔTDS versus delayed whole SPECT MUP. Non-statistically significant correlation was noted ($R^2 = 0.10$, $p = 0.166$).

RW% was also correlated with ΔTDS. Anterior RW% ($R^2 = 0.32$, $p = 0.007$) (Figure 6.190), septal RW% ($R^2 = 0.69$, $p < 0.001$) (Figure 6.193), apical RW% ($R^2 = 0.37$, $p = 0.004$) (Figure 6.194), luminal RW% ($R^2 = 0.30$, $p = 0.010$) (Figure 6.195) and whole SPECT WR% ($R^2 = 0.46$, $p < 0.001$) (Figure 6.196) correlated significantly with ΔTDS. Non-statistically significant correlation was observed between lateral RW% ($R^2 = 0.11$, $p = 0.138$) (Figure 6.191) and inferior RW% ($R^2 = 0.12$, $p = 0.127$) (Figure 6.192) and ΔTDS.
Figure 6.190: $\Delta$TDS versus anterior RW%. Statistically significant correlation was noted ($R^2 = 0.32, p = 0.007$).

Figure 6.191: $\Delta$TDS versus lateral RW%. Non-statistically significant correlation was noted ($R^2 = 0.11, p = 0.138$).
Figure 6.192: ΔTDS versus inferior RW%. Non-statistically significant correlation was noted ($R^2 = 0.12$, $p = 0.127$).

Figure 6.193: ΔTDS versus septal RW%. Statistically significant correlation was noted ($R^2 = 0.69$, $p < 0.001$).
Figure 6.194: $\Delta TDS$ versus apical RW%. Statistically significant correlation was noted ($R^2 = 0.37$, $p = 0.004$).

Figure 6.195: $\Delta TDS$ versus luminal RW%. Statistically significant correlation was noted ($R^2 = 0.30$, $p = 0.010$).
Figure 6.196: $\Delta$TDS versus whole SPECT washout. Statistically significant correlation was noted ($R^2 = 0.46$, $p < 0.001$).

123I-mIBG early and delayed TDS and $\Delta$TDS were correlated with instances of CE. Neither 123I-mIBG early (Figure 6.197) and delayed TDS (Figure 6.198) nor $\Delta$TDS (Figure 6.199) were able to differentiate between patients who suffered a CE and those who did not.

Figure 6.197: A plot demonstrating no statistically significant difference in 123I-mIBG early TDS based on CE ($p = 0.702$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Early and delayed regional uptake parameters were correlated with TL.

Statistically significant correlation was seen between TL and early luminal MUP
(R² = 0.21, p = 0.041) (Figure 6.205). Early anterior (R² = 0.04, p = 0.401) (Figure 6.200), lateral (R² = 0.02, p = 0.506) (Figure 6.201), inferior (R² = 0.07, p = 0.243) (Figure 6.202), septal (R² = 0.13, p = 0.117) (Figure 6.203) and apical (R² = 0.01, p = 0.615) (Figure 6.204) MUP did not reveal any statistically significant correlation with TL. Delayed luminal (R² = 0.25, p = 0.026) (Figure 6.211) and septal (R² = 0.22, p = 0.037) (Figure 6.209) MUP revealed a statistically significant correlation with TL. Delayed anterior (R² = 0.02, p = 0.506) (Figure 6.206), lateral (R² = 0.11, p = 0.158) (Figure 6.207), inferior (R² = 0.13, p = 0.116) (Figure 6.208) and apical (R² = 0.01, p = 0.615) (Figure 6.211) MUP did not reveal any statistically significant correlation with TL. No statistically significant correlation between RW% from anterior (R² = 0.03, p = 0.476) (Figure 6.212), lateral (R² = 0.07, p = 0.274) (Figure 6.213), inferior (R² < 0.01, p = 0.820) (Figure 6.214), septal (R² = 0.03, p = 0.451) (Figure 6.215), apex (R² = 0.01, p = 0.623) (Figure 6.216) and lumen (R² = 0.01, p = 0.620) (Figure 6.217) with TL was observed.

Figure 6.200: TL versus early anterior MUP. No statistically significant correlation was noted (R² = 0.04, p = 0.401).
Figure 6.201: TL versus early lateral MUP. No statistically significant correlation was noted ($R^2 = 0.02$, $p = 0.506$).

Figure 6.202: TL versus early inferior MUP. No statistically significant correlation was noted ($R^2 = 0.07$, $p = 0.243$).
Figure 6.203: TL versus early septal MUP. No statistically significant correlation was noted ($R^2 = 0.13$, $p = 0.117$).

Figure 6.204: TL versus early apical MUP. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.615$).
Figure 6.205: TL versus early luminal MUP. Statistically significant correlation between early luminal MUP and TL ($R^2 = 0.21$, $p = 0.041$).

Figure 6.206: TL versus delayed anterior MUP. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.704$).
Figure 6.207: TL versus delayed lateral MUP. No statistically significant correlation was noted ($R^2 = 0.11, p = 0.158$).

Figure 6.208: TL versus delayed inferior MUP. No statistically significant correlation was noted ($R^2 = 0.13, p = 0.116$).
Figure 6.209: TL versus delayed septal MUP. Statistically significant correlation was noted ($R^2 = 0.22, \ p = 0.037$).

Figure 6.210: TL versus delayed apical MUP. No statistically significant correlation was noted ($R^2 = 0.07, \ p = 0.261$).
Figure 6.211: TL versus delayed lumen MUP. Statistically significant correlation observed between delayed lumen MUP and TL ($R^2 = 0.25$, $p = 0.026$).

Figure 6.212: TL versus anterior RW%. Non-statistically significant correlation observed between anterior RW% and TL ($R^2 = 0.03$, $p = 0.476$).
Figure 6.213: TL versus lateral RW%. Non-statistically significant correlation observed between lateral RW% and TL ($R^2 = 0.07$, $p = 0.274$).

Figure 6.214: TL versus inferior RW%. Non-Statistically significant correlation observed between inferior RW% and TL ($R^2 < 0.01$, $p = 0.820$).
Figure 6.215: TL versus septal RW%. Non-statistically significant correlation observed between septal RW% and TL ($R^2 = 0.03$, $p = 0.451$).

