Right Ventricular Systolic Pressure and not Left Ventricular Systolic Function is Associated with Renal Insufficiency in Patients with Chronic Heart Failure

By

Carlos Sia Fernando

A thesis submitted in conformity with the requirements for the degree of Master of Science, Institute of Medical Science, University of Toronto

© Copyright by Carlos Sia Fernando, 2014
Abstract
Right Ventricular Systolic Pressure and not Left Ventricular Systolic Function is Associated with Renal Insufficiency in Patients with Chronic Heart Failure

Carlos Sia Fernando
Master of Science - Year 2014
Institute of Medical Science, University of Toronto

Background: Patients with heart failure (HF) with concomitant kidney disease have poor prognosis. Recent studies conducted in patients with acute HF showed that increased filling pressure causes renal vein hypertension resulting to renal insufficiency. Accordingly, this study aimed to correlate right ventricular systolic pressure (RVSP) to renal function in patients with chronic stable HF.

Method: Serum creatinine (sCr) and estimated glomerular filtration rate (eGFR) were correlated with RVSP, N-terminal-pro-Brain Natriuretic Peptide (NT-proBNP), and left ventricular ejection fraction (LVEF) in patients with chronic stable HF.

Results: Mean age 70 ± 13 years, 72% male. Mean systolic blood pressure 121 ± 20 mmHg. Both eGFR and sCr correlated with RVSP (p = 0.004 and p = 0.005, respectively) and NT-proBNP (p < 0.0001 and p < 0.0001, respectively). There were no correlations with LVEF.

Conclusion: Increased RVSP was associated with renal impairment in patients with chronic stable HF.
Acknowledgments

I would like to acknowledge my dissertation advisor, Dr. Gordon Moe for his mentorship and support for the past two years at St. Michael’s Hospital. Dr. Moe continues to teach me to think critically and rigorously as a researcher. He encouraged me in every step of my learning, and point toward new opportunities for growth. It is an honor to have such a role model as both a scientist and physician. I am also grateful for my other committee members: Dr. Howard Leong-Poi for his thoughtful advice navigating through the world of echocardiography; Dr. Abdul Al-Hesayen for his insightful guidance during committee meetings; and Dr. Kevin Thorpe for his expert advice in biostatistical analysis, this paper will not be possible without his statistical support.

I would also like to thank St. Michael’s Hospital staff: Mr. Haytham Sharar, NP, and Ms Andrea Konig, BSc (Hon.) for their assistance during the data collection, and most especially with Mr. Vene Evangelista, RDCS, for dedicating long hours of retrieving and reviewing echocardiogram files with me in the echocardiography laboratory.

I would also like to recognize the understanding and support of the Institute of Medical Science Administration, including Ms. Hazel Pollard, Ms. Michelle Rosen, and Ms. Marika Galadza. St. Michael’s Hospital Division of Cardiology, administrative secretaries Ms. Miriam Strizner and Ms. Betty Hill for arranging my program advisory committee meetings as well as my thesis defense in-order. They made my life easier arranging schedules with my Program Advisory Committee members.

And finally, I thank my wife Norita, together with my two children Gabriel and Rafael, who have stood by me through these years. Thank you for inspiring me during my difficult times completing this journey towards graduation.
Contributions

This work was supervised by a dissertation committee consisting of Professor Gordon Moe, Director of Heart Failure Clinic at St. Michael’s Hospital (supervisor), Professor Howard Leong-poi, Division Head of Cardiology at St. Michael’s Hospital (Co-supervisor), Professor Abdul Al-Hesayen, Heart Failure Specialist at St. Michael’s Hospital (Program Advisory Committee Member), and Professor Kevin Thorpe, Biostatistician at Dalla Lana School of Public Health (Program Advisory Committee Member).

The echocardiographic sample materials were collected from unknown patients was completed by Mr. Vene Evangelista, Registered Canadian Diagnostic Cardiographer at St. Michael’s Hospital Echocardiography Laboratory. Furthermore, with direct instructions from Professor Howard Leong-Poi and Professor Abdul Al-Hesayen, Mr. Evangelista assisted me in the echocardiography data collection.

Figure 6 at page 14, the Geometric Model was adapted from the work of ED Folland et.al, Circulation 1979; 60:760-766.

Professor Gordon Moe suggested the illustrations shown at page 43 (Figure 14 Mechanisms of worsening renal function in the face of circulatory congestion) and page 48 (Figure 16 Flow Diagram for the enrollment, data collection, and echocardiography review).

Ms. Andrea Konig and Mr. Haytham Sharar contributed in the initial data collection consisting of basic demography, comorbidities, and medications.

All the statistical analysis was completed by me with continuous guidance from Professor Kevin Thorpe and Professor Gordon Moe.
Professor Vasundara Venkateswaran and Professor Howard Mount, Graduate Coordinators at Institute of Medical Science - University of Toronto, reviewed this dissertation, and made suggestions in order to make this dissertation acceptable in conformity with the Institute of Medical Science standards.

Professor Nadia Giannetti of McGill University Health Centre, served as my dissertation external appraiser. Professor Darren Yuen of University of Toronto - Division of Nephrology, served as my dissertation internal appraiser. Professor Kim Connelly of University of Toronto, echo-cardiologist at St. Michael’s hospital, served as my final oral examiner. Further revisions were made as a result of their reviews emphasizing the strength and weaknesses of this paper.
# Table of Contents

Abstract ................................................................................................................................. ii  
Acknowledgments ................................................................................................................... iii  
Contributions ............................................................................................................................ iv  
List of Figures ............................................................................................................................ xii  
List of Tables ............................................................................................................................... xiv  
List of Abbreviations .................................................................................................................. xv  

Chapter I – Introduction and Background .............................................................................. 1  
1.1 Epidemiology of heart failure .............................................................................................. 1  
1.2 Syndrome of heart failure ................................................................................................. 1  
1.3 Physiology of heart failure syndrome .................................................................................. 3  
  1.3.1 Hypothesis of arterial underfilling ................................................................................. 3  
  1.3.2 Consequence of renal impairment in acute heart failure syndrome: ......................... 3  
  1.3.3 Pathogenesis of volume overload in heart failure syndrome ......................................... 4  
1.4 Worsening of chronic heart failure .................................................................................... 5  
1.5 Echocardiogram of the left heart ......................................................................................... 6  
  1.5.1 The left atrium .............................................................................................................. 6  
  1.5.2 Measurements ........................................................................................................... 7  
  1.5.3 Pressures ................................................................................................................... 8  
  1.5.4 The left ventricle ....................................................................................................... 10  
  1.5.5 Measurements ........................................................................................................... 11
1.5.6 Pressures.................................................................................................................. 11
1.5.7 Left ventricular ejection fraction ............................................................................. 15
1.5.8 The Simpson’s Biplane method of LVEF determination ........................................ 15
1.5.9 The Quinones method of LVEF determination ....................................................... 16
1.5.10 The Dumesnil method of LVEF determination ..................................................... 17

1.6. Echocardiogram of the Right Heart ......................................................................... 20
1.6.1 The Right Atrium .................................................................................................... 20
1.6.2 Measurements ........................................................................................................ 20
1.6.3 RA and RV Pressures ............................................................................................ 22
1.6.4 The Right Ventricle ............................................................................................... 26
1.6.5 Measurements ........................................................................................................ 27
1.6.6 The Right Ventricular Diastolic Function ............................................................. 29
1.6.7 The Right Ventricular Systolic Pressure ............................................................... 32

1.7 Natriuretic peptides .................................................................................................... 34
1.7.1 The history of natriuretic peptides ........................................................................ 34
1.7.2 Biological activity of natriuretic peptides .............................................................. 34
1.7.3 Factors that increases natriuretic peptides ............................................................ 36
1.7.4 Factors that lowers natriuretic peptides ............................................................... 38

1.8 Renal dysfunction in heart failure: ........................................................................... 39
1.9 Diuretics as the mainstay therapy in heart failure ....................................................... 41
1.10 The cardiorenal syndrome ....................................................................................... 42
1.10.1 Glomerular filtration rate in heart failure ................................................................. 43
1.10.2 Use of serum creatinine in heart failure ................................................................. 44
1.11 Worsening of renal function ......................................................................................... 45
  1.11.1 Venous congestion in patients with worsening of chronic heart failure .......... 45
  1.11.2 Mechanisms of worsening renal function in the face of circulatory congestion .... 47
Chapter II – Research aims and hypothesis ..................................................................... 50
Chapter III - Methodology ................................................................................................. 52
  3.1 Study population ........................................................................................................... 52
  3.2 Signs and symptoms of heart failure ........................................................................... 54
  3.3 Limitation of physical activities based on New York Heart Association Classification .. 55
  3.4 Co-morbidities ............................................................................................................ 55
  3.5 Medications .................................................................................................................. 56
  3.6 Review of the two-dimension echocardiogram ............................................................ 56
  3.7 LAVI measurement ...................................................................................................... 56
    3.7.1 Estimation of LA pressure ....................................................................................... 57
    3.7.2 Mitral inflow - mitral valve E velocity, mitral valve A velocity, E/A ratio, .......... 58
deceleration time ................................................................................................................... 58
    3.7.3 Correlation of renal function with LAVI and mitral inflow ................................. 58
    3.7.4 Correlation of left atrial size and pressure, LV diastolic function with RVSP, ..... 58
Log NT-proBNP, and LVEF ............................................................................................... 58
  3.8 Measurements of the left ventricular ejection fraction ............................................... 58
3.8.1 Stratification of LVEF based on ejection fraction ................................. 59
3.8.2 Linear regression analysis for HFpEF and HFrEF ............................... 59
3.9 Measurement of the right heart function parameters ............................. 59
3.9.1 Right atrial pressure ............................................................................. 59
3.9.2 The right ventricular systolic pressure .................................................. 60
3.10 Univariate and multivariate linear regression analysis for eGFR and sCr with RVSP, Log NT-proBNP, and LVEF .......................................................... 61
3.11 Logistic regression analysis of RVSP and NT-proBNP to eGFR and sCr .... 61
3.12 Research Ethics Board approval ................................................................. 61
3.13 Statistical analysis .................................................................................... 62
Chapter IV – Results ....................................................................................... 63
4.1 Basic demography, signs and symptoms, co-morbidities, and NYHA classifications .... 63
4.2 Medications ............................................................................................... 66
4.3 Echocardiographic and laboratory ............................................................... 67
4.3.1 Linear regression analysis performed on eGFR and sCr with left atrial volume index and left ventricular diastolic indices .............................................. 69
4.3.2 Linear regression analysis performed on LAVI, E/A ratio, E/e’ medial and........ 72
E/e’ lateral with RVSP, Log NT-proBNP, and LVEF ........................................ 72
4.3.3 Subjects stratified by LVEF ................................................................... 73
4.4 HFpEF and HFrEF linear regression analysis for eGFR and sCr with RVSP, Log NT-proBNP, and LVEF ................................................................. 76
4.5 Linear regression analysis on eGFR and sCr with RVSP, Log NT-proBNP, and LVEF 76
4.6 Multilinear regression analysis of eGFR with cardiac pressures (with Log transformed NT-proBNP) ................................................................. 80

4.7 Residuals by regression for eGFR, with RVSP, Log NT-proBNP, and LVEF .......... 81

4.8 Multilinear regression analysis of sCr with cardiac pressures (with Log .................. 81 transformed NT-proBNP) .............................................................................. 81

4.9 Multilinear regression analysis of eGFR with cardiac pressures (with NT-proBNP)..... 82

4.10 Residuals by regression for eGFR with RVSP, NT-proBNP, and LVEF................. 83

4.11 Multilinear regression analysis of sCr with cardiac pressures (with NT-proBNP)...... 84

4.12 Binary logistic regression analysis of right ventricular systolic pressure to renal function ...................................................................................... 85

4.13 Binary Logistic Regression Analysis of NT-proBNP to Renal Function ............. 86

4.14 Cohort of patients with RAP measurements ..................................................... 87

Chapter V – General Discussion ........................................................................ 89

5.1 Confirmation of the research hypothesis .......................................................... 89

5.2 Renal function correlated with cardiac filling pressure ....................................... 89

5.3 Renal function correlated with NT-proBNP .................................................... 91

5.4 Right ventricular systolic pressure to renal impairment ................................... 91

5.5 Univariate linear regression analysis of left atrial dimension, E/e’ medial, E/e’ lateral, and E/A ratio with RVSP, NT-proBNP, and LVEF ........................................ 92

5.6 HFpEF and HFrEF ......................................................................................... 93

5.7 Multiple linear regression analysis interpretations with Log NT-proBNP as one of the covariates ........................................................................... 93
5.8 Multiple linear regression analysis interpretations with NT-proBNP as one of the covariates ........................................................................................................ 95

5.9 Residuals by regression for eGFR and sCr with RVSP, LogNT-proBNP, and LVEF .... 95

5.10 Residuals by regression for eGFR and sCr with RVSP, NT-proBNP, and LVEF....... 96

5.11 Right atrial pressure did not correlate with renal function ........................................ 96

5.12 Study limitations ........................................................................................................ 97

Chapter VI – Conclusions ....................................................................................................... 98

Chapter VII - Future directions................................................................................................ 101

Chapter VII – References ....................................................................................................... 106
List of Figures

Figure 1 Left atrial measurement at apical 4 chamber view.......................................................... 7
Figure 2 Left atrial measurement at apical 2 chamber view .......................................................... 8
Figure 3 Mitral valve inflow............................................................................................................. 12
Figure 4 Tissue Doppler of the medial mitral annulus................................................................. 13
Figure 5 Tissue Doppler of the lateral mitral valve annulus ...................................................... 14
Figure 6 Geometric Model ............................................................................................................ 15
Figure 7 Left ventricular end-systolic dimension......................................................................... 18
Figure 8 Tracing of the left ventricle at end-diastolic dimension.................................................. 19
Figure 9 Apical four chamber view .............................................................................................. 21
Figure 10 Subcostal view showing normal inferior vena cava defined as diameter of < 2.1 cm 23
Figure 11 Subcostal view of the dilated inferior vena defined as diameter of > 2.1 cm............ 23
Figure 12 Pulse Doppler of the hepatic vein ................................................................................ 25
Figure 13 Tricuspid regurgitation jet with continuous wave Doppler ........................................ 33
Figure 14 Mechanisms of worsening renal function in the face of circulatory congestion ...... 47
Figure 15 Impact of venous congestion on glomerular net filtration pressure.......................... 48
Figure 16 Flow Diagram for the enrollment, data collection, and echocardiography review .... 54
Figure 17 Linear regression plots .................................................................................................. 77
Figure 18 Residuals by regression for eGFR with RVSP, LogNT-proBNP, and LVEF.............. 81
Figure 19 Residuals by regression for eGFR with RVSP, NT-proBNP, and LVEF ................. 84
Figure 20 Logistic regression plot ................................................................. 86

Figure 21 Logistic regression plot ................................................................. 87
List of Tables

Table 1 Demography, Race, and NYHA classification ............................................................... 63
Table 2 Symptoms and signs of heart failure ........................................................................ 64
Table 3 Concurrent diseases ................................................................................................. 65
Table 4 Medications ............................................................................................................. 66
Table 5 LVEF, RVSP, and Blood tests ................................................................................ 68
Table 6 Univariate linear regression analysis $y = eGFR$ .................................................. 70
Table 7 Univariate linear regression analysis $y = sCr$ ....................................................... 71
Table 8 Univariate linear regression analysis $y = LAVI$ .................................................... 72
Table 9 Univariate linear regression analysis $y = E/e’$ medial .......................................... 72
Table 10 Univariate linear regression analysis $y = E/e’$ lateral ......................................... 73
Table 11 Univariate linear regression analysis $y = E/A$ Ratio ........................................... 73
Table 12 Summary statistic stratified by LVEF ................................................................. 74
Table 13 Linear regression analysis stratified by LVEF .................................................... 75
Table 14 Multilinear regression analysis with log transformed NT-proBNP ($eGFR = y$ intercept) .................................................................................................................................................. 80
Table 15 Multilinear regression analysis with log transformed NT-proBNP ($sCr = y$ intercept) ................................................................................................................................. 82
Table 16 Multilinear regression analysis with NT-proBNP ($eGFR = y$ intercept) ............. 83
Table 17 Multilinear regression analysis with NT-proBNP ($sCr = y$ intercept) .............. 85
Table 18 Left atrial volume index and left ventricular diastolic indices descriptive summary (n=113) ............................................................................................................................... 88
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Angiotensin-Converting-Enzyme Inhibitor</td>
</tr>
<tr>
<td>AHFS</td>
<td>Acute heart failure syndrome</td>
</tr>
<tr>
<td>AVP</td>
<td>Arginine vasopressin</td>
</tr>
<tr>
<td>BNP</td>
<td>Brain or B-type natriuretic peptide</td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area</td>
</tr>
<tr>
<td>CHF</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CRS</td>
<td>Cardiorenal syndrome</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CW</td>
<td>Continuous wave</td>
</tr>
<tr>
<td>E/A V</td>
<td>Early / Late velocity ratio</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>FAC</td>
<td>Fractional area change</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>IVRT</td>
<td>Isovolumic relaxation time</td>
</tr>
<tr>
<td>LA</td>
<td>Left Atrium</td>
</tr>
<tr>
<td>LAVI</td>
<td>Left atrial volume index</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>LVEDP</td>
<td>Left ventricular end-diastolic pressure</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modified diabetic renal diet</td>
</tr>
<tr>
<td>MPI</td>
<td>Myocardial performance index</td>
</tr>
<tr>
<td>MV DT</td>
<td>Mitral valve deceleration time</td>
</tr>
<tr>
<td>MV AV</td>
<td>Mitral valve A (late) velocity</td>
</tr>
<tr>
<td>MV EV</td>
<td>Mitral valve E (early) velocity</td>
</tr>
<tr>
<td>NP</td>
<td>Natriuretic peptide</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-brain-type natriuretic peptide</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>PH</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-Angiotensin-Aldosterone System</td>
</tr>
<tr>
<td>RAP</td>
<td>Right atrial pressure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>RF</td>
<td>Renal function</td>
</tr>
<tr>
<td>RV</td>
<td>Right Ventricle</td>
</tr>
<tr>
<td>RVSP</td>
<td>Right ventricular systolic pressure</td>
</tr>
<tr>
<td>sCr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>SNFF</td>
<td>Single nephron filtration fraction</td>
</tr>
<tr>
<td>SNGFR</td>
<td>Single nephron glomerular filtration rate</td>
</tr>
<tr>
<td>SPAP</td>
<td>Systemic pulmonary artery pressure</td>
</tr>
<tr>
<td>TAPSE</td>
<td>Tricuspid annulus plane systolic excursion</td>
</tr>
<tr>
<td>TR</td>
<td>Tricuspid regurgitation</td>
</tr>
<tr>
<td>Vd</td>
<td>Diastolic wave</td>
</tr>
<tr>
<td>Vs</td>
<td>Systolic wave</td>
</tr>
<tr>
<td>WRF</td>
<td>Worsening renal function</td>
</tr>
</tbody>
</table>
Chapter I – Introduction and Background

1.1 Epidemiology of heart failure

Heart failure [HF] is foremost an emergent public health concern in Canada and the United States that affects about 5 million Americans, and over 550,000 patients are diagnosed with HF for the first time each year (American Heart Association Update., 2005). The total direct and indirect cost of HF in the US alone will be equal to $27.9 billion (American Heart Association Update., 2005). From 1990 to 1999, the annual number of hospitalizations has increased from approximately 810,000 to over 1 million for HF as a primary diagnosis and from 2.4 to 3.6 million for HF as a primary or secondary diagnosis (Koelling, Chen et al. 2004). In Canada, patients hospitalized due to congestive HF used an average of 26.9 hospital days and re-hospitalization is nearly 50% within the first year, and 16.5% of the patients with congestive HF died in hospital. In 2025, the projected number of congestive HF cases in the hospital is expected to be doubled (Johansen, Strauss et al. 2003). The incidence of HF approaches 10 per 1,000 population after age 65 (American Heart Association Update., 2005), and approximately 80% of patients hospitalized with HF are more than 65 years old (Masoudi, Havranek et al. 2002).

