# Resurgence of interest in the hemodynamic alterations of advanced heart failure

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**Voor Nele, Kaat, Saar en Teun**

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## 1. Epidemiology and definition of heart failure

Aging of the population and prolongation of the lives of cardiac patients by modern therapeutic innovations has lead to an increasing incidence of heart failure. Despite advances in heart failure therapy, patients with advanced heart failure continue to experience high rates of hospitalizations and mortality, and heart failure related costs are the most expensive expenditure of the Western World health care budget.

Repeated attempts to develop a unifying hypothesis which would explain the clinical syndrome of heart failure have been proposed but no single conceptual paradigm for heart failure has withstood the test of time. Whereas clinicians initially viewed heart failure as a problem of excessive salt and water retention that was caused by abnormalities of renal blood flow (the "cardiorenal model"), it soon became apparent that heart failure was also associated with a reduced cardiac output and excessive peripheral vasoconstriction which lead to the development of the “cardio-circulatory or hemodynamic model”. However, neither of these models explains the relentless disease progression accompanied by further activation of neurohormonal and cytokine systems, as well as a series of adaptive changes within the myocardium, referred to as LV remodeling which ultimately lead to the broad adaptation of the “neurohormonal model”.

As a result, contemporary heart failure pharmacotherapy solely focuses on preservation of neurohormonal homeostasis by suppressing the over expression of biologically active molecules that are capable of exerting toxic effects on the heart and circulation. However, in the more advanced stages hemodynamic alterations do continue to occur despite this maximum neurohormonal blockade. In addition, the clinical observation that heart failure still progresses independently of the neurohormonal status of the patient has lead to a resurgence of interest in the contributions of hemodynamic alterations of heart failure and their potential role in further disease progression.

## 2. The role of the hemodynamic alterations in advanced heart failure

Historically, risk stratification models have been constructed using datasets from clinical trials with carefully selected chronic ambulatory heart failure populations or from large registries of hospitalized patients with decompensated heart failure, all independent of hemodynamic

variables. Hence, the use of an invasive hemodynamic assessment has been largely been confined to evaluation for candidacy for cardiac transplantation. However, if hemodynamic assessment provides valuable insights into the long-term prognosis of symptomatic patients with advanced heart failure has not been examined. In addition, potential gender-specific differences in clinical presentation, prognosis and response to treatment in patients admitted with advanced decompensated heart failure are lacking. Therefore, another objective of this PhD project will be to examine potential gender-specific differences in hospitalized patients with advanced decompensated heart failure (ADHF). An important objective will be to assess the value of invasive hemodynamic measurements as an objective assessment for disease severity, and to compare potential different clinical responses to diuretic and vasoactive therapies between males and females.

Advances in medical therapies (such as neurohormonal modulation and pacing/defibrillation strategies) have significantly altered the natural history of heart failure and improved long-term outcomes. However, the pathophysiology and treatment of ADHF remains poorly understood, especially in more advanced stages when cardiac output is significantly reduced. Our treatment goal remains symptomatic relief, primarily by decreasing volume overload and attenuating pulmonary congestion with loop diuretics. In the setting of a low cardiac output, augmentation of contractility with parenteral inotropic therapy is often utilized. Classically, vasoactive drugs are administered at the expense of a potential risk of developing adverse outcomes including worsening renal function or precipitating arrhythmias. Therefore, a resurgence of interest in the use of vasodilators in the management of ADHF has emerged, particular with the recognition that a large majority of patients present with elevated rather than low blood pressures. Sodium nitroprusside (SNP) is an older intravenous vasodilator, often being used to titrate off inotropic therapy in patients with refractory heart failure but administered almost exclusively in critical care settings with careful invasive hemodynamic monitoring. Based on our large experience with SNP over many years in a heart failure intensive care unit, another aim of this PhD project will be to examine the safety and efficacy of vasodilator therapy such as SNP as part of the treatment regimen for hospitalized ADHF patients with low output states.

Although the oral vasodilators isosorbide dinitrate and hydralazine (I/H) were considered one of the earliest “evidence-based” treatment strategies for systolic heart failure based on the cardio-circulatory model of heart failure, their current use is eclipsed by the large volume of

evidence supporting the use of neurohormonal antagonists such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-adrenergic blockers (beta-blockers), and aldosterone receptor antagonists. Since ACE inhibitors/ARBs may not provide the same balance of preload and afterload reduction than I/H, we also aim to determine if addition of I/H to standard neurohormonal blockade following an episode of ADHF would be associated with sustained hemodynamic profiles and improved clinical outcomes in patients admitted with ADHF.

Finally, invasively measured pulmonary capillary wedge pressure (PCWP) has been widely used as a surrogate for left ventricular filling pressure, and is directly associated with functional capacity and prognosis in patients with heart failure. However, given the cost, potential complications, and the lack of demonstrable benefits in routine use, invasive hemodynamic assessment via pulmonary artery catheters has decreased substantially over the last decade. In contrast, transmitral flow velocity curves and other Doppler variables assessed by echocardiography have been advocated as non-invasive estimates of intracardiac filling pressures. In particular, the early transmitral velocity / tissue Doppler mitral annular early diastolic velocity (E/Ea) ratio has been shown to correlate with PCWP in a wide range of cardiac patients but none has included patients admitted with advanced heart failure and extensive reverse remodeling. Therefore, another hemodynamic goal of this PhD project will be to examine the relationship between mitral E/Ea and invasive hemodynamic measurements in patients with ADHF, a patient cohort wherein hemodynamic assessment is often considered.

## 3. Cardiorenal interactions in heart failure

The pathophysiology of the cardio-renal interaction in the setting of ADHF is poorly understood. It is commonly observed that coexisting renal dysfunction may complicate the treatment course of heart failure, and the use of intravenous loop diuretics often alleviate congestion at the cost of worsening renal function (WRF). WRF during treatment of ADHF typically occurs within days of hospitalization and is a strong independent predictor of adverse outcomes. Traditionally, WRF has been attributed to hypoperfusion of the kidney due to progressive impairment of cardiac output or intravascular volume depletion secondary to overzealous use of diuretics.

Although the majority of patients hospitalized with ADHF also present with increased central or peripheral congestion, the presence of venous congestion has been considered a secondary phenomenon due to the “backward failure” caused by impaired cardiac output. Nevertheless, experimental animal data as far back as the 1930’s have demonstrated that temporary isolated elevation of central venous pressure (CVP) can be transmitted back to the renal veins, resulting in direct impairment of renal function. However, human data regarding the differential contributions of venous congestion and cardiac output in the development of WRF during ADHF are lacking. Therefore, one of the primary aims of this PhD project will also be to test the hypothesis that WRF is more dependent on venous congestion rather than on impairment of cardiac output in patients admitted with ADHF.

There also has been increasing interest in measuring intra-abdominal pressure (IAP) in critically ill patients as elevated IAP has been associated with intra-abdominal organ dysfunction. The compliance of the abdominal wall generally limits the rise in IAP as abdominal girth increases. Therefore, once a critical volume is reached, compliance of the abdominal wall decreases abruptly. Further distention beyond this "critical IAP" results in a rapid rise in abdominal pressure and resultant organ dysfunction. Recently, during the second World Congress on Abdominal Compartment Syndrome, medical critical care specialists defined a normal IAP to be between 5–7 mmHg in critically ill adults, an elevated IAP to be $\geq$ 8 mmHg and intra-abdominal hypertension (IAH) to be $\geq$12 mmHg (7). Data regarding measurements of IAP in patients admitted with ADHF are lacking despite the potential for a substantial part of ADHF patients to present with ascites, visceral edema and impaired renal function. Therefore, the prevalence of elevated IAP in patients admitted with ADHF will be examined. In addition, the potential of hemodynamically-guided therapy to reduce IAP with corresponding positive effects on renal function will be investigated as well. With the recent interest in the role of mechanical fluid removal as a mean to alleviate congestion in ADHF, this PhD will also investigate if in selected patients with volume overload, admitted with ADHF refractory to intensive medical therapy, large-volume mechanical fluid removal might lead to resolution of otherwise elevated IAP with corresponding improvement in renal function.

## 4. Effects of cardiac resynchronization therapy on cardiac hemodynamics and molecular gene expression

Cardiac resynchronization therapy (CRT) improves cardiac function and exercise capacity leading to a better survival in patients with advanced heart failure and ventricular conduction delay. The underlying mechanisms of these beneficial effects are not fully elucidated but appear to be related to a restored coordination of the left ventricular (LV) contraction and relaxation and an improvement in functional mitral regurgitation. These effects may directly lead to augmented contractile function and reduction of LV filling pressures at resting heart rates.

In the intact normal heart, the force of contraction is augmented by an increase in heart rate. This stepwise increase in tension seen at faster rates, known as the positive staircase or Treppe phenomenon, is one of the hallmarks of LV contractility and is greatly attenuated or absent in patients with heart failure. In addition, congestive heart failure is characterized by abnormal β-adrenergic receptor and post-receptor mechanisms which diminish the adrenergically mediated contractile reserve during inotropic stimulation with dobutamine infusion. Attenuation of this force-frequency relationship (FFR) and myocardial contractile reserve (MCR) can directly lead to impairment of exercise tolerance. However, the short- and long-term effects of CRT on FFR and MCR have not been examined. Furthermore, it remains unclear whether long-term CRT can modulate the molecular underpinnings of myocardial contractility. Accordingly, an important part of this PhD project will be devoted to the investigation of the acute and chronic effects of CRT on FFR and MCR by comparing the LV dP/dtmax response at incremental heart rates during acute and long term DDD-CRT pacing with and without dobutamine infusion.

The adverse left ventricular remodeling and the reduced contractile function observed in heart failure is also associated with altered gene expression profile. One of the hallmarks of the altered molecular response is the activation of the “fetal” gene program including isoform switch in myosin heavy chain gene expression with downregulation of the fast α–myosin isoform and upregulation of natriuretic peptides. Other molecular changes include alterations in expression of genes encoding excitation-contraction coupling such as sarcoplasmic reticulum calcium ATPase 2α (SERCA) and phospholamban (PLN). End-stage heart failure is associated with decreased levels of SERCA relative to PLN as well as reduced activity, resulting in impaired calcium cycling thereby accounting for the contractile deficit of the failing heart. These changes appear to represent basic molecular mechanisms underlying LV dysfunction and heart failure.

Accordingly, it was postulated that clinical strategies should be designed to target these adverse molecular changes in order to effectively improve contractile performance of the failing myocardium. However, very few clinical studies have addressed the reversibility of adverse molecular profile in human heart failure. Moreover, alterations in the molecular fingerprint associated with this reversed remodeling after long-term CRT have never been elucidated. Accordingly, this PhD will also investigate whether functional improvement following CRT is associated with favorable changes in expression of established molecular structural and calcium regulatory markers of heart failure through gene profiling of left ventricular biopsies before and after CRT.

As with any effective therapy for heart failure, the response to CRT is often heterogeneous and patients may not see any improvement in clinical status and/or reversal of cardiac remodeling after 3-6 months of CRT. Therefore, one might postulate that "non-responders" may experience a diminished hemodynamic benefit of CRT over time. Although discordance between clinical and echocardiographic response to CRT has been observed in prior studies, the degree of hemodynamic response in the absence of a robust echocardiographic remodeling to long-term CRT has not been explored. Therefore, another objective of this PhD project will be to examine the contributions of biventricular pacing to the clinical, hemodynamic, and echocardiographic profiles of patients admitted with advanced heart failure and evidence of disease progression despite long-term CRT therapy.

Finally, the literature regarding post-implantation management of CRT is sparse, particularly long after device implantation. While the extent of the response can be heterogeneous, most studies have focused primarily on refining pre-implantation patient selection to predict favorable response (such as detecting evidence of basal dyssynchrony). However, a variety of post-implant issues besides patient selection can also contribute to suboptimal responses, although less is known about their prevalence and impact. There has been a paucity of data to systematically evaluate how to best manage patients with CRT following their implantation, and to troubleshoot their settings post-implant in order to maximize the potential of the resynchronization therapy. In particular, the feasibility and value of a systematic protocol-driven multi-disciplinary approach to diagnose potential contributors for a suboptimal response and to optimize or titrate CRT in these patients is unknown. Therefore, the final goal of this PhD project will be to describe the feasibility of a multi-disciplinary protocol-driven

approach of ambulatory CRT patients who did not experience clinical or echocardiographic improvement following CRT implantation.

## 5. Summary of objectives

The primary aim of this PhD project will be to define if a combined hemodynamic, molecular and physiological phenotyping of advanced heart failure patients might provide important clues to progression or recovery of advanced heart failure. An important objective will be to examine if progressive pump failure with resulting hemodynamic alterations is still contributing to long-term compromise and if restoration of an optimal hemodynamic balance through medical or device-based therapies might lead to improved outcomes. Novel hemodynamic insights into the pathophysiology of the cardiorenal interactions and into the role of cardiac resynchronization therapy over and beyond hemodynamic restoration will be explored in depth. Finally, the value and application of implementing invasive hemodynamic monitoring instead of non-invasive echocardiographic tools for the assessment of advanced heart failure will be examined.

# II. Novel pathophysiologic insights into the hemodynamic alterations of advanced heart failure

# II. Novel pathophysiologic insights into the hemodynamic alterations of advanced heart failure

## 1. Prognostic evaluation of ambulatory patients with advanced heart failure

Mullens W, Abrahams Z, Skouri H, Taylor D, Starling R, Young J, Francis G, Tang W. Prognostic evaluation of Ambulatory Patients with Advanced Heart Failure. Am J Cardiol 2008;101:1297-1302.

### a) Abstract

Previous heart failure (HF) risk models have included clinical and non-invasive variables, and have been largely derived from clinical trial databases or decompensated HF registries. The importance of hemodynamic assessment is less established, particularly in ambulatory patients with advanced HF. We reviewed 513 consecutive ambulatory patients (age 54±11 years, left ventricular ejection fraction 20±9%) with symptomatic HF who underwent a diagnostic right sided heart catheterization as part of outpatient assessment between 2000-2005. After a total of 1,696 patient-years of follow-up, 139 (27%) patients had died and 116 (22%) underwent cardiac transplantation. One and 2-year overall survival rate (defined as freedom from death or cardiac transplantation) was 77% and 67%, respectively. Overall, 65% of patients had elevated intracardiac filling pressures, and 40% had a cardiac index (CI) <2.2 l/min/$m^2$. In multivariate analysis, mean pulmonary artery pressure (MPA), CI, and severity of mitral regurgitation were the 3 strongest predictors for all-cause mortality and cardiac transplantation. Renal dysfunction was also an independent predictor for all-cause mortality. When a clinical model for Cox multivariate analysis of all-cause mortality was compared with a model that also included CI and MPA the chi-square score increased from 45 to 69 ($p < 0.0001$). In conclusion, in ambulatory patients with advanced HF, hemodynamic and renal function assessments remain strong independent predictors of all-cause mortality.

**b) Introduction**

Ambulatory patients with chronic systolic heart failure (HF) continue to have high rates of hospitalizations and mortality as well as correspondingly high costs of care (1-4). Recently, several risk stratification models have been constructed using datasets from clinical trials with carefully selected chronic HF populations or, from large registries of hospitalized patients with decompensated HF, all independent of hemodynamic variables (5-7). Hence, the use of invasive hemodynamic assessment has been largely confined to evaluation for candidacy for cardiac transplantation (8). The goal of this report is to examine the prognostic role of invasive hemodynamic assessment performed in ambulatory patients with advanced HF who were treated with contemporary medical and device therapy. We hypothesized that hemodynamic assessment may provide valuable insights into the long-term prognosis of symptomatic patients with advanced HF.

**c) Methods**

**Study Population.** This was a retrospective cohort study of ambulatory patients with chronic HF due to left ventricular systolic dysfunction seen at the Cleveland Clinic between January 1, 2000 and December 31, 2005. We reviewed medical records from all consecutive patients aged 18 years or older with advanced chronic (>6 months) HF that had undergone a right heart catheterization (RHC) evaluation as part of outpatient assessment. The indication for the RHC was progressive signs or symptoms of heart failure. We excluded patients with underlying complex congenital heart disease, receiving chronic inotropic drug infusions, and patients admitted to the hospital immediately following the RHC for management of decompensated HF. The Cleveland Clinic Institutional Review Board approved the study.

**Data Synthesis and Variable Definitions**. Data abstraction and adjudication was conducted by three cardiologists via manual chart review of the electronic health record. For patients who had undergone multiple RHC evaluations, only data from the initial procedure was used. Data collected included demographic characteristics, pertinent medical history, treatment regimen including drug therapies and implanted devices, hemodynamic variables obtained during RHC, routine laboratory values and underlying heart rhythm. Generally this information was within a week of the RHC. Estimated glomerular filtration rate (GFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula: GFR for men =

186 x [serum creatinine (umol/L) x 0.0113]$^{-1.154}$ x age (years)$^{-0.203}$. For women the result was multiplied by 0.742 and for African Americans by 1.210. We also collected echocardiographic data if performed within one month of the outpatient clinic visit. Left ventricular ejection fraction was calculated by biplane Simpson' technique. Left ventricular end-diastolic dimension was measured at the parasternal view. Right ventricular systolic function was visually assessed on a scale of 0 to 4 with 0 being normal and 4 severely impaired. The severity of tricuspid regurgitation and mitral regurgitation was graded semi-quantitatively by color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images.

**Hemodynamic assessment.** Central venous (CVP), pulmonary artery, and pulmonary capillary wedge (PCWP) pressures were measured at end-expiration with a balloon-tipped catheter at steady state with the patient in a supine position. A mixed central venous blood gas was taken through the tip of the catheter in the pulmonary artery and cardiac output was estimated by the Fick equation. Mean arterial pressure was calculated as (systolic blood pressure + 2 x diastolic blood pressure)/3. Systemic vascular resistance was determined by the following equation: 80 x (mean arterial pressure - right atrial pressure) / cardiac output. Pulmonic vascular resistance was determined as: (PCWP – mean pulmonary artery pressure (MPA)) / cardiac output. Elevated intracardiac filling pressures were arbitrarily defined as: CVP $\geq$ 8 mmHg, MPA $\geq$ 35 mmHg, and PCWP $\geq$ 18 mmHg.

**Endpoints.** The duration of follow-up was defined as the interval from the outpatient visit to all-cause mortality or cardiac transplantation. All-cause mortality was analyzed using data documented in the electronic health record and confirmed by the Social Security Death Index. A secondary endpoint was days to first HF hospitalization, defined as an admission of more than 12 hours for worsening HF symptoms (at the Cleveland Clinic or any other facility reported in the medical record). An admission for cardiac transplantation was not considered to be a HF hospitalization. Indication for cardiac transplantation at the Cleveland Clinic is based on transplant suitability on a case-by-case basis, which was dependent on extent of disability and disease severity (but without an upper age limit or a specific GFR cut-off).

**Data Analysis.** All data are expressed as mean ± standard deviation for continuous data and as a ratio for categorical data. Univariate and multivariate comparisons of these variables were performed between all patients for the different endpoints using SPSS for Windows, release 11.5 (SPSS Inc., Chicago, IL). An unpaired t-test for continuous data and a Pearson correlation

coefficient was used for appropriate comparisons. Variable selection in multivariate analysis was based on clinical and statistical significance of the univariate analysis. Variables entered as a stepwise fashion, included age, gender, ischemic etiology, New York Heart Association class, body mass index, diabetes mellitus, hypertension, baseline medications, heart rate and rhythm, mean arterial blood pressure, invasive hemodynamic variables (CVP, MPA / PCWP, cardiac index (CI) and pulmonic vascular resistance), echocardiographic variables (left ventricular ejection fraction, left ventricular end-diastolic diameter, right ventricular systolic function, mitral regurgitation / tricuspid regurgitation), hemoglobin, serum sodium, and serum creatinine.

To demonstrate the incremental prognostic value of invasive hemodynamic variables chi-square scores were calculated for a Cox multivariate analysis model that included only clinical and non-invasive variables (age, gender, ischemic etiology, New York Heart Association functional class, body mass index, diabetes mellitus, hypertension, baseline medications, heart rate and rhythm, mean arterial blood pressure, creatinine) and a model that in addition to the aforementioned clinical variables also included CI and MPA. To facilitate identification of high- and low risk patients in a way that could be clinically useful, Kaplan-Meier survival curves were further constructed for combined CI and creatinine values. Statistical significance was set at a two-tailed probability level of less than 0.05.

**d) Results**

**Baseline clinical characteristics.** In our study cohort, there were 784 RHC evaluations performed in the six-year period in 513 individual patients who fulfilled the inclusion and exclusion criteria (Table 1). Use of contemporary guideline based medical therapy was evident in our study population and highly comparable to that of clinical trials. Almost 35% of patients had at least chronic kidney disease stage 3 defined as a GFR of <60 mL/min/1.73m$^2$.