Figure 6.216: TL versus apical RW%. Non-statistically significant correlation observed between apical RW% and TL ($R^2 = 0.01$, $p = 0.623$).
Regional indices such as early and delayed MUP and RW% were correlated with T/S and T/S_mean. No statistically significant correlation was noted between T/S and early anterior MUP ($R^2 = 0.01, p = 0.716$) (Figure 6.218), early lateral MUP ($R^2 = 0.03, p = 0.442$) (Figure 6.219), early inferior MUP ($R^2 = 0.06, p = 0.304$) (Figure 6.220), early septal MUP ($R^2 = 0.01, p = 0.671$) (Figure 6.221), early apical MUP ($R^2 = 0.07, p = 0.271$) (Figure 6.222) and early luminal MUP ($R^2 = 0.02, p = 0.529$) (Figure 6.223). Correlation between delayed anterior MUP ($R^2 = 0.01, p = 0.704$) (Figure 6.224), delayed lateral MUP ($R^2 = 0.04, p = 0.413$) (Figure 6.225), delayed inferior MUP ($R^2 = 0.06, p = 0.304$) (Figure 6.226), delayed septal MUP ($R^2 = 0.02, p = 0.570$) (Figure 6.227), delayed apical MUP ($R^2 = 0.03, p = 0.441$) (Figure 6.228) and delayed luminal MUP ($R^2 < 0.01, p = 0.907$) (Figure 6.229) revealed no statistical significance with T/S. No statistically significant correlation between anterior ($R^2 = 0.14, p = 0.101$) (Figure 6.230), lateral ($R^2 = 0.14, p = 0.101$) (Figure 6.231), inferior ($R^2 = 0.01, p = 0.764$) (Figure 6.232), septal ($R^2 < 0.01, p = 0.909$) (Figure 6.233),
apical ($R^2 = 0.03$, $p = 0.467$) (Figure 6.234) and luminal ($R^2 = 0.01$, $p = 0.624$) (Figure 6.235) RW% and T/S was observed.

Figure 6.218: T/S versus early anterior MUP. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.716$).

Figure 6.219: T/S versus early lateral MUP. No statistically significant correlation was noted ($R^2 = 0.03$, $p = 0.442$).
Figure 6.220: T/S versus early inferior MUP. No statistically significant correlation was noted ($R^2 = 0.06$, $p = 0.304$).

Figure 6.221: T/S versus early septal MUP. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.671$).
Figure 6.222: T/S versus early apical MUP. No statistically significant correlation was noted ($R^2 = 0.07$, $p = 0.271$).

Figure 6.223: T/S versus early luminal MUP. No statistically significant correlation was noted ($R^2 = 0.02$, $p = 0.529$).
Figure 6.224: T/S versus delayed anterior MUP. No statistically significant correlation was noted ($R^2 = 0.01, p = 0.704$).

Figure 6.225: T/S versus delayed anterior MUP. No statistically significant correlation was noted ($R^2 = 0.04, p = 0.413$).
Figure 6.226: T/S versus delayed inferior MUP. No statistically significant correlation was noted ($R^2 = 0.14$, $p = 0.108$).

Figure 6.227: T/S versus delayed septal MUP. No statistically significant correlation was noted ($R^2 = 0.02$, $p = 0.570$).
Figure 6.228: T/S versus delayed apical MUP. No statistically significant correlation was noted ($R^2 = 0.03$, $p = 0.441$).

Figure 6.229: T/S versus delayed luminal MUP. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.907$).
Figure 6.230: T/S versus anterior RW%. No statistically significant correlation was noted ($R^2 = 0.01, p = 0.710$).

Figure 6.231: T/S versus lateral RW%. No statistically significant correlation was noted ($R^2 = 0.14, p = 0.101$).
Figure 6.232: T/S versus inferior RW%. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.764$).

Figure 6.233: T/S versus septal RW%. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.376$).
No statistically significant correlation was noted (R^2 = 0.02, p = 0.518).

Figure 6.234: T/S versus apical RW%. No statistically significant correlation was noted (R^2 = 0.02, p = 0.518).

Figure 6.235: T/S versus luminal RW%. No statistically significant correlation was noted (R^2 = 0.01, p = 0.640).

No statistically significant correlation was seen between T/S_mean and early anterior MUP (R^2 = 0.18, p = 0.060) (Figure 6.236), early lateral MUP (R^2 = 0.08, p = 0.223) (Figure 6.237), early inferior MUP (R^2 = 0.14, p = 0.100) (Figure 6.238), early apical MUP (R^2 = 0.18, p = 0.064) (Figure 6.240) and early luminal MUP (R^2 = 0.04, p = 0.397) (Figure 6.241). Mean early septal MUP (R^2 = 0.25, p
= 0.024) (Figure 6.239) did reveal a statistically significant correlation with T/S_mean. Delayed anterior ($R^2 = 0.05$, $p = 0.328$) (Figure 6.242), lateral ($R^2 = 0.07$, $p = 0.277$) (Figure 6.243), inferior ($R^2 = 0.07$, $p = 0.253$) (Figure 6.244), septal ($R^2 = 0.07$, $p = 0.272$) (Figure 6.245), apical ($R^2 = 0.06$, $p = 0.315$) (Figure 6.246) and luminal ($R^2 < 0.01$, $p = 0.884$) (Figure 6.247) MUP and T/S_mean did not correlate with statistical significance. No statistically significant correlation between anterior ($R^2 = 0.05$, $p = 0.348$) (Figure 6.248), lateral ($R^2 = 0.01$, $p = 0.744$) (Figure 6.249), inferior ($R^2 = 0.02$, $p = 0.520$) (Figure 6.250), septal ($R^2 < 0.01$, $p = 0.909$) Figure 6.251, apical ($R^2 = 0.03$, $p = 0.467$) (Figure 6.252) and luminal ($R^2 = 0.01$, $p = 0.624$) (Figure 6.253) RW% and T/S_mean was observed.

Figure 6.236: T/S_mean versus early anterior MUP. No statistically significant correlation was noted ($R^2 = 0.18$, $p = 0.060$).
Figure 6.237: T/S\_mean versus early lateral MUP. No statistically significant correlation was noted ($R^2 = 0.08$, $p = 0.223$).

Figure 6.238: T/S\_mean versus early inferior MUP. No statistically significant correlation was noted ($R^2 = 0.14$, $p = 0.100$).
Figure 6.239: T/S_mean versus early septal MUP. Statistically significant correlation between T/S_mean and early septal MUP ($R^2 = 0.25$, $p = 0.024$).

Figure 6.240: T/S_mean versus early apical MUP. No statistically significant correlation was noted ($R^2 = 0.18$, $p = 0.064$).
Figure 6.241: T/S_mean versus early luminal MUP. No statistically significant correlation was noted ($R^2 = 0.04$, $p = 0.397$).

Figure 6.242: T/S_mean versus delayed anterior MUP. No statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.328$).
Figure 6.243: T/S_mean versus delayed lateral MUP. No statistically significant correlation was noted ($R^2 = 0.07$, $p = 0.277$).