1.2 Syndrome of heart failure

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood (Hunt, Abraham et al. 2005). The most common clinical presentations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary
congestion and peripheral edema. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term “heart failure” is preferred over the older term “congestive heart failure (Hunt, Abraham et al. 2005).” Another terminology that is currently being used is the “acute decompensated heart failure” which is defined as the sudden or gradual onset of the signs or symptoms of heart failure requiring unplanned office visits, emergency room visits, or hospitalization (Gheorghiade, Zannad et al. 2005). The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, or great vessels, but the majority of patients with HF have symptom due to an impairment of the left ventricular (LV) myocardial function.

Volume overload or congestion is a characteristic and predominant feature for patients who present with acute heart failure syndromes (AHFS). This results from elevated left and/or right ventricular filling pressures and manifests itself clinically by symptoms such as dyspnea and orthopnea and signs such as elevated jugular venous pressure, pulmonary rales, hepatomegaly, and peripheral edema. Despite the importance of volume overload management in AHFS, the precise causes have not been fully elucidated (Pang 2010).

Coronary artery disease, hypertension, and dilated cardiomyopathy are the causes of HF in a substantial proportion of patients in the Western world. Valvular heart disease is still a common cause of HF in certain part of the world. In fact, nearly any form of heart disease may ultimately lead to the HF syndrome (Hunt, Abraham et al. 2005).
1.3. Physiology of heart failure syndrome

1.3.1 Hypothesis of arterial underfilling

This hypothesis summarizes the complex interplay among the heart, kidneys, sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and other cellular and inflammatory modulators that function to regulate intravascular volume in the human body in any low-output state (Schrier 1988, Sica 2006, Pang 2010). The body functions to maintain homeostasis of the arterial circulation is driven primarily by cardiac output and peripheral vascular resistance. When there is a decrease in arterial pressure, either by decreased cardiac output and/or vasodilation, the body reacts via neurohormonal responses to retain sodium and water to ensure arterial circulatory integrity (Schrier 1988, Pang 2010). In patients with reduced cardiac output, irrespective of cause, what begins as an adaptive response eventually becomes maladaptive, resulting in excess fluid accumulation and the HF syndrome (Pang 2010, McMurray 2010 Jan 21).

1.3.2 Consequence of renal impairment in acute heart failure syndrome:

The majority of patients admitted with AHFS have some degree of underlying renal impairment, as defined by the National Kidney Foundation, with no substantive differences based on the presence of preserved or reduced systolic function (Heywood, Fonarow et al. 2007). This baseline renal impairment reflects the confluence of comorbid conditions (i.e., diabetes, hypertension) and the AHFS state itself (Jackson, Solomon et al. 2009). An important distinction in AHFS is that the majorities of patient do not present with low cardiac output and instead have a phenotype dominated by vasoconstriction with elevated blood pressure. Whether longstanding or acute, such vasoconstriction contributes to systemic hypertension, which itself
can cause damage to the renal microvasculature and, especially among those with diabetes mellitus, impairment of afferent arteriolar autoregulation in the kidney (Inscho and K. 2009). The latter removes what in effect functions as a vasomotor (i.e., myogenic) buffer that protects the glomerulus from excessive capillary pressure, leading to glomerular injury. This effect on autoregulation, which may be compounded (especially in HF patients) by loop diuretic-mediated inhibition of the tubulo-glomerular feedback mechanism, alters the renal blood flow response to typical stimuli (i.e., RAAS, SNS, atrial and brain-type natriuretic peptides (NPs), and urine sodium concentration) and results in progressive kidney dysfunction. The progressive kidney dysfunction may have particular implications on volume status for those individuals with salt-sensitive hypertension (HJ and NE 2007). The collective pathophysiologic milieu of AHFS may result in worsening chronic kidney disease, through one or more of the following mechanisms: altered renal perfusion from progression of HF, untoward medication effects (possibly loop diuretics), continued renovascular damage caused by fluctuations in blood pressure, neurohormonal activation, and increased venous congestion (HJ and NE 2007, Ronco, Haapio et al. 2008). Venous congestion, which can be estimated clinically by central venous pressure, may be a particularly important modulator of glomerular filtration (and hence fluid balance), especially in individuals with increased right heart pressures (Damman, Navis et al. 2007, Damman, van Deursen et al. 2009).

1.3.3 Pathogenesis of volume overload in heart failure syndrome

Neurohormonal activation (particularly the RAAS system, arginine vasopressin (AVP), and the NP system), renal perfusion and intrinsic function, venous congestion, vascular compliance, extent and severity of coronary artery disease and cardiac dysfunction, as well as other
comorbid cardiac and non-cardiac conditions (Pang 2010). Additionally, dietary indiscretion (especially sodium intake) and medication noncompliance may also contribute to the development of acute or progressive volume overload (Pang 2010). Once a volume-overloaded state occurs, this congestion further activates neurohormones, impairs myocardial performance, affects ventricular chamber geometry leading to functional mitral regurgitation (Nass, Rosman et al. 1995) and increases wall stress, which may cause sub-endocardial ischemia (Gheorghiade, Filippatos et al. 2006). This exacerbates already elevated filling pressures, resulting in worsening pulmonary congestion.

1.4 Worsening of chronic heart failure

In patients with worsening chronic HF, RAAS activation maintains perfusion by actions on the vasculature, as well as the kidneys to ensure adequate volume for circulation. Of note, this activation persists well beyond the initial episode of decompensation, which may be one contributor to the high post-discharge event rate (Milo, Cotter et al. 2003, Pang 2010). The mechanism of worsening renal function following venous congestion and/or low cardiac output involves hemodynamic, neurohormonal, and inflammatory activities (Pang 2010). Initially, such RAAS activation is helpful; however, over time, it becomes increasingly detrimental and leads to a worsening of HF. Angiotensin II plays a particularly important role, acting as a direct vasoconstrictor and a mediator of both AVP and aldosterone release, leading to further retention of sodium and water. Higher levels of serum angiotensin II are associated with worse prognosis, presumably due to its consequential adverse effects on peripheral and central components of the circulatory system (Baker, Booz et al. 1992). In addition to stimulation by angiotensin II, release of vasopressin from the posterior pituitary gland is driven by receptors for both serum osmolality and blood pressure (Finley, Konstam et al. 2008). Vasopressin has
multiple functions, affecting fluid and osmolality regulation through its effect on free water absorption. AVP acts on the collecting ducts of the kidney via Vasopressin 2 (V₂) receptors, leading to increased free water reabsorption. It also acts as a vasoconstrictor and has been implicated in ventricular remodeling (Finley, Konstam et al. 2008).

1.5 Echocardiogram of the left heart

1.5.1 The left atrium

Left atrium is the chamber of the heart that receives oxygenated blood from the lungs through the pulmonary vein then forces the blood to the left ventricle upon opening of the mitral valve. The atrium modulates ventricular filling through its reservoir, conduit, and pump functions (Lang, Bierig et al. 2006). During ventricular systole and isovolumic relaxation, when the atrioventricular (AV) valves are closed, atrial chambers work as distensible reservoirs accommodating blood flow from the venous circulation (reservoir volume is defined as left atrium (LA) passive emptying volume minus the amount of blood flow reversal in the pulmonary veins with atrial contraction. The atrium is also a pumping chamber, which contributes to maintaining adequate left ventricle (LV) end-diastolic volume by actively emptying at end-diastole (LA stroke volume is defined as LA volume at the onset of the electrocardiographic P wave minus LA minimum volume). Finally, the atrium behaves as a conduit that starts with AV valve opening and terminates before atrial contraction and can be defined as LV stroke volume minus the sum of LA passive and active emptying volumes. The reservoir, conduit, and stroke volumes of the left atrium can be computed and expressed as percentages of LV stroke volume (Lang, Bierig et al. 2006).
1.5.2 Measurements

The measurement of LA volume is feasible and reliable in most echocardiographic studies, with the most accurate measurements obtained using the apical 4-chamber and 2-chamber views (Figure 1 and 2) (Sherif F. Nagueh February 2009). This assessment is clinically important, because there is a significant relation between LA remodeling and echocardiographic indices of diastolic function (Sherif F. Nagueh February 2009). However, Doppler velocities and time intervals reflect filling pressures at the time of measurement, whereas LA volume often reflects the cumulative effects of filling pressures over time (Appleton and Kovács 2009).

Figure 1 Left atrial measurement at apical 4 chamber view.

![Image of left atrial measurement](image)

Courtesy of Vene Evangelista, RDCS - SMH Echo Lab (2014)

Left atrial measurement taken at apical 4 chamber view. LA area measured at end-systole by tracing the endocardial lining from medial MV annulus along interatrial septum, then superior LA towards the lateral endocardial border. The LA length was measured from the annulus to the superior LA wall.
Left atrial measurement taken at apical 2 chamber view. LA area measured at end-systole by tracing the internal LA cavity from the inferior annulus to the anterior annulus of the mitral valve.

1.5.3 Pressures

Symptomatic patients with diastolic dysfunction usually have increased pulmonary artery (PA) pressures. Therefore, in the absence of pulmonary disease, increased PA pressures may be used to infer the presence of elevated LV filling pressures. Correlation between PA systolic pressure and LV filling pressure has been noted in one study (Prioli, Marino et al. 1998). The peak velocity of the tricuspid regurgitation (TR) jet by continuous-wave (CW) Doppler together with systolic right atrial (RA) pressure are used to derive systolic PA pressure (Bouchard, Aurigemma et al. 2008). In patients with severe TR and low systolic right ventricular–RA pressure gradients, the accuracy of the PA systolic pressure calculation is dependent on the reliable estimation of systolic RA pressure. Likewise, the end-diastolic velocity of the
pulmonary regurgitation (PR) jet can be applied to derive diastolic PA pressure (Bouchard, Aurigemma et al. 2008). The estimation of RA pressure is needed for both calculations and can be derived using inferior vena cava diameter and its change with respiration, as well as the ratio of systolic to diastolic flow signals in the hepatic veins (Bouchard, Aurigemma et al. 2008). PA diastolic pressure by Doppler echocardiography usually correlates well with invasively measured mean pulmonary wedge pressure and may be used as its surrogate (Brutsaert, Sys et al. 1993).
1.5.4 The left ventricle

Left ventricle is the strongest chamber of the heart. It receives blood from the left atrium upon opening of the mitral valve and the forces the blood to the systemic circulation through the aortic valve. The ventricle has two alternating functions: systolic ejection and diastolic filling. Furthermore, the stroke volume must increase in response to demand, such as exercise, without much increase in LA pressure (Rapp, Lange et al. 2001). The theoretically optimal LV pressure curve is rectangular, with an instantaneous rise to peak and an instantaneous fall to low diastolic pressures, which allows for the maximum time for LV filling. This theoretically optimal situation is approached by the cyclic interaction of myofilaments and assumes competent mitral and aortic valves. Diastole starts at aortic valve closure and includes LV pressure fall, rapid filling, diastasis (at slower heart rates), and atrial contraction (Rapp, Lange et al. 2001). Elevated filling pressures are the main physiologic consequence of diastolic dysfunction. Filling pressures are considered elevated when the mean pulmonary capillary wedge pressure (PCWP) is >12 mm Hg or when the left ventricular end-diastolic pressure (LVEDP) is >16 mm Hg (Brutsaert, Sys et al. 1993). Filling pressures change minimally with exercise in healthy subjects. Exercise-induced elevation of filling pressures limits exercise capacity and can indicate diastolic dysfunction. LV filling pressures are determined mainly by filling and passive properties of the LV wall but may be further modulated by incomplete myocardial relaxation and variations in diastolic myocardial tone (Sherif F. Nagueh February 2009).
1.5.5 Measurements

Primary measurements of mitral inflow include the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the isovolumic relaxation time (IVRT), derived by placing the cursor of PW Doppler in the left ventricular outflow tract (LVOT) to simultaneously display the end of aortic ejection and the onset of mitral inflow. Secondary measurements include mitral A-wave duration (obtained at the level of the mitral annulus), diastolic filling time, the A-wave velocity-time integral, and the total mitral inflow velocity-time integral (and thus the atrial filling fraction) with the sample volume at the level of the mitral annulus (Paulus, Tschope et al. 2007) (Figures 3, 4 and 5). Mid-diastolic flow is an important signal to recognize. Low velocities can occur in normal subjects, but when increased (20 cm/s), they often represent markedly delayed LV relaxation and elevated filling pressures (Appleton, Jensen et al. 1997). Age is a primary consideration when defining normal values of mitral inflow velocities and time intervals. With increasing age, the mitral E velocity and E/A ratio decrease, whereas DT and A velocity increase. A number of variables other than LV diastolic function and filling pressures affect mitral inflow, including heart rate and rhythm; PR interval, cardiac output, mitral annular size, and LA function. Age-related changes in diastolic function parameters may represent a slowing of myocardial relaxation, which predisposes older individuals to the development of diastolic heart failure (Sherif F. Nagueh February 2009).

1.5.6 Pressures

LV filling pressures as measured invasively include mean pulmonary wedge pressure or mean left atrial (LA) pressure (both in the absence of mitral stenosis), LVEDP; the pressure at the
onset of the QRS complex or after A-wave pressure), and pre-A LV diastolic pressure. Although these pressures are different in absolute terms, they are closely related, and they change in a predictable progression with myocardial disease, such that LVEDP increases prior to the rise in mean LA pressure (Sherif F. Nagueh February 2009).

**Figure 3 Mitral valve inflow**

![Mitral valve inflow](image)

Courtesy of Vene Evangelista, RDCS - SMH Echo Lab (2014)

Mitral valve inflow is performed by taking the velocity of the mitral valve by placing the pulse wave (pw) sample volume Doppler of the mitral valve. (The first rapid diastolic filling is the peak E velocity. The 2nd wave is the peak A velocity that correspond to the atrial kick. The line drawn from the peak E velocity to the base is called the deceleration time.
Figure 4 Tissue Doppler of the medial mitral annulus

Tissue Doppler measuring e’ velocity by first downward deflection during diastole.
Figure 5 Tissue Doppler of the lateral mitral valve annulus

Tissue Doppler measuring lateral e’ velocity by first downward deflection during diastole.
1.5.7 Left ventricular ejection fraction

Ejection fraction is the amount of blood ejected from the ventricle during contractions. It is measured by percentage. Clinicians can approximate the left ventricle on the basis of its size to how much smaller the ventricle is during the period of systole. Several methods are currently being used in determining left ejection fraction.

1.5.8 The Simpson’s Biplane method of LVEF determination

The Simpson’s method was derived from the Simpson’s rule which is a numerical method that approximates the value of a definite integral by using quadratic polynomials. Simpson's rule is described as the left ventricle considered the sum of a cylinder (from the base of the heart to the mitral valve), a truncated cone (from the level of the mitral valve to the level of the papillary muscles), and below this another cone to the cardiac apex. These three sections were arbitrarily assumed to be of equal height (L/3). The paucity of reproducible landmarks precluded the use of more than three sections (as would ideally be the case in a true Simpson's rule application) (E D Folland 1979).

Formulation: \[ V = \left[ A_m \right] \frac{L}{3} + \left[ \frac{1}{2} (A_m + A_p) \right] \frac{L}{3} + \frac{1}{3} \left[ A_p \right] \frac{L}{3} \]

Figure 6 Geometric Model

ED Folland et.al., Circulation 1979;60:760-766
The Simpson’s Biplane method is by far the most commonly used in determining left ventricular ejection fraction. It is calculated by obtaining biplane LV end-diastolic volume minus the end-systolic volume divided by the end-diastolic volume times one hundred.

\[
\text{Equation: } EF = \left[\left(ED_{vol} - ES_{vol}\right) / ED_{vol}\right] \times 100
\]

**1.5.9 The Quinones method of LVEF determination**

Left ventricular ejection fraction (LVEF) measurement using the Quinones method is the measurement of eight averaged LV internal dimensions at different levels of the LV in the parasternal long-axis, apical 4 chamber, and long-axis views at end-diastole (LVEDD) (Figure 8) and end-systole (LVESD) (Figure 7) adjusting for contraction in long-axis. Approximating the correction of apical contraction (%ΔL) is as follows: +15% for normal apex contraction, +5% for hypokinetic apex, +0% for akinetic apex, -5% for slightly dyskinetic apex, and finally -15% for frankly dyskinetic apex. The formula for Quinones method is as follows: First, Percent change in two dimensions (%ΔD\(^2\)) = square of Average LV end-diastolic dimension squared (LVEDD\(^2\)) minus square of Average LV end-systolic dimension (LVESD\(^2\)) divided by the square of Average LV end-diastolic dimension squared (LVEDD\(^2\)). Then, calculate for the LVEF by Percent change in two dimensions (%ΔD\(^2\)) plus the sum of one minus Percent change in two dimensions (%ΔD\(^2\)) multiplied to the correction of apical contraction (Yock and Popp 1984). Equation is written as:

a) %ΔD\(^2\) = (LVEDD\(^2\) - LVESD\(^2\)) / LVEDD\(^2\)

b) LVEF = (%ΔD\(^2\)) + [(1-%ΔD\(^2\))(%ΔL)]

%ΔL Correction for apical contraction:

+15% Normal apex
+5% Hypokinetic apex
+0% Akinetic apex
-5% Slightly dyskinetic apex
-15% Frankly dyskinetic apex
1.5.10 The Dumesnil method of LVEF determination

The Dumesnil method of calculating left ventricular ejection fraction (LV EF) consists of dividing Doppler derived stroke volume (SV) in the LV outflow track (LVOT) by LV end-diastolic volume (LVEDV) calculated by Teichholz’s formula: (Nagueh, Middleton et al. 1997)

Firstly, determine the Stroke Volume (SV) by multiplying pi (π) with the square of the half of left ventricular outflow tract diameter, then multiply it with left ventricular outflow tract sub-valvular velocity time integral. Secondly, determine the left ventricular end-diastolic volume by dividing the cube of left ventricular end-diastolic dimension time seven with the left ventricular end-diastolic dimension plus 2.4. Finally, Determining left ventricular ejection fraction by dividing the stoke volume with left ventricular end-diastolic volume (Nagueh, Middleton et al. 1997). Equation is written below:

\[
\begin{align*}
SV &= \pi \times (\text{LVOT}/2)^2 \times \text{VTI}1 \\
\text{LVEDV} &= (7 \times \text{LVEDD}^3) / (2.4 + \text{LVEDD}) \\
\text{LVEF} &= \frac{SV}{\text{LVEDV}}
\end{align*}
\]

Definition of terms: LVEDD (left ventricular end-diastolic dimension; LVOT (left ventricular outflow tract diameter); VTI1 (left ventricular outflow tract subvalvular velocity time integral); SV (stroke volume); LVEDV (left ventricular end-diastolic volume); and LVEF (left ventricular ejection fraction [%])
Figure 7 Left ventricular end-systolic dimension

Parastral long axis measuring the smallest LV and LA antero-posterior dimension at the end-systole.
Figure 8 Tracing of the left ventricle at end-diastolic dimension

Parasternal long axis view measuring the LV dimension during the dimension during diastole.
1.6. Echocardiogram of the Right Heart

1.6.1 The Right Atrium

The right atrium is the chamber of the heart that receives unoxygenated blood from the systemic circulation via superior and inferior vena cava then pushes the blood into the right ventricle upon opening of the tricuspid valve.