**Baseline hemodynamic profile.** Table 2 illustrates the hemodynamic and echocardiographic profiles of the overall study cohort. All patients had complete hemodynamic data, and echocardiography data was available in 436 patients (85%). None of the patients had serious complications directly related to the RHC procedure. Figure 1 illustrates the distribution of the hemodynamic profile seen in our ambulatory cohort. Overall, 65% patients had elevated intracardiac filling pressures, including 48% with CVP $\geq$ 8 mmHg, 25% with MPA $\geq$ 35 mmHg, and 51% with PCWP $\geq$ 18 mmHg. In addition, 40% had a CI $\leq$ 2.2 l/min/m$^2$.

**Long-term Outcomes.** Patients were followed for a mean duration of 40 ± 26 months (range 0.1 to 85 months), and the 513 individual patients contributed to 1,696 patient years of observation. Complete follow-up data was available for all patients, and there were 139 deaths (27%) and 116 cardiac transplantations (22%) during the follow-up period. The average time to death or cardiac transplantation was 29 ± 21 months and 14 ± 15 months, respectively. During the first year of follow-up, 38% of patients had to be admitted for worsening HF. Overall, 57% of patients had to be admitted during the total follow-up period with the average time to first HF hospitalization being 12 ± 15 months.

The overall survival rate (defined as freedom from all-cause mortality or cardiac transplantation) and overall event-free rate (freedom from all-cause mortality, cardiac transplantation and HF re-hospitalization) was 77% vs. 51% at 1 year, and 67% vs. 35 % at 2 years, respectively.

**Predictors of adverse clinical events.** On univariate analysis, the presence of elevated intracardiac filling pressures, impaired systolic ventricular function, valvular regurgitation, and renal dysfunction (all $p < 0.001$) were associated with adverse clinical events. Predictors of adverse outcomes on multivariate analysis are provided in Table 3.

When a clinical model for Cox multivariate analysis of all-cause mortality was compared with a model that also included CI and MPA the chi-square score increased from 45 to 69 ($p < 0.0001$). Similar incremental values can be found when cardiac transplantation and HF hospitalizations were used as end-points (data not shown).

Kaplan-Meier curves of survival stratified according to quartiles of patients for CI and serum creatinine are shown in Figure 2. At 1 and 5 year follow-up all-cause mortality increased from 3% and 15% in patients with serum creatinine <1.25 mg/dl and CI >2.4 l/min/$m^2$ to 22% and 53% in those with serum creatinine >1.25 mg/dl and CI <2.4 l/min/$m^2$, respectively (adjusted odds ratio: 0.391; 95% confidence interval: 0.219 to 0.698, $p = 0.001$). Patients with serum creatinine >1.25 mg/dl also had higher CVP (9 ±5 versus 7 ±5 mmHg, $p = 0.01$) and higher PCWP (19 ±9 versus 16 ±8 mmHg, $p < 0.001$) compared to those with serum creatinine <1.25 mg/dl.

No significant correlation between renal impairment and CI or left ventricular ejection fraction was observed. Also, serum sodium and hemoglobin levels were not predictive of all-cause mortality or cardiac transplantation. However if a combined endpoint of all-cause

mortality and cardiac transplantation was considered a serum sodium level of <140 mmol/l was associated with worse outcome (p =0.02). Patients implanted with an implantable cardioverter defibrillator or cardiac resynchronization therapy with defibrillator showed a trend towards reduced all-cause mortality (23% versus 30%, p =0.07) but had increased cardiac transplantation rates (30% versus 16%, p <0.001).

Predictors for HF hospitalization on univariate analysis were limited to higher intracardiac filling pressures together with a lower CI as well as impaired renal function (not shown). However, as shown in Table 4, only 3 variables were statistically significant in a multivariate model. A HF hospitalization itself was associated with a higher mortality rate after the index hospitalization (22% versus 31%; adjusted odds ratio: 1.752; 95% confidence interval: 1.361 to 2.256, p <0.001).

**e) Discussion**

From our large cohort of ambulatory patients with advanced HF who have been treated with contemporary therapies, we demonstrated that hemodynamic and renal function abnormalities are valuable determinants of long-term prognosis. When a prognostic model that includes only clinical and non-invasive variables is directly compared to a model where hemodynamic information is added for this patient population, we note an incremental prognostic value when adding invasive hemodynamic data to risk models. This observation confirms the hypothesis that an invasive hemodynamic assessment is an important tool in long-term risk assessment in patients with advanced HF, which can be safely performed in an outpatient fashion.

Our patient cohort with advanced ambulatory HF was derived from a tertiary care heart transplant referral center being treated with contemporary guideline-based HF therapies that generally included angiotensin converting enzyme inhibitors, beta-adrenergic blockers, and aldosterone receptor antagonists, as well as with implanted devices and surgical therapies. Nevertheless, the overall prognosis observed in this ambulatory HF population remains poor, with up to 38% of patients subsequently admitted to the hospital for HF within one year.

There has been a longstanding notion that clinical outcomes may improve when hemodynamic targets can be achieved (9,10,11). Therefore, the challenge is to better identify those patients with concerning hemodynamic compromise that might not be clinically apparent

in the ambulatory care setting and to optimize their medications when possible (such as incorporating oral vasodilator therapy like hydralazine and nitrate therapy). As seen in Figure 1, a substantial proportion of patients in our cohort still presented with predominantly elevated intracardiac filling pressures rather than strikingly low cardiac indices. This may represent a population that despite receiving evidence-based therapies for HF is experiencing ongoing disease progression, leading to the progressive hemodynamic and renal compromise. In fact, the hemodynamic and clinical profile of this group of patients can be characterized in HF jargon as the "walking wounded". In the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) these patients are referred to as being at Level 6 (some may even be at Level 5), which means their conditions may even be advanced enough to be considered for interventions to improve their altered hemodynamics (12).

Our study provides an important rationale for routine invasive hemodynamic evaluation in this patient population, as there was an increased predictive value of invasive hemodynamic variables when they were added to a risk-model that only included clinical variables. Information obtained from this procedure should enable physicians to better assess patients' risk. This, in turn, identifies individuals in need of a closer follow-up or perhaps even a more aggressive intervention. Moreover, some ambulatory patients have surprisingly altered hemodynamics, which may not be fully appreciated by history and physical examination alone. Our data also demonstrated that a RHC performed by an experienced cardiologist in an outpatient setting could be done safely without significant risk of complications. It must also be emphasized that despite improvement in echocardiographic and thoracic impedance monitoring techniques (or other non-invasive evaluation of cardiac performance), none has yet demonstrated the ability to replace RHC as a tool to provide hemodynamic assessment for staging the severity of heart failure (13,14). Nevertheless, our data provide preliminary "evidence" of altered hemodynamics being prevalent in an outpatient HF population, thereby emphasizing the need for further research on the use of implantable hemodynamic monitors and the potential benefits of add-on vasodilator therapy.

Our study differs from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial in several aspects. The ESCAPE trial prospectively compared therapy in congestive HF patients that was directed either by pulmonary artery catheter insertion or clinical assessment only (15). Patients, however, had the clinical

indication for hospital admission with a diagnosis of acute exacerbation of HF. In contrast, our patient population remained in the ambulatory setting after their RHC. Furthermore, the baseline hemodynamic measurements in the ESCAPE trial were more severely altered when compared to that in our patient population. The role of hemodynamic variables in assessing the prognosis of HF has only been evaluated prior to the broad adoption of neurohormonal antagonists. It is therefore reassuring to observe that there was still a significant correlation between hemodynamic alterations, even though less severely deranged than usually reported, and risk for adverse clinical events.

Therapies for advanced HF have evolved with widespread use of ACE inhibitors and use of beta-blockers in more than 70% of our patients. The common use of vasodilating medications is reflected in a lower estimated systemic vascular resistance (mean of 1433 dynes.s/cm$^2$ in our population) compared to that seen in other studies (generally over 1800 dynes.s/cm$^2$) (16,17). However, progression of renal dysfunction and diuretic resistance commonly limits vasodilating and neurohormonal therapy (18). Although mean serum creatinine levels in our database were only 1.25 mg/dl (versus 1.8 mg/dl in a large decompensated heart failure registry (19)), the probability of survival is reduced even by minor reductions in renal function (Hazard ratio of 2.0). In addition, we demonstrated that the relationship between serum creatinine levels and prognosis was sustained over a wide range of serum creatinine values, probably because most clinical trials exclude patients with significant or severe renal dysfunction. It was not unexpected to find renal function not being predictive of subsequent cardiac transplantation, since most patients who had significant renal insufficiency were not eligible for transplantation. Finally, the absence of a correlation between renal impairment and any index of left ventricular performance corroborate the hypothesis that renal dysfunction may have a pathophysiologic role in the progression of HF, independent from myocardial performance per se (20,21,22). The fact that a more impaired renal function was associated with higher right and left sided filling pressures and with subsequent increased HF re-hospitalizations, at least on univariate analysis, further supports this hypothesis.

Comprehensive follow-up, review of events, and adjudication by manual chart review has minimized the potential for missed or misclassified outcomes, but limitations inherent to the retrospective study design should still be considered when our findings are interpreted. Reliable echocardiographic data with regards to derived peak pulmonary artery pressure and tissue-

Doppler-derived measurements of left ventricular diastolic function were available only in a small subset of patients and therefore not used. Only half of the patients had implanted devices since its widespread use was only noted after 2002. For those patients with an implanted device, prognosis may be better in the future, as we have already witnessed a trend towards reduced all-cause mortality in patients implanted with such devices. To analyze cardiac output, a standard resting metabolic rate was assumed but overall cardiac output assessed by Fick were comparable with those assessed by thermodilution technique. An important confounding factor that may influence the true extent of the disease progression lies in the fact that a substantial proportion of patients (22%) underwent cardiac transplantation during the follow-up period. This may also explain why our patient population was younger than that noted in many patient registries, epidemiologic studies, and some clinical trials. Nevertheless, we analyzed all-cause mortality and cardiac transplantation separately and in combination to illustrate the consistently incremental prognostic values of hemodynamic assessment in an otherwise unique patient population.

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**Table 1. Baseline patient characteristics (n=513)**

| **Variable** | |
|---|---|
| Age (years) | 54 ± 11 |
| New York Heart Association class III / IV | 92 / 8 % |
| Ischemic cardiomyopathy | 48 % |
| Idiopathic dilated cardiomyopathy | 44 % |
| Body mass index ($kg/m^2$) | 28.4 ± 3.6 |
| Male | 78 % |
| Caucasian / African-American | 84 / 16 % |
| Smoking | 52 % |
| Diabetes Mellitus | 28 % |
| Hypertension (>140/90 mmHg) | 76 % |
| Hyperlipidemia (LDL > 130 mg/dl) | 63 % |
| Previous cardiac valve surgery | 12 % |
| Previous left ventricular remodeling surgery | 3 % |
| Previous coronary by-pass surgery | 27 % |
| Implantable cardiac defibrillator | 38 % |
| CRT – ICD | 10 % |
| **Drugs Used** | |
| Aspirin / Warfarin | 47 / 42 % |
| ACE-I / ARB | 72 / 18 % |
| Digoxin | 68 % |
| Beta-blockers | 70 % |
| Spironolactone | 38 % |
| Loop diuretics | 92 % |
| Hydralazine / Isosorbide dinitrate | 12 / 33 % |
| Statin | 47 % |
| Amiodarone | 17 % |
| Oral anti-diabetic | 12 % |

**Table 2. Baseline hemodynamic (n=513) and echocardiographic (n=436) variables**

| | |
|---|---|
| **Hemodynamics** | |
| Heart rate (bpm) | 80 ± 17 |
| Mean arterial blood pressure (mmHg) | 85 ± 14 |
| Central venous pressure (mmHg) | 8 ± 6 |
| Mean pulmonary artery pressure (mmHg) | 28 ± 11 |
| Pulmonary capillary wedge pressure (mmHg) | 18 ± 9 |
| Cardiac output (l/min) | 4.6 ± 1.3 |
| Cardiac index (l/min/m2) | 2.3 ± 0.6 |
| Systemic vascular resistance (dynes.s/cm2) | 1433 ± 442 |
| Pulmonic vascular resistance (Woods Unit) | 2 ± 2 |
| **Echocardiography** | |
| Left ventricular ejection fraction | 20 ± 9 % |
| Left ventricular end-diastolic volume (ml) | 217 ± 96 |
| Left ventricular end-diastolic diameter (cm) | 6.6 ± 1.1 |
| Right ventricular systolic dysfunction ≥ moderate | 59 % |
| Mitral valve regurgitation grade ≥ 2 | 53 % |
| Tricuspid valve regurgitation ≥ 2 | 31 % |

**Table 3. Predictors of all-cause mortality and cardiac transplantation on univariate analysis**

| VARIABLE | All-cause mortality | | | Cardiac transplantation | | |
|---|---|---|---|---|---|---|
| | Alive | Death | p value | No | Yes | p value |
| Ischemic etiology | 47 % | 49 % | ns | 48 % | 50 % | ns |
| Male | 73 % | 83 % | 0.009 | 75 % | 75 % | ns |
| Age (years) | 53 ± 11 | 57 ± 11 | 0.002 | 54 ± 11 | 54 ± 10 | ns |
| Caucasian | 85 % | 81 % | ns | 84 % | 84 % | ns |
| Body mass index (kg/m2) | 28 ± 6 | 28 ± 5 | ns | 29 ± 6 | 26 ± 5 | < 0.001 |
| Diabetes mellitus | 26 % | 30 % | ns | 27 % | 27 % | ns |
| Hypertension | 74 % | 82 % | 0.024 | 78 % | 78 % | ns |
| Hyperlipidemia | 63 % | 64 % | ns | 64 % | 64 % | ns |
| Cardiac defibrillator | 39 % | 36 | ns | 36 % | 45 % | ns |
| Cardiac resynchronization therapy + defibrillator | 10 % | 6 % | ns | 7 % | 18 % | 0.003 |
| Beta blockers | 71 % | 65 % | ns | 70 % | 65 % | ns |
| Angiotensin converting enzyme inhibitor / angiotensin receptor blocker | 71 / 18 % | 74 / 17 % | ns | 72 / 16 % | 70 / 22 | ns |
| Digoxin | 66 % | 69 % | ns | 70 % | 64 % | ns |
| Spironolactone | 39 % | 35 % | ns | 35 % | 47 % | 0.019 |
| Isordil / Hydralazine | 37 % | 55 % | 0.019 | 41 % | 37 % | ns |
| Loop Diuretics | 90 % | 95 % | ns | 90 % | 97 % | 0.012 |

| | | | | | | |
|---|---|---|---|---|---|---|
| New York Heart Association class | 2.9 ± 0.3 | 3.1 ± 0.4 | ns | 3.0 ± 0.3 | 3.1 ± 0.2 | ns |
| Heart rate (bpm) | 80 ± 18 | 79 ± 17 | ns | 79 ± 17 | 82 ± 19 | ns |
| Atrial fibrillation | 7 % | 9 % | ns | 8 % | 8 % | ns |
| Mean arterial blood pressure (mmHg) | 85 ± 15 | 86 ± 14 | ns | 86 ± 14 | 84 ± 12 | ns |
| Central venous pressure (mmHg) | 7 ± 6 | 10 ± 6 | 0.007 | 8 ± 5 | 10 ± 5 | 0.012 |
| Mean pulmonary artery pressure (mmHg) | 26 ± 10 | 31 ±10 | 0.022 | 26 ± 10 | 33 ± 10 | < 0.001 |
| Pulmonary capillary wedge pressure (mmHg) | 17 ± 9 | 19 ± 8 | 0.013 | 16 ± 8 | 22 ± 8 | < 0.001 |
| Cardiac index (l/min/m2) | 2.5 ± 0.6 | 2.2 ± 0.4 | < 0.001 | 2.5 ± 0.6 | 2.0 ± 0.5 | < 0.001 |
| Pulmonic vascular resistance (Woods Unit) | 2.2 ± 1.4 | 2.8 ± 1.8 | 0.005 | 2.2 ± 1.5 | 2.7 ± 1.7 | 0.004 |
| Systemic vascular resistance (dynes/cm) | 1415 ± 443 | 1480 ± 439 | ns | 1389 ± 422 | 1581 ± 479 | 0.001 |
| Left ventricular ejection fraction | 20 ± 10 % | 19 ± 9 % | ns | 21 ± 10 % | 17 ± 7 % | < 0.001 |
| Left ventricular end-diastolic diameter (cm) | 6.5 ± 1.0 | 6.9 ± 1.4 | 0.009 | 6.5 ± 1.1 | 6.8 ± 1.0 | 0.013 |
| Right ventricular systolic dysfunction ≥ moderate | 56 % | 64 % | 0.02 | 51 % | 85 % | < 0.0001 |
| Mitral valve regurgitation grade ≥ 2 | 48 % | 65 % | < 0.0001 | 49 % | 68 % | 0.001 |
| Tricuspid valve regurgitation grade ≥ 2 | 27 % | 41 % | 0.004 | 27 % | 46 % | 0.002 |
| Hemoglobin (g/dl) | 13.5 ± 1.5 | 13.4 ± 2.0 | ns | 13.5 ± 1.7 | 13.4 ± 1.6 | ns |

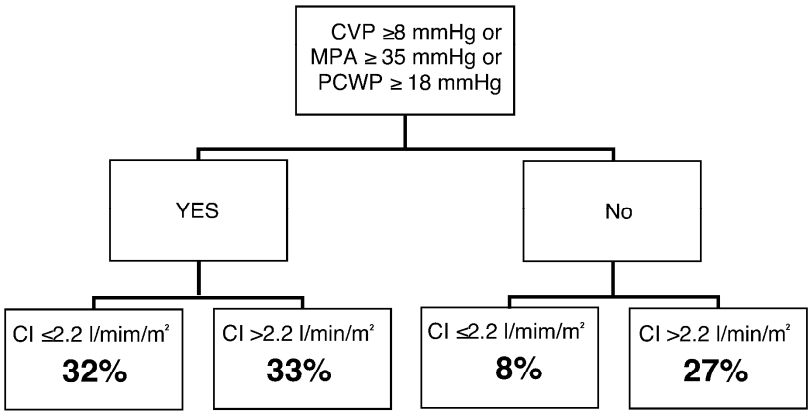
**Table 4. Predictors of all-cause mortality, cardiac transplantation and heart failure hospitalization on multivariate analysis**

| All-cause mortality | Hazard Ratio | 95% Confidence Interval | p-Value |
|---|---|---|---|
| Cardiac index | 0.46 | 0.299-0.707 | < 0.001 |
| Mean pulmonary artery pressure | 1.021 | 1.001-1.004 | 0.04 |
| Mitral valve regurgitation | 1.3 | 1.116-1.514 | 0.001 |
| Creatinine | 2.032 | 1.461-2.827 | < 0.001 |
| Age | 1.024 | 1.005-1.044 | 0.014 |

| Cardiac transplantation | Hazard Ratio | 95% Confidence Interval | p-Value |
|---|---|---|---|
| Cardiac index | 0.431 | 0.278-0.668 | < 0.001 |
| Mean pulmonary artery pressure | 1.075 | 1.033-1.078 | < 0.001 |
| Mitral valve regurgitation | 1.273 | 1.121-1.457 | 0.001 |

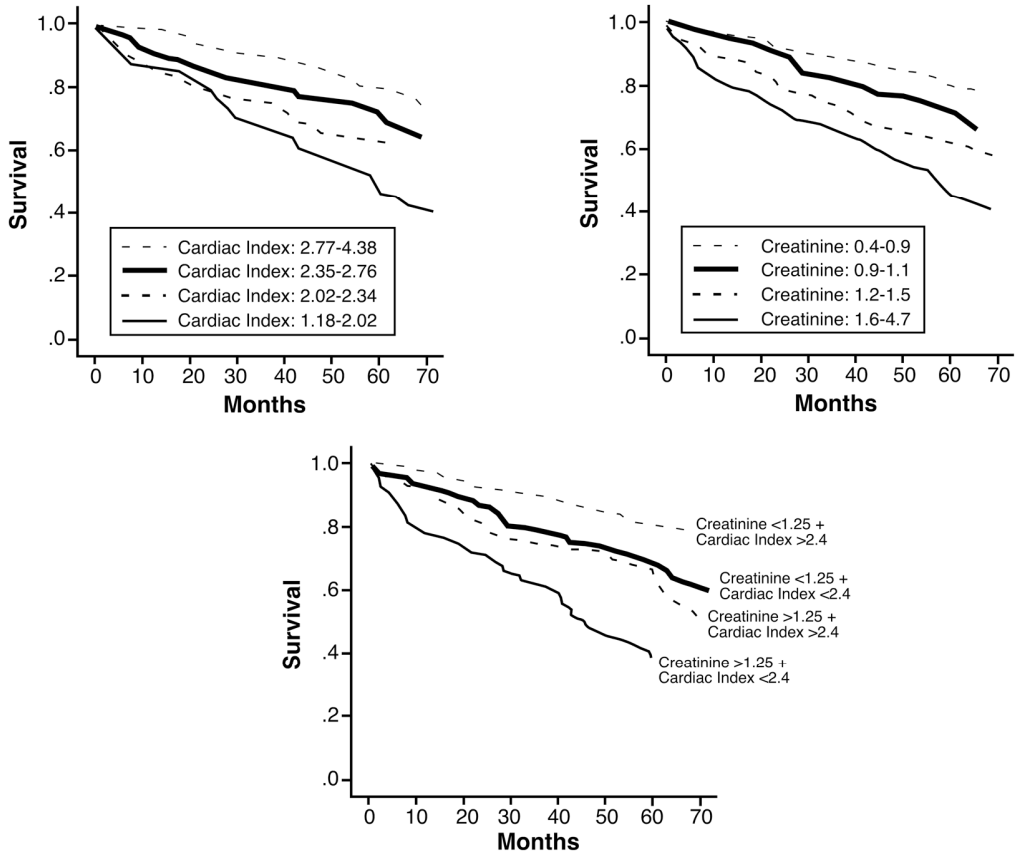
| Heart failure hospitalization | Hazard Ratio | 95% Confidence Interval | p-Value |
|---|---|---|---|
| Cardiac index | 0.702 | 0.518-0.951 | 0.023 |
| Mean pulmonary artery pressure | 1.027 | 1.007-1.044 | 0.007 |
| Mitral valve regurgitation | 1.19 | 1.077-1.316 | 0.001 |

**Figure 1. Patient population according to hemodynamic variables.**




PCWP: pulmonary capillary wedge pressure, CVP: central venous pressure, MPA: mean pulmonary artery pressure, CI: cardiac index.