Figure 6.244: T/S_mean versus delayed inferior MUP. No statistically significant correlation was noted ($R^2 = 0.07$, $p = 0.253$).
Figure 6.245: T/S_mean versus delayed septal MUP. No statistically significant correlation was noted ($R^2 = 0.07$, $p = 0.272$).

Figure 6.246: T/S_mean versus delayed apical MUP. No statistically significant correlation was noted ($R^2 = 0.06$, $p = 0.315$).
Figure 6.247: T/S_mean versus delayed lumen MUP. No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.884$).

Figure 6.248: T/S_mean versus anterior RW%. No statistically significant correlation was noted ($R^2 = 0.05$, $p = 0.348$).
Figure 6.249: T/S_mean versus lateral RW%. No statistically significant correlation was noted ($R^2 = 0.01$, $p = 0.744$).

Figure 6.250: T/S_mean versus inferior RW%. No statistically significant correlation was noted ($R^2 = 0.02$, $p = 0.520$).
Figure 6.251: T/S\_mean versus septal RW\%.
No statistically significant correlation was noted ($R^2 < 0.01$, $p = 0.909$).

Figure 6.252: T/S\_mean versus apical RW\%.
No statistically significant correlation was noted ($R^2 = 0.03$, $p = 0.467$).
Regional uptake and RW% was correlated with instances of CE. No statistically significant correlation was noted between CE and early anterior MUP (p = 0.170) (Figure 6.254), early lateral MUP (p = 0.952) (Figure 6.255), early inferior MUP (p = 0.571) (Figure 6.256), early septal MUP (p = 0.878) (Figure 6.257), early apical MUP (p = 0.718) (Figure 6.258) and early luminal MUP (p = 0.440) (Figure 6.259). No statistically significant discriminatory power of delayed anterior (p = 0.081) (Figure 6.260), lateral (p = 0.778) (Figure 6.261), inferior (p = 0.470) (Figure 6.262), septal (p = 0.832) (Figure 6.263), apical (p = 0.409) (Figure 6.264) and luminal (p = 0.452) (Figure 6.265) MUP was noted in being able to differentiate between patients who suffered CE and those who did not. RW% from lateral (p < 0.001) (Figure 6.267) and inferior wall (p < 0.001) (Figure 6.268) correlated with higher chance of CE (p < 0.001). Other RW% from anterior wall (p = 0.375) (Figure 6.266), septum (p = 0.797) (Figure 6.269), apex (p = 0.367) (Figure 6.270) and lumen (p = 0.389) (Figure 6.271) did not correlate statistically significantly with CE.
Figure 6.254: A plot demonstrating no statistically significant difference in early anterior MUP based on CE. (p = 0.170). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.255: A plot demonstrating no statistically significant difference in early lateral MUP based on CE (p = 0.952). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.256: A plot demonstrating no statistically significant difference in early inferior MUP based on CE ($p = 0.571$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.257: A plot demonstrating no statistically significant difference in early septal MUP based on CE ($p = 0.878$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.258: A plot demonstrating no statistically significant difference in early apical MUP based on CE ($p = 0.718$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.259: A plot demonstrating no statistically significant difference in early luminal MUP based on CE ($p = 0.440$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.260: A plot demonstrating no statistically significant difference in delayed anterior MUP based on CE ($p = 0.081$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.261: A plot demonstrating no statistically significant difference in delayed lateral MUP based on CE ($p = 0.778$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.262: A plot demonstrating no statistically significant difference in delayed inferior MUP based on CE (p = 0.470). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.263: A plot demonstrating no statistically significant difference in delayed septal MUP based on CE (p = 0.832). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.264: A plot demonstrating no statistically significant difference in delayed apical MUP based on CE (p = 0.409). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.265: A plot demonstrating no statistically significant difference in delayed luminal MUP based on CE (p = 0.452). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.266: A plot demonstrating no statistically significant difference in anterior washout based on CE (p = 0.375). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.267: A plot demonstrating a statistically significant difference in lateral washout based on CE (p < 0.001). This observation is supported by the non-overlapping of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.268: A plot demonstrating a statistically significant difference in inferior washout based on CE ($p < 0.001$). This observation is supported by the non-overlapping of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.269: A plot demonstrating no statistically significant difference in septal washout based on CE ($p = 0.797$). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.270: A plot demonstrating no statistically significant difference in apical washout based on CE (p = 0.367). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Figure 6.271: A plot demonstrating no statistically significant difference in luminal washout based on CE (p = 0.389). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Areas of MI are not a source of arrhythmias in patients with HF. However often they are the areas with the least uptake of 123I-mIBG and greatest washout, thus confounding the calculations. In order to eliminate this, mean regional
uptake and washout was calculated only for areas with perfusion on the rest 99mTc-MIBI scan. These were then correlated with instances of CE. When CE was evaluated against the mean delayed MUP from non-infarcted segments, it was seen that the correlation did not have a statistical significance (p = 0.434) (Figure 6.272). Correlation between a mean washout from non-infarcted segments and CE revealed a statistically significant relationship between them (p = 0.015) (Figure 6.273). When the mean non-infarcted MUP was categorised into low and high based on a threshold of 1.2. In patients with a mean non-infarcted MUP of less than 1.2 the OR was 1.8 of having a CE than those with a mean non-infarcted MUP of more than or equal to 1.2 (p = 0.650) (Table 6.23). Upon categorisation of the washout from the non-infarcted segments into low and high based on a threshold of 40%, the OR of CE in patients with a washout of more than 40% was 11 as compared to those in whom the washout from the non-infarcted segments was less than or equal to 40% (p = 0.029) (Table 6.24).

Figure 6.272: A plot demonstrating no statistically significant difference in mean delayed non-infarcted MUP based on CE (p = 0.434). This observation is supported by the considerable overlap of the 95% CIs represented by the top and bottom portion of the diamonds.
Figure 6.273: A plot demonstrating a statistically significant difference in the mean washout from the non-infarcted segments based on CE (p = 0.015). This observation is supported by the minimal overlap of the 95% CIs represented by the top and bottom portion of the diamonds.

Table 6.23: Contingency table of mean non-infarct MUP < 1.2 and CE (p = 0.650). The OR of CE in patients with a mean non-infarct MUP < 1.2 was 1.8.

<table>
<thead>
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<td>N</td>
<td>Y</td>
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<td>CE</td>
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<td>N</td>
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<td>9</td>
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<td></td>
<td>3</td>
<td>19</td>
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</tbody>
</table>

Table 6.24: Contingency table of mean non-infarct washout > 40% and CE (p = 0.029). The OR of CE in patients with a mean non-infarct washout > 40% was 11 times more than those with a mean non-infarct washout ≤ 40%.