The right atrium (RA) assists in filling the right ventricle by acting as a (Lang, Bierig et al. 2005) reservoir for systemic venous return when the tricuspid valve is closed (Forman, Goodin et al. 1984) passive conduit in early diastole when the tricuspid valve is open, and active conduit in late diastole during atrial contraction (Gaynor, Maniar et al. 2005). To date, only a few studies have focused on the role of the right atrium in disease states. RA dilatation was documented in patients with atrial arrhythmias by both two-dimensional (2D) and three-dimensional (3D) echocardiography (Muller, Burri et al. 2008) and reverse remodeling occurred following radiofrequency ablation treatment of atrial fibrillation (Muller, Noble et al. 2008).

1.6.2 Measurements

The primary transthoracic window for imaging the right atrium is the apical 4-chamber view (Figure 9). From this window, RA area is estimated by planimetry (Otto 2007). The maximal long-axis distance of the RA is from the center of the tricuspid annulus to the center of the superior RA wall, parallel to the interatrial septum. A mid-RA minor distance is defined from the mid-level of the RA free wall to the interatrial septum, perpendicular to the long axis. RA area is traced at the end of ventricular systole (largest volume) from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area between the leaflets and annulus,
following the RA endocardium, excluding the IVC and superior vena cava and RA appendage (Rudski, Lai et al. 2010). Note that RA dimensions can be distorted and falsely enlarged in patients with chest and thoracic spine deformities. RA dimensions should be considered in all patients with significant RV dysfunction in whom image quality does not permit for the measurement of RA area. Because of the paucity of standardized RA volume data by 2D echocardiography, routine RA volume measurements are not currently recommended (Rudski, Lai et al. 2010).

**Figure 9 Apical four chamber view**

![Apical four chamber view demonstrating septal deviation towards LA during end systole showing increased in RAP.](image)

*Courtesy of Vene Evangelista, RDCS - SMH Echo Lab (2014)*
1.6.3 RA and RV Pressures

RA pressure is most commonly estimated by inferior vena cava (IVC) diameter and the presence of inspiratory collapse (Moreno, Hagan et al. 1984). As RA pressure increases; this is transmitted to the IVC, resulting in reduced collapse with inspiration and IVC dilatation (Figures 10 and 11). Combining these two parameters result in a good estimation of RA pressure within a limited number of ranges in a majority of patients. Secondary indices of RA pressure may be useful in such scenarios to further refine estimates. In patients being ventilated using positive pressure, the degree of IVC collapse cannot be used to reliably estimate RA pressure, and RA pressure measured by transduction of a central line should be used if available. An IVC diameter ≤ 12 mm in these patients, however, appears accurate in identifying patients with RA pressures < 10 mm Hg.11 If the IVC is small and collapsed, this suggests hypovolemia (Rudski, Lai et al. 2010).
Figure 10 Subcostal view showing normal inferior vena cava defined as diameter of < 2.1 cm

Figure 11 Subcostal view of the dilated inferior vena defined as diameter of > 2.1 cm
The subcostal view is most useful for imaging the IVC, with the IVC viewed in its long axis (Feigenbaum H 2005). The measurement of the IVC diameter should be made at end-expiration and just proximal to the junction of the hepatic veins that lie approximately 0.5 to 3.0 cm proximal to the ostium of the right atrium (Rudski, Lai et al. 2010). To accurately assess IVC collapse, the change in diameter of the IVC with a sniff and also with quiet respiration should be measured, ensuring that the change in diameter does not reflect a translation of the IVC into another plane (Feigenbaum H 2005, Otto 2007, Rudski, Lai et al. 2010). Although a distended IVC usually denotes elevated RA pressures, in patients with otherwise normal exam results, reassessing the IVC size and collapsibility in the left lateral position may be useful to avoid the potentially erroneous inference of increased RA filling pressure (Rudski, Lai et al. 2010).

The IVC may also be dilated in normal young athletes, and in this population, it may not reflect elevated RA pressure. Hepatic vein flow patterns provide complementary insights into RA pressure. At low or normal RA pressures, there is systolic predominance in hepatic vein flow, such that the velocity of the systolic wave (Vs) is greater than the velocity of the diastolic wave (Vd) (Figure 12). At elevated RA pressures, this systolic predominance is lost, such that Vs is substantially decreased and Vs/Vd is <1. The hepatic vein systolic filling fraction is the ratio Vs/(Vs + Vd), and a value < 55% was found to be the most sensitive and specific sign of elevated RA pressure (Nagueh, Kopelen et al. 1996).
Figure 12 Pulse Doppler of the hepatic vein

Shown are the normal systolic and diastolic flows. The 1st marker is the normal systolic flow and the 2nd marker is the diastolic flow.

Other 2D signs of increased RA pressure include a dilated right atrium and an interatrial septum that bulges into the LA throughout the cardiac cycle. These are qualitative and comparative, and do not allow the interpreter to assign an RA pressure but if present should prompt a more complete evaluation of RA pressure as well as a search for possible etiologies (Rudski, Lai et al. 2010). For simplicity and uniformity of reporting, it is recommended that specific values of RA pressure, rather than ranges, should be used in the determination of systolic pulmonary artery pressure (SPAP). IVC diameter ≤ 2.1 cm that collapses >50% with a sniff suggests a normal RA pressure of 3 mm Hg (range, 0-5 mm Hg), whereas an IVC diameter > 2.1 cm that collapses <50% with a sniff suggests a high RA pressure of 15 mm Hg (range, 10-20 mm Hg). In indeterminate cases in which the IVC diameter and collapse do not
fit this paradigm, an intermediate value of 8 mm Hg (range, 5-10 mm Hg) may be used, or, preferably, secondary indices of elevated RA pressure should be integrated. These include restrictive right-sided diastolic filling pattern, tricuspid E/E´ ratio > 6, and diastolic flow predominance in the hepatic veins (which can be quantified as a systolic filling fraction < 55%). In indeterminate cases, if none of these secondary indices of elevated RA pressure are present, RA pressure may be downgraded to 3 mm Hg. If there is minimal IVC collapse with a sniff (<35%) and secondary indices of elevated RA pressure are present, RA pressure may be upgraded to 15mmHg. If uncertainty remains, RA pressure may be left at the intermediate value of 8 mm Hg. In patients who are unable to adequately perform a sniff, an IVC that collapses < 20% with quiet inspiration suggests elevated RA pressure. This method of assigning an RA pressure is preferable to assuming a fixed RA pressure value for all patients (Moreno FL 1984).

1.6.4 The Right Ventricle

The right ventricle is the chamber in the heart that receives unoxygenated blood from the right atrium upon opening of the tricuspid valve and then forces the blood to the lungs via pulmonary artery. The right ventricle (RV) is composed of 3 distinct portions: the smooth muscular inflow (body), the outflow region, and the trabecular apical region. Volumetric quantification of RV function is challenging because of the many assumptions required. As a result, many physicians rely on visual estimation to assess RV size and function (Rudski, Lai et al. 2010). Standardization remains insufficient for RV systolic function when measured using visual assessment. There are several simple and reproducible methods of assessing RV systolic function that should be incorporated into the routine echocardiographic assessment. These are fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), pulsed
tissue Doppler S’, and myocardial performance index (MPI). Combining more than one measure of RV function, such as S´ and MPI, may more reliably distinguish normal from abnormal function (Miller, Farah et al. 2004). It is strongly recommended by that at least one of the above quantitative measures be incorporated into the routine echocardiographic examination and report, and this is particularly important when RV dysfunction is suspected and or when the clinical indication for the study relates to a condition that may affect the right ventricle (Rudski, Lai et al. 2010).

1.6.5 Measurements
Quantitative assessment of RV size and function has proven to be of important clinical value in a number of cardiac and pulmonary diseases. Numerous publications have demonstrated the prognostic significance of RV function. The normal right ventricle is accustomed to low pulmonary resistance and because of its thin walls is relatively compliant. Hence, conditions that acutely increase pulmonary vascular resistance (PVR) such as pulmonary embolism result in increases in RV size prior to the augmentation of pulmonary pressures, which ultimately may result as the ventricle hypertrophies (Cresci and Goldstein 1992, Rudski, Lai et al. 2010). Dilatation of the right ventricle thus is the first marker of increases in PVR. As the right ventricle hypertrophies to overcome the elevated PVR, RV size, indicated by diameter or volumes, can decrease, and the RV free wall thickness increases with ultimate increase in right ventricular systolic pressure (RVSP).

In patients with acute pulmonary embolism, initial increases in RV volume and diameters are often accompanied by a specific pattern of abnormal regional wall motion in which the mid RV free wall becomes dyskinetic with relative sparing of the base and apex (McConnell, Solomon
et al. 1996). In patients with long standing pulmonary vascular disease or other forms of secondary PH (including from chronic obstructive pulmonary disease, emphysema, or other forms of pulmonary parenchymal disease), the right ventricle tends to hypertrophy and normalize volumes at first, followed by eventual and progressive dilatation (Ferlinz 1982).

RV size and function can also be adversely affected by diseases intrinsic to the left ventricle. Patients with LV dysfunction secondary to myocardial infarction or heart failure are at increased risk for both RV dilatation and dysfunction (Gorcsan, Murali et al. 1996). Indeed, RV dysfunction is one of the most powerful independent predictors of outcome following myocardial infarction, even in the absence of overt RV infarction (Anavekar, Skali et al. 2008). Similar findings have been shown in patients with chronic heart failure and in stable survivors a year after infarction (Khush KK 2009). Data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) suggest that elevation in pulmonary pressures directly may contribute to alterations in RV size and function in patients with heart failure (Khush, Tasissa et al. 2009). Moreover, sleep apnea in patients with heart failure may also contribute substantially to alterations in RV function and size (Romero-Corral A 2007).

RV size and function can also be affected by diseases affecting the tricuspid valve resulting in substantial TR. These include carcinoid disease in which the tricuspid leaflets can retract and become functionally incompetent; rheumatic tricuspid disease (Romero-Corral, Somers et al. 2007); myxomatous degeneration of the tricuspid valve; or any other situation in which the tricuspid valve becomes incompetent. The volume overload that ensues with TR leads to dilatation of the right ventricle, which can itself result in further TR.
The most common congenital abnormality that affects the right ventricle in adult cardiology is atrial septal defect. The increased flow resulting from the shunt can lead to elevation in pulmonary pressures and RV dilatation. The population of patients with postoperative tetralogy of Fallot with severe pulmonary regurgitation presenting with severe RV dilatation and diminished function is increasing. Other congenital abnormalities, such as Ebstein anomaly, and more complex congenital disorders can affect the right ventricle. Situations in which RV morphology appears to be particularly unusual should raise the suspicion of more complex congenital heart disease (Rudski, Lai et al. 2010).

1.6.6 The Right Ventricular Diastolic Function

The right ventricle is more than a passive chamber. Acute injury to the right ventricle, most notably in the context of RV myocardial infarction, results in marked diastolic dysfunction with elevated filling pressures and clinically apparent jugular venous distension (Yilmaz, Erol et al. 2003). Pathophysiology of RV diastolic dysfunction is much more complex than simply measuring the thickness of the myocardium (Weber, Janicki et al. 1981). A growing number of acute and chronic conditions have been associated with RV diastolic dysfunction, including both pressure and volume overload pathologies, primary lung disease, ischemic heart disease, congenital heart disease, cardiomyopathies, LV dysfunction (via ventricular interdependence), systemic diseases, and the physiologic aging process (Rudski, Lai et al. 2010).

The parameters used to assess RV diastolic function are essentially the same as those used to assess the left side. Those that have been most validated are Doppler velocities of the transtricuspid flow (E, A, and E/A), tissue Doppler velocities of the tricuspid annulus (E’, A’,
E′/A′), deceleration time, and isovolumic relaxation time (IVRT). The tricuspid E/E′ ratio, RA area or volume, and diastolic strain rate appear promising (Rudski, Lai et al. 2010).

There is a modest correlation (r = 0.30) between the E/A ratio and increasing age. The E/A ratio decrease by approximately 0.1 per decade (Innelli, Esposito et al. 2009). Inspiration causes an increase in E and therefore an increase in the E/A ratio. Tachycardia causes an increase in E but a relatively greater increase in A and therefore a decrease in the E/A ratio (Yu, Lin et al. 2003). When comparing Doppler parameters between patients or in the same patient, one must consider the effect of these hemodynamic variables on the observed parameters. Because of its thin wall, the right ventricle is very sensitive to afterload (wall stress), especially in the presence of RV myocardial disease such as ischemia or infarction (Berman, Green et al. 1979).

It is also sensitive to changes in preload, whereby a reduction in preload causes a decrease in E but a relatively smaller decrease in A and therefore a decrease in E/A (O'Sullivan, Duncan et al. 2005). Tissue Doppler is less load dependent, because a reduction in preload causes an equal decrease in E′ and A′ and therefore an unchanged E′/A′ ratio. Importantly, tissue Doppler should be used to differentiate normal from pseudonormal filling patterns with elevated filling pressures as are hepatic vein flow patterns and vena cava size and collapse (Nagueh, Kopelen et al. 1996).

Last, the physiologic response to exercise is to increase both early rapid filling and atrial contribution. In ischemic patients, the pathophysiologic response is a failure of the early rapid
filling to increase and a heightened dependency on atrial contribution and consequent elevated RA pressure (Heywood, Grimm et al. 1990).

A small number of studies have evaluated the clinical impact of RV diastolic dysfunction. The tricuspid E/E’ ratio and RA volume have been shown to correlate well with hemodynamic parameters (Rudski, Lai et al. 2010). An E/E’ ratio ≥ 4 had high sensitivity and specificity for predicting RA pressure ≥ 10 mm Hg in non-cardiac surgery intensive care unit patients (Mittal and Goozar 2001), while an E/E’ ratio > 8 had good sensitivity and specificity for predicting RA pressure ≥ 10 mm Hg in cardiac transplantation patients (Sade, Gulmez et al. 2007).

In patients with chronic HF and PH, the presence of RV diastolic dysfunction was associated with worse functional class and was an independent predictor of mortality (Sallach, Tang et al. 2009). Diastolic filling patterns reflect response to therapy, improving with successful treatment of a variety of cardiac conditions (Gan, Holverda et al. 2007).

Finally, studies of RV diastolic dysfunction may be clinically useful because it serves as an early and more easily quantifiable marker of subclinical RV dysfunction. Multiple studies have shown that RV diastolic dysfunction is usually present before apparent systolic dysfunction and before RV dilatation or RVH. It is highly recommended that measurement of RV diastolic function should be considered in patients with suspected RV impairment as a marker of early or subtle RV dysfunction, or in patients with known RV impairment as a marker of poor prognosis. Transtricuspid E/A ratio, E/E’ ratio, and RA size have been most validated and are the preferred measures. Grading of RV diastolic dysfunction should be done as follows: tricuspid E/A ratio < 0.8 suggests impaired relaxation, a tricuspid E/A ratio of 0.8 to 2.1 with
an E/E’ ratio > 6 or diastolic flow predominance in the hepatic veins suggests pseudonormal filling, and a tricuspid E/A ratio > 2.1 with a deceleration time < 120 ms suggests restrictive filling (as does late diastolic antegrade flow in the pulmonary artery) (Rudski, Lai et al. 2010).

1.6.7 The Right Ventricular Systolic Pressure

Right ventricular systolic pressure (RVSP) is estimated through determination of tricuspid regurgitation (TR) velocity (Figure 13) with the addition of right atrial pressure (RAP), assuming no significant right ventricular outflow tract obstruction (Rudski, Lai et al. 2010). It is recommended to use the RA pressure estimated from IVC and its collapsibility, rather than arbitrarily assigning a fixed RA pressure as stated earlier. In general, TR velocity > 2.8 to 2.9 m/s, corresponding to SPAP of approximately 36 mmHg, assuming an RA pressure of 3 to 5 mmHg, indicates elevated RV systolic and PA pressure. SPAP may increase, however, with age and in obesity (Rudski, Lai et al. 2010). In the study by Kevin Shrestha et al., in 144 patients with chronic systolic HF, they performed comprehensive echocardiography of right-sided cardiac structure and performance and 5-year follow-up, and measured plasma cystatin C (CysC) and sCr as markers of renal function. They have found that an increased RAP and RVSP predicted longer, outcomes after adjustment for each other (Shrestha, Dupont et al. August 2012).
Figure 13 Tricuspid regurgitation jet with continuous wave Doppler

Complete Doppler profile: Shown (arrow) is the peak velocity of TR jet.

Courtesy of Vene Evangelista, RDCS - SMH Echo Lab (2014)
1.7 Natriuretic peptides

1.7.1 The history of natriuretic peptides

A series of experiments done in the mid-1950s established the heart as an endocrine organ. First, Kisch and colleagues detected secretory granules in guinea pig atria (Pearce 1956). Henry and Pearce subsequently described increased urinary flow after balloon stretch of the canine left atrium (de Lemos, McGuire et al. 2003). In an experiment done 25 years later, de Bold injected homogenized atrial tissue into rats and noted increased sodium excretion and urinary volume (Kisch 1956). In 1984, the structure of atrial natriuretic peptide (ANP) was identified (de Bold, Borenstein et al. 2001) and in 1988 a compound was isolated from pig brain that caused natriuretic and diuretic responses similar to ANP (Sudoh T 1988). Although this peptide was called brain (B-type) natriuretic peptide (BNP), the primary site of BNP synthesis is ventricular myocardium (Kangawa, Fukuda et al. 1984, Hosoda, Nakao et al. 1991).