**Figure 2. Kaplan-Meier curves of survival by quartiles of patients for cardiac index (upper panel), quartiles of patients for creatinine level (middle panel) and for medians of serum creatinine and cardiac index (lower panel).**




Log-Rank for all curves $p < 0.0001$. Cardiac index expressed as $l/min/m^2$, serum creatinine expressed as mg/dl.

## 2. Gender differences in patients admitted with advanced decompensated heart failure

Mullens W, Abrahams Z, Sokos G, Francis G, Starling R, Young J, Taylor D, Tang W. Gender Differences in Patients Admitted with Advanced Decompensated Heart Failure. Am J Cardiol 2008;102:454-458.

### a) Abstract

Broad population studies of stable ambulatory heart failure patients have associated female gender with a better age-adjusted survival. This study investigates whether there are gender-specific differences in clinical presentation, response to intensive medical therapy and outcomes in patients admitted with advanced (cardiac index < 2.4 l/min.m$^2$) decompensated heart failure (ADHF). We reviewed 278 consecutive patients (age 54 ±12 years, cardiac index 1.7 ±0.4 l/kg.m$^2$, pulmonary capillary wedge pressure 26 ±9 mmHg, serum creatinine 1.4 ±0.8 mg/dl) with ADHF treated with intensive medical therapy guided by pulmonary artery catheter in a dedicated heart failure intensive care unit between 2000-2006. Compared to men (n=226), women (n=52) had similar baseline characteristics with the exception of a higher prevalence of non-ischemic etiology. No differences in medical therapy on admission, during intensive medical therapy or at discharge were observed. Intensive medical therapy was associated with significant hemodynamic improvement independent of gender. All-cause mortality and heart failure rehospitalization rates were similar among genders. However, adjusted for etiology, women with ischemic cardiomyopathy had higher all-cause mortality rates (50 vs 37%, HR:1.95; p=0.05; 95% CI 0.98-3.90) and with nonischemic cardiomyopathy lower all-cause mortality rates (19% vs. 40%, HR:0.40; p=0.01; 95% CI 0.17-0.96) than men. In conclusion, women presenting with ADHF have similar baseline characteristics and response to therapy than men. Overall outcomes are comparable between men and women though subgroup analysis suggests a better survival for women with nonischemic etiology.

### b) Introduction

Women with heart failure have been reported to have a better age-adjusted survival rate than men with the same condition (1,2,3,4). Although earlier studies indicated that this benefit is

limited to women with nonischemic heart failure, recent data suggest that the survival benefit is sustained irrespective of etiology, including women with heart failure and preserved left ventricular systolic function (5,6,7). However, most studies interrogated datasets from clinical trials or large natural history databases with carefully selected stable and ambulatory chronic heart failure populations, independent of hemodynamic variables. In addition, potential gender-specific differences in clinical presentation, prognosis and response to treatment in patients admitted with advanced decompensated heart failure (ADHF) are lacking. Therefore, the aim of our study was to examine potential gender-specific differences in hospitalized patients with ADHF. An important objective was to compare invasive hemodynamic measurements as an objective assessment for disease severity, and to compare clinical responses to diuretic and vasoactive therapies between males and females.

**c) Methods**

**Subject Population**. We reviewed the electronic medical records of consecutive patients, age ≥18 years, with chronic (>6 months) systolic heart failure (New York Heart Association functional class III-IV), who underwent a right heart catheterization for evaluation of ADHF at the Cleveland Clinic between January 1, 2000 and December 31, 2006. From this large cohort, we narrowed our study population to include only patients admitted to the heart failure intensive care unit for intensive medical therapy. The inclusion criteria included: 1) impaired cardiac output, defined by cardiac index <2.4 l/min.$m^2$; and 2) evidence of congestion as determined by pulmonary capillary wedge pressure (PCWP) >18 mmHg and/or central venous pressure (CVP) >8 mmHg. Exclusion criteria included patients: 1) on mechanical ventilation; 2) on renal replacement therapy; 3) on intravenous inotropic support on admission; 4) with congenital heart disease; 5) recipients of heart transplantation. Institutional Review Board approval of this research project was obtained, and informed consent was obtained for hospitalization, treatment and all invasive procedures and documented in the medical records, according to protocol and Cleveland Clinic policy.

**Intensive Medical Therapy.** The hemodynamic goals and pharmacologic approach of intravenous therapy in a dedicated heart failure intensive care unit have been previously described (8). Briefly, optimal hemodynamic response was defined as a decrease in PCWP to <18 mmHg, decrease in CVP to <8 mmHg, and improvement in cardiac index to ≥2.4 l/min/$m^2$,

all while maintaining mean arterial pressure >65-70 mmHg. In order to achieve these hemodynamic goals, all subjects were treated according to standardized protocols included intravenous loop diuretics in combination with intravenous vasodilators (and/or inotropic agents), while continuing and optimizing evidence-based therapies as tolerated. Standard patient education materials and counseling were given to the patient at the time of admission, and post-discharge follow-up was provided by a heart failure disease management clinic.

**Data Collection and Renal Assessment.** Two experienced heart failure cardiologists manually collected hemodynamic data. Additional data were recorded including demographic characteristics, medical history, and treatment information. Sequential serum creatinine values were recorded on admission and daily throughout the hospitalization period including the day of discharge. Glomerular filtration rate (GFR) in ml/min was estimated daily using the four-variable Modification of Diet in Renal Disease equation (9). Normal or mild renal insufficiency as described by the National Kidney Foundation was defined as GFR $\geq$60 ml/min.1.73m$^2$. Moderate renal insufficiency was defined as GFR 30-59 ml/min.1.73m$^2$ and severe renal insufficiency as GFR <30 ml/min.1.73m$^2$.

**Hemodynamic Assessment.** Complete hemodynamic assessment was collected in all subjects before the start of intensive medical therapy, and again at the end of intensive medical therapy before removing the pulmonary artery catheter. The CVP and PCWP were assessed at end-expiration with a balloon-tipped catheter at steady state with the subject in a supine position. Cardiac index was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. The systemic blood pressure was measured non-invasively by an automatic cuff sphygmomanometer.

**Endpoints.** Three prespecified end-points were analyzed and compared between males and females during follow-up: all-cause mortality, all-cause mortality or cardiac transplantation, and first readmission for heart failure following discharge. Death was determined using data documented in the medical record and confirmed by surveying the Social Security Death Index.

**Statistical analysis.** All data are expressed as mean ± standard deviation for continuous variables and as a ratio for categorical data. Univariate and multivariate comparisons of these variables were performed between genders for the different endpoints using SPSS for Windows, Release 13.0 (SPSS Inc., Chicago, Illinois). A paired and unpaired t-test for continuous data and

the chi-square test for categorical variables were used for appropriate comparisons. The Cox Proportional hazards regression model was used to determine which variables were related significantly to the different endpoints during the follow-up period. Variable selection in multivariable modeling was based on statistical significance of the univariate analysis or identified as important in other studies (age, New York Heart Association functional class, ischemic etiology, diabetes mellitus, arterial hypertension, smoking, heart rhythm, renal function and race). In addition, adjusted hazard ratios for all-cause mortality comparing genders for prespecified patient subgroups defined by etiology, diabetes mellitus, race, heart rhythm, smoking and arterial hypertension were calculated. Kaplan-Meier curves were constructed for the different end-points. Statistical significance was set at a two-tailed probability level of less than 0.05. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**d) Results**

**Sex and baseline characteristics.** A total of 278 patients (19% women) fulfilled all inclusion and exclusion criteria (Table 1). Incidence of atrial fibrillation was similar among genders (15%). Female patients with ischemic etiology were older than females with idiopathic dilated etiology (58±9 years vs 51±12 years, p=0.02).

**Use of Concomitant Medications.** As shown in Table 2 adherence to optimal pharmacological therapy was high on admission and discharge, and except for isosorbide dinitrate comparable among genders. There was a trend toward more use of inotropic agents at the time of discharge in male patients. Use of spironolactone was lower while use of digoxin was higher in males at discharge.

**Hemodynamic Assessment.** As shown in Table 3, all patients had severe hemodynamic derangements with the female patients presenting with higher CVP, while demonstrating a similarly low cardiac index and high PCWP. Furthermore, the average mean arterial pressure at baseline was slightly lower in females than in males. When compared with the initial hemodynamic assessment, statistically significant reductions of right and left sided filling pressures and increase in cardiac index were achieved in both gender groups. However, the total reduction in intracardiac pressures and increase in cardiac index was slightly higher in the female patients. A significant reduction in mean arterial pressures was noticed in both cohorts during

treatment, but overall mean arterial pressure on discharge was comparable between two groups. Of note, none of the patients had complications during insertion of the pulmonary artery catheter and none of the early deaths could be directly attributed to catheter related complications.

**Clinical Outcomes.** Patients were followed for a median duration of 54 months after the index hospitalization. No patient was lost to follow-up. There were 104 (38%) deaths and 69 (25%) cardiac transplantations. Female gender was not associated with worse outcomes as defined by all-cause mortality (unadjusted HR: 0.84; 95% CI 0.45-1.42; p=0.5), all-cause mortality / cardiac transplantation (unadjusted HR: 0.86; 95% CI 0.56-1.29; p=0.5) or heart failure hospitalization (unadjusted HR: 1.06; 95% CI 0.68-1.63; p=0.8) (Figure 1). Both early and late all-cause mortality (defined as within or after 30 days of admission) were similar in females compared with males.

To further validate our findings, we performed a sub-analysis to compare hazard ratios for all-cause mortality comparing genders for prespecified patient subgroups adjusted for treatment group (Figure 2). Compared with men, women with ischemic cardiomyopathy had higher all-cause mortality (50 vs 37%, p=0.05) and women with dilated cardiomyopathy had lower all-cause mortality (19% vs. 40%, p=0.01), which could not be attributed to differences in baseline characteristics between groups. There were no differences in crude mortality rate or hazard ratio for the other pre-specified variables.

On uni- and multivariate analysis, the absence of a beta-adrenergic blocker on admission, the presence of inotropic therapy during admission or at discharge and lower GFR on admission, peak or discharge were all associated with higher all-cause mortality (all p <0.03), and this independent of gender. However, adjusted for different degrees of renal impairment on admission, peak or discharge indicated that degree of renal dysfunction was not associated with a higher or lower hazard ratio in women compared with men (Figure 3).

**e) Discussion**

The unique setting of a dedicated heart failure intensive care unit operated by experienced heart failure specialists and where patients are treated with intensive medical therapy guided by pulmonary artery catheter enabled us to examine the effect of gender in a large cohort of patients with ADHF. The key clinical implication is that guideline recommended care is well tolerated by females and can be safely administered to achieve significant hemodynamic

improvement. Crude clinical outcomes do not differ among males and females, though a small survival benefit is seen in females with nonischemic etiology of heart failure. Taken together, female patients with ADHF tolerate guideline recommend care as well as their male counterparts leading to overall similar outcomes.

The prognosis for male and female patients is similar even when corrected for several baseline characteristics that reflect known markers of prognosis in heart failure, though these may differ between men and women, including race, diabetes mellitus, hypertension, smoking, heart rhythm and renal dysfunction. A small survival benefit was apparent in females with nonischemic heart failure, while there was a trend toward worse survival in ischemic heart failure (though the confidence interval for ischemic heart failure was wider). Fundamental differences in response to the underlying etiology, probably related to different sex hormones, may account for these observed outcome differences (10). It also has been well-established in animal and human models that the progression of heart failure, especially in nonischemic models, is attenuated in females compared with males (11,12,13,14,15,16). The findings reported here are consistent with previous work that gender-related differences are dependent on the cause of heart failure rather than the treatment given. The fact that both gender groups had advanced and long-standing severe heart failure with similar hemodynamic dearangments on presentation nullifies the argument that the study findings could have resulted from differences in the timing of presentation or severity of disease. In addition, all patients were closely followed in a dedicated heart failure clinic after discharge thereby ensuring compliance to medical therapy.

The presence of a low cardiac output and elevated intracardiac filling pressures in the setting of ADHF represents a very high-risk patient. The ability to safely add intensive medical therapy to standard optimal medical therapy irrespective of gender is of great reassurance. Of particular importance, we observed no greater incidence of hypotension or worsening renal dysfunction during hospitalization in female patients. In addition, our study clearly indicates the overall hemodynamic improvement after intensive medical treatment are similar, if not greater, in women than in men.

Obvious limitations inherent to the retrospective study design should be considered when these findings are interpreted. Comprehensive follow-up, review of events, and centralized adjudication minimized the potential for missed or misclassified outcomes. Pre- or postmenopausal status could not be obtained since sex hormone levels are not routinely

measured. The mechanism of death could not be ascertained, but other studies of advanced heart failure suggest that a majority of patients die of progressive pump failure (17). Accurate estimates about previous heart failure hospitalizations, coronary artery disease severity, and duration of vasoactive therapies administered and medication doses could not be retrieved due to logistic limitations.

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**Table 1. Baseline patient characteristics**

| Variable | Female (n=52) | Male (n=226) | p-value |
|---|---|---|---|
| Age (years) | 54±12 | 55±12 | ns |
| Caucasian | 79 % | 81 % | ns |
| African-American | 21 % | 19 % | ns |
| NYHA Classification III / IV | 38 % / 62 % | 37 % / 63 % | ns |
| Hypertension | 61 % | 66 % | ns |
| Hyperlipidemia | 52 % | 58 % | ns |
| Diabetes | 29 % | 31 % | ns |
| Smoking | 26 % | 58 % | < 0.001 |
| ICD / CRT-D | 42 % / 18 % | 41 % / 20 % | ns |
| Ischemic etiology | 39 % | 55 % | 0.02 |
| Idiopathic dilated etiology | 61 % | 45 % | 0.02 |
| Left ventricular ejection fraction | 17±8 % | 16±7 % | ns |
| Hemoglobin (g/dl) | 12.5±2.1 | 12.9±1.9 | ns |
| Sodium (mmol/l) | 134±17 | 136±4 | ns |
| Creatinine admission (mg/dl) | 1.3±0.9 | 1.5±0.7 | 0.09 |
| GFR admis(ml/min/1.72.m2) | 63±31 | 63±28 | ns |
| Creatinine peak (mg/dl) | 1.4±0.9 | 1.7±0.8 | 0.013 |
| GFR peak (ml/min/1.72.m2) | 62±31 | 60±29 | ns |
| Creatinine discharge (mg/dl) | 1.2±0.7 | 1.5±0.7 | 0.004 |
| GFR disch (ml/min/1.72.m2) | 70±38 | 64±27 | ns |
| Brain natriuretic peptide (pg/ml) | 1386±1076 | 1204±1115 | ns |

**Table 2. Use of medication on admission, during hospitalization and at discharge**

| | Female (n=52) | Male (n=226) | p-value |
|---|---|---|---|
| **On admission** | | | |
| Aspirin / Clopidogrel | 38 % | 45 % | ns |
| Coumadin | 51 % | 48 % | ns |
| Angiotensin converting enzyme inhibitor / angiotensin receptor blocker | 70 % | 74 % | ns |
| Digoxin | 51 % | 54 % | ns |
| Beta-blocker | 65 % | 65 % | ns |
| Spironolactone | 40 % | 38 % | ns |
| Loop Diuretic | 90 % | 94 % | ns |
| Hydralazine | 17 % | 16 % | ns |
| Isosorbide dinitrate | 16 % | 28 % | 0.02 |
| Statin | 44 % | 46 % | ns |
| Insulin | 14 % | 15 % | ns |
| **During hospitalization** | | | |
| Nitroprusside | 48 % | 46 % | ns |
| Dopamine | 5 % | 2 % | ns |
| Dobutamine | 23 % | 30 % | ns |
| Milrinone | 28 % | 26 % | ns |
| Dobutamine or milrinone | 51 % | 52 % | ns |
| Norepinephrine | 1 % | 1 % | ns |
| Intra-aortic balloon pump | 3 % | 2 % | ns |
| Ultrafiltration / Dialysis | 2 % | 2 % | ns |
| **On discharge** | | | |
| Aspirin / Clopidogrel | 37 % | 50 % | ns |
| Warfarin | 48 % | 41 % | ns |
| Angiotensin converting enzyme inhibitor / angiotensin receptor blocker | 85 % | 86 % | ns |
| Digoxin | 46 % | 65 % | 0.03 |

| | | | |
|---|---|---|---|
| Beta-blocker | 65 % | 61 % | ns |
| Spironolactone | 70 % | 52 % | 0.02 |
| Loop Diuretic | 88 % | 96 % | ns |
| Hydralazine | 37 % | 40 % | ns |
| Isosorbide dinitrate | 55 % | 57 % | ns |
| Statin | 41 % | 44 % | ns |
| Dobutamine | 3 % | 8 % | 0.04 |
| Milrinone | 12 % | 11 % | ns |
| Dobutamine or milrinone | 13 % | 16 % | ns |

**Table 3. Hemodynamics on admission and time of pulmonary-artery catheter removal**

| | Female (n=52) | | | Male (n=226) | | |
|---|---|---|---|---|---|---|
| | **Admission** | **Discharge** | **p-value** | **Admission** | **Discharge** | **p-value** |
| Mean arterial pressure (mmHg) | 80±10 | 73±8 | 0.005 | 83±12 | 74±9 | <0.001 |
| Systolic blood pressure (mmHg) | 108±16 | 103±15 | 0.005 | 111±17 | 105±10 | <0.001 |
| Central venous pressure (mmHg) | 16±6 | 7±5 | 0.01 | 14±10 | 10±6 | <0.001 |
| Systolic pulmonary artery pressure (mmHg) | 54±20 | 44±12 | 0.005 | 56±15 | 46±13 | <0.001 |
| Pulmonary capillary wedge pressure (mmHg) | 26±10 | 15±6 | 0.006 | 26±8 | 19±5 | <0.001 |
| Cardiac index (l/min/m2) | 1.7±0.3 | 2.4±0.5 | <0.001 | 1.7±0.3 | 2.3±0.5 | <0.001 |
| Systemic vascular resistance (dynes/cm5) | 1671±593 | 1180±397 | <0.001 | 1607±486 | 1238±1438 | 0.01 |