<table>
<thead>
<tr>
<th>Mean non-infarct washout &gt; 40%</th>
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<td>CE</td>
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<td>N</td>
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Survival analysis using regional uptake parameters revealed that only delayed mean inferior and anterior MUP revealed differences in the instances of CE. The mean delayed inferior uptake of 1.09 was statistically significant discriminator for patients who suffered from CE as opposed to those who did not (p = 0.040) (Figure 6.275). When a delayed anterior uptake of 1.3 was used as threshold, a non-statistically significant difference in the CE was noted in those with delayed anterior MUP less than 1.30, than those with a delayed anterior MUP more than or equal to 1.30 (p = 0.142) (Figure 6.274). Delayed luminal MUP also displayed a non-statistically significant difference in CE when a threshold of 0.74 was employed (p = 0.256) (Figure 6.276).

![Kaplan–Meier survival curves of CE](image)

Figure 6.274: Kaplan–Meier survival curves of CE in study subjects divided into 2 groups according to delayed anterior MUP. Patients with delayed anterior MUP < 1.30 had more CE than those with delayed anterior MUP ≥ 1.30 (p = 0.142).
Figure 6.275: Kaplan–Meier survival curves of CE in study patients divided into 2 groups based on delayed inferior MUP. Patients with delayed inferior MUP < 1.09 had more CE than those with delayed inferior MUP ≥ 1.09 (p = 0.040).

Figure 6.276: Kaplan–Meier survival curves of CE study patients divided into 2 groups based on delayed inferior MUP. Patients with delayed luminal MUP < 0.74 had more CE than those with delayed luminal MUP ≥ 0.74 (p = 0.256).

The role of RW% in predicting CE was explored. The only statistically significant RW% was 45% from the inferior wall (p = 0.005) (Figure 6.277). RW% threshold of 20% from the anterior wall (p = 0.085) (Figure 6.278), 25% from lateral wall (p = 0.085) (Figure 6.279) and 25% from the lumen (p = 0.150) (Figure 6.280) revealed non-statistically significant difference in CE. RW% from apex or septum had no ability in predicting CE.
Figure 6.277: Kaplan-Meier survival curves for instances of CE based on RW% from inferior wall. RW% of 45% from the inferior wall was a statistically significant threshold for predicting CE (p = 0.005).

Figure 6.278: Kaplan–Meier survival curves in study patients divided into 2 groups according to anterior RW%. RW% of 20% from the anterior wall was not statistically significant in predicting CE (p = 0.085).
Figure 6.279: Kaplan–Meier survival curves of study patients divided into 2 groups according to lateral RW%. RW% of 25% from the lateral wall was not statistically significant in predicting CE (p = 0.085).

Figure 6.280: Kaplan–Meier survival curves of study patients divided into 2 groups according to luminal RW%. RW% of 25% from the lateral wall was not statistically significant in predicting CE (p = 0.150).

In order to reduce the influence of infarcted segments in confounding the regional uptake and washout statistics, mean delayed MUP of lateral wall and septum and RW% was used in patients with inferior wall MI and apical and mean inferior wall and apex MUP in those whom the inferior wall was not infarcted. In non-infarcted segments, mean regional MUP was unable to predict
survival in a statistically significant manner, while mean regional RW% of ≥ 40% was able to predict survival (p = 0.035) (Figure 6.281).

Figure 6.281: RW% of 40% from non-infarcted segments was a statistically significant predictor of CE (p = 0.035).
Chapter 7

Discussion
7.1 DISCUSSION

Krum et al. (2006) have described HF as the “Cinderella” of health issues, as it has failed to register on the radar of the health care providers. This has been primarily attributed to the true magnitude of the problem not yet being delineated (Ambrosy et al., 2014; Cleland, Khand, & Clark, 2001; Krum & Stewart, 2006). A number of important factors include the lack of a simple and universally acceptable definition, difficulty in diagnosis because of varied presentations with absence of classical signs and symptoms in a number of patients, and frequent presence of co-morbidities (Choudhary et al., 2013; Hawkins et al., 2009; F. D. R. Hobbs, 2002; Oudejans et al., 2011).

A major challenge presented by HF is an increasing global incidence and prevalence, and an increasing burden to the national health budgets on account of frequent hospitalisation required by the patients (Ambrosy et al., 2014; Dunlay et al., 2011; Fonseca, 2006). Additionally HF is characterised by a markedly reduced quality of life and survival (Ambrosy et al., 2014; Choudhary et al., 2013; Fonseca, 2006; D. S. Lee et al., 2009). Roger et al. (2013) have reported the 5-year survival at 50% and the median survival 1.6 years.

New and improved pharmacological therapies have been introduced which have reduced morbidity and mortality, many patients tend to remain symptomatic with ongoing progression of the underlying disease (Cleland et al., 2013). SCD in HF remains a challenge and prophylactic implantation of an ICD has shown to be of benefit (Satake et al., 2015; Tomaselli & Zipes, 2004).
The NYHA classification is the most commonly employed classification method for HF (Currie et al., 2011). The correlation between the ventricular function and severity of symptoms however, is poor (McMurray et al., 2012). A patient's NYHA class may regress, without any underlying change in the disease, on the basis of a change in therapy or development of co-morbidity (McMurray et al., 2012). An alternate classification criterion has been devised by ACC/AHA which is based on underlying cardiac abnormality (Hunt et al., 2005). Nonetheless, the NYHA is the standard for justifying ICD use.

Existing criteria for the implantation of ICD is a LVEF of less than or equal to 35% and a NYHA class of II or III (Krum et al., 2006), and this criteria is generally universal. The limitation of this criterion is that the decision to implant or deny an ICD solely on change in symptoms may not reflect the underlying pathology (Gerson et al., 2010). Only a third of patients who are eligible for an ICD suffer from SCD, while only a third of SCD are in patients who fulfil the existing criteria for an ICD (Gerson et al., 2010). This means that a better criterion for implantation for ICD is required.

Increased SNS overdrive has been implicated in a raised incidence of arrhythmias (Kelesidis & Travin, 2012). Cardiac SNS imaging with 123I-mIBG has the potential to be an effective tool for determining HF patients at risk of SCD. A significant body of work has been undertaken in this regard, however, the approach to date has been to assess the heart globally. This is perhaps a prohibitive barrier to employing 123I-mIBG in the HF management guidelines. It is believed by the author that a regional approach using 123I-mIBG SPECT has a higher sensitivity and specificity for this purpose. That is, an insight into
regional myocardial sympathetic innervation may provide greater stratification of those patients at risk of SCD and in whom, independently of LVEF or NYHA classification, would benefit from an ICD.