1.7.2 Biological activity of natriuretic peptides

In the setting of volume expansion or pressure overload, the resulting wall stress initiates synthesis of pre–proBNP in the ventricular myocardium. Subsequently, the peptide is cleaved first to proBNP1-108, then to the biologically active BNP1-32 and the inactive amino-terminal fragment (NT-proBNP) (Harada, Saito et al. 1998). The release of BNP results in improved myocardial relaxation and serves an important regulatory role in response to acute increases in ventricular volume by opposing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin-angiotensin aldosterone system (Daniels and Maisel 2007). The biological actions of NPs are mediated through membrane-bound natriuretic peptide receptors.
(NPRs) that are linked to a cyclic guanosine monophosphate-dependent signaling cascade, including NPR-A, which preferentially binds ANP and BNP, and NPR-B, which preferentially binds C-type NP. Clearance of NPs from the blood is mediated by NPR-C. In addition, BNP is degraded by neutral endopeptidase, which opens the ring structure and inactivates the peptide. Direct renal filtration and passive excretion might be responsible for some BNP clearance as well (Daniels and Maisel 2007).

Although blood levels of NPs rise to very high levels in the setting of acute HF, recent studies support the notion that HF patients actually manifest a state of BNP insufficiency, due to both a deficiency of biologically active BNP\textsubscript{1-32} and resistance to its effects (Nakagawa O 1995). Evidence for a state of deficiency comes from molecular analysis of BNP in subjects with acute HF, which reveals 2 distinct circulating forms of BNP: a high-molecular weight form, thought to be proBNP\textsubscript{1-108}, and a low-molecular weight form, the 32-amino acid active BNP\textsubscript{1-32} (Chen 2007). Instead of recognizing BNP\textsubscript{1-32} or NT-proBNP alone, recent studies have shown that the standard NP assays also recognize the high molecular weight proBNP\textsubscript{1-108}, which comprises a significant percentage of immunoreactive BNP in HF patients yet seems to have less biologic activity than BNP\textsubscript{1-32}, thus explaining the paradox of HF as an NP-deficient state despite high levels of these biomarkers.(Shimizu, Masuta et al. 2002, Liang, O'Rear et al. 2007). Abnormal processing of proBNP into less active forms might also factor into the state of relative BNP insufficiency (Hawkridge, Heublein et al. 2005). In addition, HF patients seem to suffer some degree of BNP resistance. Animal studies have implicated an up-regulation of phosphodiesterase in HF, causing impaired cyclic-GMP activity despite high stimulation of the NPRs by NPs (Lam, Burnett et al. 2007). Taken together, these studies help explain the paradox of high measurable BNP and NT-proBNP levels in HF patients who nonetheless suffer
physiologically from a state of BNP deficiency and its attendant fluid and salt retention (Daniels and Maisel 2007).

1.7.3 Factors that increases natriuretic peptides

Natriuretic peptide levels are clearly age- and gender specific. Two studies looked at NP levels in normal subjects without cardiovascular disease or ventricular (systolic or diastolic) dysfunction and found increased levels with age and in women (Redfield, Rodeheffer et al. 2002, Forfia, Lee et al. 2007). Therefore, “normal” values vary. As a general guideline, in young, healthy adults, 90% will have NT-proBNP 70 pg/ml (Wang, Larson et al. 2002). For acutely dyspneic patients, some have suggested cutoffs NT-proBNP 300 pg/ml to rule out HF (Maisel, Krishnaswamy et al. 2002, Daniels, Allison et al. 2008).

The natriuretic peptides have become important diagnostic tools for assessing patients who present acutely with dyspnea. The PRIDE (ProBNP Investigation of Dyspnea in the ED) study was a similar study performed with NT-proBNP, measured in 600 patients who presented to a single ED with dyspnea. In this study, NT-proBNP was sensitive and specific for the diagnosis of congestive heart failure (CHF) (AUC 0.94). Patients with acute HF had a median NT-proBNP of over 4,000 pg/ml compared to 130 pg/ml in those without acute HF. An NT-proBNP with a cut-point of 300 pg/ml was proposed to “rule-out” a diagnosis of HF, whereas higher age-dependent cut-points were suggested to “rule-in” HF (AUC 0.94) (Maisel, Krishnaswamy et al. 2002).
Similar improvements in diagnosis and cost savings were seen in the IMPROVE-CHF (Improved Management of Patients With Congestive Heart Failure) study of NT-proBNP use in the ED (Moe, Howlett et al. 2007).

Several conditions that cause high cardiac outputs, including sepsis, cirrhosis, and hyperthyroidism, can contribute to elevated NP levels. Although the mechanisms are unclear, patients with severe sepsis or shock might have markedly elevated NP levels (Yamaguchi, Yoshida et al. 2004) possibly due to induction by endotoxin or other inflammatory mediators (Rudiger, Gasser et al. 2006) or due to underlying myocardial dysfunction (Ma, Ogawa et al. 2004).

NT-proBNP, which is not cleared by the NPR-C receptor or neutral endopeptidase, is very sensitive to reduced renal filtration and clearance (DeFilippi, Fink et al. 2005). In a study of breathless patients, there was a stronger relationship between glomerular filtration rate (GFR) and NT-proBNP levels ($r = 0.55$) although the relationship was somewhat attenuated among patients with acute CHF ($r = 0.33$ for NT-proBNP) (Lamb, Vickery et al. 2006). Because of this renal influence, interpretation of NT-proBNP levels might be more difficult in patients with a GFR 60 ml/min/1.7 m$^2$ (AM, MG et al. 1998). However, an analysis from the PRIDE study showed that NT-proBNP levels in patients with GFR 60 ml/min/1.7 m$^2$ were still the strongest independent predictor of outcome and suggested the higher cut-point of NT-proBNP >1,200 pg/ml for diagnosing HF in such patients (Lamb, Vickery et al. 2006). The relationship of NP with filling pressures and prognosis in patients with elevated creatinine still applies even if a higher cut-point is required (DeFilippi, Fink et al. 2005). In relatively healthy subjects with only mild renal impairment, in contrast, there seems to be no significant relationship between
NT-proBNP levels and GFR (Knudsen CW 2005). Thus, NT-proBNP might have additional as yet undiscovered modes of clearance, such as degradation by nonspecific peptidases.(Harada, Saito et al. 1998, Anwaruddin, Lloyd-Jones et al. 2006).

1.7.4 Factors that lowers natriuretic peptides

Low levels of NPs are interestingly noted in some patients. Some studies have found that NT-proBNP levels might be lower in obese patients, despite the fact that NT-proBNP is not believed to be cleared by NPR-C (Das, Drazner et al. 2005, Daniels, Clopton et al. 2006). Other investigator, however, have found that the degree of impact of body mass index on NT-proBNP was minimal (Knudsen, Omland et al. 2005). A recent study of post-bariatric surgery patients hypothesized that, because NT-proBNP levels increased after weight loss, decreased NP production and not increased clearance might be the responsible mechanism (Krauser, Lloyd-Jones et al. 2005). Despite the lower circulating levels, NPs retain their prognostic capacity in obese patients (van Kimmenade, van Dielen et al. 2006) although lower NP cut-points are needed for diagnosing HF in patients with a high body mass index (Wang, Larson et al. 2004).

Several studies have shown that NP levels in patients presenting with HF are predictive of future adverse outcomes. Monitoring NP levels in the outpatient setting might improve patient care and outcomes, although prospective studies of this have shown conflicting results. For patients regularly followed in clinic, it might be beneficial to establish their “dry” NP level, i.e. the NP level that corresponds to their optimized fluid status. Knowing a patient’s steady state NP level might be helpful for management in both the inpatient and outpatient settings, because baseline NP levels can vary on the basis of the patient’s underlying severity of disease and
NYHA functional class (Horwich, Hamilton et al. 2006). Significant deviations above this steady state value might prove more helpful than traditional cut-points for diagnosing HF exacerbations in those individuals who are closely followed as outpatients and whose NP levels tend to stay elevated, whereas values much lower than their steady state level might signal a patient who is over-diuresed or intravascularly depleted.

A post-discharge rise in NP level can be an important marker for repeat hospital stay. How high an NP level must raise over baseline before a patient is deemed “clinically relevant” is not entirely clear because as noted previously, there is a certain amount of individual variation in NP levels, and certainly the clinical picture is important in this regard. However, an increase by at least 50% over one’s steady state NP level might be a reasonable benchmark for triggering an evaluation for confirmatory signs and symptoms followed by more aggressive treatment (Harada, Saito et al. 1998).

1.8 Renal dysfunction in heart failure:

The function, regulation, and adjustments of the heart and vasculature are closely linked to those of the kidneys. Renal dysfunction adversely affects cardiovascular function, which in turn influences renal function. Because of the physiological adjustments required of the kidneys to maintain adequate renal function in heart failure, this organ system in chronic HF is vulnerable to pharmacological, haemodynamic, or structural disturbances (Januzzi 2011).

Serum creatinine is a poor guide of GFR because it is highly dependent on muscle mass and is insensitive to changes in renal function until a level where the GFR is substantially reduced. Prediction equations, such as the Cockcroft–Gault (CG) or Modified Diet in Renal Disease (MDRD) equations (Petrie, Mark et al. 2008) based primarily on creatinine and age are more
practical. In patients with chronic kidney disease (CKD), the MDRD formula is more accurate (less bias and greater precision) in predicting GFR than other equations (Petrie, Mark et al. 2008) but it should be recognized that the validation sample was drawn from the 1628 patients in the MDRD study, thus the performance of this equation in different populations may not be the same. Those without renal disease, diabetics receiving insulin treatment and those >70 years old were excluded and it has not been validated in those with extreme values of serum albumin (Petrie, Mark et al. 2008). Based on the Kidney Disease Quality Outcome Initiative guidelines, moderate renal insufficiency is defined as a GFR 30–60 ml/min per 1.73 m², severe renal insufficiency 15–30 ml/min per 1.73 m², and renal failure ≤15 ml/min per 1.73 m², or dialysis dependency (Levey, Bosch et al. 1999).

Any fall in cardiac output, effective blood volume, and renal blood flow is accompanied by activation of the sympathetic nervous system (SNS) and renin secretion from the juxtaglomerular apparatus, with consequent angiotensin II (AG II) production (Januzzi 2011). Vasoconstriction of the post glomerular efferent arterioles in preference to the pre glomerular afferent arterioles restores glomerular capillary pressure and thereby maintains GFR despite a reduced perfusion pressure. Preferential constriction of the efferent arteriole by angiotensin II in addition to dilatation of the afferent arteriole by natriuretic peptides and prostaglandins appears to be the major mechanisms for maintaining GFR as renal blood flow declines. The mechanisms adjusting renal vascular resistance and blood flow in Chronic HF are not the same as those influencing the vascular resistance and blood flow in other regions of the body. It is also influenced by a number of local mechanisms and substances, including modulators of vascular tone such as nitric oxide, endothelin, prostaglandins and tubulo-glomerular feedback.
1.9 Diuretics as the mainstay therapy in heart failure

Diuretic relieve congestion but at the expense of increasing neurohormonal activation, which in turn may reduce glomerular perfusion pressure. This is probably via reduced “effective” blood volume, flow, or pressure, and if over diuresis occurs, a significant reduction in renal blood flow and GFR can result. As renal function declines, so does the response to diuretics and this “diuretic resistance” is associated with a poorer prognosis (Ezekowitz, McAlister et al. 2003).

The balance between a desire to achieve an adequate diuresis and the ever apparent danger of worsening renal function is a constant therapeutic challenge. High diuretic doses may increase the risk of arrhythmia caused by electrolyte depletion and decrease the tolerability of proven therapies such as ACE inhibitors. Diuretic resistance and worsening renal function may also be a marker, rather than a mechanism for poor outcomes (Neuberg, Miller et al. 2002).

Loop diuretics (e.g. furosemide) are 1st line therapy and in those with “diuretic resistance” the synergistic action of a thiazide diuretic (e.g. metolazone) often results in improved diuresis (Januzzi 2011). In hospitalized patients loop diuretics are usually given intravenously. Continuous infusion of loop diuretics can achieve better diuresis than intermittent bolus injections and perhaps should be used more often for fluid removal in heart failure (Adams, Fonarow et al. 2005). These strategies require careful monitoring of serum electrolytes and from a practical stand-point, salt and fluid restriction is crucial and one often needs to accept a transient deterioration in renal function in association with diuretics when treating decompensated heart failure (Januzzi 2011). Damman et al. recently showed that GFR is also determined by venous congestion, and (in a multivariate analysis) both right atrial pressure and RBF were independent determinants of GFR, and suggest that if diuretic therapy is tailored to
reduce venous congestion it may actually benefit GFR and perhaps improve prognosis (Damman, Navis et al. 2007).

**1.10 The cardiorenal syndrome**

The cardiorenal syndrome (CRS) manifests a complex pathophysiology with dismal clinical outcomes. The proposal of a comprehensive definition that incorporates first the bidirectional nature of the organ interaction and the multiplicity of compensatory mechanisms involved represents a significant paradigm shift (Ronco, Haapio et al. 2008, Iyngkaran, Schneider et al. 2012).

The cardio-renal interaction is primary via the circulatory system (hemodynamic factors) or secondary to underlying endogenous humoral or exogenous factors that are associated with disease of either organ or a combination of both (Shlipak, Chertow et al. 2003). This interaction can occur in normal organs (acute dysfunction) or diseased organs (acute or chronic dysfunction), and in one or both organs or a combination. The causation and temporality of this interaction in terms of kidney damage and subsequent clinical deterioration is unpredictable. This is compounded by a lack of symptoms, the unpredictable time lapse between injury and clinical manifestation, and the narrow therapeutic window between insult and implementing renal protective strategies. Importantly adequacy of renal function (RF) may be a primary determinant of compensation in patients with HF, and therapy capable of improving RF may delay progression of HF (Dries, Exner et al. 2000, Heywood, Fonarow et al. 2007, Noppert and Mayer 2009, Ronco, McCullough et al. 2010, Tang and Mullens 2010).
The details of renal blood flow medullary and cortical nephrons share differential blood flows to maintain a cortico-medullary solute gradient. Despite receiving 25% of cardiac output, only 10% supply the medulla. The juxtamedullary cortex and outer medulla receive the majority of renal blood flow (Shlipak, Chertow et al. 2003). With greater density of neural innervations it can modulate acute changes. The precise mechanisms that regulate medullary blood flow (RBF) are unknown, but evidence supports a lack of counter-regulatory control in normal physiology (Shlipak, Chertow et al. 2003).

Relationship of renal blood flow and GFR represents the net filtration of all functioning nephrons. RBF is the most important contributor of GFR in patients with congestive heart failure (CHF) on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. There is a parallel decline in GFR with declining RBF despite having a stable filtration fraction over almost the full range of RBF (Noppert and Mayer 2009). In addition, GFR is determined by various intrarenal and extrarenal factors, for example, prerenal (cardiac pump failure, excessive vasoconstriction, hypovolemia, pregnancy, and drug therapy), renal (afferent and efferent capillary flow and intrinsic renal disease), or postrenal (increased venous filling pressures) factors. This makes GFR an insensitive marker to detect onset, follow-up progression or remission in early renal disease, or establish differential diagnosis Dries, Exner et al. (2000).

1.10.1 Glomerular filtration rate in heart failure

In HF renal perfusion, filtration coefficient and compensatory changes (hyperfiltration, hypertrophy, and sclerosis) are affected by many factors, for example, systemic hypertension (diastolic heart failure), systemic hypotension (systolic heart failure), advanced disease
(hypoalbuminemia and altered oncotic pressure), and comorbidities such as diabetic nephropathy (underlying glomerular disease) (Shlipak, Chertow et al. 2003). Single nephron glomerular filtration rate (SNGFR) is critical in maintaining overall RF. Many CHF patients have baseline renal impairment, and already may have single nephron filtration fraction (SNFF) and SNGFR functioning at capacity (Dries, Exner et al. 2000, Noppert and Mayer 2009). To compensate for the inability to predict corticomedullary compensation or monitor the many factors threatening to diminish RBF, the ability to anticipate injury and thus potential renal insufficiency is a great armament for early intervention (Shlipak, Chertow et al. 2003) (Figure 2.13).

1.10.2 Use of serum creatinine in heart failure

Serum creatinine (sCr) is the most used marker for renal function (RF) assessment in practice, usually is produced at fairly constant rates. Excretion occurs predominately by filtration; however, distal tubular secretion may account for up to 10% to 40%. In addition, delays in achieving steady state (which may take up to 7 days) and varying levels make it an unreliable measure for accurate and temporal information (Shlipak, Chertow et al. 2003). It is also considered best retrospective window for renal injury and dysfunction (Smilde, Damman et al. 2009).

On the other hand, GFR is considered the best overall measure of RF. It can be estimated from sCr and demographic and clinical variables, such as age, sex, ethnicity, and body size. Physiological decline with age (1 mL/min/1.73m² per year after 40 years) needs to be taken into account. Estimated GFR (eGFR) based on an endogenous marker is extremely useful in daily clinical practice, and recent studies have validated these as providing reliable estimates of

1.11 Worsening of renal function

Worsening renal function (WRF), usually defined as an increase in serum creatinine levels $\geq 0.3$ mg/dL (or 26.52 umol/L) from values at admission, has also been shown to be an independent prognostic determinant (Klein, Massie et al. 2008, Metra, Davison et al. 2012). Most of these data were, however, based on retrospective analyses and they are, therefore, subject to a detection bias. For example, sicker patients who are more congested and have a longer hospital stay tend to have more creatinine measurements done and hence have a greater likelihood of showing a creatinine increase. Second, increases in serum creatinine levels may just be caused by renal hemodynamic abnormalities and diuretic therapy (Pang 2010, P and G 2011). In all of these cases, an increase in serum creatinine would be simply a marker of more severe HF rather than of real WRF. In accordance with this hypothesis, studies based on serial measurements of serum creatinine levels, done independently from patients’ clinical conditions, have failed to show a prognostic value for the changes of this variable, different from absolute serum creatinine levels, either on admission or at discharge (Nohria, Hasselblad et al. 2008).

1.11.1 Venous congestion in patients with worsening of chronic heart failure.

Reduced cardiac output is traditionally believed to be the main determinant of worsening renal function (WRF) in advanced decompensated heart failure (ADHF) (Mullens, Abrahams et al. 2009). In one study showed venous congestion, rather than impairment of cardiac output, is
primarily associated with the development of WRF in ADHF. A small number of patients (145) admitted with acute decompensated heart failure (ADHF) treated with intensive medical therapy guided by pulmonary artery catheter were studied. The authors concluded that patients who developed WRF had a higher central venous pressure on admission (CVP, 18 ±7 versus 12 ±6 mmHg, p<0.001) and after intensive medical therapy (11 ±8 versus 8 ±5 mmHg, p=0.04). The development of WRF occurred less frequently in patients that achieved a CVP <8 mmHg (p=0.01). Furthermore, the ability of CVP to stratify risk for development of WRF was apparent across the spectrum of systemic blood pressure, pulmonary capillary wedge pressure, cardiac index (CI), and estimated glomerular filtration rates. Hence, the study concluded that venous congestion is the most important hemodynamic factor driving WRF in decompensated patients with advanced heart failure (Mullens, Abrahams et al. 2009).
1.11.2 Mechanisms of worsening renal function in the face of circulatory congestion

The notion of renal impairment driven by poor cardiac output has always been the underlying theory in the context of circulatory congestion. However, this theory has been challenged by few clinical trials depicting the presence of venous congestion to be the root source of the problem. Venous congestion will give rise to an increase of central venous pressure as well as in right atrial pressure. This will also trigger the bulging of the inter-ventricular septum towards the left ventricle causing some impairment in its function such as restriction to ventricular filling as a response to physiologic stress. Right heart function will produce some feedback mechanism to the renal veins resulting in an increased in renal vein pressure and thereby causing a decreased in renal filtration (Figure 14). In Figure 15, the difference in glomerular net filtration pressure is shown between a normal individual and a patient with increased RAP. As a result from poor glomerular-capillary hydrostatic pressure in patients with poor RAP, the net filtration pressure was only 4 mmHg as compared with normal RA.
pressure which is 14 mmHg. This figure demonstrated the importance of RAP in renal circulation.