**Figure 1. Kaplan Meier curve for different end-points stratified to gender.**

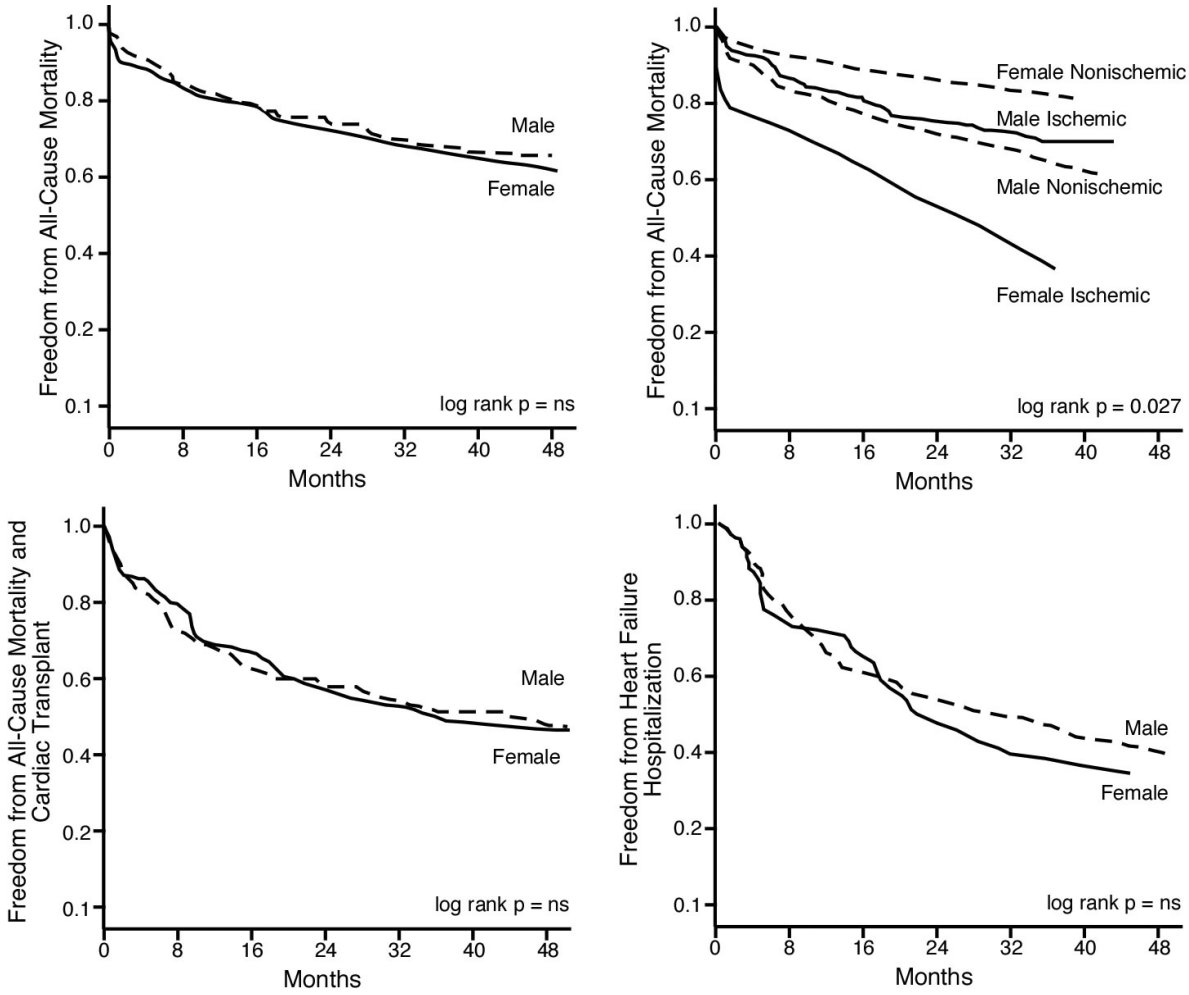


**Figure 2. Hazard ratios for all-cause mortality comparing genders for presecified patient subgroups adjusted for treatment group.**

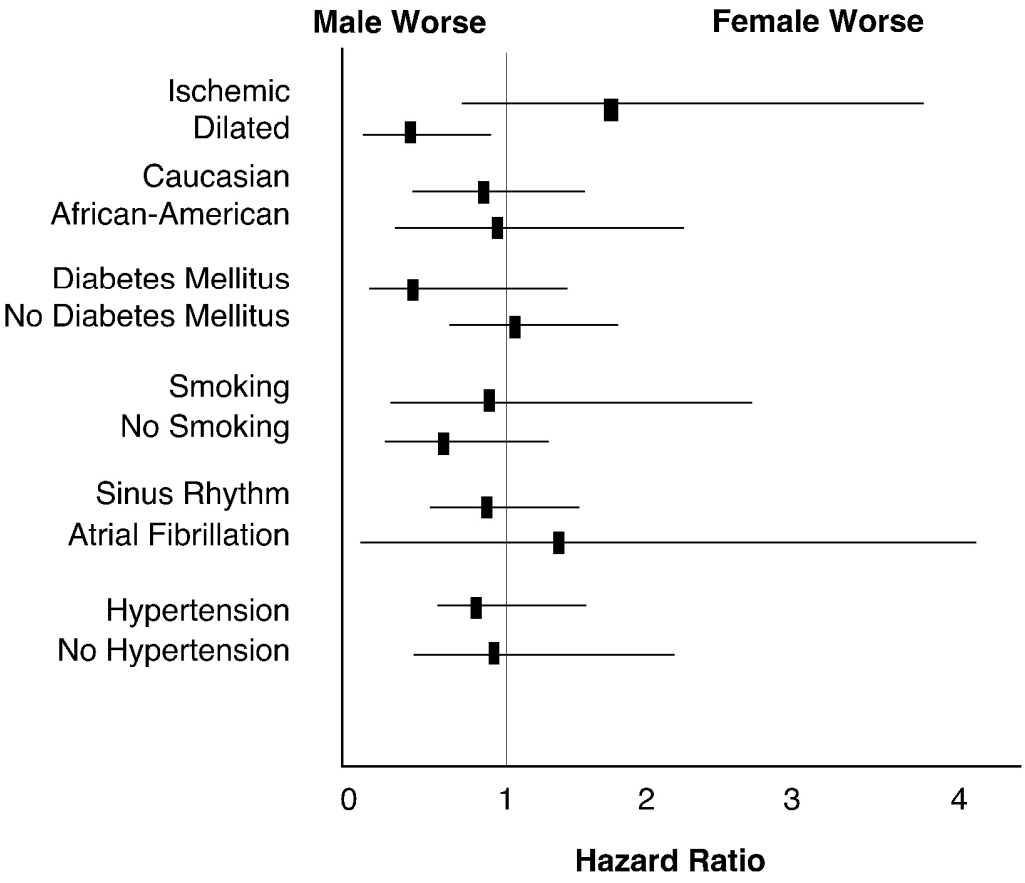
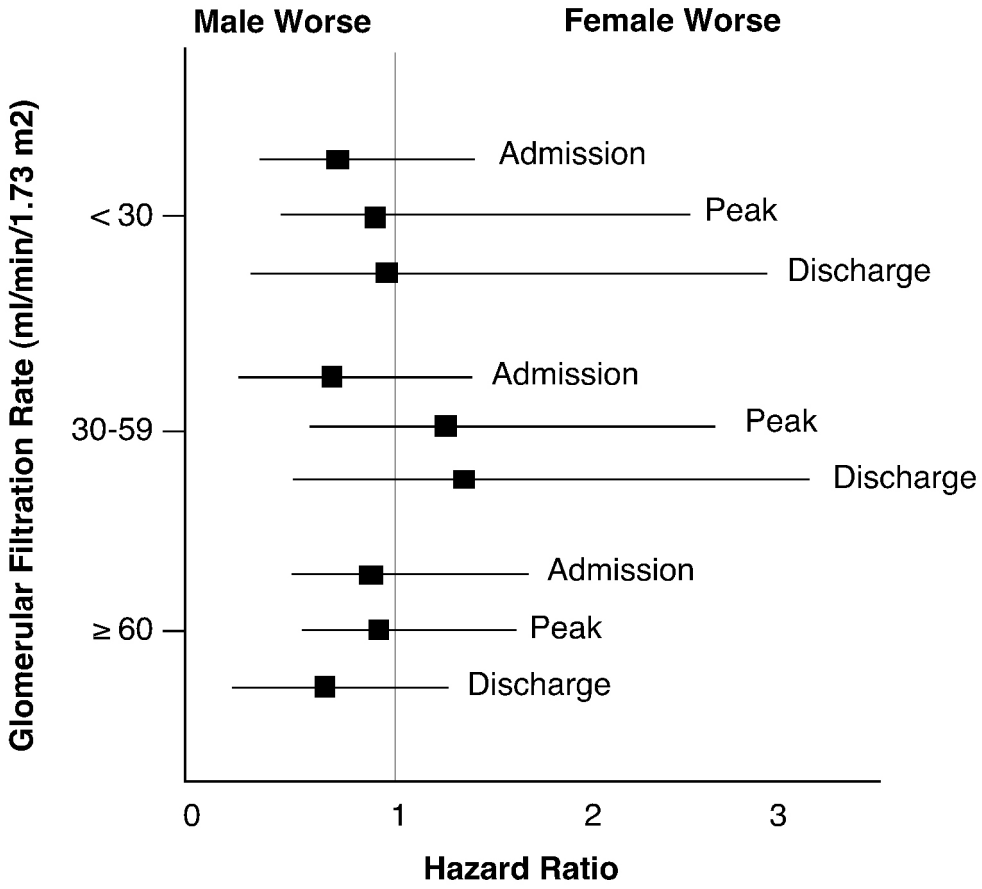


**Figure 3. Hazard ratios for all-cause mortality comparing genders for prespecified renal function subgroups on admission, peak level during hospitalization, and discharge.**



## 3) Sodium nitroprusside for advanced low-output heart failure

Mullens W, Abrahams Z, Skouri H, Taylor D, Starling R, Young J, Francis G, Tang W. Sodium Nitroprusside for Advanced Low-Output Heart. J Am Coll Card 2008;52:200-7.


**a) Abstract**

**Objectives:** To examine the safety and efficacy of sodium nitroprusside (SNP) for patients with acute decompensated heart failure (ADHF) and low output states.

**Background:** Inotropic therapy has been predominantly used in the management of patients with ADHF presenting with low cardiac output.

**Methods:** We reviewed all consecutive patients with ADHF admitted between 2000-5 with a cardiac index $\leq$ 2L/min/$m^2$ for intensive medical therapy including vasoactive drugs. Administration of SNP was chosen by the attending clinician, non-randomized and titrated to a target mean arterial pressure of 65-70 mmHg.

**Results:** Compared to controls (n=97), cases treated with SNP (n=78) had significantly higher mean central venous pressure (15 vs. 13 mmHg; p=0.001), pulmonary capillary wedge pressure (29 vs. 24 mmHg; p=0.001), but similar demographics, medications, and renal function at baseline. Use of SNP was not associated with higher rates of inotropic support or worsening renal function during hospitalization. Patients treated with SNP achieved greater improvement in hemodynamic measurements during hospitalization, had higher rates of oral vasodilator prescription at discharge, and had lower rates of all-cause mortality (29% versus 44%; OR: 0.48; p=0.005; 95% CI 0.29-0.80) without increase in re-hospitalization rates (58% versus 56%; p=ns).

**Conclusion**: In patients with advanced, low-output heart failure, vasodilator therapy used in conjunction with optimal current medical therapy during hospitalization might be associated with favorable long-term clinical outcomes irrespective of inotropic support or renal dysfunction and remains an excellent therapeutic choice in hospitalized ADHF patients.


**b) Introduction**

Advances in medical therapies (such as neurohormonal modulation and pacing/defibrillation strategies) have significantly altered the natural history of heart failure and

improved long-term outcomes (1-5). However, the pathophysiology and treatment of acute decompensated heart failure (ADHF) remains poorly understood, especially in more advanced stages when cardiac output is significantly reduced. Our treatment goal remains symptomatic relief, primarily by decreasing volume overload and attenuating pulmonary congestion with loop diuretics. In the setting of a low cardiac output, augmentation of contractility with parenteral inotropic therapy is often utilized. However, vasoactive drugs are often administered at the expense of a potential risk of developing adverse outcomes including worsening renal function or precipitating arrhythmias (6,7,8). Concern has also arisen from post-hoc observations that short-term infusions of newer drugs like levosimendan, milrinone, and nesiritide in hospitalized ADHF patients might negatively impact long-term outcomes (9,10,11).

There is a resurgence of interest in the use of intravenous vasodilators in the management of ADHF, particular with the recognition that a large majority of patients present with elevated rather than low blood pressures (12). The latest clinical guidelines from the Heart Failure Society of America advocate the use of intravenous vasodilators as part of the treatment strategy for ADHF (level of evidence C) (13). Despite these guideline recommendations, only about 18% of all patients hospitalized for ADHF received these agents and <1% received sodium nitroprusside (SNP) (14).

Sodium nitroprusside is an older intravenous vasodilator, often being used to titrate off inotropic therapy in patients with refractory heart failure (15). It is administered almost exclusively in critical care settings with careful invasive hemodynamic monitoring due to the risk of inducing hypotension. Furthermore, prolonged use of SNP has been associated with the risk of thiocyanate toxicity. These concerns have hindered the general enthusiasm in using SNP in the contemporary management of ADHF, even though the favorable hemodynamic effects have been well documented.

Based on our large experience with SNP over many years in a heart failure intensive care unit, the primary aim of this paper was to examine the safety and efficacy of vasodilator such as SNP as part of the treatment regimen for hospitalized ADHF patients with low output states. An important objective is to characterize the group selected to receive SNP and compare it to those patients treated with alternative strategies, and to determine if there were any short-term and long-term differences in treatment patterns and clinical outcomes between the two groups. There are no similar data currently available in the contemporary literature.

**c) Methods**

**Patient population**. We reviewed the electronic medical records of consecutive patients, age ≥18 years, with chronic (>6 months) systolic heart failure (New York Heart Association class III-IV), who underwent a right heart catheterization for evaluation of ADHF at the Cleveland Clinic between January 1, 2000 and December 31, 2005. From this large cohort, we narrowed our study population to include only patients actually admitted to the heart failure intensive care unit for intensive medical therapy (15). The inclusion criteria included: 1) impaired cardiac output defined by cardiac index ≤2.0 L/min/$m^2$; and 2) elevated filling pressures, as defined by pulmonary capillary wedge pressure (PCWP) ≥18 mmHg and/or right atrial pressure ≥8 mmHg. Exclusion criteria included: 1) use of inotropic infusion at the time of cardiac catheterization; 2) use of nesiritide during admission; 3) mean systemic arterial pressure (MAP) ≤60 mmHg at the time of cardiac catheterization. The Cleveland Clinic Institutional Review Board has approved this project.

**Protocol for intensive medical therapy.** The pharmacologic approach and hemodynamic goals of intravenous therapy for ADHF have been previously described (16). Briefly, optimal hemodynamic response is defined as a decrease in PCWP to ≤18 mmHg, decrease in mean pulmonary arterial pressure (mPAP) by at least 20%, decrease in right atrial pressure to ≤8 mmHg and improvement in cardiac index to ≥2.2 l/min/$m^2$, all while maintaining MAP >65 mmHg. The systemic blood pressure was generally measured non-invasively by an automatic cuff sphygmomanometer every 15 minutes. In order to achieve the hemodynamic goals, most patients were treated with simultaneous intravenous diuretics in combination with either vasodilators or inotropic agents while continuing previous therapies with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta-adrenergic blockers, hydralazine, isosorbide dinitrate and spironolactone as tolerated. Some patients received both SNP and inotropic drugs, and for purposes of this analysis are considered in the SNP group.

**Sodium nitroprusside infusion protocol.** The decision to use SNP and/or inotropic therapy was at the discretion of the physician caring for the patient and no randomization scheme was employed. In addition, there might have been some selection bias towards more use of vasodilators in case of higher blood pressure although we also often use vasodilators to wean people from inotropic or IABP support. SNP was administered intravenously by a continuous infusion at a dose of 10-400 mcg/min (without bolus) as needed to improve hemodynamics

(Figure 1). Titration of SNP dose was based on achieving a target MAP of 65-70 mmHg and mainly done by nursing staff who are well-trained and experienced in the use of SNP, and are able to titrate drugs without continuous physician input. Once MAP goals achieved (usually within 24 hours), and optimal hemodynamic measures maintained, SNP infusion was gradually weaned by instructing the MAP to be maintained at 65-70 mmHg. Doses of neurohormonal antagonists, and/or a combination of hydralazine and isosorbide dinitrate were continued or up-titrated to guideline recommended therapeutic doses. Titration of oral drugs follows standard protocols (Figure 1) in our intensive care unit, but the sequence of drugs was also at the attending cardiologist's discretion. The duration of infusions of intravenous agents in the intensive care unit varied widely, but typically between 24-72 hours. Standard patient education materials and counseling were given to the patient at the time of admission, and post-discharge follow-up was provided by a heart failure disease management clinic.

**Hemodynamic assessment.** Central venous pressure, right atrial pressure, systolic, diastolic, mPAP, and PCWP were assessed on admission at end-expiration with a balloon-tipped catheter at steady state with the patient in a supine position. Cardiac output was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. All initial measurements were performed at the cardiac catheterization laboratory for consistency of results reporting.

**Endpoints.** Three pre-specified end-points were analyzed and compared between cases and controls during follow-up: all-cause mortality, cardiac transplantation, and first readmission for HF following discharge. A combined endpoint of all-cause mortality and cardiac transplantation was also analyzed. The duration of total follow-up was defined as the interval from the index right heart catheterization on the day of admission to all-cause mortality or cardiac transplantation. Death was determined using data documented in the medical record and confirmed by surveying the Social Security Death Index.

**Statistical Analysis.** All data are expressed as mean ± standard deviation for continuous variables and as a ratio for categorical data. Univariate and multivariate comparisons of these variables were performed between both treatment groups for the different endpoints using SPSS for Windows, Release 11.5 (SPSS Inc., Chicago, Illinois). A paired and unpaired t-test for continuous data and chi-square or Fisher's exact test for categorical data was used for appropriate comparisons. All continuous variables were assessed for normal distribution and

otherwise non-parametric tests were employed. The Cox Proportional hazards regression model was used to determine which variables were related significantly to the different endpoints during the follow-up period. Variable selection in multivariable modeling was based on statistical significance of the univariate analysis. Statistical significance was set at a two-tailed probability level of less than 0.05. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**d) Results**

**Baseline characteristics.** A total of 175 patients fulfilled all inclusion and exclusion criteria. Of these, 78 received SNP during their hospitalization (cases) and 97 did not receive SNP (controls). Baseline clinical characteristics were similar among patients in the two study groups (Table 1). Mean intensive care and hospital duration was 3.5 ±1 and 8 ±7 days respectively and was also similar between groups. Brain natriuretic peptide measurements within 3 days of admission were available in 32% eligible subjects, and were comparable between SNP-treated and non-SNP-treated patients (median;25%-75%: 823;577-1445 vs 987;571-1200 pg/ml).

**Hemodynamic Assessment.** As shown in Table 2A the patients treated with SNP presented with higher baseline filling pressures and systemic- and pulmonic vascular resistance, while demonstrating a lower cardiac output and cardiac index. Furthermore, the average mean arterial blood pressure and systolic blood pressure at baseline was slightly higher in the SNP cases than in controls. Mean LVEF, LV end-diastolic diameter and severity of mitral regurgitation (assessed within three days of admission) were similar between the two groups. Of note, none of the patients had complications during insertion of the pulmonary artery catheter (PAC) and none of the early deaths could be directly attributed to catheter related complications.

Hemodynamic assessments at the time of removal of the PAC were retrievable in 63% of the study patients (Table 2B). Missing data were due to incomplete recording of hemodynamic data in the charts and not attributable to futility in achieving hemodynamic targets. When compared with the initial hemodynamic assessment, statistically significant reduction of mPAP and increase in cardiac index were achieved in both groups. However, reduction in intracardiac pressures and the increase in cardiac index were higher in the SNP treated patients, though the overall mean hemodynamic measurements at the time of PAC removal were similar between the two groups. Only cardiac index at this time was higher in the SNP treated patients (p=0.0156).

In the same cohort of patients, we also retrieved the last MAP measured before discharge from the hospital after optimization with oral medications. A significant reduction in MAP was noticed in both cohorts, but overall MAP on discharge was similar between the two groups.

**Use of Concomitant Medications.** As shown in Table 3, adherence to optimal pharmacological therapy was high on admission and discharge, and comparable between the two groups. Patients treated with SNP had higher use of beta-adrenergic blockers on admission but not on discharge. The percentage of patients treated with other agents during hospitalization was similar in both groups. There was a trend towards more use of inotropic agents at discharge in patients not treated with SNP. The use of isosorbide dinitrate and hydralazine separately and/or in combination at the time of discharge was significantly higher in patients treated with SNP. Use of oral vasodilators did not differ between Caucasian or African-American patients.