The mean age of the study patients of 72 years corresponded well with The EuroHeart Failure survey programme where the average age of the patients was 71 and the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult, which state that 80% of HF patients are more than 65 years of age (Cleland et al., 2003; Hunt et al., 2005). Similarly all the study patients were male, which is also concordant with the ADMIRE-HF trial where 80.1% of HF patients were males (Jacobson et al., 2010). Fifty-four percent of the patients developed HF secondary to IHD which is similar to the CHARM-Preserved Trial and the ADMIRE-HF study where 56.4% and 66.0% of the HF patients respectively had IHD (Jacobson et al., 2010; Yusuf et al., 2003).

The mean LVEF was 41.9%, while the end-diastolic volume of 157 ml which was similar to the data published by Kasama et al (2008), but lower than some of the other published HF studies (Bleeker et al., 2005; Sutton et al., 2003). When patients were classified on the basis of LVEF-5%, the statistical correlation between LVEF-5% and CE was much more significant than the correlation between LVEF and CE. The OR for CE where the LVEF decreased by 5% from baseline compared to patients without a change in LVEF was 11.7. This is concordant with studies by Aronow (2006), Vasan et al. (1999), Cowburn et al. (1998), and Cohn et al. (1988). No correlation was seen between the age of the patients and the LVEF at the time of diagnosis, and the instances of CE.
The index event also did not have any significant influence on the patients having a CE. Similarly the LVEF of the patients was not determined by the aetiology of HF. That is, the risk of a CE was not predictable by age, LVEF or underlying pathology.

A significant percentage of the patients experienced a CE (41%), compared to a CE rate of 25% in the ADMIRE-HF study and 26% in the study by Agostini et al (2008). This may be attributed to a selection bias where the asymptomatic patients were less inclined to participate in a study where a radiotracer is injected (Jacobson et al., 2010). One patient (4.5%) suffered SCD, the only mortality, which compares to 8% (which included non-cardiac deaths) in the ADMIRE-HF study and the mean time between the scan and CE was almost 10 months (Jacobson et al., 2010).

Of the time-domain indices available in the 24-hour Holter studies, SDNN and rms-SD, which are indices of cardiac parasympathetic activity, showed a statistically significant correlation with instances of CE and substantial reduction in LVEF. In our study there was a higher instance of CE and a substantial reduction in LVEF in patients with increased HRV. This is contrary to the findings of Kurtoglu et al (2014), however, they did not use CE as an end point and only included patients with non-ischaemic HF. Yamada et al (2003) also concluded that time-domain indices of HRV were unrelated to CE.

The evaluated genetic biomarkers did not correlate with any of the collected demographic data. Thirteen patients underwent ACE genotype analysis which failed to establish any statistically significant correlation with any of the study
parameters or instances of CE. The published literature differs on which genotype (I or D) is a risk factor for heart disease and that is why there is no correlation with any of the study parameters (Bauters & Amouyel, 1998; Butler, 2000; Harrap et al., 1993; Ueda et al., 1998; A. G. Williams et al., 2000). UCP SNPs rs1800849, rs660339 and rs659366 genotypes were available for 19 patients. No correlation was found between the UCP SNPs and any of the other study parameters or instance of CE. Polymorphism in UCP has been linked to obesity and metabolic syndrome (H.-J. Lee et al., 2008; Liu, Zhao, Kang, & Zhang, 2013; Salpea et al., 2010). Studies that have observed the levels of UCP 3 in HF have conflicting opinions with regards to its up or down regulation in a failing heart (Murray, Anderson, Watson, Radda, & Clarke, 2004; Razeghi et al., 2002). Nonetheless, no relationship between UCP polymorphism and HF has been established in literature.

Telomere data was available for 20 study patients. TL, T/S and T/S_mean all revealed a non-statistically significant decreased with ageing. The results concordant with other studies (Bischoff et al., 2006; S. E. Harris et al., 2006; Martin-Ruiz, Gussekloo, van Heemst, von Zglinicki, & Westendorp, 2005) who have suggested that telomere is merely an indicator of cellular age and there is no link between patients’ age and telomere length. Studies that suggested a link between IHD and TL, also failed to find any connection between systemic inflammation and TL, which is a hallmark of HF (Brouilette et al., 2007; Starr et al., 2007; Weischer et al., 2012). A study where the IHD patients cohort had a shorter TL length compared to age matched controls, and the IHD cohort had low LVEF, raised NTproBNP and hsCRP levels (Spyridopoulos et al., 2009), used a different method for measurement of TL, flow cytometry–fluorescent in
situ versus quantitative polymerase chain reaction. The difference in the method used may be the source of difference in results as suggested by Gutierrez-Rodrigues et al. (2014). Hemann et al. (2001) have suggested that the shortest telomere and not the average telomere length is the critical factor and the telomere parameters in this study are the average length rather than the shortest.

The planar global parameters of the study population revealed a mean early H:M (1.53) and delayed H:M (1.41) which are consistent with published data, while the washout (23.87%) was lower than published data (Imamura et al., 2001; Jacobson et al., 2010). Quite a wide variation is seen in literature regarding these parameters as they are influenced by various factors such as dosage, acquisition parameters such as timing of the early and delayed scanning, the calibration of the gamma camera, the collimator and the patient’s body habitus. In addition to the 159 keV photopeak, I-123 has a 529 keV photopeak that has been reported to degrade images due to septal penetration. Use of a MEGP instead of a LEHR collimator to minimise scatter has been suggested (Edwards & Zhuang, 2014) and employed in some of the MIBG studies (Asghar et al., 2015; Snay, Treves, & Fahey, 2011; K. Yamada, Shiraishi, Hamasaki, & Kuratsu, 2010). Conversely Nicholas et al. (2014) in their study have concluded that using a LEHR with iterative reconstruction is superior to the use of a MEGP collimator on account of better count statistics and contrast resolution. A similar conclusion has been drawn by Dobbeleir et al. (1999) when conducting quantitative neuroreceptor imaging. Consequently, there are mixed reports and protocols which are likely to have a small impact on the H:M figures but which should not impact on washout.
Patient age, LVEF and EDV had no effect on the global uptake and washout. Non-statistically significant correlation was observed between the global 123I-mIBG uptake and washout and the 24-hour Holter parameters. No statistically significant correlation was seen between the global uptake and washout parameters and the biomarkers. The only exception was a statistically significant reduction of early and delayed global H:M that was observed with increased T/S_mean. These findings have a probable basis in the observation by Hemann et al (2001) that the shortest telomere and not the average telomere length is the critical factor and that global parameters are not as sensitive as regional ones.