**Figure 15 Impact of venous congestion on glomerular net filtration pressure**

An illustration of the afferent and efferent pressures at a glomerular capillary in a patient with normal hemodynamics and a patient with increased right atrial (RA) pressure and venous congestion. $P_{BC} =$ hydrostatic pressure in Bowman’s capsule; $P_{GC} =$ glomerular capillary hydrostatic pressure; GC = oncotic pressure in glomerular capillaries.


In the normal condition, 85% of the total plasma volume resides in the venous circulation; and only 15% is maintained in the arterial circuit. The primary regulation of renal sodium and water excretion and, thus, body fluid homeostasis, is modulated by the smaller arterial circulation, enabling the system responsible for the perfusion of the body’s vital organs to respond to small changes in body fluid volume (RW, 2006).

Arterial hypoperfusion inactivates the high pressure baroreceptors in the aortic arch and coronary sinus, attenuates the tonic inhibition of afferent parasympathetic signals to the central nervous system, and enhances sympathetic efferent tone, with subsequent activation of the RAAS and non-osmotic release of AVP (RW, 2006)
In the kidney, increased angiotensin II causes renal efferent arteriolar vasoconstriction, resulting in decreased renal blood flow and increased filtration fraction. Together with renal nerve stimulation, the increased peritubular capillary oncotic pressure and reduced peritubular capillary hydrostatic pressure augment sodium reabsorption in the proximal tubule. Angiotensin II also directly stimulates proximal sodium reabsorption by activating sodium bicarbonate co-transporters and apical sodium-hydrogen exchangers (RW, 1990). Finally, angiotensin II promotes aldosterone secretion, which boosts sodium reabsorption in the distal nephron (RW, 2006).

Importantly, increased proximal sodium reabsorption decreases distal sodium and water delivery, stimulating macula densa cells to increase synthesis of renin that further amplifies neurohormonal activation (Castrop H, 2004). Enhanced renal sodium and water reabsorption predominantly fills the compliant venous circulation, increasing CVP and atrial pressures. Normally, an increase in atrial pressure suppresses AVP release and enhances water diuresis, decreases renal sympathetic tone, and augments natriuretic peptide secretion. In patients with HF, these atrial–renal reflexes are overwhelmed by neurohormonal activation, evidenced by persistent renal sodium and water retention despite elevated atrial pressures (RW, 2006). Transmission of venous congestion to the renal veins further impairs the glomerular filtration rate (GFR) (Fig. 15).

The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, right atrial pressure emerged as the only hemodynamic variable correlated with baseline renal function, an independent predictor of mortality and HF hospitalization (Nohria, Hasselblad et al. 2008).
Chapter II – Research aims and hypothesis

In the clinical setting where attending physicians manages patients with acute onset of heart failure or worsening of heart failure, the mainstay in the management is the administration of diuretics. Patients who are diagnosed as having chronic stable heart failure are closely followed up in the programmed care heart failure or heart function clinic and are treated with evidence-based heart failure medications. This include beta blockers, angiotensin converting enzyme inhibitor or ACEI, or angiotensin receptor blocking agent (ARB), mineralocorticoids receptor antagonist (MRA), and finally, the use of diuretics such as furosemide and thiazides. These agents are very potent in treating patients with acute onset of heart failure. Patients who are given these medications are not necessarily stable in the sense that a little alteration of the patient’s health would require adjustments in the intake of these medications. Worried about the effects on the kidneys sometimes put the clinician in a dilemma of not giving the appropriate regimen.

Not many published papers have demonstrated the relationship of cardiac and renal systems affecting one another. The balance in their management often results in an injury to one organ or sometimes to both. The question of which comes first is the issue. Almost all patients with a renal disorder will eventually have a cardiac compromise. On the other hand, almost all patients with heart failure will eventually have kidney impairment. Although prior studies on acute heart failure have supported the relationship of renal function using serum creatinine and estimated glomerular filtration rate with either central venous pressure or right atrial pressure, none have use the right ventricular systolic pressure. We therefore thought of establishing the relationship of renal function with right ventricular systolic pressure, since this parameter is
readily available in the routine echocardiographic examination. However, in the absence of tricuspid regurgitation, estimation of the inferior vena cava would be critically unavailable. However, these mechanisms for renal impairment have not been explored in patients with chronic stable HF. Therefore, the objective of our study was to correlate right ventricular systolic pressure and N-Terminal pro-Brain Natriuretic Peptide to renal function represented by estimated glomerular filtration rate and serum creatinine in patients with chronic stable HF. Using statistical analysis, we hoped to establish the relationship of RVSP and NT-proBNP to renal impairment.
Chapter III - Methodology

3.1 Study population

We reviewed 246 patients diagnosed with chronic stable HF followed in a HF clinic at St. Michael’s Hospital from September 2008 to October 2013. These patients signed a Research Ethics Board approved consent form prior to data collection. Basic demography was collected and a physical examination was performed by the qualified investigator. Further review of the patient medical history included clinic chart and hospital electronic records were such information as age, sex, race, blood pressure, weight and height were taken. Comorbidities were also captured. Of these 246 patients, one patient withdrew because of busy follow-up schedules with other medical professional. Hence, echocardiogram was not done for this patient.

During the enrollment visit, the patient’s vital signs were obtained, which include systolic and diastolic blood pressure measured by millimeters of mercury, heart rate per minute, as well as weight in pounds. In order to get an accurate blood pressure reading, the patient was asked to sit relaxed on a chair for at least 10 minutes. An appropriate size blood pressure cuff was wrapped on the patient’s arm. An electronic blood pressure machine that is regularly calibrated was used in this study.

Diagnostic test results including an echocardiogram and blood tests such as NT-proBNP, serum sodium, potassium, creatinine, estimated, blood urea nitrogen, chloride, and bicarbonate were also determined. Estimated glomerular filtration rate was calculated using the modified renal diabetic diet calculation by Modified Diet in Renal Disease (MDRD) equations (Colin J. Petrie 2008).
There were three patients whose echocardiograms were not performed here are St. Michael’s Hospital. A total of 242 patient’s echocardiograms were reviewed. We group these patients based on LVEF. Those patients whose LVEF was more than 40% were labeled as Heart Failure with Preserved Ejection Fraction (HFpEF) and those patients whose LVEF was equal or less than 40% were labeled as Heart Failure with Reduced Ejection Fraction (HFrEF).

The American Society of Echocardiography (ASE) released its mandate in 2010 on the review of the right heart quantification. Patients who were enrolled earlier than 2010 had incomplete reviews based on the ASE recommendation in 2010 since there were no standardized methods of capturing these images at that time. We therefore grouped those patients enrolled between the period 2010 and 2013. We have 113 patients enrolled during this period. Right atrial pressure, left atrial volume index, and left ventricular diastolic indices were captured in this group of patients. We performed statistical analysis to explore relationships with each variable. A flow diagram on how the enrollment, data collection, and echocardiographic review were made below (Figure 16).
3.2 Signs and symptoms of heart failure

Symptoms of heart failure were identified in each of the subject. These included shortness of breath at minimal exertion, shortness of breath at moderate exertion, shortness of breath at rest, paroxysmal nocturnal dyspnea, orthopnea, and fatigue. Signs of congestive heart failure such as increased jugular venous pressure, pulmonary rales, S₃ gallop, pulmonary edema, bipedal edema, and heart murmurs were also determined.
3.3 Limitation of physical activities based on New York Heart Association Classification

New York Heart Association Classification (NYHA) was determined in each of the patients seen on the day of the visit. Based on the classification according to the Heart Failure Society of America: Class I, there is no limitation of physical activity, ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath); Class II (Mild), there is slight limitation of physical activity, comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea; Class III (Moderate), there is marked limitation of physical activity, comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea; and Class IV (Severe), there is unable to carry out any physical activity without discomfort, symptoms of cardiac insufficiency at rest, and if any physical activity is undertaken, the discomfort is increased (Hunt, Baker et al. 2001).

3.4 Co-morbidities

In the medical history of each patient, we identified the presence or absence of coronary artery disease (CAD) which include anginal symptoms and myocardial infarction (MI); we also identified patients with valvular heart disease, and those who underwent surgical procedures such as valvular surgery, coronary artery bypass graft (CABG) surgery, and percutaneous transluminal coronary angioplasty (PTCA). The frequency of risk factors and relevant comorbid conditions, including hypertension, diabetes mellitus, dyslipidemia, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, stroke, kidney disease, and ethanol consumption, were also determined. Patient’s smoking history were also determined.
3.5 Medications

The medications that the patients were prescribed for treatment of HF were recorded; these include diuretics, digitalis, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blocker (ARB), beta-blockers, and aldosterone antagonists. In addition, the use of other medications such as acetylsalicylic acid, statins, calcium channel blockers, antiarrythmias, and coumadin.

3.6 Review of the two-dimension echocardiogram

We reviewed again the video clips and defined other parameters for LV diastolic function. We reviewed closest available echocardiogram to the enrollment date for each patient. Parameters obtained included the left atrial volume indexed (LAVI), for body surface area using biplane area-length method. In order to obtain these parameters we used the on-line calculator Cardiomath with permission from the creator Dr. Chi-Ming Chow of St. Michael’s Hospital. Other parameters were mitral valve E (early diastolic) velocity, mitral valve A (late diastolic) velocity, to calculate the E/A ratio. Furthermore, we obtained the mitral valve deceleration time. We also obtained mitral valve septal or medial e’, mitral valve lateral e’ using tissue Doppler, and then calculated the mitral valve E/e’ medial ratio as well as the mitral valve lateral E/e’ ratio.

3.7 LAVI measurement

We reviewed LAVI and left ventricular diastolic indices of 113 subjects enrolled from 2010 to 2013. LA size which is measured at the end-ventricular systole (maximum LA size). Precautions were taken in order not to foreshortening the measurement. Planimetry was
performed, excluding the LA confluences of the pulmonary veins and the LA appendage. The length (L) remained the LA long-axis length determined as the distance of the perpendicular line measured from the middle of the plane of the mitral annulus to the superior aspect of the LA. In the area-length formula, the length was measured in both the 4- and 2-chamber views and the shortest of these 2 length measurements was used in the formula. $A_1$ is defined as the maximum planimetered LA area in apical 4-chamber view, $A_2$ is the maximum planimetered LA area in apical 2-chamber view. The formula is as follows:

$$\text{LA volume} = \frac{8}{3} \sqrt[3]{A_1 \times A_2} / L \; \text{or} \; (0.85) \times \frac{(A_1 \times A_2)}{L} \; \text{(corrected for BSA)}$$

The reference ranges of LAVI are as follows: normal is between 16 and 28 mL/m$^2$, mildly abnormal is between 29 and 33 mL/m$^2$, moderately abnormal is between 34 and 39 mL/m$^2$, and severely abnormal is more than or equal to 40 mL/m (Lester, Ryan et al. 1999, Lang, Bierig et al. 2005, Sade, Gulmez et al. 2007).

### 3.7.1 Estimation of LA pressure

We reviewed the e prime ($e'$) by tissue Doppler imaging (TDI) of the septal and lateral sides of the mitral annulus. We also obtained the average $e'$ velocity from the septal and lateral sides of the mitral annulus, then we calculated for the $E/e'$ ratio. It is worth mentioning that because septal $e'$ velocity is usually lower than lateral $e'$ velocity, the $E/e'$ ratio using septal signals is usually higher than the ratio derived by lateral $e'$, and the different cutoff values should be applied on the basis of age, as well as $e'$ location. $E/e'$ ratio < 8 is usually associated with normal LV filling pressures (PCWP < 15 mmHg), while a ratio > 15 is associated with increased filling pressures (PCWP > 15 mmHg). Between 8 and 15, there is a gray zone with overlapping of values for filling pressures (Sherif F. Nagueh February 2009).
3.7.2 Mitral inflow - mitral valve E velocity, mitral valve A velocity, E/A ratio, deceleration time

The mitral valve E and A velocities were determined using the Pulsed-wave echocardiography. Primary measurements of mitral inflow include the peak early filling (E wave) and late diastolic filling (A wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity derived by placing the PW sample volume at the tip of the mitral leaflets in apical four chamber view.

3.7.3 Correlation of renal function with LAVI and mitral inflow

We explored the relationships of LAVI and left ventricular diastolic indices with renal function by performing univariate linear regression analysis using eGFR and sCr as the outcome variables while LAVI and mitral inflow as the predictors.

3.7.4 Correlation of left atrial size and pressure, LV diastolic function with RVSP, Log NT-proBNP, and LVEF

We looked at the association of the left atrial size by performing linear regression analysis between the outcome variable LAVI and the predictors RVSP, Log NT-proBNP, and LVEF (Table 9). We also looked at the association of the left atrial pressure represented by E/e’ medial and E/e’ lateral and the left ventricular diastolic function represented by E/A ratio and deceleration time with the same predictors.

3.8 Measurements of the left ventricular ejection fraction

More importantly, we reviewed the left ventricular ejection fraction of each subject. There are common methods used at the center in measuring LVEF: Qualitative measurement such as the
“eyeballing’ or visual estimation, and the quantitative measurement such as the Quinones and Dumesnil methods, and the Biplane Simpson’s method. Although “eye balling” is very subjective, the reader’s technical and clinical experience are required in order to obtain more accurate LVEF estimation. Simpson’s biplane method was further improved with the use of contrast agent.

3.8.1 Stratification of LVEF based on ejection fraction

Subjects with ejection fraction (EF) of more than 40% was grouped to HFpEF, and subjects with EF of equal or less than 40% was grouped to heart failure with reduced ejection fraction. We performed descriptive statistics for each group.

3.8.2 Linear regression analysis for HFpEF and HFrEF

Univariate linear regression analysis was performed in these two groups. Renal function eGFR and sCr as the outcome variables while RVSP, Log NT-proBNP, and LVEF as the predictor variables.

3.9 Measurement of the right heart function parameters

3.9.1 Right atrial pressure

The ASE right heart quantification update in 2010 includes the routine evaluation of right heart function (Rudski, Lai et al. 2010). We followed the suggested way of reading RA pressure which is the specific values of RAP rather than ranges should be used. The two most important parameters are the size and collapsibility of IVC. IVC diameter \( \leq 2.1 \) cm that collapses \( >50\% \)
with a sniff suggests normal RA pressure of 3 mm Hg (range, 0-5 mm Hg), whereas IVC diameter > 2.1 cm that collapses < 50% with a sniff suggests high RA pressure of 15 mm Hg (range, 10-20 mm Hg). In scenarios in which IVC diameter and collapse do not fit this pattern, an intermediate value of 8 mm Hg (range, 5-10 mm Hg) was used or. Other indices of increased RA pressure are dilated right atrium, deviation of the atrial septum to the left atrium, was integrated to downgrade or upgrade to the normal or high values of RA pressure (Rudski, Lai et al. 2010).

3.9.2 The right ventricular systolic pressure

Right ventricular systolic pressure (RVSP) can be estimated by measuring the TR jet maximum velocity by continuous wave (CW) spectral Doppler. If there is no significant stenosis at the right ventricular outflow tract, or the pulmonic valve, the RVSP is equivalent to the systolic pulmonary artery pressure (SPAP).

Normal resting values are usually defined as a peak TR gradient of 2.8 to 2.9 m/s or a peak systolic pressure of 35 to 36 mmHg, assuming an RA pressure of 3 to 5 mmHg. SPAP may increase with age and increasing body surface area and this should be considered when estimations are at the upper limits of normal. Some cardiologists who care for patients with congenital heart disease will consider SPAP greater than two thirds of the systemic blood pressure as indicative of severe pulmonary hypertension (Dumesnil, Dion et al. 1995, Rudski, Lai et al. 2010).
RVSP = \(4(\text{TR V}_{\text{Max}})^2 + \text{RA pressure}\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR V(_{\text{Max}})</td>
<td>TR Max Jet Velocity (m/sec)</td>
</tr>
<tr>
<td>RA Pressure</td>
<td>Choose between 3, 8, or 15 mmHg, or other (mmHg)</td>
</tr>
<tr>
<td>RVSP</td>
<td>Right ventricular systolic pressure (mmHg)</td>
</tr>
</tbody>
</table>

3.10 Univariate and multivariate linear regression analysis for eGFR and sCr with RVSP, Log NT-proBNP, and LVEF

To confirm if RVSP and Log NT-proBNP can predict renal impairment, we performed univariate linear regression analysis using eGFR and sCr as the outcome variable and RVSP and Log NT-proBNP as the predictors. We performed similarly with LVEF as the outcome variable contradicting relationship with renal impairment.

3.11 Logistic regression analysis of RVSP and NT-proBNP to eGFR and sCr

We performed logistic regression analysis using the median of RVSP and NT-proBNP to eGFR and sCr and obtained the odds ratio, confidence interval, and p values.

3.12 Research Ethics Board approval

The study was approved by the St. Michael’s Hospital Research Ethics Board. Informed consent was signed by each patients enrolled into the study.
3.13 Statistical analysis

Patient characteristics are presented with values of mean ± standard deviation, blood test and echocardiographic reports were also presented with mean ± standard deviation as well as median and interquartile ranges. Other data reported as the percentage of patients where indicated. Univariate and multivariate linear regression as well as binary logistic regression were performed using SAS Enterprise Guide 6.1 and R version 2.15.1 statistical softwares. A full model was constructed including the exposure and the outcome variables. We performed log transformation for variable NT-proBNP in order to achieve linearity. From the final model, we obtained odds ratios (OR) and 95% confidence intervals (CI) as well as p values. P values of ≤ 0.05 were accepted as statistically significant.
Chapter IV – Results

4.1 Basic demography, signs and symptoms, co-morbidities, and NYHA classifications

We have found that the mean age was 70 ± 13 years, 72% (177) were males, systolic blood pressure 121 ± 20 mmHg (Table 1). The majority of the study patients were Caucasian comprising 67%, followed by Chinese at 19%, South Asian 9%, and Black 5% (Table 2). Majority of the patients was classified as NYHA Class II (66%), followed by Class III (33%), Class IV (0.8%) and NYHA Class I (1%) (Table 1).