**Clinical Outcomes.** Patients were followed for a median duration of 25.7 months (379 patient years) after the index right heart catheterization. No patient was lost to follow-up. There were 66 (38%) deaths and 60 (34%) cardiac transplantations. Primary outcome differences between two cohorts are shown in Table 4. Treatment with SNP during hospitalization was associated with lower all-cause mortality (OR: 0.48; p=0.005; 95% CI 0.29-0.80) and all-cause mortality / cardiac transplantation (OR: 0.64; p=0.016; 95% CI 0.45-0.92) when compared to those not treated with SNP (Figure 2). Both early and late all-cause mortality (defined as within or after 30 days after admission) were significantly lower in the SNP treated patients (both p values <0.01). The two treatment groups did not differ in cardiac transplantation or heart failure re-hospitalization rates. Median time to first heart failure re-hospitalization, cardiac transplantation and death were 8, 8.6, and 17.3 months, respectively, and did not differ significantly between the two cohorts. Use of SNP was not associated with an increased use of inotropic therapy, nor did it contribute to worsening renal dysfunction during hospitalization. Blood sampling for thiocyanate toxicity was not routinely performed. However, no clinical signs of thiocyanate toxicity were noted in any patient receiving SNP.

To further validate our findings, we performed a sub-analysis to include only the patients with a MAP of $\leq$ 85 mmHg. In this cohort, use of SNP was still associated with reduced all-cause mortality (p=0.0001) and the combined endpoint of all-cause mortality plus cardiac transplantation (p=0.02). Also, if patients who received an inotropic agent at discharge were excluded from the analysis, use of SNP was still associated with reduced all-cause mortality

(p=0.003) and all-cause mortality / cardiac transplantation (p=0.03). Finally, although the use of oral vasodilators was not associated with improved outcomes on univariate analysis, a successful transition from SNP to oral vasodilators at the time of discharge was associated with reduced all-cause mortality independent from race (p=0.03).

On univariate analysis, the absence of diabetes mellitus, presence of beta-adrenergic blocker on admission, absence of inotropic therapy during admission, lower creatinine during hospitalization and at discharge, and SNP use during hospitalization were all associated with lower all-cause mortality and all-cause mortality / cardiac transplantation (all $p < 0.01$). When these parameters were entered in a multivariate model for all-cause mortality, SNP use remained an independent predictor of survival (Table 5).

**e) Discussion**

The key finding of our retrospective, non-randomized case-control series is that vasodilator therapy with SNP, in an in-patient setting of guideline recommended care, can be safely administered to achieve hemodynamic improvement in patients presenting with advanced low output heart failure. Importantly, our observations suggest that the use of SNP according to a clinical protocol based on achieving a target MAP is associated with more hemodynamic improvement that may facilitate the institution of a more aggressive oral vasodilator regimen over standard neurohormonal antagonists at the time of discharge. Taken together, the use of SNP was associated with significantly lower all-cause mortality and fewer clinical adverse events at long-term follow-up, irrespective of the use of inotropic therapy or underlying renal function. These data underscore the importance of assessing the potential for adding vasodilator therapy in patients with advanced low output heart failure yet seemingly reasonable mean arterial blood pressure.

Despite clinical evidence suggesting hemodynamic and concordant clinical improvement, there has been limited data on the impact of continuous infusion of SNP on long-term outcomes in ADHF. Furthermore, SNP is infrequently used today for ADHF exacerbations especially when the cardiac output is significantly depressed and blood pressure is marginal (17,18,19). The dual arteriolar and venous effects of SNP appear to contribute to the immediate hemodynamic response of the drug (20). Dilation of the arterial resistance vessels reduces LV afterload and allows the severely compromised LV to eject more blood. The venodilator effect increases

venous capacitance and reduces congestion. Both effects lead to an increase in cardiac output in patients with heart failure and often reduce the basal tachycardia. We expect there is a reluctance of physicians to use SNP in hospitalized ADHF patients with low cardiac output or marginal blood pressure. This stems from the misguided belief that vasodilatation could potentially be risky if systemic vascular resistance is reduced without any compensatory increase in CO, leading to significant hypotension and downward spiraling of detrimental hemodynamic support. This concept, however, is an oversimplification of the usual cardiac hemodynamics observed, typically in patients with severe LV systolic dysfunction with increased ventricular volumes. The substantial improvement in cardiac output more than offsets any fall in blood pressure under most circumstances. As a result, a reduction in afterload or wall stress during SNP administration usually leads to a marked increase in cardiac output, preventing the development of significant hypotension. Our data corroborate this hypothesis, as we observed that the SNP treated patients had a statistically greater increase in cardiac index without substantial reduction in MAP when compared to the non-SNP treated control cohort.

Alternative treatment strategies in these critically ill hospitalized ADHF patients include intravenous infusion of inotropic therapy. These drugs can lead to symptomatic and hemodynamic improvement, but at the cost of increased risk for ischemic events, tachyarrhythmias, and long-term mortality (14,21). In contrast to inotropic therapies, SNP is energetically neutral and reduces myocardial oxygen consumption by a reduction in LV wall tension. Furthermore, increased coronary perfusion pressure via coronary vasodilatation can lead to a protective effect on the already compromised myocytes (22,23,24). Likely SNP improves cardiac output, but not at the expense of increased myocardial oxygen demand.

The presence of a low cardiac output and elevated intracardiac filling pressures in the setting of ADHF represents a very high-risk individual, and the ability to safely add SNP to standard optimal medical therapy, is of great reassurance. It is important to emphasize that the profile of our patient population has important differences from recent large scale clinical registries like ADHERE (Acute Decompensated Heart Failure National Registry), and from the recently published ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) (12,25). With an annual mortality plus cardiac transplantation rate as high as 50%, our patient cohort likely has far more advanced disease than those in ADHERE registry or even ESCAPE trial. While the ESCAPE trial has raised concerns

about the risk-benefit ratio of *routine* invasive hemodynamic monitoring in patients hospitalized with ADHF, our study at least lends some credit of using invasive monitoring when adding intravenous vasoactive drug therapy in this advanced heart failure population. Of particular importance, we observed no greater incidence of hypotension or worsening renal dysfunction during hospitalization. Furthermore, there was a trend toward less use of inotropic drugs in the SNP-treated group. However, since selection bias may have entered the decision to use SNP, this difference might also be the result of the non-treated SNP patients being 'sicker'.

Recent reports have also highlighted the important prognostic value of systemic blood pressure in ADHF (12,26). The use of SNP versus inotropic agents may have been biased in part because of a higher MAP or systolic blood pressures at baseline, a known predictor of better outcomes in the setting of ADHF. Additionally, patients with higher blood pressure are assumed to be more tolerant of SNP. However, as we excluded patients with low MAPs, and the presence of equivalent post-treatment hemodynamics and MAPs between both patient groups, our findings suggest that the administration of vasodilator therapy primarily targets any potentially "reversible" contributions of hemodynamic alteration. Also, sub-analysis of the patients with MAP $\leq$ 85 mmHg still demonstrated a better outcome in the SNP-treated group, thus suggesting that low blood pressure per se should not necessarily dissuade physicians from using SNP.

The early and continuous separation of the mortality curves for the two cohorts implies a continued and increasing benefit of vasodilator therapy throughout the follow-up period. We hypothesize that this is secondary to the ability to establish an early optimal hemodynamic balance with SNP, allowing the institution of longer-term oral vasodilator therapy bridged by SNP titration. Thus, use of early intravenous and late oral vasodilators exerts an improved short-term hemodynamic benefit and a long-term survival benefit. The fact that this benefit was observed in patients already treated with maximal neurohormonal blockade lends credence to the suggestion that the combination of agents is exerting an effect via mechanisms incremental to neurohormonal antagonism. Indeed oral vasodilators have proven to enhance NO bioavailability (27), myocardial metabolism (28) and energy regulation (29), to have potent antioxidant effects (30) and reduce LV hypertrophy (31) and remodeling (32), in addition to significant morbidity and mortality benefit when utilized in an African Americans with advanced heart failure (33). Our results provide additional support for the beneficial use of these vasodilators (hydralazine and nitrates) in patients with advanced heart failure, independent of race (33,34,35).

**Study Limitations.** Obvious limitations inherent to the retrospective study design should be considered when findings are interpreted. Comprehensive follow-up, review of events, and centralized adjudication minimized the potential for missed or misclassified outcomes. However, selection bias probably entered the decision to treat or not treat patients with SNP which trended toward the use of SNP in patients with higher systemic, right- and left sided filling pressures and lower cardiac output. This may suggest that the SNP group was more hemodynamically compromised, "tipping the scales" in favor of standard therapy. Also, only half of the patients had implantable cardioverter defibrillator or cardiac resynchronization therapy with defibrillator since widespread use of the devices only started after 2002. The mechanism of death could not be ascertained, but other studies of advanced heart failure suggest that a majority of patients die of progressive pump failure (36). Accurate estimates about duration of vasoactive therapies administered, medication doses and how many patients achieved hemodynamic goals in both treatment arms could not be retrieved due to logistic limitations. It should also be emphasized that our patient population was younger than the overall heart failure population thereby explaining the higher cardiac transplantation rate. Lastly, our single-center data was achieved while patients were hospitalized in a specialized heart failure intensive care unit, which included medical and nursing staff that are experienced in the use of SNP. Recognizing all the aforementioned limitations we believe that the information provided in this manuscript is a well-balanced description of our long standing, in general, positive experience with use of SNP in advanced decompensated heart failure patients. Together with the ongoing controversy with another vasodilator, nesiritide (37), and potential detrimental effects of inotropic agents, we hope our data will provide some insights into the potential for reviving an age-old concept of a vasodilator-based approach to low cardiac output in carefully selected patients that may tolerate such strategy. Careful interpretation of our findings should be based on the applicability of our protocols, and further studies are needed to examine the safety and efficacy of SNP-based intensive medical therapy in this vulnerable population.

## f) Conclusion

In our single-center study, we demonstrated that intravenous SNP could be safely administered in selected patients admitted with advanced low output heart failure to achieve an optimal hemodynamic profile. The use of SNP as part of intensive medical therapy, and the

transition to oral vasodilators in patients already treated with neurohormonal antagonists was associated with improved long-term clinical outcomes irrespective of inotropic drug usage or renal dysfunction during admission.

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**Table 1. Baseline patient characteristics**

| | | No Nitroprusside n=97 | Nitroprusside n=78 | p-value |
|---|---|---|---|---|
| **Demographics** | | | | |
| | Age (y) | 55±11 | 55±11 | Ns |
| | Men (% ) | 80 | 84 | Ns |
| | Caucasian (%) | 80 | 76 | Ns |
| | African-American (%) | 19 | 22 | Ns |
| **NYHA Classification (%)** | | | | |
| | III | 44 | 42 | Ns |
| | IV | 56 | 58 | Ns |
| **Medical History (%)** | | | | |
| | Hypertension | 77 | 70 | Ns |
| | Hyperlipidemia | 51 | 61 | Ns |
| | Diabetes | 28 | 27 | Ns |
| | Smoking | 47 | 55 | Ns |
| | Previous CABG | 28 | 36 | Ns |
| | ICD | 42 | 46 | Ns |
| | CRT-D | 16 | 13 | Ns |
| **Etiology Heart Failure (%)** | | | | |
| | Ischemic | 48 | 52 | Ns |
| | Idiopathic Dilated | 39 | 39 | Ns |
| | Valvular | 8 | 5 | Ns |
| | Other | 5 | 3 | Ns |
| **Serology** | | | | |
| | Hemoglobin (g/dl) | 13.3±1.8 | 13.2±1.9 | Ns |
| | BUN (mg/dl) | 31±17 | 31±21 | Ns |
| | Sodium (mmol/l) | 136±4 | 137±4 | Ns |

| | | | | |
|---|---|---|---|---|
| | Creat. BL (mg/dl) | 1.4±0.5 | 1.3±0.5 | Ns |
| | Creat. P (mg/dl) | 1.5±0.6 | 1.4±0.6 | Ns |
| | Creat. D (mg/dl) | 1.3±0.5 | 1.3±0.5 | Ns |

NYHA indicates New York Heart Association functional class, CABG: coronary by-pass surgery, ICD: implantable cardioverter defibrillator, CRT-D: cardiac resynchronization therapy with defibrillator, BUN: blood urea nitrogen, Creat: serum creatinine, BL: baseline, P: peak, D: discharge. Values are mean ± SD or n (%).

**Table 2 A. Baseline hemodynamic and echocardiograph variables**

| | | No Nitroprusside n=97 | Nitroprusside n=78 | p-value |
|---|---|---|---|---|
| **Hemodynamics** | | | | |
| | Sinus Rhythm (%) | 82 | 90 | ns |
| | Heart Rate (bpm) | 86±20 | 81±18 | ns |
| | MAP (mmHg) | 82±11 | 86±11 | 0.01 |
| | Systolic BP (mmHg) | 106±14 | 110±15 | 0.05 |
| | CVP (mmHg) | 13±7 | 15±5 | 0.002 |
| | Systolic PA (mmHg) | 51±15 | 63±14 | <0.001 |
| | DiastolicPA(mmHg) | 26±9 | 32±7 | <0.001 |
| | PCWP (mmHg) | 24±8 | 29±7 | <0.001 |
| | CO (l/min) | 3.6±0.8 | 3.2±0.7 | 0.002 |
| | CI (l/min/m2) | 1.7±0.2 | 1.6±0.2 | 0.005 |
| | SVR (dynes/cm5) | 1601±419 | 1846±567 | 0.002 |
| | PVR (Woods Unit) | 2.9±1.4 | 4.3±2.6 | <0.001 |
| **Echocardiography** | | | | |
| | EF (%) | 15±7 | 15±5 | ns |
| | LVEDD (cm) | 7±1 | 7±1 | ns |
| | MR (grade) | 2±1 | 2±1 | ns |

MAP: mean arterial pressure, BP: blood pressure, CVP: central venous pressure, PA: pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CO: cardiac output, CI cardiac index, SVR: systemic vascular resistance, PVR: pulmonary vascular resistance, EF: ejection fraction, LVEDD: left ventricular end diastolic diameter, MR: mitral regurgitation. Values are mean ± SD or n (%).

**Table 2 B. Hemodynamics at admission and time of pulmonary-artery catheter removal (CI and PA) and discharge from hospital (MAP) between who did and did not receive SNP during hospitalization**

| | No Nitroprusside (n=49) | | | Nitroprusside (n=60) | | |
|---|---|---|---|---|---|---|
| | **Admission** | **Discharge** | **p-value** | **Admission** | **Discharge** | **p-value** |
| **MAP (mmHg)** | 82±12 | 74±8 | <0.001 | 87±12 | 74±11 | <0.001 |
| **Systolic PA (mmHg)** | 55±14 | 41±13 | <0.001 | 65±13 | 42±12 | <0.001 |
| **Diastolic PA (mmHg)** | 28±8 | 20±7 | <0.001 | 33±7 | 19±6 | <0.001 |
| **CI (l/min/m2)** | 1.6±0.2 | 2.4±0.5 | <0.001 | 1.6±0.2 | 2.6±0.5 | <0.001 |

Abbreviations as in Table 2A.

**Table 3. Use of medication on admission, during admission and on discharge**

| | | No Nitroprusside n=97 | Nitroprusside n=78 | p-value |
|---|---|---|---|---|
| **At admission (%)** | | | | |
| | Aspirin / Clopidogrel | 37 | 47 | Ns |
| | Coumadin | 55 | 44 | Ns |
| | ACE-I / ARB | 88 | 83 | Ns |
| | Digoxin | 70 | 68 | Ns |
| | Beta-blockers | 62 | 77 | 0.038 |
| | Spironolactone | 37 | 35 | Ns |
| | Loop Diuretic | 94 | 96 | Ns |
| | Hydralazine | 11 | 16 | Ns |
| | Isosorbide dinitrate | 28 | 26 | Ns |
| | Statin | 35 | 44 | Ns |
| | Amiodarone | 28 | 17 | Ns |
| | Insulin | 16 | 12 | Ns |
| **During Admission (%)** | | | | |
| | Nitroglycerine | 1 | 5 | Ns |
| | Dopamine | 4 | 3 | Ns |
| | Dobutamine | 36 | 38 | Ns |
| | Milrinone | 37 | 25 | Ns |
| | Dobutamine or milrinone | 64 | 60 | Ns |
| | Norepinephrine | 1 | 0 | Ns |
| | IABP | 5 | 2 | Ns |
| | Dobutamine or milrinone or IABP | 67 | 61 | Ns |
| | UF/Dialysis | 1 | 2 | Ns |
| **At discharge (%)** | | | | |
| | Aspirin / Clopidogrel | 44 | 50 | Ns |

| | | | | |
|---|---|---|---|---|
| | Warfarin | 50 | 37 | Ns |
| | ACE-I / ARB | 93 | 94 | Ns |
| | Digoxin | 72 | 73 | Ns |
| | Beta-blockers | 50 | 56 | Ns |
| | Spironolactone | 55 | 56 | Ns |
| | Loop Diuretic | 92 | 96 | Ns |
| | Hydralazine | 28 | 54 | 0.001 |
| | ISDN | 50 | 69 | 0.017 |
| | Hydralazine or ISDN | 52 | 75 | 0.004 |
| | Hydralazine and ISDN | 26 | 48 | 0.006 |
| | Statin | 33 | 45 | Ns |
| | Amiodarone | 36 | 27 | Ns |
| | Insulin | 13 | 10 | Ns |
| | Dobutamine | 5 | 2 | Ns |
| | Milrinone | 7 | 3 | Ns |
| | Dobutamine or milrinone | 12 | 6 | 0.08 |

ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, IABP: intra-aortic balloon pump, UF: ultrafiltration, ISDN: isosorbide dinitrate.

**Table 4. Primary outcomes**

| Primary outcome % (n) | No Nitroprusside n=97 | Nitroprusside n=78 | p-value |
|---|---|---|---|
| **All cause mortality** | 44 (43) | 29 (23) | 0.005 |
| **Cardiac transplant** | 35 (34) | 33 (26) | ns |
| **All cause mortality + transplant** | 79 (77) | 63 (49) | 0.016 |
| **Heart failure re-hospitalization** | 56 (54) | 60 (47) | ns |

**Table 5. Predictors of all-cause mortality on multivariate analysis**

| | Hazard Ratio | 95%Confidence Interval | p-value |
|---|---|---|---|
| Sodium nitroprusside | 0.54 | 0.33-0.88 | 0.015 |
| Beta-blocker | 0.48 | 0.29-0.78 | 0.03 |
| Diabetes mellitus | 1.13 | 0.62-2.07 | 0.7 |
| Inotropic agent | 2 | 1.36-3.6 | 0.01 |
| Creatinine | 2.16 | 1.56-3.24 | 0.001 |

**Figure 1: Standard Medication Protocols for the Cleveland Clinic Heart Failure Intensive Care Unit.**

**Sodium Nitroprusside**

Begin at 10 – 40 mcg/min (without bolus)

↑ as tolerated to achieve desired hemodynamic goals, targeting MAP 65-70 mmHg

Do not ↑ dose beyond 400 mcg/min

To wean off: ↓ infusion gradually as tolerated while maintaining MAP goals and initiating/increasing oral vasodilators

**Captopril**

Incremental ↑ 6.25→12.5→25→50 mg

Begin at 6.25-12.5 mg orally

After 2 hours, if initial dose tolerated, ↑ incrementally to next dose

After 2 hours, if previous dose tolerated, ↑ incrementally to next dose

After 6 hours, if previous dose tolerated, then 50 mg po TID*

**Isosorbide Dinitrate**

Begin 10 mg orally

After 2 hours, if initial dose tolerated, ↑ to 20 mg

After 8 hours, if 20 mg tolerated, ↑ to 40 mg

After 8 hours, if 40 mg tolerated, ↑ to 60 mg

After 8 hours, if 60 mg tolerated, then 60 mg po TID*

**Hydralazine**

Begin 25 mg orally (or 10 mg if MAP is low or patient is labile condition)