Based on the criterion established in the ADMIRE-HF study (Jacobson et al., 2010) and the study by Yamada et al (2003), the participants of this study were grouped into those who had low and high H:M (the threshold being a delayed H:M of 1.6) or a low or high washout (patients with washout of less than equal to or more than 27%). In this study a high global washout was the sole statistically significant predictor of CE, which is concordant with observations of other key studies (Abdallah & Gerson, 2012; Kasama et al., 2008; Zhao et al., 2001). The OR for a CE in patients with high washout as compared to those with a low washout was 44. Washout is thought to be robust against variations in protocol, conditions and underlying pathology.

Survival analysis conducted using the delayed H:M threshold of 1.6 was unable to statistically differentiate between patients who experienced a CE and those who did not. In our study, when this threshold was adjusted to 1.5, there was a
statistically significant difference in survival between those with delayed H:M of more than 1.5 with those with delayed H:M of less than or equal to 1.5 (p = 0.046). 123I-mIBG uptake values have varied widely in the literature; from 1.85 – 1.6 even in large studies. This is probably due to the variation in the study population, the use of different types of collimators, the difference in ambient temperature, and the variation in injected dose among other possible factors. The lower cut-off in this study reflects higher ambient temperatures during uptake and the use of LEHR collimation. Nonetheless, a washout of 27% was able to, with a high degree of statistical significance, differentiate between patients experiencing a CE in the follow up period (p = 0.003). These results are in congruence with some of the published studies (Nagamatsu, Momose, Kobayashi, Kusakabe, & Kaskanuki, 2007; T. Yamada et al., 2003) indicating that the washout is more robust to procedural and patient variation.

Global SPECT uptake and washout in this study were compared to other study parameters. As expected the early and delayed global SPECT uptake and washout parameters correlated statistically with planar early (p < 0.001) and delayed H:M (p < 0.001) and washout (p = 0.013) significantly. No statistically significant correlation was noted between age, ∆LVEF, ∆LVEF-5% or the 24-hour Holter study parameters with the global SPECT uptake and washout. Statistically significant correlation was noted between early and delayed global SPECT uptake and LVEF. In order to study the effect of heart size as a confounding factor in the calculation of global SPECT uptake and washout, they were correlated with EDV as a measure of the heart size, but no statistically significant difference was noted. This is important because it is possible that a small heart with little contribution of lumen to the pixel size of the region of
interest may indicate higher uptake than a larger heart with prominent lumen that artificially decreases the overall counts per pixel of a global region. Washout may be similarly diluted in effect. Nonetheless, none of the hearts in this study were considered small and the limitation to a male only population may have masked this effect. Further analysis in a gender balanced study would be warranted.

Of the biomarkers, a statistically significant correlation between mean early whole SPECT uptake and T/S\_mean was observed. No other biomarker revealed any statistically significant correlation with the global SPECT uptake and washout parameters. Global SPECT uptake and washout have, in our study, had no more predictive power than planar global.

The limitation of both global planar and global SPECT approaches is the nature of pathology HF is a regional disease and thus global parameters are unlikely to adequately predict risk of SCD. For example, patients with a MI may demonstrate low global uptake due to the lack of uptake in the region of the MI yet the infarcted segments are unlikely to be a source of arrhythmias. Conversely, a small region of MI without the global dilution effect could offer normal results despite an adjacent region of decreased mIBG uptake (with washout) that is suggestive of a higher risk of SCD. Washout from the non-infarcted segments is the parameter most likely to predict CE in HF.

123I-mIBG SPECT imaging in HF studies have, to date, used either a visual quantitative approach or global uptake and washout. Very few studies have undertaken semi-quantitative regional uptake and washout by employing polar
maps. Still fewer have factored in the results from MPS. In the studies that have calculated regional 123I-mIBG parameters, very few utilised CE as an end point, thus they have perhaps erroneously concluded that regional SPECT SNS imaging lacked a robust role in HF (Jacobson et al., 2010; Zhao et al., 2001). Consequently there has been a need for a study that utilised regional 123I-mIBG uptake and washout, in conjunction with MPS, to predict CE in patients with HF. This is the first study to evaluate 123I-mIBG regional uptake and washout parameters in that detail.

Patients’ were assessed for risk of SCD based on the global and regional uptake and washout combined with the perfusion pattern (Table 7.1). The results demonstrated that the regional SCD parameters were better able to predict which patients would suffer a CE and those that would not as compared to the global SCD risks. When sensitivity, specificity, positive predicted values and negative predicted values were calculated, the sensitivity for both modalities was 100%, while the specificity of the regional SCD was 75% as compared to the global SCD whose specificity was 17%. Positive predictive value of global SCD risk was 50%, while that of regional SCD risk was 77%. Negative predictive of both the parameters were 100% (Table 7.2). The sensitivity of the global approach is likely to reflect a “sweeping net” approach that errs on the side of predicting a CE and this is reflected by the poor specificity. The power of improved specificity allows more accurate identification of those patients who are more likely to benefit from an ICD.
Table 7.1: Summary of correlation between risk of SCD based on global and regional criterion and the actual CE. It is observed that the instances of CE correlated much better with the regional SCD risk factors than the global ones.

<table>
<thead>
<tr>
<th>No.</th>
<th>Risk of SCD global</th>
<th>Risk of SCD regional</th>
<th>CE</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>Y</td>
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<tr>
<td>4</td>
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<td>5</td>
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<td>6</td>
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<td>7</td>
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<td>9</td>
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<td>12</td>
<td>Y</td>
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<td>21</td>
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<tr>
<td>22</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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</table>

Table 7.2: Summary of sensitivity, specificity, positive and negative predictive value of the global planar and regional SCD risk.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of SCD global</td>
<td>100%</td>
<td>17%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Risk of SCD regional</td>
<td>100%</td>
<td>75%</td>
<td>77%</td>
<td>100%</td>
</tr>
</tbody>
</table>

The 123I-mIBG early and delayed TDS were also concordant with published data (Arora et al., 2003; Kasama et al., 2006). Although various authors have used different scoring methods, with 3, 4, 5 and 6-point scoring systems being employed, the use of the 5-point scale has become a standard as it is
recommended by the EANM guidelines for standardisation 123I-mIBG cardiac sympathetic imaging (Flotats et al., 2010). Being visual assessment scores, these are quite subjective, thus there is a wide variation between different studies and as stated earlier perhaps the aetiological factors (Zhao et al., 2001).