Table 1 Demography, Race, and NYHA classification

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean ± SD years</strong></td>
<td>70 ± 13</td>
</tr>
<tr>
<td>Male</td>
<td>177 (72%)</td>
</tr>
<tr>
<td>SBP</td>
<td>121 ± 20</td>
</tr>
<tr>
<td>DBP</td>
<td>67 ± 13</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>166 (67%)</td>
</tr>
<tr>
<td>Black</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>South Asian</td>
<td>42 (9%)</td>
</tr>
<tr>
<td>Chinese</td>
<td>46 (19%)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>162 (66%)</td>
</tr>
<tr>
<td>III</td>
<td>82 (33%)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>
We found that majority of the patient had shortness of breath at moderate exertion (82%), followed by shortness of breath at minimal exertion (43%), and then fatigue (58%), orthopnea (10%), shortness of breath at rest (9%), and finally paroxysmal nocturnal dyspnea (5%) (Table 2). The most common sign of heart failure in this study population was leg edema comprising 39%, followed by increased jugular venous pressure at 22%, then heart murmurs at 15%, rales at 8%, S₃ Gallop at 2%, and finally pulmonary edema at 1%. (Table 2)

**Table 2 Symptoms and signs of heart failure**

<table>
<thead>
<tr>
<th>Symptoms of Heart Failure</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of Breath at Minimal Exertion</td>
<td>105 (43)</td>
</tr>
<tr>
<td>Shortness of Breath at Moderate Exertion</td>
<td>202 (82)</td>
</tr>
<tr>
<td>Shortness of Breath at Rest</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Paroxysmal Nocturnal Dyspnea</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>25 (10)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>142 (58)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs of Heart Failure</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased jugular venous pressure</td>
<td>54 (22)</td>
</tr>
<tr>
<td>Murmurs</td>
<td>36 (15)</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>97 (39)</td>
</tr>
<tr>
<td>Rales</td>
<td>20 (%)</td>
</tr>
<tr>
<td>S₃ gallop</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>
Co-morbidities for HF include hypertension (66%), diabetes mellitus (44%), dyslipidemia (60%), chronic obstructive pulmonary disease (11%), chronic kidney disease (14%). Additionally, 56% were non-smokers, 31% were previous smokers, and 13% had no smoking history. (Table 3)

Table 3 Concurrent diseases

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>162 (66)</td>
</tr>
<tr>
<td>Coronary Artery Bypass Graft / Percutaneous Transluminal Coronary Angioplasty</td>
<td>75 (31)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>146 (60)</td>
</tr>
<tr>
<td>Diabetes Mellitus II</td>
<td>107 (44)</td>
</tr>
<tr>
<td>Angina</td>
<td>95 (39)</td>
</tr>
<tr>
<td>Bronchial Asthma</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>102 (42)</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>38 (16)</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>27 (11)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>34 (14)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>69 (28)</td>
</tr>
</tbody>
</table>
Table 4 Medications

<table>
<thead>
<tr>
<th>Medications</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>221 (91)</td>
</tr>
<tr>
<td>Angiotensin Converting Enzyme Inhibitors</td>
<td>164 (67)</td>
</tr>
<tr>
<td>Angiotensin Receptor blockers</td>
<td>55 (22.4)</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>53 (22)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>228 (93)</td>
</tr>
<tr>
<td>Thiazide</td>
<td>33 (13)</td>
</tr>
<tr>
<td>Statins</td>
<td>167 (68)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>40 (16)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>56 (23)</td>
</tr>
<tr>
<td>Oral Hypoglycemic Agents</td>
<td>70 (29)</td>
</tr>
<tr>
<td>Insulin</td>
<td>35 (14)</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>28 (11)</td>
</tr>
<tr>
<td>Anti-platelet</td>
<td>115 (47)</td>
</tr>
</tbody>
</table>

4.2 Medications

We found that most of the patients were prescribed diuretics specifically furosemide at 93.1% as compared to thiazides which was only 13.5%. Beta-blocker were prescribed at 90.2%, while ACE inhibitors were used more frequently than angiotensin receptor blockers (ARB) at 66.9%
and 22.5% respectively. Statins 68.2%, anti-platelet agent at 46.9%, coumadin at 40.4%, calcium channel blockers at 21.6%, digitalis at 16.3%, vasodilators at 11.8, anti-arrhythmic agents at 11.4%, and oral hypoglycemic agents at 28.6% versus insulin at 14.3% (Table 4).

### 4.3 Echocardiographic and laboratory

Out of 246 patients, 242 of the patients had echocardiogram available at St. Michael’s Hospital. The average time in which echocardiogram was performed from study enrollment was 165 days ± 202, median was 89 days (IQR 25, 217). There were three patients without echocardiogram available at St. Michael’s Hospital. One patient withdrew the consent prior to the echocardiogram at St. Michael’s Hospital.

There were 43 patients whom RVSP was not measured because of the absence of TR jet velocity. There were 6 patients whose septal or medial e’ prime and 7 patients whom lateral e’ was not measured because of mitral valve prosthesis. There were 4 patients whom deceleration time could not distinguish because of fused E and A flow velocities. There were 78 patients whom MV A velocity was not measured due to cardiac arrhythmia mostly because of atrial fibrillation.

The mean LVEF was 40.74% ± 15, median was 40 (IQR 27, 55); the mean RVSP was 42.5 mmHg ± 15, median was 40 (IQR 32, 51); the mean NT-proBNP was 3379.6 pg/ml ± 4758.9, median was 1614 pg/ml; sCr was 123.4 ± 73 umol/L, median was 104 (IQR 83, 139); and eGFR was 59 ml/min/1.73m² ± 27, median was 58 (IQR 39, 76) (Table 5).

Other laboratory findings revealed mean blood urea nitrogen of 10.3 ± 6.6 mmol/L, median was 8.4 (IQR 5.9, 12.4); the mean serum sodium of 137.5 ± 3 mmol/L, median was 138 (IQR 136,
the mean serum potassium of 4.3 ± 0.5 mmol/L, median was 4.3 (IQR 4, 4.6); the mean serum chloride of 102 ± 4.5 mmol/L, median was 102 IQR 100, 105); and the mean serum bicarbonate of 27.4 ± 2.9 mmol/L, median was 27 (IQR 26, 29). (Table 5)

Table 5 LVEF, RVSP, and Blood tests

<table>
<thead>
<tr>
<th>Blood Test</th>
<th>Mean, SD</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>40.74 % ± 15</td>
<td>40 (27, 55)</td>
</tr>
<tr>
<td>RVSP</td>
<td>42.5 mmHg ± 15</td>
<td>40 (32, 51)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>3379.6 pg/mL ± 4758.9</td>
<td>1614 (702, 4130)</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>123.4 umol/L ± 73</td>
<td>104 (83,139)</td>
</tr>
<tr>
<td>estimated Glomerular Filtration Rate</td>
<td>59 ml/min/1.73m² ± 26</td>
<td>58 (39, 76)</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>10.3 mmol/L ± 6.6</td>
<td>8.4 (5.9, 12.4)</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>137.5 mmol/L ± 3.0</td>
<td>138 (136, 140)</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>4.3 mmol/L ± 0.5</td>
<td>4.3 (4, 4.6)</td>
</tr>
<tr>
<td>Serum Chloride</td>
<td>102 mmol/L ± 4.5</td>
<td>102 (100, 105)</td>
</tr>
<tr>
<td>Serum Bicarbonate</td>
<td>27.4 mmol/L ± 2.9</td>
<td>27 (26, 29)</td>
</tr>
</tbody>
</table>

NT-proBNP = N-terminal pro-B-type natriuretic peptide; LVEF = Left ventricular ejection fraction; RVSP = Right ventricular systolic pressure; mmHg = millimeter mercury; pg/mL = picogram per milliliter; umol/L = micromole per liter; mmol/L = millimole per liter
4.3.1 Linear regression analysis performed on eGFR and sCr with left atrial volume index and left ventricular diastolic indices

We tried to explore the relationships between the renal function and the left atrial volume index, as well as with left ventricular diastolic indices. It showed that only eGFR is associated with mitral valve deceleration time ($r^2 = 0.079$, $p = 0.003$) in the univariate linear regression analysis (Table 6), while sCr showed association not only with mitral valve deceleration time ($r^2 = 0.144$, $p < 0.001$) but also with mitral valve E velocity ($r^2 = 0.057$, $p = 0.01$), mitral valve E/e’ Lateral ($r^2 = 0.095$, $p = 0.001$), and mitral valve E/e’ average ($r^2 = 0.046$, $p = 0.02$) (Tables 6).
Table 6 Univariate linear regression analysis  $y = eGFR$

<table>
<thead>
<tr>
<th>Predictors</th>
<th>$r^2$</th>
<th>p values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA VI</td>
<td>0.001</td>
<td>0.738</td>
<td>-0.05</td>
<td>57.9</td>
</tr>
<tr>
<td>MV E velocity</td>
<td>0.027</td>
<td>0.082</td>
<td>-0.09</td>
<td>64.7</td>
</tr>
<tr>
<td>MV Deceleration time</td>
<td>0.079</td>
<td>0.003*</td>
<td>-0.09</td>
<td>74.2</td>
</tr>
<tr>
<td>MV A velocity</td>
<td>0.021</td>
<td>0.21</td>
<td>-0.13</td>
<td>64.6</td>
</tr>
<tr>
<td>E/A Ratio</td>
<td>0.000</td>
<td>0.97</td>
<td>0.13</td>
<td>55.2</td>
</tr>
<tr>
<td>MV e' (Lateral)</td>
<td>0.006</td>
<td>0.42</td>
<td>0.29</td>
<td>53.9</td>
</tr>
<tr>
<td>MV E/e' (Lateral)</td>
<td>0.0198</td>
<td>0.14</td>
<td>-0.58</td>
<td>63.4</td>
</tr>
<tr>
<td>MV e' (medial)</td>
<td>0.010</td>
<td>0.28</td>
<td>-0.48</td>
<td>59.3</td>
</tr>
<tr>
<td>MV E/e' (medial)</td>
<td>0.008</td>
<td>0.36</td>
<td>-0.21</td>
<td>60.1</td>
</tr>
<tr>
<td>MV E/e' average</td>
<td>0.016</td>
<td>0.19</td>
<td>-0.46</td>
<td>63.6</td>
</tr>
</tbody>
</table>

p value < 0.05*

LA VI = Left atrial volume index; MV = Mitral valve; E = Early; A = Late
Table 7 Univariate linear regression analysis \( y = sCr \)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>( r^2 )</th>
<th>p values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA VI</td>
<td>0.002</td>
<td>0.64</td>
<td>-0.21</td>
<td>138.4</td>
</tr>
<tr>
<td>MV E velocity</td>
<td>0.057</td>
<td>0.01*</td>
<td>0.42</td>
<td>82.2</td>
</tr>
<tr>
<td>MV Deceleration time</td>
<td>0.144</td>
<td>&lt; 0.001*</td>
<td>0.38</td>
<td>52.5</td>
</tr>
<tr>
<td>MV A velocity</td>
<td>0.013</td>
<td>0.33</td>
<td>0.34</td>
<td>108.7</td>
</tr>
<tr>
<td>E/A Ratio</td>
<td>0.002</td>
<td>0.696</td>
<td>4.0</td>
<td>127</td>
</tr>
<tr>
<td>MV e' (Lateral)</td>
<td>0.006</td>
<td>0.44</td>
<td>-0.9</td>
<td>136.9</td>
</tr>
<tr>
<td>MV E/e' (Lateral)</td>
<td>0.095</td>
<td>0.001*</td>
<td>4.02</td>
<td>81</td>
</tr>
<tr>
<td>MV e' (medial)</td>
<td>0.014</td>
<td>0.22</td>
<td>1.7</td>
<td>118.4</td>
</tr>
<tr>
<td>MV E/e' (medial)</td>
<td>0.0097</td>
<td>0.30</td>
<td>0.76</td>
<td>114.1</td>
</tr>
<tr>
<td>MV E/e' average</td>
<td>0.046</td>
<td>0.02*</td>
<td>2.47</td>
<td>90.6</td>
</tr>
</tbody>
</table>

p value < 0.05

LA VI = Left atrial volume index; MV = Mitral valve; E = Early; A = Late
4.3.2 Linear regression analysis performed on LAVI, E/A ratio, E/e’ medial and E/e’ lateral with RVSP, Log NT-proBNP, and LVEF

LAVI, E/e’ medial, E/e’ lateral and E/A ratio were all correlated with RVSP and Log NT-proBNP. However, no association was noted among LAVI, E/e’ medial, E/e’ lateral, and E/A ratio with LVEF (Table 8, 9, 10, and 11).

Table 8 Univariate linear regression analysis  \( y = \text{LAVI} \)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>( r^2 )</th>
<th>p values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVSP</td>
<td>0.19</td>
<td>&lt; 0.0001*</td>
<td>0.56</td>
<td>22.3</td>
</tr>
<tr>
<td>Log NT</td>
<td>0.07</td>
<td>0.005*</td>
<td>3.5</td>
<td>16.5</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.004</td>
<td>0.52</td>
<td>0.07</td>
<td>40.2</td>
</tr>
</tbody>
</table>

p value < 0.05*

Table 9 Univariate linear regression analysis  \( y = \text{E/e’ medial} \)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>( r^2 )</th>
<th>p values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVSP</td>
<td>0.07</td>
<td>0.008*</td>
<td>0.22</td>
<td>10.96</td>
</tr>
<tr>
<td>Log NT</td>
<td>0.04</td>
<td>0.03*</td>
<td>1.64</td>
<td>6.47</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.03</td>
<td>0.05</td>
<td>-0.13</td>
<td>24</td>
</tr>
</tbody>
</table>

p value < 0.05*
Table 10 Univariate linear regression analysis  \( y = E/e' \) lateral

<table>
<thead>
<tr>
<th>Predictors</th>
<th>( r^2 )</th>
<th>p values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVSP</td>
<td>0.09</td>
<td>0.003*</td>
<td>0.14</td>
<td>6.4</td>
</tr>
<tr>
<td>Log NT</td>
<td>0.05</td>
<td>0.02*</td>
<td>1.06</td>
<td>3.9</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.006</td>
<td>0.42</td>
<td>-0.03</td>
<td>13.2</td>
</tr>
</tbody>
</table>

p value < 0.05*

Table 11 Univariate linear regression analysis  \( y = E/A \) Ratio

<table>
<thead>
<tr>
<th>Predictors</th>
<th>( r^2 )</th>
<th>p values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVSP</td>
<td>0.18</td>
<td>0.0006*</td>
<td>0.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Log NT</td>
<td>0.10</td>
<td>0.005*</td>
<td>0.25</td>
<td>-0.354</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.0007</td>
<td>0.82</td>
<td>-0.002</td>
<td>1.6</td>
</tr>
</tbody>
</table>

p value < 0.05*

4.3.3 Subjects stratified by LVEF

We grouped the patients into two, those LVEF above 40 % and used the term HFP EF and those patients with LVEF equal or lower than 40% and called them HFrEF. There were 118 HFP EF and 124 HFrEF (Table 12).
### Table 12 Summary statistic stratified by LVEF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heart failure with preserved ejection fraction (HFpEF) n = 118</th>
<th>Heart failure with reduced ejection fraction (HFrEF) n = 124</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD Median (IQR)</td>
<td>mean ± SD Median (IQR)</td>
</tr>
<tr>
<td>RVSP</td>
<td>41 mmHg 14 38 (29, 49)</td>
<td>39.8 mmHg 13.6 38 (29, 49)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>3127.7 pg/mL 3729.6 1699.5 (489, 4786)</td>
<td>4436.8 pg/mL 5306.8 2612 (1054, 4694)</td>
</tr>
<tr>
<td>LVEF</td>
<td>53.7% 6.9 55 (49, 55)</td>
<td>28.4% 8.2 30 (20, 35)</td>
</tr>
<tr>
<td>eGFR</td>
<td>51.5 ml/min/1.73m² 25 48 (34, 69)</td>
<td>60 ml/min/1.73m² 24.6 63 (41, 75)</td>
</tr>
<tr>
<td>sCr</td>
<td>139.1 umol/L 95.1 116 (89, 163)</td>
<td>120 umol/L 59.1 100 (80, 236)</td>
</tr>
<tr>
<td>RAP</td>
<td>7.4 5.1 5.5 (3, 15)</td>
<td>7.1 mmHg 4.8 8 (3, 8)</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate; RVSP = Right ventricular systolic pressure; sCr = Serum creatinine; HFpEF = Heart failure with preserved ejection fraction; HFrEF = Heart failure with reduced ejection fraction; LVEF = Left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RAP = Right atrial pressure
### Table 13 Linear regression analysis stratified by LVEF

<table>
<thead>
<tr>
<th>Variables</th>
<th>$r^2$</th>
<th>P values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR vs RVSP</td>
<td>0.1066</td>
<td>0.0011*</td>
<td>-0.6815</td>
<td>83.82</td>
</tr>
<tr>
<td>sCr vs RVSP</td>
<td>0.0721</td>
<td>0.0078*</td>
<td>1.76</td>
<td>56.06</td>
</tr>
<tr>
<td>eGFR vs Log NT-proBNP</td>
<td>0.21</td>
<td>&lt; 0.0001*</td>
<td>-8.2</td>
<td>114.7</td>
</tr>
<tr>
<td>sCr vs Log NT-proBNP</td>
<td>0.12</td>
<td>0.0002*</td>
<td>18.3</td>
<td>-2.27</td>
</tr>
<tr>
<td>eGFR vs LVEF</td>
<td>0.0097</td>
<td>0.2898</td>
<td>0.3450</td>
<td>37.71</td>
</tr>
<tr>
<td>sCr vs LVEF</td>
<td>0.0130</td>
<td>0.2188</td>
<td>-1.2017</td>
<td>192.95</td>
</tr>
</tbody>
</table>

### Univariate linear regression analysis for HFrEF

<table>
<thead>
<tr>
<th>Variables</th>
<th>$r^2$</th>
<th>P values</th>
<th>B coefficient</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR vs RVSP</td>
<td>0.0179</td>
<td>0.1734</td>
<td>-0.2192</td>
<td>69.67</td>
</tr>
<tr>
<td>sCr vs RVSP</td>
<td>0.0236</td>
<td>0.1178</td>
<td>0.6670</td>
<td>92.19</td>
</tr>
<tr>
<td>eGFR vs Log NT-proBNP</td>
<td>0.15</td>
<td>&lt; 0.0001*</td>
<td>-9.0</td>
<td>129.6</td>
</tr>
<tr>
<td>sCr vs Log NT-proBNP</td>
<td>0.14</td>
<td>&lt; 0.0001*</td>
<td>22.6</td>
<td>-51.5</td>
</tr>
<tr>
<td>eGFR vs LVEF</td>
<td>0.0025</td>
<td>0.5803</td>
<td>-0.1743</td>
<td>65.75</td>
</tr>
<tr>
<td>sCr vs LVEF</td>
<td>0.0007</td>
<td>0.7745</td>
<td>0.2330</td>
<td>114.32</td>
</tr>
</tbody>
</table>

p value is < 0.05*

eGFR = estimated glomerular filtration rate; RVSP = Right ventricular systolic pressure; sCr = Serum creatinine; HFrEF = Heart failure with reduced ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide
4.4 HFpEF and HFrEF linear regression analysis for eGFR and sCr with RVSP, Log NT-proBNP, and LVEF

We performed linear regression analysis in this cohort of patients. In the HFpEF, the correlation of eGFR and sCr with RVSP and Log NT-proBNP showed significant p value of less than 0.05 while with LVEF did not. In the HFrEF, only the eGFR and sCr with Log NT-proBNP showed relationships (Table 13).