After 2 hours, if initial dose tolerated, ↑ to 50 mg

After 6 hours, if 50 mg tolerated, ↑ to 75 mg

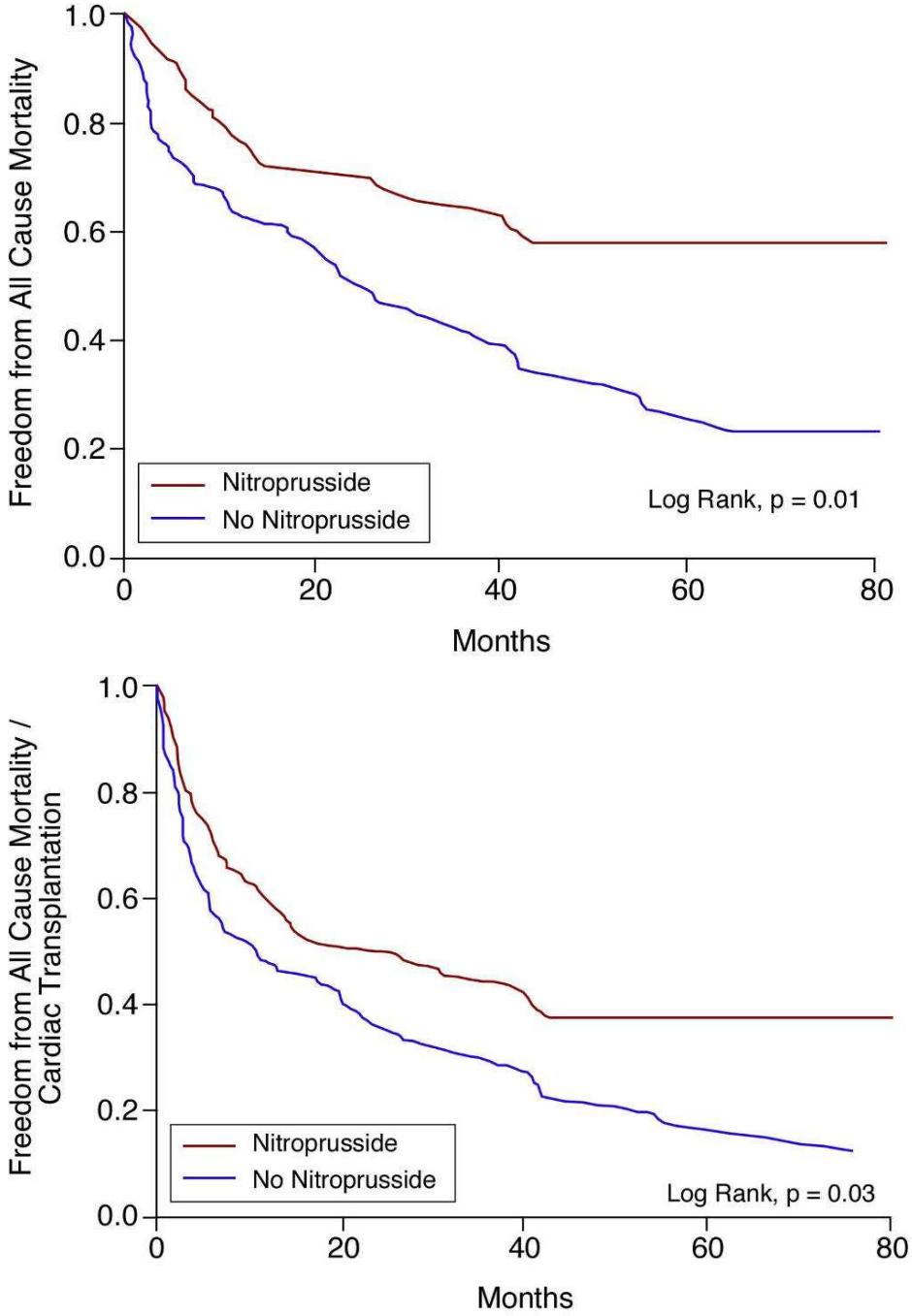
After 6 hours, if 75 mg tolerated, ↑ to 100 mg

After 6 hours, if 100 mg tolerated, then 100 mg QID*

* if previous dose is not tolerated, administer highest dose tolerated TID or QID

MAP = mean arterial pressure; TID = three times daily; QID = four times daily

**Figure 2. Kaplan-Meier curves of all cause mortality (2A) and the combined endpoint of all-cause mortality and cardiac transplantation (2B) between patients who did and did not receive intravenous sodium nitroprusside during hospitalization**



## 4) Isosorbide dinitrate and hydralazine in patients admitted with advanced decompensated heart failure

Mullens W, Abrahams Z, Francis G, Sokos G, Taylor D, Young J, Starling R, Tang W. Isosorbide dinitrate and hydralazine in patients admitted with advanced decompensated heart failure. Am J Card 2009;103:1113-9.

### a)Abstract

**Objectives:** To determine if addition of oral isosorbide dinitrate and/or hydralazine (I/H) to standard neurohormonal blockade in patients discharge from advanced decompensated heart failure (ADHF) is associated with better hemodynamic profiles and improved clinical outcomes.

**Background:** Data supporting the use of I/H as add-on therapy to standard neurohormonal antagonists in ADHF are limited, especially in the non-African American population.

**Methods:** We reviewed consecutive patients with ADHF admitted between 2003-6 with a cardiac index $\leq$ 2.2 L/min/$m^2$ admitted for intensive medical therapy. Patients discharged with angiotensin converting enzyme inhibitors (ACE-I) and/or angiotensin receptor blockers (ARB) (control group) were compared with those receiving ACE-I/ARB plus I/H (I/H group).

**Results:** The control (n=97) and I/H (n=142) groups had similar demographic characteristics, baseline blood pressure, and renal function. Patients in the I/H group had a significantly higher estimated systemic vascular resistance (SVR: 1,660 versus 1,452 dynes/$cm^5$, p<0.001) and lower cardiac index (1.7 versus 1.9 l/min.$m^2$, p<0.001) on admission. The I/H group achieved a similar reduction in intra-cardiac filling pressures and discharge blood pressures than controls, but had greater improvement in cardiac index and SVR. Use of I/H was associated with lower rates of all-cause mortality (34% versus 41%; OR: 0.65; 95% CI 0.43-0.99; p=0.04) and all-cause mortality / heart failure re-hospitalization (70% versus 85%; OR: 0.72; 95% CI 0.54-0.97; p=0.03), irrespective of race.

**Conclusions**: In patients discharged from advanced low-output heart failure, the addition of I/H to neurohormonal blockade is associated with a more favorable hemodynamic profile and long-term clinical outcomes regardless of race.

**b) Introduction**

Despite significant advances in our understanding of heart failure pathophysiology and the many drug and device therapies available, many patients with systolic heart failure continue to experience progression in their disease states, with significant morbidity and mortality. Although isosorbide dinitrate and hydralazine (I/H) were considered one of the earliest "evidence-based" treatment strategies for systolic heart failure based on the cardio-circulatory model of heart failure (1,2), its current use is eclipsed by the large volume of evidence supporting the use of neurohormonal antagonists such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-adrenergic blockers (beta-blockers), and aldosterone receptor antagonists.

Recently, the African-American Heart Failure Trial (A-HeFT) demonstrated a significant reduction in adverse clinical outcomes in response to therapy with a fixed-dose formulation of I/H on top of neurohormonal blockade in ambulatory African-American patients who were highly symptomatic (New York Heart Association [NYHA] functional class III-IV) and had significant cardiac impairment and remodeling (3). As a result, the latest clinical guidelines advocate the use of a combination of I/H as "a reasonable option" as part of the treatment strategy for patients with stable but advanced systolic heart failure (level of evidence A in African-American patients, level of evidence C in non-African American patients) who remain symptomatic (NYHA III-IV) despite optimal standard therapy (4,5).

Perhaps the major benefit of neurohormonal antagonist is to delay the disease progression of the heart failure syndrome. It is therefore conceivable that hemodynamic perturbations may only be delayed (rather than diminished) as the disease progresses. Since ACE inhibitors/ARBs may not provide the same balance of preload and afterload reduction than I/H, the primary aim of this study was to determine if addition of I/H to standard neurohormonal blockade following an episode of ADHF would be associated with sustained hemodynamic profiles and improved clinical outcomes in patients admitted with advanced systolic heart failure.

**c) Methods**

**Patient population**. We reviewed consecutive patients, age ≥18 years, with chronic (>6 months) systolic heart failure (New York Heart Association class III-IV), who underwent intensive medical therapy guided by pulmonary artery catheter at the Cleveland Clinic in a dedicated heart failure intensive care unit between January 1, 2003 and December 31, 2006. From this cohort, we narrowed our study population to include only patients discharged from the hospital following therapy. Subjects who met the additional inclusion criteria at the time of admission were enrolled in the study: 1) impaired left ventricular systolic function as defined by left ventricular ejection fraction (LVEF) < 30%; 2) impaired cardiac output, defined by cardiac index (CI) ≤ 2.2 l/min/$m^2$; and 3) evidence of congestion as determined by pulmonary capillary wedge pressure (PCWP) > 18 mmHg and/or central venous pressure (CVP) > 8 mmHg. Exclusion criteria included those: 1) with congenital heart disease; 2) recipients of heart transplantation; 3) mean arterial pressure (MAP) <65 mmHg. Institutional Review Board approval of this research project, and informed consent were obtained for hospitalization, treatment and all standard invasive procedures and documented in the medical records, according to protocol and Cleveland Clinic policy.

**Hemodynamic assessment.** The systemic blood pressure was generally measured non-invasively by an automatic cuff sphygmomanometer and central hemodynamic parameters were derived from pulmonary artery catheter measurements every 15 minutes (except for CI which was calculated at 4 hour intervals). Complete hemodynamic information was collected in all subjects prior to starting intensive medical therapy, and again before removing the pulmonary artery catheter. The CVP and PCWP were assessed at end-expiration with a balloon-tipped catheter at steady state with the subject in a supine position. CI was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. The estimated systemic vascular resistance (SVR) was calculated according to the formula: 80 x (MAP - right atrial pressure) / CO.

**Protocol for intensive medical therapy.** The pharmacologic approach and hemodynamic goals of intravenous therapy for ADHF have been described previously (6,7). Briefly, optimal hemodynamic response was defined as a decrease in PCWP to ≤18 mmHg, decrease in CVP to ≤8 mmHg and improvement in CI to ≥2.2 l/min/$m^2$, all while maintaining

mean arterial pressure (MAP) >65-70 mmHg and/or systolic blood pressure >85 mmHg. In order to achieve the hemodynamic goals, most patients were treated with either parental vasodilators or inotropic agents with or without intravenous loop diuretic therapy. Oral drug regimens including angiotensin converting-enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARB), beta-blockers, and spironolactone were continued at their admitting doses as tolerated (except in the case of intravenous dobutamine or vasodilator administration where beta-blockers or I/H would be stopped, respectively). The duration of infusions of intravenous agents in the intensive care unit was typically between 24-48 hours.

**Oral vasodilator protocol.** Upon stabilization, the decision to use I/H in addition to an ACE-I (or ARB) versus further up-titration of ACE-I (or ARB) alone was at the discretion of the physician caring for the patient and no randomization scheme was employed. Regardless, titration of oral drugs was aimed to wean off parental therapy and based on maintaining a target MAP of 65-70 mmHg and/or systolic blood pressure >85 mmHg. Titration of oral vasodilator drugs followed standard protocols established in our heart failure intensive care unit and conducted by highly trained nursing staff experienced in the care of advanced heart failure patients (Figure 1), but the sequence of drugs was also at the attending cardiologist's discretion. The systemic blood pressure is generally measured non-invasively by an automatic cuff sphygmomanometer every 15 minutes. If hypotension occurred during the titration protocol, the previously tolerated dose will be administered without further up-titration. Once blood pressure goals were achieved and optimal hemodynamic measures maintained, patients are discharged from the intensive care unit to a regular nursing floor (usually within 48-72 hours). Neurohormonal antagonists and I/H are further titrated, as tolerated, to guideline recommended therapeutic doses if not already achieved in the heart failure intensive care unit. Standard heart failure patient education materials and counseling are given to the patient during the admission, and post-discharge follow-up is provided by a heart failure disease management clinic.

**Endpoints.** Three end-points were analyzed and compared between patients who received ACE-I or ARB alone (control group) and those who received I/H plus ACE-I or ARB (I/H group) at discharge: all-cause mortality, cardiac transplantation, and first re-admission for heart failure following index hospitalization discharge. A combined endpoint of event-free survival (time to all-cause mortality and first heart failure re-admission) was also analyzed.

Death was determined using data documented in the medical record and confirmed by surveying the Social Security Death Index.

**Statistical Analysis.** All data are expressed as mean ± standard deviation for continuous variables and as a ratio for categorical data. A paired and unpaired t-test for continuous data and chi-square, and Fisher's exact test for categorical data was used for appropriate comparisons. The Cox Proportional hazards regression model was used to determine which variables were related significantly to the different endpoints during the follow-up period and Kaplan-Meier survival curves were constructed using SPSS for Windows, release 13.0 (SPSS Inc., Chicago, Illinois). Variable selection in multivariable modeling was based on statistical significance of the univariate analysis. Statistical significance was set at a two-tailed probability level of less than 0.05. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**d) Results**

**Baseline characteristics.** A total of 266 consecutive patients fulfilled all inclusion and exclusion criteria, including 142 I/H and 97 controls. The remaining 27 patients [referred to as "Other"] did not receive an ACE-I at discharge, typically because of chronic renal insufficiency as evidenced by a higher serum creatinine throughout the admission. No patient received the combination of ACE-I and ARB in our study cohort. Baseline clinical characteristics were similar among patients in the two study groups except for a higher serum creatinine at discharge in the I/H group (see Table 1). Mean intensive care and hospital duration was 3.5 ±1 days and 8 ±7 days, respectively and was similar between the I/H and control groups.

**Hemodynamic Assessment.** As shown in Table 2, the average systolic blood pressure was similar between two treatment groups as were right- and left-sided filling pressures. Mean LVEF, LV end-diastolic diameter and severity of mitral regurgitation (assessed within three days of admission) were also similar between the two groups. However, when reviewing the hemodynamic data, we observed that the I/H group presented with a higher estimated SVR, while demonstrating a lower cardiac output and CI when compared with control patients.

Compared to baseline hemodynamic assessment, a statistically significant reduction of right- and left-sided filling pressures together with an increase in CI was achieved in both groups. However, a statistically significant reduction in estimated SVR and systolic blood

pressure was only documented in the I/H group and not as apparent in the control group. In addition, the increase in cardiac output (2.1±1.9 versus 1.4±1.6 l/min, p=0.005) and CI (1.05±0.8 versus 0.65±0.6 l/min/$m^2$, p=0.005) was greater in I/H treated patients, though the overall mean hemodynamic measurements at the time of PAC removal were similar between the two groups. Only estimated SVR at this time was lower in the ACE-I plus I/H treated patients.

**Use of Concomitant Medications.** As shown in Table 3, adherence to optimal pharmacological therapy was high on admission and discharge, and comparable between the two groups with >65% use of beta-blockers at discharge. Patients in the I/H group had greater use of sodium nitroprusside during hospitalization than the control group. However, the percentages of patients treated with other agents during hospitalization were similar in both groups. There was a non-significant trend toward less use of inotropic agents in the I/H group at discharge.

**Clinical Outcomes.** Patients were followed for a median duration of 26.3 months (total of 584 patient-years) after the index hospital admission. No patient was lost to follow-up. There were 104 (39%) deaths and 52 (20%) cardiac transplantations. Primary outcome differences between two cohorts are shown in Table 4. Patients in the I/H group had a lower all-cause mortality (34% versus 41%; OR: 0.65; 95% CI 0.43-0.99; p=0.04) and lower all-cause mortality / heart failure re-hospitalization (70% versus 85%; OR: 0.72; 95% CI 0.54-0.97; p=0.03) compared to the control group (Figure 2). The two treatment groups did not differ in overall cardiac transplantation or heart failure re-hospitalization rates during the entire study period. The more favorable outcome in the I/H group was irrespective of race though there was a trend towards more significance for the African-American population (all-cause mortality for whites in I/H group: OR: 0.66; 95% CI 0.4-0.98; p=0.05, all-cause mortality for African-Americans in I/H group: OR: 0.44; 95% CI 0.23-0.85; p=0.01). Interestingly, early separation of the outcome curves started after three months and was mainly driven by a reduction in heart failure re-hospitalizations while a mortality benefit was noted after only six months of therapy.

To further validate our findings, we performed a sub-analysis to include only those patients with an admission MAP of 65-85 mmHg (n=141). In this cohort, use of I/H plus ACE-I or ARBs was still associated with reduced all-cause mortality (OR: 0.55; 95% CI 0.31-0.97; p=0.03) and all-cause mortality / heart failure re-hospitalization (OR: 0.66; 95% CI 0.44-0.97; p=0.03). Finally, the addition of I/H to ACE-I in patients previously not on I/H (n=87) was also

associated with reduced all-cause mortality (OR: 0.58; 95% CI 0.37-0.93; p=0.02) and all-cause mortality / heart failure re-hospitalization (OR: 0.61; 95% CI 0.45-0.85; p=0.003).

**e) Discussion**

The key finding of our non-randomized, single-center, case-control series of patients with advanced heart failure is that careful, protocol-driven administration of oral isosorbide dinitrate / hydralazine can provide favorable hemodynamic improvements that are incremental to standard neurohormonal therapy despite similar systemic blood pressure targets. Furthermore, we demonstrated that add-on I/H to standard neurohormonal blockade might be associated with significantly lower all-cause mortality and fewer clinical adverse events at follow-up compared to standard neurohormonal blockade alone. We also found this effect to be independent of race. Therefore, while neurohormonal blockade can effectively delay disease progression in advanced heart failure, adding oral vasodilators in those with evidence of hemodynamic derangements and adequate systemic blood pressures allows restoration of optimal hemodynamic balance, which might translate into incremental intermediate- and long-term benefits.

With the broad adoption of the neurohormonal hypothesis following the head-to-head comparison between enalapril and I/H (8), vasodilator therapy has taken a less prominent role in the armamentarium of pharmacologic therapy in chronic systolic heart failure. While add-on aldosterone receptor antagonists and ARBs have been advocated recently, their benefits have largely assumed to be associated with a more comprehensive blockade of the "aldosterone escape" or "angiotensin escape" rather than optimization of hemodynamic derangements. Also, it is important to emphasize that the profile of our patient population has important differences from V-HeFT and A-HeFT (1,2). Patients analyzed in our study cohort were not stable or ambulatory, but were admitted with ADHF and were recently stabilized with parenteral vasoactive therapy. With an average systolic blood pressure of 110 mmHg, and mean LVEF of 16%, our patient cohort has far more advanced disease and is highly vulnerable to repeat hospitalizations. By demonstrating the potential advantages of using add-on vasodilators over up-titration of standard neurohormonal antagonists, we revisited the concept of "hemodynamic dependence" in the setting of progressive pump failure.

There is reluctance of physicians to use vasodilators (parental and/or oral) in addition to neurohormonal blockers in hospitalized patients with advanced heart failure and low cardiac

output. This may stem from the belief that vasodilatation may lead to significant hypotension if SVR is reduced without the ability to provide compensatory increase in cardiac output. Some even considered ACE inhibitors/ARBs as effective vasodilators themselves as they are effective anti-hypertensive agents. Indeed, indiscriminant use of vasodilator therapy has raised concerns of potential adverse consequences in prior studies (9,10). Instead, our data corroborate the hypothesis that a reduction in afterload or wall stress during vasodilator administration can lead to a marked increase in cardiac output with effective SVR reduction, preventing the development of significant hypotension. Despite similar systemic blood pressures at discharge, I/H group had a more favorable hemodynamic profile compared to that achieved in the control group. Furthermore the patients with MAP $\leq$ 85 mmHg also demonstrated a better outcome in the I/H-treated group. These observations may imply that there may be differential effects of various oral heart failure therapies on central hemodynamics even independent of their blood pressure lowering effects.

Post-hoc analyses of several trials have suggested a potential biological difference of lower ambient renin activity in African American patients to explain the reduced efficacy of ACE-I. Hence, the beneficial effects of I/H may be explained primarily on the basis of more pronounced blood pressure reduction particularly in African-Americans (11-13). Nevertheless, a recent sub-analysis of the A-HeFT trial demonstrates that although the beneficial effects of I/H were similar among patients with baseline systolic blood pressure above or below the median of 126 mmHg, I/H did not further reduce systolic blood pressure in patients with baseline systolic blood pressure below the median (13). The lack of a clear difference in hemodynamic profiles or long-term outcomes between African-American and non-African American patients in our study further supports the presence of a biological process responsive to oral vasodilator therapy in advanced heart failure that is common to all races.

Although invasive measurements were obtained in our study, it is not our intention to imply the need for invasive monitoring, but more to illustrate the relative mechanistic contributions of I/H in the improvement of hemodynamic compromise in the setting of ADHF. In this report, we demonstrated that add-on I/H to guideline-recommended care with high adherence to ACE-I (100%), beta-blocker (65%), and spironolactone (52%) can further reduce all-cause mortality and adverse events. Importantly, the benefit of I/H is apparent at three months and is mainly driven by a reduction in heart failure re-hospitalization while a mortality benefit is

seen at just six months of therapy. The short-term benefit of reduced heart failure re-hospitalization likely relates to achieving a more favorable hemodynamic profile (lesser SVR / higher CI).