Early and delayed 123I-mIBG TDS did not correlate statistically with any of the global SPECT parameters, except for correlation between delayed 123I-mIBG TDS and global SPECT washout. Of the regional uptake and washout parameters, weak but statistically significant correlation was noted between the regional washout from anterior, inferior, septum with global washout. ΔTDS correlated statistically significantly with early and delayed regional uptake and anterior, septal, apical, luminal and whole SPECT washout.

Regional uptake, regional washout and global washout, as predictors for CE proved to be statistically significant as compared to global uptake, which is in agreement with the published research (Imamura et al., 2001; Kasama et al., 2002; T. Yamada et al., 2003; Zhao et al., 2001). The two regions that were able to predict CE when there was a reduced 123I-mIBG uptake were the (non-infarcted) inferior and the lateral walls. This may be explained by the fact that HF is perhaps not a global phenomenon at the onset, but more of a regional disease that progresses to become a global cardiac disease. This phenomenon has already been reported in diabetic CAN (Scott & Kench, 2004).

There is a paucity of studies that have used semi-quantitative analysis of the 123I-mIBG SPECT. One of the aims of this study was to evaluate parameters that may be of value in early detection of risk of CE in HF. Regional uptake in
the inferior wall and the septum were seen to have significant power to predict CE.

Regional washout from inferior (p < 0.001) and lateral (p < 0.001) wall had a statistically significant ability to predict CE. Similarly, a statistically significant difference in Kaplan-Meier survival curves was observed in cases of low washout from the inferior wall (p = 0.005). This is consistent with the observation that HF is a regional disease with substantial CAN, leading to frequent arrhythmias, which are a major source of morbidity and mortality. There is evidence that CAN (just like in DM) starts in the inferior wall and then progresses towards the anterior wall via the lateral wall and or septum (Scott & Kench, 2004). In this study it has been observed that it is the inferior wall and the lateral wall that are significant markers of CE in HF. Thus it is most likely that CAN in HF starts in the (non-infarcted) inferior wall and progresses to the lateral wall after which it envelops the rest of the heart.

One of the common causes of HF is a prior MI, and it was present in 55% of the cases in this study (Bui, Horwich, & Fonarow, 2011; Velagaleti et al., 2008). One issue that plagues the use of 123I-mIBG in accurately predicting morbidity and mortality in HF is the fact that infarcted segments have, on account of a poor blood supply and lack of functional autonomic neurons, low uptake and high washout. These segments however, have lost innervation and thus are incapable of causing arrhythmias. This is probably why different studies have come up with different global planar and global SPECT uptake and washout thresholds for predicting CE, based on their study population characteristics. This issue may be overcome by using SPECT regional imaging and calculating
uptake and washout from segments that are not infarced on the MPS. Washout of more than 40% from non-infarced segments in our study has proved to have a statistically significant ability in predicting CE. Patients who have a high washout from non-infarced segments are 11 times more likely to suffer a CE as compared to those in whom the washout is less than 40%.

This finding may have a major impact on the management of patients with HF. Especially those in whom ICD implantation is considered, as a high washout from non-infarced segments is perhaps the best indicator of SCD in patients with HF. This finding is independent of the LVEF or NYHA class of the patient. This will mean that as many as two-thirds of HF patients with LVEF less than 35% and NYHA class of II or III, who are unlikely to suffer from an SCD will be spared the added procedure and expense of an ICD implantation, while many patients who are ineligible for an ICD under the current regimen, but suffer from SCD will benefit from an ICD implantation. The mortality, morbidity and cost implications of this approach are significant nationally and globally.

A number of studies have observed increased incidence and poorer prognosis of HF with a reduction in TL (Chimenti et al., 2003; Serrano & Andrés, 2004). This may be in part due to acceleration of apoptosis in patients with shorter TL (Hemann et al., 2001; Leri et al., 2003; Oh et al., 2003). Regional uptake and washout parameters failed to correlate statistically significantly correlate with TL, except for luminal uptake. Luminal uptake (blood compartment) may be an indicator of either poor uptake or washout (or combination of the two), from the myocardium, accounting for the statistically significant relationship.
7.2 LIMITATIONS

While there were a number of limitations identified in this research, none were thought to threaten internal or external validity. While a larger patient sample would improve statistical power, the smaller sample is not thought to limit identification of statistically significant relationships. Indeed, a number of key relationships were identified despite the smaller population. The study was a single centre trial that required minimally invasive procedures, significant time commitment, no change in management, and longitudinal follow-up which limited volunteers.

A number of key biomarkers were identified for analysis and correlation including NTproBNP, hsCRP, IL-6 and TNF-α. All of these markers have been suggested in literature as being useful for diagnosis and follow up in patients with HF. Unfortunately a technical issue with the third party undertaking blood collection was prohibitive of serum biochemical analysis. Thus this study only includes genetic analysis from the cellular part of the blood for those study participants where sample integrity permitted.

An unexpected limitation, but one that provides an important insight, was ambient temperature. The ambient temperature in the department in which the 123I-mIBG studies was performed was relatively high (23 degrees Celsius) and, as discussed below, resulted in a decrease in 123I-mIBG uptake.

One patient who was required to be imaged twice yielded quite different early and delayed uptake and global washout values. One set of imaging occurred four days prior to the second set and in a different department where the
ambient temperature was a much lower 19 degrees Celsius. The early and delayed H:M were 2.21 and 2.15 and the global washout was 30.0%, while the second study it was 1.52 and 1.43 respectively with a washout of 30.8%. The patient had no change in symptoms or medication and underwent the exact same pre-scan routine. The only difference between those two instances was the ambient temperature with the second scan being performed in a department with an ambient temperature set at 23 degrees Celsius (the former at 19 degrees Celsius). This phenomena was noticed when patients scanned (in second department with higher temperature) showed consistently low uptake values. Further investigation revealed the temperature issue.

The temperature dependent cardiac uptake of 123I-mIBG may be due to rich sympathetic innervation and high mitochondrial density of cardiac tissue. This is similar to brown adipose tissue, which has shown to have increased sympathetic outflow in response to cold temperature (Blumberg, Sokoloff, & Kirby, 1997; Kirov, Talan, & Engel, 1996). Furthermore studies have suggested a link between low ambient temperature and increased levels of cardiac sympathetic activity (Barnett et al., 2005; Ootsuka & McAllen, 2006; Vuori, 1987). Since mIBG is a NE analogue, any factor that influences the cardiac SNS activity is likely to cause a change in the uptake of 123I-mIBG, since both NE and 123I-mIBG share the uptake mechanism in the sympathetic pre-synaptic neurons.

In this study a LEHR collimator was employed rather than a MEAP. While some septal penetration was expected (Figure 7.1 and Figure 7.2) impacting on the
H:M, this approach was consistent with the more recent literature, reduces the cut-off employed and has no bearing on washout.