4.5 Linear regression analysis on eGFR and sCr with RVSP, Log NT-proBNP, and LVEF

In order for us to see the relationships between renal function and cardiac filling pressure, we performed univariate linear regression using eGFR and sCr as the outcome variables, while RVSP, Log NT-proBNP, and LVEF as the predictors. We conducted eGFR and sCr separately and found the following results:

It showed that eGFR was associated with RVSP ($r^2 = 0.04, p = 0.004$) and Log NT-proBNP ($r^2 = 0.16, p < 0.0001$). Also, sCr was associated with RVSP ($r^2 = 0.04, p = 0.005$) and Log NT-proBNP ($r^2 = 0.12, p < 0.0001$). On the other hand, there was no association between eGFR and LVEF ($r^2 = 0.004, p = 0.32$), and between sCr and LVEF ($r^2 = 0.0004, p < 0.77$) (Figure 17).
Figure 17 Linear regression plots

Linear regression analysis for eGFR with RVSP

$r^2 = 0.04$
$p = 0.004$
$\beta = -0.4$
$y$ intercept = 73.6

$r^2 = R$ square; $p = p$ value; $\beta$ = beta coefficient; eGFR = estimated glomerular filtration rate; RVSP = right ventricular systolic pressure; mm Hg = millimeters mercury; mL = milliliters; min = minute; m² = meter squared

Linear regression analysis for eGFR with LogNT

$r^2 = 0.16$
$p = <0.0001$
$\beta = -7.97$
$y$ intercept = 117.8

$r^2 = R$ square; $p = p$ value; $\beta$ = beta coefficient; eGFR = estimated glomerular filtration rate; Log NT = log transformed N terminal pro-brain natriuretic peptide; pg = picogram; mL = milliliters; min = minute; m² = meter squared
Figure 17 Linear Regression Plots (cont.)

Linear regression analysis for sCr with RVSP

\[ r^2 = 0.04 \]
\[ p = 0.005 \]
\[ \beta = 1.03 \]
\[ y \text{ intercept} = 81.4 \]

RVSP (mmHg)

sCr (umol/L)

\( r^2 \) = R square; \( p \) = p value; \( \beta \) = beta coefficient; RVSP = right ventricular systolic pressure; mm Hg = millimeters mercury; sCr = serum creatinine; umol = micromol; L = liter

Linear regression analysis for sCr with LogNT

\[ r^2 = 0.12 \]
\[ p = < 0.0001 \]
\[ \beta = 18.8 \]
\[ y \text{ intercept} = -14.8 \]

Log NT

sCr (umol/L)

\( r^2 \) = R square; \( p \) = p value; \( \beta \) = beta coefficient; sCr = serum creatinine; Log NT = log transformed N-Terminal pro-brain natriuretic peptide; pg = picogram; mL = milliliters; umol = micromol; L = liter
Figure 17 Linear regression plots (cont.)

Linear regression analysis for eGFR with LVEF

$r^2 = 0.004$
$p = 0.32$
$\beta = -0.11$
$y$ intercept = 63.3

cGFR (mL/min/1.73m²)

LVEF (%)

Linear regression analysis for sCr with LVEF

$r^2 = 0.0004$
$p = 0.77$
$\beta = 0.09$
$y$ intercept = 120.4

sCr (umol/L)

LVEF (%)

$r^2 = R$ square; $p = p$ value; $\beta = \beta$ coefficient; eGFR = estimated glomerular filtration rate; mL = milliliters; min = minute; m² = meter squared; LVEF = left ventricular ejection fraction; % = percent
4.6 Multilinear regression analysis of eGFR with cardiac pressures (with Log transformed NT-proBNP)

In the multiple linear regression analysis, the model showed an r square of 0.19 with significant p value of < 0.0001. The outcome variable eGFR was 140.2 ml/min/1.73m² and the predictor variables showed the following beta coefficient after adjustments with other covariates: RVSP (β-coefficient -0.17 p = 0.16); Log NT-proBNP (β-coefficient -8.3, p < 0.0001); LVEF (β-coefficient -0.3, p = 0.008) (Table 14).

Table 14 Multilinear regression analysis with log transformed NT-proBNP (eGFR = y intercept

<table>
<thead>
<tr>
<th>Number of Observations</th>
<th>246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Observations used</td>
<td>202</td>
</tr>
<tr>
<td>Number of observations with missing values</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R-square</th>
<th>0.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>y intercept (eGFR)</td>
<td>140.2 mL/min/1.73m²</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RVSP</td>
<td>-0.17</td>
<td>0.16</td>
</tr>
<tr>
<td>Log NT-proBNP</td>
<td>-8.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.3</td>
<td>0.008</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate; RVSP = right ventricular systolic pressure; Log NT-proBNP = log transformed N-terminal pro-brain natriuretic peptide; LVEF = left ventricular systolic pressure.
4.7 Residuals by regression for eGFR, with RVSP, Log NT-proBNP, and LVEF

In order to evaluate the multilinear regression model, we analyzed the residual plots for the dependent variable eGFR with the three independent variables RVSP, log transformed NT-proBNP, and the LVEF. It revealed that there were no definite patterns that can be described with all of the three plots (Figure 18), which indicates good fit for the multilinear regression model.

Figure 18 Residuals by regression for eGFR with RVSP, LogNT-proBNP, and LVEF

![Residual plots](image)

RVSP = right ventricular systolic pressure; logNT = log transformed N-terminal pro-brain natriuretic peptide; LVEF = left ventricular systolic pressure

4.8 Multilinear regression analysis of sCr with cardiac pressures (with Log transformed NT-proBNP)

In the multiple linear regression analysis, the model showed an r square of 0.14 with significant p value of 0.0000. The outcome variable sCr was 69.7 umol/L and the predictor variables showed the following beta coefficient after adjustments with other covariates: RVSP (β-
coefficient 0.5 p = 0.15); Log NT-proBNP (β-coefficient 19.9, p < 0.0001); LVEF (β-coefficient 0.54, p = 0.11) (Table 15).

Table 15 Multilinear regression analysis with log transformed NT-proBNP (sCr = y intercept)

<table>
<thead>
<tr>
<th>Number of Observations</th>
<th>246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Observations used</td>
<td>202</td>
</tr>
<tr>
<td>Number of observations with missing values</td>
<td>44</td>
</tr>
<tr>
<td>R-square</td>
<td>0.14</td>
</tr>
<tr>
<td>P value</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>y intercept (sCr)</td>
<td>69.7 umol/L</td>
<td>0.06</td>
</tr>
<tr>
<td>RVSP</td>
<td>0.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Log NT-proBNP</td>
<td>19.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.54</td>
<td>0.11</td>
</tr>
</tbody>
</table>

4.9 Multilinear regression analysis of eGFR with cardiac pressures (with NT-proBNP)

Similarly, in order to show the difference when NT-proBNP was not log transformed, we also performed the multiple linear regression analysis using the non-transformed NT-proBNP. The model showed an $r$ square of 0.10 with significant $p$ value of 0.0002. The outcome variable eGFR was 83.5 ml/min/1.73m$^2$ and the predictor variables showed the following beta
coefficient after adjustments with other covariates: RVSP (β-coefficient -0.3, p = 0.02); NT-proBNP (β-coefficient -0.001, p = 0.002); LVEF (β-coefficient -0.2, p = 0.08) (Table 16).

Table 16 Multilinear regression analysis with NT-proBNP (eGFR = y intercept)

<table>
<thead>
<tr>
<th>Number of Observations</th>
<th>246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Observations used</td>
<td>202</td>
</tr>
<tr>
<td>Number of observations with missing values</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R-square</th>
<th>0.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>y intercept (eGFR)</td>
<td>83.5 mL/min/1.73m²</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RVSP</td>
<td>-0.3</td>
<td>0.02</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>-0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.2</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* eGFR = estimated glomerular filtration rate; RVSP = right ventricular systolic pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; LVEF = left ventricular systolic pressure

4.10 Residuals by regression for eGFR with RVSP, NT-proBNP, and LVEF

In order to evaluate the multilinear regression model, we analyzed the residual plots for the dependent variable eGFR with the three independent variables RVSP, NT-proBNP, and the LVEF. It revealed that there were no definite patterns that can be described with RVSP and LVEF plots. However, there was a cluster of data along the left hand corner of in NT-proBNP plot which can indicate questionable fit for the multilinear regression model (Figure 19).
**Figure 19 Residuals by regression for eGFR with RVSP, NT-proBNP, and LVEF**

RVSP = right ventricular systolic pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; LVEF = left ventricular systolic pressure

### 4.11 Multilinear regression analysis of sCr with cardiac pressures (with NT-proBNP)

In this multiple linear regression analysis, the model showed an r square of 0.11 with significant p value of 0.0000. The outcome variable sCr was 63.2 umol/L and the predictor variables showed the following beta coefficient after adjustments with other covariates: RVSP ($\beta$-coefficient 0.7 p = 0.04); NT-proBNP ($\beta$-coefficient 0.004, p = 0.0001); LVEF ($\beta$-coefficient 0.37, p = 0.27) (Table 17).
Table 17 Multilinear regression analysis with NT-proBNP (sCr = y intercept)

<table>
<thead>
<tr>
<th>Number of Observations</th>
<th>246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Observations used</td>
<td>202</td>
</tr>
<tr>
<td>Number of observations with missing values</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R-square</th>
<th>0.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>y intercept (sCr)</td>
<td>63.2 umol/L</td>
<td>0.0048</td>
</tr>
<tr>
<td>RVSP</td>
<td>0.7</td>
<td>0.04</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.004</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.37</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*eGFR = estimated glomerular filtration rate; RVSP = right ventricular systolic pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; LVEF = left ventricular systolic pressure

4.12 Binary logistic regression analysis of right ventricular systolic pressure to renal function

We used the median values for RVSP, eGFR and sCr and performed binary logistic regression. We have found that those patients having RVSP of more than 40 mmHg would have a higher chance of having renal impairment [OR 2.0, CI 1.5 – 3.6, p = 0.01 (eGFR) and OR 2.6, CI 1.5 – 4.5, p = 0.001 (sCr)]. In contrast to patients with RVSP equal or less than 40 mmHg who are less likely to have renal impairment [OR 0.49, CI 0.28 – 0.86, p = 0.01 (eGFR) and OR 0.39, CI 0.22 – 0.60, p = 0.001 (sCr)]. (Figure 20)
4.13 Binary Logistic Regression Analysis of NT-proBNP to Renal Function

We performed logistic regression analysis using NT-proBNP with renal function. We used the median value of 1614 pg/ml for NT-proBNP, and we found that patients who have an NT-proBNP of 1614 pg/ml or more, are more likely to have renal impairment [OR 2.9, CI 1.7–4.8, p = 0.0001 (eGFR) and OR 3.3, CI 1.95–5.57, p < 0.0001 (sCr)]. While those who had NT-proBNP equal or lower than 1614 pg/ml had a lower chance of developing renal impairment [OR 0.35, CI 0.21-0.59, p = 0.001 (eGFR) and OR 0.30, CI 0.18-0.51, p < 0.0001 (sCr)]. (Figure 21)
4.14 Cohort of patients with RAP measurements

There were 113 subjects who had their echocardiogram performed during the period of 2010 and 2013. Out of this 113, four subjects had a very poor window that we were not able to determine the IVC. There were 54 subjects whose RAP was 3 mm Hg, 28 subjects had RAP of 8 mm Hg, and 27 subjects had RAP of 15 mm Hg. The mean RAP was 7.26 mm Hg ± 4.9, the mean LVEF was 40.53% ± 14.8, mean RVSP was 40.37 mm Hg ± 13.7, mean NT-proBNP was 3811.18 pg/ml ± 4647.34, mean serum creatinine was 129.13 ± 78.6, and finally, the mean eGFR was 55.96 ml/min/1.73m² ± 25.
The study by Guglin and her group demonstrated relationship of RAP with renal function. It is important to validate in our dataset this published result. Hence, we performed univariate linear regression analysis using RAP as the predictor variable, and eGFR and sCr as the outcome variables. The statistical analysis showed no correlation between eGFR and RAP ($r^2 = 0.007, p = 0.39, \beta = 0.40, \text{Intercept} = 52.6$). Similarly, there was also no correlation between sCr and RAP ($r^2 = 0.0004, p = 0.83, \beta = -0.32, \text{Intercept} = 130.8$).

Table 18 Left atrial volume index and left ventricular diastolic indices descriptive summary (n=113)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (±SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA VI</td>
<td>43.0 (±16.9)</td>
<td>39 (33, 51)</td>
</tr>
<tr>
<td>MV E velocity</td>
<td>94.9 (±44.9)</td>
<td>89.7 (65, 109)</td>
</tr>
<tr>
<td>MV Dec time</td>
<td>199.8 (±78.2)</td>
<td>190 (140, 230)</td>
</tr>
<tr>
<td>MV A velocity</td>
<td>71.2 (±29.4)</td>
<td>71.5 (45.5, 92.5)</td>
</tr>
<tr>
<td>E/A Ratio</td>
<td>1.5 (±1.0)</td>
<td>1.1 (0.8, 2)</td>
</tr>
<tr>
<td>MV e’ (Lateral)</td>
<td>9.0 (±6.6)</td>
<td>8.45 (6, 10.4)</td>
</tr>
<tr>
<td>MV E/e’ (Lateral)</td>
<td>11.9 (±6.1)</td>
<td>10.7 (7.8, 14)</td>
</tr>
<tr>
<td>MV e’ (medial)</td>
<td>5.9 (±5.4)</td>
<td>5.4 (4, 6.5)</td>
</tr>
<tr>
<td>MV E/e’ (medial)</td>
<td>18.9 (±10.2)</td>
<td>16.4 (12.6, 22)</td>
</tr>
<tr>
<td>MV E/e’ average</td>
<td>15.3 (±6.8)</td>
<td>13.7 (10.4, 20.2)</td>
</tr>
</tbody>
</table>

LA VI = Left atrial volume index; MV = Mitral valve; E = Early; A = Late
Chapter V – General Discussion

5.1 Confirmation of the research hypothesis

To our knowledge, this is one of the first studies in patients with chronic stable HF to demonstrate the correlation between eGFR and serum creatinine with RVSP and NT-proBNP. Higher RVSP and NT-proBNP are associated with renal insufficiency. On the other hand, LVEF does not correlate with renal function.

Our findings further show correlation when we stratified LVEF based on HFpEF and HFrEF. HFpEF group demonstrated that cardiac filling pressure is associated with renal function. However, in the HFrEF group, only the NT-proBNP was related to renal function. To date, there have been no publications in reference to these findings.

Furthermore, our data showed that LAVI, MV E/e’ medial, MV E/e’ lateral and LV diastolic function showed relationship with RVSP and Log NT-proBNP, but not with LVEF.

5.2 Renal function correlated with cardiac filling pressure

Our data analysis suggests that renal function represented by eGFR and sCr has a significant relationship with RVSP ($r^2 = 0.04$, $p = 0.004$, and $r^2 = 0.04$, $p = 0.005$, respectively) (Figure 17). Although the $r^2$ showed weak values, the hypothesis was clearly answered by these results.

No available publications regarding studies on RVSP in association with renal function to date. However, other cardiac filling pressures such as the CVP and the RAP have been studied.
These studies were mostly conducted in patients with acute heart failure rather than chronic heart failure.

In the study of Guglin and her colleague in 2011, they focused on the CVP rather than the RVSP and correlated with renal function. The question of which one is more important in the development of renal insufficiency: Was it because of the low cardiac output? Or was it because of the mere presence of elevated CVP. Guglin and her group conducted a study in 178 patients with ADHF. All of these patients underwent right heart catheterization for evaluation of HF. Also, they determined renal function by performing sCr in the blood and calculate for eGFR. The authors found significant relationship ($r = 0.27$, $p = 0.015$ and $r = 0.22$, $p = 0.001$, respectively). However, if one considers the $r^2$ in their result, it was also a weak one. Moreover, the authors have also found that there was no significant relationship between LVEF and renal function (Maya Guglin 2011) (Maya Guglin, 2011). The latter findings was consistent with the results presented in this paper, that the LVEF had no relationship with renal function {p values 0.32 (eGFR) and 0.77 (sCr)}. Again, these results demonstrated week relationships ($r^2 = 0.004$ and 0.0004, respectively).

Another study uses RAP instead of CVP in correlating with renal function. This was a sub-study from the ESCAPE trial. The authors reviewed 194 patients randomized either to the pulmonary artery catheter–guided therapy with treatment based or clinical assessment alone in patients admitted with advanced HF. Similarly, the authors reported a weak correlation between sCr and eGFR with RAP ($r = 0.165$, $p = 0.03$ and $r = 0.195$, $p = 0.01$, respectively).
5.3 Renal function correlated with NT-proBNP

In order to achieve linearity of the data, log transformation was performed. Linear regression analysis of eGFR and sCr with Log NT-proBNP showed significant relationships ($r^2 = 0.16$, $p < 0.0001$ and $r^2 = 0.12$, $p < 0.0001$, respectively) (Figure 17). Additionally, patients who had an NT-proBNP of more than 1614 pg/ml are more likely to develop renal impairment [OR 2.9, CI 1.7–4.8, $p = 0.0001$ (eGFR) and OR 3.3, CI 1.95–5.57, $p < 0.0001$ (sCr)]. Natriuretic peptides were discovered decades ago and its existence in heart function was clearly proven to be an essential biologic marker in the management of patients either with acute or chronic HF.

In the PRIDE study, the authors examined the interaction between renal function and NT-proBNP levels. A total of 599 dyspneic patients with glomerular filtration rate as low as 14.8 ml/min were analyzed. They have found that renal insufficiency was associated with risk factors for congestive heart failure, and patients with renal insufficiency were more likely to have congestive heart failure ($p < 0.003$). It was noted that NT-proBNP and GFR were inversely and independently related ($p < 0.001$) (Anwaruddin S 2006).

5.4 Right ventricular systolic pressure to renal impairment

Interaction with patients whose RVSP is more than 40 mmHg would have a higher chance of developing renal impairment [OR 2.0, CI 1.5 – 3.6, $p = 0.01$ (eGFR) and OR 2.6, CI 1.5 – 4.5, $p = 0.001$ (sCr)]. This finding definitely shows a strong renal correlation with cardiac filling pressure, and thus far has never been reported in previous papers. Shrestha K et al. demonstrated in 144 patients with chronic systolic HF (LVEF ≤ 35%, NYHA II-IV), that high RVSP (≥ 39 mmHg) is associated with renal insufficiency after adjustment for RAP (67). This study is consistent with our results revealing a direct relationship. However, in our paper we
showed linearity between renal function and RVSP. RVSP is somehow a reflection of RAP after adding the TR velocity provided that the left ventricular outflow tract is unobstructed. We have demonstrated for the first time with the use of RVSP instead of RAP, that higher RVSP could predict renal impairment (figure 19).