Previous studies have suggested that the delayed survival benefit can be attributed to further inhibition of left ventricular remodeling (2,14-16). Indeed, the fact that this benefit was observed in patients already treated with neurohormonal antagonism lends credence to the suggestion that the combination of agents may provide benefits beyond blockade of the renin-angiotensin-aldosterone system. Neurohormonal blockers slow the progression of left ventricular dysfunction, retard the structural left ventricular remodeling and reduce the rate of death and complications among patients with heart failure. Impaired bioavailability of nitric oxide, and increased oxidant stress leading to endothelial dysfunction may also contribute to the remodeling process in heart failure (18,19). Therefore, it has been postulated that combining the nitric oxide donor (isosorbide dinitrate) with the antioxidant (hydralazine) may provide an alternative or supplemental approach to slow or reverse progressive heart failure. Based on our data, we cannot confirm or exclude the potential benefits of incremental I/H benefit beyond their role in hemodynamic optimization. Nevertheless our patient characteristics were consistent with the clinical profile of "direct vasodilator responders," particularly in those with dilated ventricles whereby reduction of left ventricular impedance (or enhanced systolic ejection) and reduction in regurgitant volume may lead to wall stress reduction (20). However, our observations may encourage future investigations to better understand the mechanistic underpinnings of such a strategy and further clarify our understanding of the complex role of nitric oxide and oxidative stress in advanced heart failure.

**Study Limitations.** Obvious limitations inherent to the retrospective study design should be considered when findings are interpreted. Comprehensive follow-up, review of events, and centralized adjudication minimized the potential for missed or misclassified outcomes. However, selection bias probably entered the decision to treat or not treat patients with I/H, which may have trended towards the use of I/H in patients with more deranged hemodynamic measurements. Nevertheless, the decision to use I/H in addition to neurohormonal blockade may have been driven in part because of a higher systemic blood pressure at baseline, a known predictor of better outcomes in the setting of ADHF (21). Accurate estimates about duration of vasoactive therapies administered and medication doses and tolerance to incremental dosing

could not be retrieved due to logistic limitations from a chart review process. It should also be emphasized that our patient population was relatively younger than the overall heart failure population, perhaps explaining the higher cardiac transplantation rate. Since none of our patients had add-on ARB therapy, the relative differences between add-on I/H versus add-on ARB cannot be compared. Lastly, patients were hospitalized in a specialized heart failure intensive care unit, which included medical and nursing staff that was experienced in the use of vasodilator therapies.

Recognizing all the aforementioned limitations we believe that the information provided represents a well-balanced description of our long-standing, and overall positive experience of adding vasodilators to standard therapy in advanced decompensated heart failure patients. These findings await verification in a proper controlled trial before a refined clinical approach using these commonly utilized drugs can be advocated.

**f) Conclusion**

In patients admitted with advanced low-output heart failure and hemodynamic compromise, the addition of isosorbide dinitrate / hydralazine to background neurohormonal therapy was associated with improved hemodynamic profiles and long-term clinical outcomes. Our findings may warrant further investigations into the appropriate use of oral vasodilators as add-on therapy in this advanced heart failure population.

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**Table 1. Baseline patient characteristics**

| | **Control group n=97** | **I/H group n=142** | **p-value control vs I/H group** | **Other n=27** |
|---|---|---|---|---|
| Age (y) | 55±11 | 54±12 | ns | 62±11 |
| Men (%) | 80 | 80 | ns | 80 |
| Caucasian (%) | 79 | 80 | ns | 73 |
| African-American (%) | 21 | 20 | ns | 27 |
| Hypertension | 70 | 70 | ns | 66 |
| Hyperlipidemia | 54 | 58 | ns | 70 |
| Diabetes | 28 | 33 | ns | 37 |
| Smoking | 47 | 52 | ns | 50 |
| Previous CABG | 33 | 35 | ns | 34 |
| ICD | 38 | 42 | ns | 38 |
| CRT-D | 18 | 15 | ns | 21 |
| LV ejection fraction (%) | 17±7 | 16±6 | ns | 17±8 |
| Ischemic etiology | 53 | 55 | ns | 62 |
| Idiopathic Dilated etiology | 47 | 45 | ns | 48 |
| Hemoglobin (g/dl) | 12.7±2.1 | 13.0±2.0 | ns | 11.7±1.8 |
| BNP (pg/ml) | 1016±1210 | 996±988 | ns | 1367±1254 |
| Sodium (mmol/l) | 136±4 | 137±4 | ns | 135±6 |
| Creatinine admission (mg/dl) | 1.3±0.6 | 1.4±0.7 | ns | 2.0±1.0 |
| Creatinine peak (mg/dl) | 1.4±0.7 | 1.5±0.8 | ns | 2.2±1.1 |
| Creatinine discharge (mg/dl) | 1.2±0.5 | 1.4±0.5 | 0.005 | 1.9±0.9 |

Abbreviations: ACE-I: angiotensin converting enzyme inhibitor, I: isosorbide dinitrate, H: hydralazine, CABG: coronary artery by-pass surgery, ICD: implantable cardioverter defibrillator, CRT-D: cardiac resynchronization therapy with defibrillator, LV: left ventricle, BNP: brain natriuretic peptide. Values are mean ± SD or n (%).

**Table 2. Baseline and follow-up hemodynamic measures**

| | Control group (n=97) | | | I/H group (n=142) | | |
|---|---|---|---|---|---|---|
| | **Admission** | **Follow-Up** | **p-value** | **Admission** | **Follow-Up** | **p-value** |
| Systolic BP (mmHg)[1] | 107±15 | 105±10 | Ns | 110±17 | 106±13 | 0.001 |
| Heart Rate (bpm)[2] | 81±15 | 80±14 | Ns | 85±13 | 83±13 | ns |
| CVP (mmHg)[2] | 12±6 | 9±6 | <0.001 | 13±6 | 9±5 | <0.001 |
| Systolic PA (mmHg)[2] | 53±17 | 44±14 | <0.001 | 55±16 | 43±11 | <0.001 |
| PCWP (mmHg)[2] | 24±8 | 18±7 | 0.01 | 25±8 | 17±5 | <0.001 |
| CO (l/min)[2] | 3.9±0.8* | 5.1±1.2 | <0.001 | 3.5±0.9 | 5.2±1.4 | <0.001 |
| CI (l/min/$m^2$)[2] | 1.9±0.4* | 2.4±0.4 | <0.001 | 1.7±0.4 | 2.5±0.5 | <0.001 |
| SVR (dynes/cm5)[2] | 1452±477* | 1553±249* | Ns | 1660±571 | 1030±339 | <0.001 |

Abbreviations: ACE-I: angiotensin converting enzyme inhibitor, I: isosorbide dinitrate, H: hydralazine, BP: blood pressure, CVP: central venous pressure, PA: pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CO: cardiac output, CI cardiac index, SVR: systemic vascular resistance. [1] Follow-up = at discharge from hospital, [2] follow-up = at moment of removal pulmonary artery catheter, * $p < 0.001$ between both treatment groups at same time. Values are mean ± SD.

**Table 3. Use of medication on admission, during hospitalization and at discharge**

| | | Control group (n=97) | I/H group (n=142) | p-value |
|---|---|---|---|---|
| **On admission (%)** | | | | |
| | Aspirin / Clopidogrel | 43 | 46 | ns |
| | Coumadin | 50 | 44 | ns |
| | ACE-I / ARB | 81 | 87 | ns |
| | Digoxin | 60 | 64 | ns |
| | Beta-blockers | 67 | 69 | ns |
| | Spironolactone | 47 | 34 | 0.03 |
| | Loop Diuretic | 92 | 94 | ns |
| | Hydralazine | 4 | 20 | <0.001 |
| | Isosorbide dinitrate | 8 | 34 | <0.001 |
| | Statin | 44 | 45 | ns |
| | Amiodarone | 22 | 22 | ns |
| **During Hospitalization (%)** | | | | |
| | Lasix | 73 | 79 | ns |
| | Nitroprusside | 34 | 54 | 0.002 |
| | Dopamine | 2 | 2 | ns |
| | Dobutamine or milrinone | 41 | 42 | ns |
| | Intra-aortic balloon pump | 3 | 2 | ns |
| **On discharge (%)** | | | | |
| | Aspirin / Clopidogrel | 54 | 52 | ns |
| | Warfarin | 43 | 43 | ns |
| | ACE-I / ARB | 100 | 100 | ns |
| | Digoxin | 58 | 62 | ns |
| | Beta-blockers | 66 | 65 | ns |
| | Spironolactone | 57 | 52 | ns |
| | Loop Diuretic | 92 | 92 | ns |

| | | | | |
|---|---|---|---|---|
| | Hydralazine | 0 | 79 | <0.001 |
| | Isosorbide dinitrate | 0 | 94 | <0.001 |
| | Statin | 41 | 43 | ns |
| | Amiodarone | 27 | 30 | ns |
| | Dobutamine or milrinone | 10 | 6 | ns |

Abbreviations: ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, I: isosorbide dinitrate, H: hydralazine. Values are expressed in % patients.

**Table 4. Primary outcomes**

| Primary outcome % | Control group (n=97) | I/H group (n=142) | p-value |
|---|---|---|---|
| **All cause mortality** | 41 | 34 | 0.04 |
| **Cardiac transplant** | 19 | 22 | ns |
| **Heart Failure Re-hospitalization** | 64 | 59 | ns |
| **All cause mortality + heart failure re-hospitalization** | 85 | 70 | 0.007 |

Abbreviations: ACE-I: angiotensin converting enzyme inhibitor, I: isosorbide dinitrate, H: hydralazine.

**Figure 1. Standard oral medication protocols for the Cleveland Clinic Heart Failure Intensive Care Unit.**

**Captopril**

Incremental ↑ 6.25→12.5→25→50 mg

Begin at 6.25-12.5 mg orally

After 2 hours, if initial dose tolerated, ↑ incrementally to next dose

After 2 hours, if previous dose tolerated, ↑ incrementally to next dose

After 6 hours, if previous dose tolerated, then 50 mg po TID*

**Isosorbide Dinitrate**

Begin 10 mg orally

After 2 hours, if initial dose tolerated, ↑ to 20 mg

After 8 hours, if 20 mg tolerated, ↑ to 40 mg

After 8 hours, if 40 mg tolerated, ↑ to 60 mg

After 8 hours, if 60 mg tolerated, then 60 mg po TID*

**Hydralazine**

Begin 25 mg orally (10 mg if systemic blood pressure low or patient in labile condition)

After 2 hours, if initial dose tolerated, ↑ to 50 mg

After 6 hours, if 50 mg tolerated, ↑ to 75 mg

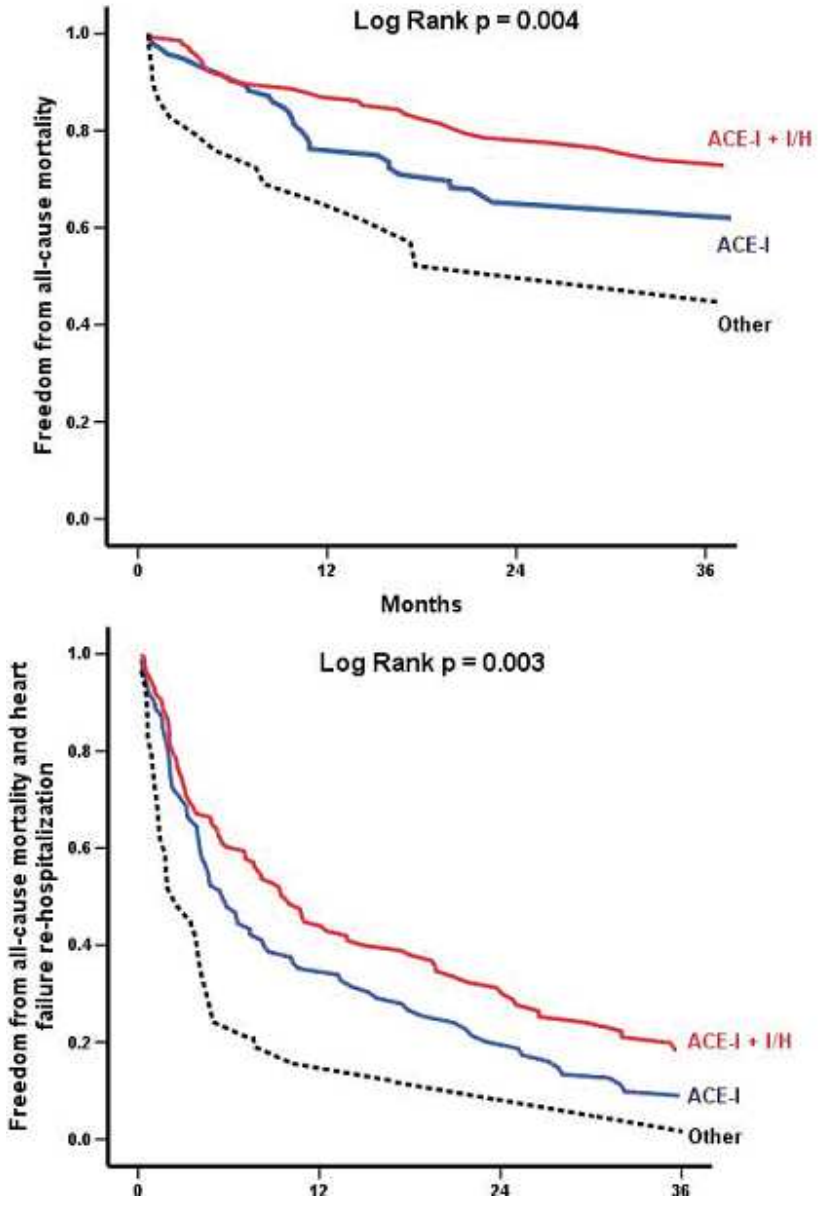
After 6 hours, if 75 mg tolerated, ↑ to 100 mg

After 6 hours, if 100 mg tolerated, then 100 mg QID*

* if previous dose is not tolerated, administer highest dose tolerated TID or QID

TID = three times daily; QID = four times daily

**Figure 2. Kaplan-Meier curves of all cause mortality and the combined endpoint of all-cause mortality and heart failure re-hospitalization between patients who were on ACE-I or ARB, ACE-I or ARB plus I/H or no ACE-I or ARB (=other).**



## 5) Limited value of tissue Doppler imaging in the estimation of left ventricular filling pressure in advanced decompensated heart failure

Mullens W, Borowski A, Curtin R, Thomas J, Tang W. Limited value of Tissue Doppler Imaging in the Estimation of Left Ventricular Filling Pressure in Advanced Decompensated Heart Failure. Circulation 2009;119:62-70.

### a) Abstract

**Background**: Early transmitral velocity / tissue Doppler mitral annular early diastolic velocity (E/Ea) has been correlated with pulmonary capillary wedge pressure (PCWP) in a wide variety of cardiac conditions. The objective of this study was to determine the reliability of mitral E/Ea for predicting PCWP in patients admitted for advanced decompensated heart failure (ADHF).

**Methods and Results:** Prospective consecutive patients with ADHF (ejection fraction [EF] ≤30%, NYHA class III-IV symptoms) underwent simultaneous echocardiographic and hemodynamic evaluation on admission and after 48 hours of intensive medical therapy. A total of 106 patients were included (mean age 57 ±12 years, EF 24 ±8%, PCWP 21 ±7 mmHg, mitral E/Ea 20 ±12). There was a lack of correlation between mitral E/Ea and PCWP, particularly in those with larger LV volumes, more impaired cardiac indices, and the presence of cardiac resynchronization therapy. Overall, mitral E/Ea was similar among patients with PCWP > and ≤ 18 mmHg, and sensitivity and specificity for mitral E/Ea > 15 to identify a PCWP > 18 mmHg was 66% and 50%, respectively. Contrary to prior reports, we did not observe any direct association between changes in PCWP and changes in mitral E/Ea.

**Conclusion:** In decompensated patients with advanced systolic heart failure, tissue Doppler derived mitral E/Ea may not be as reliable in predicting intracardiac filling pressures, particularly in those with larger LV volumes, more impaired cardiac indices, and the presence of cardiac resynchronization therapy.

**b) Introduction**

Invasively measured pulmonary capillary wedge pressure (PCWP) has been widely used as a surrogate for left ventricular (LV) filling pressure, and is directly associated with functional capacity and prognosis in patients with heart failure (1,2,3). However, given the cost, potential complications, and the lack of demonstrable benefits in routine use, hemodynamic assessment via pulmonary artery catheters has decreased substantially over the last decade (4,5,6).

Conventional echocardiography plays a critical role in the management of heart failure as it serves as a non-invasive bedside tool to determine abnormalities in cardiac structure and performance. Transmitral flow velocity curves and other Doppler variables have been utilized as non-invasive estimates of intracardiac filling pressures, albeit with limitations. In particular, the early transmitral velocity / tissue Doppler mitral annular early diastolic velocity (E/Ea) ratio has been shown to correlate with PCWP in a wide range of cardiac patients (7,8,9,10,11,12,13). However, while some smaller studies have included patients with depressed LV systolic function, none has included patients admitted with advanced heart failure and extensive reverse remodeling (14,15,16,17,18,19). Therefore, the primary goal of our study was to examine the relationship between mitral E/Ea and hemodynamic measurements in patients with advanced decompensated heart failure (ADHF) – a patient cohort wherein hemodynamic assessment is often considered. We further aimed to explore the potential clinical utility of serial mitral E/Ea assessment in estimating changes in intracardiac filling pressures in response to intensive medical therapy in the ADHF setting.

**c) Methods**

**Study Population.** We prospectively enrolled consecutive patients, aged 18 years or older, with symptomatic chronic (>6 months) heart failure, who underwent a right heart catheterization (RHC) due to concerns regarding hemodynamic derangements at the Cleveland Clinic heart failure intensive care unit between September 15, 2006 and October 15, 2007. The inclusion criteria included: 1) markedly impaired systolic left ventricular (LV) function defined by LV ejection fraction (LVEF) $\leq$ 30%; and 2) New York Heart Association class III-IV symptoms. Exclusion criteria included: 1) patients on artificial ventilation; 2) status post aortic- and/or mitral valve repair or prosthesis; 3) status post cardiac transplantation. A previous cardiac resynchronization therapy with defibrillator (CRT-D) implant was not an exclusion criterium,

and all data provided in the results for patients previously implanted with a CRT-D device are with the device ON. The Cleveland Clinic Institutional Review Board approved this research project, and informed consent was prospectively obtained in all subjects.

**Hemodynamic Study Design.** Hemodynamic and echocardiographic data were simultaneously collected at baseline (within 12 hours of admission) and at follow-up (after 48 hours of intensive medical therapy) if the pulmonary artery catheter was still in place. Hemodynamic data including systemic blood pressure, central venous pressure (CVP), and PCWP (wedge position was verified by fluoroscopy and phasic changes in pressure waveforms), represent the average of 5 cycles, and with balanced transducers (0 level at the mid-axillary line). The CVP and PCWP were assessed at end-expiration with a balloon-tipped catheter at steady state with the patient in a supine position by an investigator unaware of the echocardiographic measurements. Cardiac index (CI) was determined using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates.

The hemodynamic goals and pharmacologic approach to intravenous therapy in the specialized heart failure intensive care unit have been previously described (20). Briefly, optimal hemodynamic response was defined as a decrease in PCWP $\leq$ 18 mmHg, decrease in CVP to $\leq$ 8 mmHg and improvement in CI to $\geq$ 2.2 l/min/$m^2$, while maintaining mean arterial pressure > 65 mmHg. In order to achieve the hemodynamic goals, most patients were treated with intravenous loop diuretics in combination with vasodilators and/or inotropic agents while continuing or intensifying previous therapies with angiotensin converting enzyme inhibitors, anti-adrenergic blockers, aldosterone receptor antagonists, and other vasodilators as indicated and as tolerated.

**Transthoracic Echocardiography.** A comprehensive two-dimensional echocardiographic exam dedicated for research was performed with a commercially available system (Vingmed, System Seven, General Electric, USA) by a single American Society of Echocardiography Registered Diagnostic Cardiac Sonographer (AB). Images were acquired in the left lateral decubitus position using a phased array transducer in the standard parasternal and apical views. Standard two-dimensional and Doppler data, triggered to the QRS complex, were digitally stored in a cine-loop format.

**Echocardiographic Analysis.** The analysis was performed offline by two independent investigators experienced with echocardiographic measurements, blinded to hemodynamic data at the time of analysis. All reported echocardiographic measurements were averaged from three consecutive cycles. Left ventricular volumes, left ventricular ejection fraction, mitral regurgitation, and left atrial maximum volume were assessed as recommended by the American Society of Echocardiography (21). Mitral inflow was analyzed for peak E (early diastolic) and peak A (late diastolic) velocities, E/A ratio, and deceleration time (DT) of E velocity. Ea septal and lateral mitral annulus velocities were measured, and the dimensionless ratio mitral E/Ea for the septal and lateral annulus was calculated (7,8,15). Inter-ventricular mechanical dyssynchrony (VMD) was assessed as the difference between the pre-ejection intervals from QRS onset to the beginning of ventricular ejection at the pulmonic and aortic valve levels using pulsed-wave Doppler and intra-VMD by the opposing wall time-to-peak myocardial velocity intervals in a 4-segment model using color tissue-Doppler imaging.