Figure 7.1: Early (left) and delayed (right) planar 123I-mIBG scans using MEAP showing less septal penetration (background).

Figure 7.2: Early (left) and delayed (right) planar 123I-mIBG scans of the same patient as Figure 7.1 showing lower H:M due to increased background from septal penetration but the same washout.

### 7.3 CASE STUDY

A 77 year old male presented with an inferior wall MI, NYHA class III, a LVEF of 32% and an EDV of 210 ml. Global planar mIBG imaging demonstrated a delayed H:M of 2.33 (normal) and washout of 38.3% (high) (Figure 7.3). Based on the LVEF and NYHA class he was eligible for an ICD. Regional SPECT analysis, however, demonstrated that the high washout was limited to regions of infarction (Table 7.3). The regional analysis otherwise suggested the patient was at low risk of SCD and he elected to forgo the ICD. At two year follow up the patient remained event free and did not escalate (symptoms, LVEF, NYHA
classification, perfusion pattern). Furthermore, the patient remains event free at 4 years.

The uptake itself, including global and regional, is not a good indicator of SCD risk. A regional approach in consideration of the individual patient conditions demonstrate the same pattern of 123I-mIBG uptake and stage of disease despite slightly lower uptake (Table 7.4), while washout rates appear to be robust to those confounders.

<table>
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<th>MUP</th>
<th>RW%</th>
<th>MUPI</th>
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<tbody>
<tr>
<td>Early anterior</td>
<td>1.67</td>
<td>40.9%</td>
<td>0.93</td>
</tr>
<tr>
<td>Delayed anterior</td>
<td>1.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early lateral</td>
<td>0.85</td>
<td>33.9%</td>
<td>0.83</td>
</tr>
<tr>
<td>Delayed lateral</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early inferior</td>
<td>0.58</td>
<td>56.9%</td>
<td>1.29</td>
</tr>
<tr>
<td>Delayed inferior</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early septal</td>
<td>1.47</td>
<td>34.1%</td>
<td>0.84</td>
</tr>
<tr>
<td>Delayed septal</td>
<td>1.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early apex</td>
<td>1.02</td>
<td>46.2%</td>
<td>1.02</td>
</tr>
<tr>
<td>Delayed apex</td>
<td>1.00</td>
<td></td>
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</tbody>
</table>
Figure 7.3: Base-line early (left) and delayed (middle) 123I-mIBG scan and resting perfusion (right) of the case study patient showing poor 123I-mIBG uptake and washout is matched with the perfusion defect.

Figure 7.4: Two year follow-up early (early) and delayed (middle) 123I-mIBG scan and resting perfusion (right) of the case study patient.
Table 7.4: Comparison of the baseline and two year follow-up regional MUP, RW% and MUPI.

<table>
<thead>
<tr>
<th></th>
<th>MUP</th>
<th>RW%</th>
<th>MUPI</th>
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7.4 RECOMMENDATIONS

A larger multicentre trial with appropriate controls is required to evaluate the role of regional SPECT analysis. This should include SPECT/CT systems for better delineation of the cardiac outline (regional ROIs placement) and this may be especially beneficial in patients with relatively low cardiac 123I-mIBG uptake and for delineating the boundaries between infarcted and non-infarcted tissue. There is also a pressing need for a robust studies cost benefit analysis of including 123I-mIBG SPECT as a standard evaluation test for ICD implantation.

Ambient temperature seems to have an influence on the cardiac uptake of mIBG. There is a need for controlled studies in animal models to understand the impact on changes to ambient conditions during uptake and washout, and between normal and diseased myocardium, on the cardiac uptake of 123I-mIBG.
Based on the findings of this study the protocol of implanting an ICD in HF patients should be modified so that $^{123}$I-mIBG SPECT may be utilised for stratification of at-risk patients. Such a protocol may be:

- Patients fulfilling the diagnostic criteria for HF.
- Patients diagnosed as ACC/AHA class C.
- If presenting with history of ischaemia or infarction, then a MPS scan.
- A reduction in LVEF of 5% or more on follow up.
- $^{123}$I-mIBG SPECT regional washout in inferior or lateral walls (non infarcted) or in tissues adjacent to MI of 40% or more.

### 7.5 CONCLUSION

HF is a complex, multi-factorial progressive disease that appears to start in the inferior wall of the heart, progress to the lateral wall and then involves the whole heart. The role of the autonomic nervous system, especially the sympathetic nervous system, is central to the clinical course of the disease, especially the incidence of SCD. $^{123}$I-mIBG provides a valuable tool in not just imaging the global sympathetic innervation of the heart, but also in assessing the regional distribution. This allows earlier diagnosis and stratifications of patients at risk of cardiac events, in particular SCD. Improved identification of risk allows more appropriate use of ICDs. While previous reports indicate that delayed washout offers identification of risk, the key marker is regional washout of $^{123}$I-mIBG from non infarcted myocardium.
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## Appendix 1

**Jadad-Currie evaluation form**

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<th>1. Was the study described as randomised?</th>
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<td>2. Was the randomisation protocol detailed and appropriate?</td>
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<tr>
<td>3. Was the study described as double-blind?</td>
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<td>4. Was the blinding process detailed and appropriate?</td>
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<tr>
<td>5. Did the study have a control group? Are all variables and confounders identified and controlled?</td>
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<tr>
<td>6. Was the control detailed and appropriate (eg. placebo)?</td>
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<td>7. Was there an adequate exclusion criteria?</td>
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<td>8. Was there a description of withdrawals and dropouts?</td>
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<td>9. Was the intervention used at a therapeutic dose and appropriate duration?</td>
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<tr>
<td>10. Were the data clearly and adequately reported?</td>
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<td>11. Is the sampling method appropriate, free of sampling bias and valid externally?</td>
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<tr>
<td>12. Is the report current? Are the results and instruments valid today?</td>
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<td>13. Is the sample size sufficient for statistical power in all cohorts? Is the sample size sufficiently large to be representative and statistically valid?</td>
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<td>14. Are the outcomes of interest identified and appropriately evaluated?</td>
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<td>15. Are statistical methods appropriate and adequately explained?</td>
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<td>16. Was data collected prospectively?</td>
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<td>17. Is an appropriate gold standard employed and justified?</td>
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<td>18. Were study limitations identified and discussed?</td>
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<tr>
<td>19. Is the study sample sufficiently broad that the results are valid to other populations?</td>
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<td>20. Are the conclusions consistent with the actual results?</td>
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| Total | /20 |
Appendix 2

Performa for SPECT image analysis

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SA: ¼ from apex
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