5.5 Univariate linear regression analysis of left atrial dimension, E/e’ medial, E/e’ lateral, and E/A ratio with RVSP, NT-proBNP, and LVEF.

Left atrial size and pressures as well as left ventricular diastolic indices were explored for possible relationships with the predictors RVSP, NT-proBNP, and LVEF. In the study of Rosi A. et al. in 2002, the prognostic implications of having an increased LA was associated with poorer survival incremental to LV end-diastolic volume, diastolic dysfunction, and mitral regurgitation (A., M. et al. 2002). Furthermore, in the study of Beinart R. et al., in 2004, that an LA VI of > 32 mL/m² is a powerful marker for increased all-cause mortality, independent of other measures of LV systolic and diastolic function after an acute myocardial infarction (Moller JEMP 2003, Beinart R 2004).

In the recent findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) Trial. Cardiac structure and function and prognosis in HFpEF showed that among 244 patients who experienced the primary composite outcome of cardiovascular death, HF hospitalization, or aborted cardiac arrest, and its components. Elevated LV filling pressure (E/e’; adjusted HR 1.05 per 1 integer increase; 95% CI 1.02-1.07) with two other parameters (LV hypertrophy [LVH; adjusted HR 1.52, 95% CI 1.16-2.00] and higher pulmonary artery pressure assessed by the TR velocity [HR 1.23 per 0.5 m/sec increase; 95% CI 1.02-1.49]) were associated with the composite outcome and HF hospitalization alone after adjusting for clinical and laboratory variables. The risk of
adverse outcome associated with LVH was additive to the risk associated with elevated E/e’ (Shah, Claggett et al. 2014).

In this paper, we demonstrated the relationship of LA VI, E/e’ medial, E/e’ lateral and E/A ratio with RVSP ($r^2 = 0.19$, p = < 0.0001; $r^2 = 0.07$, p = 0.008; $r^2 = 0.09$, p = 0.003; and $r^2 = 0.18$, p = 0.0006, respectively) and Log NT-proBNP ($r^2 = 0.07$, p = 0.005; $r^2 = 0.04$, p = 0.03; $r^2 = 0.05$, p = 0.02; $r^2 = 10$, p = 0.005, respectively) but did not show relationship with LVEF (Table 9, 10, 11, & 12).

5.6 HFP EF and HFr EF

In the sub-analysis stratified subjects according to LVEF. Patients with LVEF > 40 % were defined as patients with heart failure with preserved ejection fraction (HFP EF) and patients with LVEF ≤ 40 % were defined as patients with heart failure with reduced ejection fraction (HFr EF) (Table 13). In the HFP EF group, it showed that RVSP and NT-proBNP showed significant relationship with renal insufficiency represented by eGFR and sCr, while LVEF did not show any relationship. However, in the HFr EF group, only the NT-proBNP showed significant relationship (Table 14).

5.7 Multiple linear regression analysis interpretations with Log NT-proBNP as one of the covariates

Multiple linear regression was performed which included the outcome variable eGFR and sCr against the predictors RVSP, Log NT-proBNP, and LVEF. The model with $r^2$ of 0.19 and p < 0.0001 (eGFR) and $r^2$ of 0.14 and p value of 0.0000 (sCr) was statistically significant at 95%
confidence. We expected that the outcome variable would show correlation with all of the predictors except for LVEF since these were evident in the univariate linear regression results.

To better meet the assumption of normal distribution, transformation of some of the input variables, in this case is the NT-proBNP, was necessary. The log transformation of the NT-proBNP reflected to the β coefficient and p value of not only the RVSP, but also the LVEF. The eGFR y intercept was 140.2 mL/min/1.73m2 with p value of <0.0001. The predictor RVSP showed insignificant p value (0.16) after adjustment with other covariate. However, the direction of the β coefficient was negative (-0.17) which explains that the higher the RVSP, the lower the eGFR. Log NT-proBNP showed significant p value at < 0.0001 after adjustment with other covariates. Its β coefficient was also towards the negative direction (-8.3). It again explained that the higher NT-proBNP the patient has, the poorer renal function is expected.

For the LVEF, the p value showed significant 0.008 after adjustment with other covariate. This is opposite to the result shown in the univariate linear regression. Its β coefficient was negative (-0.3) which means, the higher the LVEF, the poorer renal function. This is an example that any variables included in a multilinear regression model would sometimes produce unexpected results after adjustments with each variable. This provides difficulties for the statistician in interpreting each result. To date, there have been no published data regarding normal or preserved LVEF associated with renal impairment.

The interpretations with sCr against the predictors RVSP, Log NT-proBNP, and LVEF was somewhat obscured. The y intercept did not show statistically significant (p = 0.06). Moreover, that the RVSP and LVEF were definitely deranged after the NT-proBNP was log transformed making it more difficult to interpret the statistical results.
5.8 Multiple linear regression analysis interpretations with NT-proBNP as one of the covariates

A repeat of the multilinear regression analysis was performed, eGFR as the outcome variable, and the other covariates were RVSP, LVEF and this time, we used the NT-proBNP that was not log transformed. The model with $r^2$ of 0.10 and $p$ 0.0002 was significant at 95% confidence. The y intercept (eGFR) was 83.5 mL/min/m$^2$ with $p$ value of < 0.0001. The predictor RVSP showed significant $p$ value (0.02) after adjustment with other covariate (β coefficient -0.3) NT-proBNP showed significant $p$ value at 0.002 after adjustment with other covariates (β coefficient -0.001). For the LVEF, the $p$ value showed insignificant at 0.08 after adjustment with other covariate (β -0.2).

These results in this section are consistent with the analysis performed using univariate regression correlating eGFR with the covariates stated above. The inverse relationship between the outcome and the predictors showed the consistency of our hypothesis that RVSP is associated with renal impairment using eGFR as well as with NT-proBNP, while LVEF did not show any relationship (Table 16).

Similar to the model using sCr as y intercept, it is consistent with the analysis performed using univariate linear regression (Table 17).

5.9 Residuals by regression for eGFR and sCr with RVSP, LogNT-proBNP, and LVEF

We examined the residuals by regression for eGFR with the predictors RVSP, Log transformed NT-proBNP, and LVEF in order to check if the model fits the data (Figure 19). The plots showed no clear patterns and randomly placed all along the zero mark or line. This implies that
the data fits the multilinear regression model. However, some of the residuals are large which is not ideal. Several outliers have also been observed that could potentially affect the results leading to a weaker regression analysis.

5.10 Residuals by regression for eGFR and sCr with RVSP, NT-proBNP, and LVEF

Similarly, we also examined the residuals by regression for eGFR with RVSP, LVEF, and this time with the non-transformed NT-proBNP (Figure 20). There were no significant patterns shown on the RVSP and LVEF plots. However, in the NT-proBNP, it showed clusters of residuals on the left hand side of the box.

5.11 Right atrial pressure did not correlate with renal function

The assessment of RAP is required in the echocardiography laboratory for the estimation of systolic right ventricular and pulmonary artery pressures. The study in 2011 by Guglin and her group showed the relationship of RAP with renal function representing eGFR and sCr in 178 patients evaluated for right heart catheterization. However, contrary to our findings, that in the cohort of 113 subjects there were no relationships between RAP and eGFR ($r^2 = 0.007$, $p = 0.39$, $\beta = 0.40$, Intercept = 52.6), and between RAP and sCr ($r^2 = 0.0004$, $p = 0.83$, $\beta = -0.32$, Intercept = 130.8).

It is known that RAP and RVSP are included in the collective term called cardiac filling pressures. Accordingly, there was no statistical analysis performed between these two variables simply because it is unrealistic to compare systolic pressure with mean atrial pressure.
RVSP is the measurement of the right ventricle’s pressure during contraction or systolic phase and it is further described as the velocity of the tricuspid regurgitation with the addition of RAP. While RAP is described as the measurement of inferior vena cava diameter and its collapsibility during sniff test.

5.12 Study limitations

Echocardiographic reports were captured with an average 165 days (±202) from the time of patient’s enrollment into the study, while the blood tests for renal function were performed during the patient enrollment. The time between echocardiographic studies and laboratory results constitute a limitation.

Quantitative measurement of RVSP was not captured in about 20% of the study population. This substantial amount of echocardiographic reports that were missed would pose weakness in the regression analysis. Several factors could potentially pose risks in the accuracy of RVSP estimate. These include technical difficulties such as proper positioning of the beam through the tip of the mitral valve straight to the right ventricle and underestimate or overestimate when graphing the velocity curve.
Chapter VI - Conclusions

We hypothesize that RVSP is associated with renal impairment and not left ventricular systolic pressure in patients with chronic stable heart failure. It has been a known knowledge that patients with reduced cardiac output can result to poor renal perfusion thereby causing impairment in renal function. Few studies have been published demonstrating association of cardiac filling pressure represented either by right atrial pressure or central venous pressure with renal function represented by sCr or eGFR in the setting of acute heart failure. No studies have been done on chronic heart failure.

In our knowledge, this is the first paper demonstrating the relationship of right ventricular systolic pressure in patients with chronic stable heart failure. Additionally, we showed that NT-proBNP was also associated with renal impairment. Furthermore, we also showed that there was no association of the left ventricular systolic pressure with renal function.

Interestingly, after we stratified the subjects into two groups: heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. A total of 124 subjects with heart failure with reduced ejection fraction and 118 subjects with heart failure with preserved ejection fraction. Using similar statistical analysis, we further confirmed that our hypothesis is also true in patients with heart failure with preserved ejection fraction, that RVSP and NT-proBNP were associated with renal impairment, while LVEF did not show any relationships. Moreover, in the group of heart failure with reduced ejection fraction group, only the NT-proBNP showed association with renal function.
We were not fully surprised with the NT-proBNP showing relationships with renal impairment. NT-proBNP is known to excrete via the kidneys through the glomerulus. It has a longer half-life of between 1-2 hours as compared with active form BNP which is only 20 minutes (DeFilippi, Fink et al. 2005). Comparison with BNP was not established in this paper, since only NT-proBNP was the only available test at the center.

We have demonstrated the relationship of renal impairment with RVSP through univariate and multivariate linear regression analysis and logistic regression analysis. The results showed weak but statistically significant. Adjustment has to be made to the variables in order to fit the data in the statistical model. As the data presented, particularly with NT-proBNP, showed non-normal distribution, thus, log transformation was done. This is one of the situations in statistical analysis wherein sometimes the unpredicted number will come out. This could either be the beta coefficient and/or the p values. Therefore, interpretation has to be carefully reviewed.

We cannot ignore the statistical strength of the confounding variables such as age, gender, comorbidities and medications used. To date, there is no specific statistical test to use in identifying confounding variables. We could only theoretically identify them, and incorporating confounding variables into the multivariate analysis would definitely affect the statistical outcome. Additionally, it would be ideal to use confounding variables when there were two or more sets of data to compare. It would be more meaningful to interpret the results as the confounding variables will take its effect significantly with the comparing data set. However, in this paper, we only captured the baseline dataset. Hence, the interpretations of the
results would only provide further confusions and uncertainties if confounding variables were included.

The lack of correlations between LVEF and renal function challenges the traditional knowledge that, in heart failure (HF), renal insufficiency usually represents hypoperfusion of the kidney as the result of poor forward flow or overzealous diuresis (Guyton AC 1973) These intriguing observations raise questions about the current management strategy for acute or chronic HF, which has been to lower cardiac filling pressures while maintaining or enhancing cardiac index as well as maintaining normal renal function (guideline 2006). The exact mechanisms by which venous congestion worsens renal function, and why is vigorous diuresis alone so often ineffective has to be explained and clarified (Jessup M. 2009).
Chapter VII - Future directions

A larger group of study population in chronic heart failure will strengthen our hypothesis that cardiac filling pressure is the underlying cause of renal dysfunction in patient with chronic stable heart failure. This theory could also be true in patients with acute heart failure as well.

This future plan can be obtained by collaborating with other centers in Toronto and/or other hospitals in Canada. Heart failure clinic or heart function clinic (as they call them in other centers) across Canada has been very active in terms of establishing databases. Thus, sharing vital information with other centers would give the heart failure community a better understanding about cardiac filling pressures and its relationship with renal function.

An interesting approach is to formulate a prospective observational clinical trial. A study looking at all echocardiographic parameters involving right and left heart functions as well as filling pressure in patients with chronic heart failure. Potential subjects will be invited to participate during their visit at the heart failure clinic. Upon signing of the Research Ethics Board approved consent form, collections of basic demography and medical history will be performed. A blood test will be done which includes test for NT-proBNP, renal function such as serum creatinine, and calculate for the eGFR. An echocardiogram procedure will be scheduled as soon as possible or at least within 2 weeks from the randomization visit. Blood test will be performed in two or three different time-points in order to see renal progression as the patient follows up in the clinic. A second echocardiogram procedure will take place on month 3 or month 6 following randomization. The patient follow-up could last up to 12 months. I think that in this method, we would be able to collect important echocardiographic parameters and monitor its changes as we follow up with the patient clinically.
Measurement of right heart function in echocardiogram has becoming a routine component of echocardiographic studies not only in patients with HF, but also in patients suffering from other conditions such as post-myocardial infarction, pulmonary hypertension, and other disease entities involving right heart failure. Future studies on right atrium in relation to its volume index using different parameters similar to the one used in the left atrium would be very interesting to know. Important left ventricular diastolic indices such as the E/e’ medial and E/e’ lateral that measures LA pressures, E/A ratio and deceleration time that specifically measures LV diastolic function. LAVI is also an important parameter of the left atrium size which is more accurate because of its calculation based on patient’s body surface area. In this paper, we have established the relationships of these indices with RVSP and NT-proBNP but not with LVEF. However, the mechanism that influences each activity is still uncertain to us, which is another avenue that we can certainly look for.

LVEF has recently been used to classify patients with heart failure. Patients whose LVEF is equal or less than 40% are now called Heart Failure with Reduced Ejection Fraction (HFrEF), and patients whose LVEF are more than 40% are now called Heart Failure with Preserved Ejection Fraction (HFpEF). The current trend in the heart failure clinical trials often based on population whose LVEF is either HFrEF or HFpEF. In one of our findings in correlating renal function with RVSP, NT-proBNP, and LVEF. It did show different outcome. HFpEF showed significant relationships with RVSP and NT-proBNP but not with LVEF. However in HFrEF, only NT-proBNP was found to be associated with renal function and not with RVSP and LVEF. These findings in both groups demonstrated some degree of difference in terms of heart function its renal correlation. Its mechanism is still unclear.
Recent biological markers for kidney function are being introduced into the market. This includes Cystatin C. Cystatin C was proposed to be such a marker because it purportedly is produced by all nucleated cells at a constant rate, is filtered at the glomerulus, and is taken up and degraded by the proximal tubular cells of the kidney (Curhan 2005). It has been used in detection and staging patients with chronic kidney disease. In contrast with serum creatinine, cystatin C is not affected by muscle mass, hence, it require less adjustments for factors like age, sex, and race. A recent study conducted by the Chronic Kidney Disease Prognosis Consortium (CKD-PC), authors tried to determine whether the addition of an eGFR that was calculated with the use of the Cystatin C equations would strengthen the relationships between various eGFR categories and adjusted risks of death from any cause, death from cardiovascular causes, and end-stage renal disease, as compared with the use of creatinine-based eGFR. The authors found that the use of Cystatin C improves the role of eGFR in risk categorization, as judged by the risk of death from any cause and to a lesser extent the risks of death from cardiovascular causes and end-stage renal disease. Most notably, reduced values for Cystatin C–based eGFR and eGFR based on combined measurements of creatinine and Cystatin C had a consistent linear association with increased risks of death from any cause and from cardiovascular causes for all eGFR levels below approximately 85 ml per minute per 1.73 m², which is well above the threshold of 60 ml per minute per 1.73 m² for the detection of chronic kidney disease with a creatinine-based eGFR. These findings show that eGFR equations that are based on the measurement of Cystatin C can be used to detect increased risks of adverse outcomes that are not detected with creatinine-based calculation of the eGFR (Michael G. Shlipak, Johan Ärnlöv et al. 2013).
Another potential biologic marker is the Neutrophil gelatinase-associated lipocalin (NGAL). NGAL is also known as *lcn2*, is one of the most upregulated genes in the early post-ischaemic mouse kidney (Devarajan, Mishra et al. 2003, Supavekin, Zhang et al. 2003). These findings leads to several translational studies evaluating NGAL as a novel biologic marker in human acute and chronic kidney injury (Devarajan 2008). One study has shown its role as a marker of severity and prognosis in patients with HF (Pronschinske, Qiu et al. 2014). In another study were authors evaluated the role of NGAL in predicting in-hospital WRF and post-discharge follow-up during six months period in patients with acute HF. They found that admission NGAL measurement appears to be a sensible tool for in-hospital WRF prediction as well as an early marker for adverse outcome during post discharge vulnerable phase (Palazzuoli, Ruocco et al. 2014).

Another highly upregulated protein in the proximal tubule of the kidney after injury is the Kidney injury molecule-1 or KIM-1. KIM-1 is a phosphatidylserine receptor which recognizes apoptotic cells directing them to lysosomes. It also serves as a receptor for oxidized lipoproteins and hence is important for uptake of components of the tubular lumen which may be immunomodulatory and/or toxic to the cell. KIM-1 is unique in being the first molecule, not also present on myeloid cells, that transforms kidney proximal epithelial cells into semi-professional phagocytes. Data suggests that KIM-1 expression is protective during early injury, whereas in chronic disease states, prolonged KIM-1 expression may be maladaptive and may represent a target for therapy of chronic kidney disease (Bonventre 2014).

Cystatin C, NGAL, and KIM-1 are just some of the recently introduced biologic marker that can be explored. Their potential use in screening, diagnostics, and prognosticating renal injury will soon be the focus of many researches in the future. Their advantage over the sCr or eGFR
will become apparent in the near future that could probably lead to the minimal if not negligible use of sCr and eGFR.

As we move forward to using biologic markers, there will always be an opportunity to explore their relationship with cardiovascular diseases including heart failure in particular along with the echocardiographic parameters available, finding their relationship with each variable that can potentially be useful in clinical setting.
Chapter VII – References


Ma, K. K., T. Ogawa and A. J. de Bold (2004). "Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase." J Mol Cell Cardiol 36(4): 505-513.


Maya Guglin, M., PhD; Abel Rivero, MD; Fadi Matar, MD; Marcos Garcia, MD ; Clin. Cardiol. (2011). "Renal Dysfunction in Heart Failure Is Due to Congestion but Not Low Output." Clin. Cardiol. 34, 2, 113-116


Sherif F. Nagueh, M., Chair, Christopher P. Appleton, MD, Thierry C. Gillebert, MD, Paolo N. Marino, MD, Jae K. Oh, MD, Otto A. Smiseth, PhD, Alan D. Waggoner, MHS, Frank A. Flachskampf, MD, Co-Chair, Patricia A. Pellikka, MD, and Arturo Evangelista, MD (February 2009). "Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography." Journal of the American Society of Echocardiography.