To ensure optimal accuracy of mitral E/Ea in patients with advanced heart failure and possible regional wall motion abnormalities, all analysis provided are based on the mitral E/Ea ratio, computed from the average of the septal and lateral Ea (16). Pulsed wave and not color TDI was used, since temporal resolution is higher with pulsed wave TDI. Second, low gain and filter settings were applied so the onset of mitral Ea could be reliably identified. Third, the scale was adjusted as needed to range from -15 to 20 to +15 to 20 cm/s, and the sweep speed was set at 100 mm/s to achieve the optimal spectral display of myocardial velocities. Finally, identical R-R intervals (<5 ms) were chosen, to minimize potential differences in diastolic time intervals and subsequent differences in interpretation at slightly different R-R cycle lengths.

**Statistical Analysis.** All data are expressed as mean ± standard deviation for continuous data and as a ratio for categorical data. Univariate comparisons of these variables were performed between baseline and follow-up variables, and between patients with and without previous CRT-D implantation. A paired and unpaired t-test for continuous data and a Spearman correlation coefficient was used for appropriate comparisons. Receiver-operating characteristic (ROC) curves were constructed to determine optimal sensitivity and specificity for predicting PCWP >18 mm Hg using mitral E/Ea. A PCWP of 18 mmHg was chosen as the cut-off value, since this was the target according to treatment protocol. Based on previous studies, a cut-off value PCWP of 15 mmHg was analyzed also. Statistical significance was set at a two-tailed

probability level of less than 0.05. All analyses were performed using SPSS for Windows, release 13.0 (SPSS Inc., Chicago, Illinois). The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**d) Results**

**Patient Characteristics.** A total of 110 patients met eligibility criteria during the study period of which 4 patients refused to be enrolled. Baseline characteristics and treatment of the final 106 patients enrolled during admission are summarized in Table 1. All patients (93% of whom were in sinus rhythm at the time of exam, 7% in atrial fibrillation with an additional 14% having a history of atrial fibrillation) were classified as NYHA class III-IV, with a mean LVEF of 24 ±8%. The median length of intensive medical therapy in the heart failure intensive care unit was 3.5 days. Fifty-one patients (49%) had a CRT-D device at the time of inclusion in our study with overall comparable baseline characteristics (except QRS width) and treatment patterns compared to patients without previous CRT-D implantation.

**Hemodynamic and Echocardiographic Measurements.** Adequate mitral inflow, tissue Doppler signals and hemodynamic variables were obtained in all patients. Table 2 presents the hemodynamic and echocardiographic measurements at the time of the baseline assessment for all patients, stratified according to the presence or absence of CRT-D implantation. Overall, both patients groups had similar baseline hemodynamic derangements except for a higher heart rate in patients without CRT-D. Compared to those without CRT-D, patients with previous CRT-D implant had larger LV end-diastolic volumes, and longer mitral deceleration times. Mitral Ea and E/Ea ratios for different annular regions were similar between those with versus without CRT-D. In addition, septal and lateral Ea for ischemic and idiopathic dilated cardiomyopathy patients were also similar (5.1 ±3.2 vs 5.1 ±2.4 cm/sec, p = 0.9 and 7.5 ±5.7 vs 7.3 ±3.4 cm/sec, p = 0.8 respectively). Overall, 22% of patients had more than moderate mitral regurgitation at baseline. Compared to patients with mild or moderate mitral regurgitation, these patients had a non-significant trend towards higher PCWP and higher mitral E/Ea. Finally, inter-VMD and intra-VMD was only 19±26 and 36±38 ms respectively.

The relationships between PCWP and different Doppler variables are shown in Table 3. There was a weak but statistically significant negative correlation between PCWP and mitral DT as well as a weak positive correlation between PCWP and mitral E velocity, only in patients

without previous CRT-D implantation. However, no correlation was observed between PCWP and mitral Ea in the septal annulus, lateral annulus, or when averaged over both annular regions. Furthermore, the ratio mitral E/Ea (using all definitions for Ea just mentioned) showed no significant correlation with PCWP. As illustrated in Figure 1, even an elevated mitral E/Ea could be associated with a relatively low PCWP and vice versa. Interpretable pulmonary vein (PV) Doppler tracings were obtained in 66% of patients at baseline (Systolic PV: 33 ±8 cm/s, diastolic PV: 56 ±19 cm/s and Atrial PV: 27 ±9 cm/s). However, no significant correlation could be detected among PV doppler tracings and PCWP (r for systolic PV: -0.01, diastolic PV: 0.1, systolic/diastolic PV: -0.04)

Only 53% of patients with a PCWP > 18 mmHg had a mitral E/Ea ratio > 15. Figure 2 compares mean mitral E/Ea values in patients with PCWP > 15 or 18 mmHg versus ≤ 15 or 18 mmHg and stratified by the presence or absence of previous CRT-D implant. Overall, averaged mitral E/Ea was similar among patients with normal versus elevated PCWP. Only patients without previous CRT-D implant had a modestly (but significantly) higher mitral E/Ea when PCWP > 15 or 18 mmHg.

**Clinical Accuracy of Mitral E/Ea ratio to Predict Pulmonary Capillary Wedge Pressure.** As illustrated in Figure 3, sensitivity and specificity for mitral E/Ea > 15 to identify a PCWP > 18 mmHg was 66% and 50%. The predictive value was similar when patients with atrial fibrillation were excluded from the analysis. However, a mitral E/Ea > 15 provided better accuracy in predicting PCWP > 18 mmHg in patients without previous CRT-D implantation (sensitivity 72%, specificity 54%) than in patients with previous CRT-D implantation (sensitivity 59%, specificity 52%). Sensitivity and specificities of mitral E/Ea > 15 to predict a PCWP > 15 mmHg in patients without previous CRT-D implantation (sensitivity 63%, specificity 57%) and in patients with previous CRT-D implantation (sensitivity 58%, specificity 50%) was poorer.

To further analyze the potential importance of a cutoff value for mitral E/Ea, patients were divided into 3 groups. Of the patients with mitral E/Ea < 8, E/Ea 8-15 and E/Ea > 15, average PCWP were similar (19±4, 19±7, 20±6 mmHg respectively). We also tested a previously derived equation (PCWP = 2 + 1.3 mitral E/Ea) to predict measured PCWP in our study cohort but no correlation was observed (r = 0.03, p = ns).

**Relation of Mitral E/Ea with Cardiac Structure and Performance.** In order to better understand the lack of correlation between mitral E/Ea and PCWP, echocardiographic and

hemodynamic variables were compared among 2 groups according to presence or absence of concordant mitral E/Ea > 15 and PCWP > 18 mmHg (Figure 4). Interestingly, the only variables that demonstrated statistically significant differences between concordant versus discordant mitral E/Ea-PCWP measurements were LV end-diastolic volume and cardiac index. In particular, those with discordant mitral E/Ea-PCWP measurements had significantly larger LV volumes and lower cardiac indices. Left atrial volume or severity of mitral regurgitation did not differ among the groups.

**Follow-Up Measures.** Fifty-one (49%) patients underwent also simultaneous Doppler and hemodynamic measurements at follow-up. The absolute change in mean PCWP levels ranged from -24 to + 16 mmHg. No correlation between absolute change in PCWP and change in mitral E/Ea was observed (Figure 1).

**e) Discussion**

In the present study, we report for the first time the reliability of the mitral E/Ea ratio to estimate PCWP in a large, well-characterized "cold and wet" patient population admitted with decompensation from advanced systolic heart failure (LV ejection fraction ≤30%). Using simultaneously measured echocardiographic and invasive hemodynamic variables, we found the predictive value of baseline mitral E/Ea in estimating PCWP in this population to be less robust than previously reported, especially in patients with cardiac resynchronization therapy. Furthermore, we were unable to identify any reliable direct correlation between changes in mitral E/Ea and PCWP. We further explored this complex relationship and observed the discordance of mitral E/Ea and PCWP to be linked to larger left ventricular dimensions, more impaired cardiac output, and the presence of cardiac resynchronization therapy. With increasing acceptance of mitral E/Ea as a surrogate measure of diastolic function and as a reliable estimate of intracardiac filling pressures, our observations provide an important refinement in the clinical interpretation of the mitral E/Ea ratio as it applies to patient populations where confounders such as alterations in myocardial structure, severity of systolic dysfunction, or the presence of synchronized pacing may influence its predictive value. Our data also caution the use of serial mitral E/Ea assessment for titration of diuretic therapy in such conditions.

Conventional Doppler recording of mitral inflow velocities and pulmonary vein velocities have shown to be useful in estimating PCWP though significant difficulties arise with alterations

in loading conditions, mitral valve disease, aging, tachycardia and atrial fibrillation (22,23,24,25,26). Although LV filling is initiated and enhanced by augmentable myocardial relaxation in healthy individuals, it is driven by a high filling pressure in patients with heart failure because myocardial relaxation is reduced (27). Our data corroborate these findings, since we too found modest relations between PCWP and mitral inflow velocities and deceleration times in our study cohort. This relatively low correlation is an unexpected finding, probably attributable to the confounding effects of LV relaxation, LV stiffness, left atrial pressure, mitral valve function, and annular recoil in this advanced heart failure population which will impact mitral inflow velocities and deceleration times to a greater extent than in normal or less advanced heart failure patients. As a result, the mitral E and DT which are recorded early diastole are only a very rough estimate of PCWP. To better account for relaxation, mitral annular velocity Ea has been shown to be not as dependent on pressure gradients as blood flow (27,28,29). As a consequence, the ratio of mitral E/Ea, which can be easily measured by standard equipment without extensive post-processing, has been proposed as a surrogate for PCWP in patients with a variety of cardiac abnormalities including diastolic heart failure, mitral valve disease, hypertrophic cardiomyopathy, atrial fibrillation and sinus tachycardia (7,8,9,10,11,12,13). The increasing acceptance is reflected by the endorsement of mitral E/Ea as a marker for LV filling pressure by a consensus statement from the European Society of Cardiology on the assessment of diastolic function (30).

The sensitivity and specificity for previously described cutoff value of mitral E/Ea > 15 to detect elevated PCWP was far lower in our study population than described in prior studies, especially in those patients receiving cardiac resynchronization therapy. However, it is important to emphasize that the profile of our patient population has important differences from several published reports that advocated mitral E/Ea for estimation of LV filling pressures in patients with depressed systolic function (14,15,16,17,18,19). Not only was our sample size much larger, our patient population by design experienced worsening of their clinical status just preceding evaluation and had significantly more cardiac dysfunction and LV remodeling (mean LVEF 24 ±7%, mean CI 2.1 ±0.7 l/min/m2, mean LVEDV 263 ±117 ml) than prior studies. We also describe for the first time the impact of pacing on the accuracy of mitral E/Ea, as shown by the poorer correlation of this measure with PCWP in patients with biventricular pacing, though even without pacing we failed to find a robust relationship. To better illustrate the potential

confounding aspects of this analysis, consider the two patients in Figure 5. The top panel is from a patient with dilated cardiomyopathy presenting with low-output in whom a high mitral E/Ea (27.3 for septal Ea, 22.4 for lateral Ea, and 24.6 for the mean) is seen with a relatively low PCWP of 14 mmHg. In contrast, the lower panel shows very elevated PCWP (23 mmHg) in a patient with ischemic cardiomyopathy, cardiac resynchronization therapy, low-output and relatively modest mitral E/Ea elevations (17.7 for septal Ea, 7.3 for lateral Ea, and 10.3 for the mean).

We did not confirm the previously reported finding that changes in the mitral E/Ea track changes in PCWP in ADHF (14). Patients with a reduction in mitral E/Ea could still have significantly elevated PCWP and vice versa at follow-up. Therefore, a potential reduction in mitral E/Ea during serial echocardiographic assessment should not be considered a surrogate for a drop in PCWP in advanced heart failure patients. Importantly, based on the findings of our study, mitral E/Ea should not be used as the only initial or continuing assessment of LV filling pressure to titrate diuretic therapy in the setting of decompensation or advanced systolic heart failure. Figure 6 illustrates a case with dilated cardiomyopathy treated with loop diuretics and vasodilators where a fall in PCWP and increase in CI elicited a contradictory increase in mitral E/Ea. One issue here is the patient's tachycardia and low cardiac output, causing a hyperdynamic state with increased movement and subsequent velocities of the lateral mitral annulus (high lateral E'). Furthermore, a patient's treatment may vary significantly over time, particularly in relation to the use of inotropic medications, which may have independent effects on annular motion. Clearly, many confounders may be at play to influence the predictive value of mitral E/Ea.

We further highlight the complex relationships between cardiac structure and performance as we observed that the discordance of mitral E/Ea and PCWP was linked to larger LV dimensions, and more impaired cardiac output in patients with ADHF. The presence of more severe LV remodeling seems to indicate the presence of a 'disconnect' between LV diastolic function and actual LV filling pressure in patients with ADHF, which limits the clinical utility of mitral E/Ea in estimating filling pressures in patients admitted with ADHF. Conversely, the lack of a significant correlation between mitral E/Ea and PCWP in patients with ADHF can also be explained by the presence of a more pronounced, irreversible, diastolic and systolic dysfunction. Patients with advanced heart failure often have severe LV fibrosis and impaired cardiac output

which could restrict systolic and subsequent early diastolic mitral annular motion such that the relationship between left atrial driving pressure (E) and LV relaxation kinetics (Ea) within the LV could become defective, resulting in discordance between echocardiographically measured mitral E/Ea and invasively measured PCWP. In addition, both mitral E and Ea are occurring in early diastole and reflect a host of factors relating to recoil, suction, intraventricular pressure gradients and the previous systolic contraction whereas PCWP is a mean value of diastolic pressure. Taken together, it is therefore not surprising that mitral E/Ea is only a very rough measure of LV end-diastolic pressure. In other words, mitral E/Ea has lower accuracy in assessing PCWP, especially at the more severe end of the heart failure syndrome spectrum because E and Ea are probably altered by volume shifts to a different degree than in cases with less severe heart disease.

**Study Limitations**. There were no direct hemodynamic measurements of LV end-diastolic or left atrial pressure performed, although PCWP is accepted as a well-validated surrogate considering the clinical condition of the patients and the need for serial monitoring (1,31,32). Wedge position was verified by changes in pressure waveforms without fluoroscopic guidance or measured venous blood oxygen content with balloon inflation. To analyze cardiac output, a standard resting metabolic rate was assumed, but overall cardiac outputs assessed by the Fick equation were comparable with those assessed by the thermodilution technique. Regional wall motion abnormalities in severely dilated and/or ischemic ventricles might have altered Ea. However, instead of analyzing only the septal or lateral Ea, we also considered the average of both walls (16). The exact mechanism through which CRT-D influences mitral E and Ea is not known, but pacing the heart leads to altered inter- and intra-ventricular activation sequences with subsequent alterations in wall segmental loading and contraction which probably influences Doppler parameters. Finally, the main aim of the study was to evaluate mitral E/Ea as a surrogate for PCWP, and we did not evaluate the reliability of combinations of different Doppler variables (including pulmonary vein signals) in estimating LV filling pressures. Our data do not imply in any way that Doppler evaluation is not useful in ADHF but merely support the notion of a stepwise approach incorporating all available echocardiographic data (11,16). We also did not evaluate the role of these measurements on the assessment of LV diastolic function of the failing myocardium. Although this is the largest reported cohort of patients with ADHF (especially with LVEF ≤30% and with serial measurements), and the sample size was

substantially larger compared with prior reports involving invasive hemodynamic validations, the sample size is still relatively small, notably for sub-group analyses.

**f) Conclusion**

In decompensated patients with advanced systolic heart failure, tissue Doppler derived mitral E/Ea alone may not be reliable in predicting intracardiac filling pressures, particularly in those with larger LV volumes, more impaired cardiac indices, and the presence of cardiac resynchronization therapy. Our observations underscore a need for a refinement in the broad clinical use of mitral E/Ea to estimate filling pressures, and caution the direct inference of such relationships to patients in the decompensated state with significant LV systolic dysfunction, cardiac remodeling, or biventricular pacing.

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**Table 1.** Demographics and Vital Statistics

| | **All Patients (n = 106)** | **Patients without CRT-D (n = 55)** | **Patients with CRT-D (n = 51)** |
|---|---|---|---|
| Age (y) | 57 ±12 | 56 ±13 | 59 ±12 |
| Men (%) | 76 | 72 | 78 |
| Weight (kg) | 81 ±22 | 82 ±22 | 78 ±22 |
| QRS width (msec) | 141 ±34 | 123 ±29 | 160 ±29* |
| Hypertension (%) | 58 | 56 | 60 |
| Hyperlipidemia (%) | 59 | 59 | 63 |
| Diabetes (%) | 32 | 34 | 27 |
| Ischemic etiology (%) | 42 | 44 | 39 |
| LV Ejection Fraction (%) | 24 ±8 | 25 ±8 | 24 ±9 |
| Hemoglobin (g/dl) | 11.7 ±2 | 11.7 ±2 | 11.8 ±2 |
| Creatinine (mg/dl) | 1.8 ±1.1 | 1.7 ±0.7 | 1.9 ±1.3 |
| BNP (pg/ml) | 1710 ±1406 | 1628 ±1247 | 1734 ±1386 |
| **Medical Treatment During Admission (%)** | | | |
| Beta Blockers | 58 | 54 | 62 |
| ACE inhibitors / ARB | 54 | 56 | 52 |
| Spironolactone | 44 | 39 | 48 |
| Loop Diuretic | 85 | 84 | 78 |
| Digoxin | 22 | 17 | 24 |
| Hydralazine | 38 | 40 | 35 |
| Isosorbide dinitrate | 37 | 37 | 37 |
| Inotropic Drugs | 35 | 38 | 32 |
| Nitroprusside | 41 | 44 | 40 |

Values are mean ± SD or n (%). *Abbreviations:* CRT-D: cardiac resynchronization therapy with defibrillator, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker.

* $p<0.01$ for comparison between patients with and without CRT-D

**Table 2.** Initial Hemodynamic and Echocardiographic Measurements

| | **All Patients (n = 106)** | **Patients without CRT-D (n = 55)** | **Patients with CRT-D (n = 51)** |
|---|---|---|---|
| Body Mass Index (kg/m2) | 27 ±8 | 28 ±6 | 27 ±6 |
| Heart Rate (bpm) | 75 ±29 | 84 ±24 | 67 ±32* |
| MAP (mmHg) | 75 ±11 | 76 ±13 | 74 ±9 |
| CVP (mmHg) | 12 ±7 | 13 ±6 | 11 ±8 |
| MPA (mmHg) | 34 ±11 | 34 ±11 | 36 ±10 |
| PCWP (mmHg) | 21 ±7 | 21 ±6 | 20 ±7 |
| CI (l/min.m2) | 2.1 ±0.7 | 2.0 ±0.7 | 2.1 ±0.8 |
| LV mass (g) | 376 ±134 | 367 ±130 | 395 ±145 |
| LV mass index (g/m2) | 183 ±63 | 177 ±59 | 196 ±68 |
| Left atrial volume (ml) | 92 ±38 | 89 ±39 | 96 ±38 |
| Left atrial volume index (ml/m2) | 45 ±16 | 43 ±17 | 47 ±14 |
| LVEDV (ml) | 252 ±114 | 210 ±85 | 294 ±124* |
| LVEDV index (ml/$m^2$) | 124 ±57 | 104 ±45 | 142 ±62* |
| Mitral E velocity (cm/s) | 96 ±28 | 97 ±25 | 96 ±32 |
| Mitral A velocity (cm/s) | 43 ±14 | 45 ±16 | 42 ±20 |
| Mitral E/A | 2.4 ±0.9 | 2.5±0.9 | 2.3 ±0.7 |
| Mitral DT (ms) | 150 ±45 | 136 ±38 | 164 ±46* |
| Mitral Ea septal annulus (cm/s) | 5.1 ±2.8 | 4.9 ±2.1 | 5.2 ±3.2 |
| Mitral E/Ea septal annulus | 23 ±12 | 24 ±11 | 22 ±13 |
| Mitral Ea lateral annulus (cm/s) | 7.4 ±4.6 | 7.2 ±3.1 | 7.5 ±5.8 |
| Mitral E/Ea lateral annulus | 17 ±11 | 17 ±10 | 17 ±12 |
| Mitral Ea average (cm/s) | 6.1 ±3.6 | 5.9 ±2.5 | 6.3 ±4.4 |

| | | | |
|---|---|---|---|
| Mitral E/Ea average | 20 ±12 | 21 ±11 | 19 ±12 |

Values are mean ± SD. *Abbreviations:* CRT-D: cardiac resynchronization therapy with defibrillator, MAP: mean systemic arterial pressure, CVP: central venous pressure, MPA: mean pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac index, LV: left ventricle, EDV: end-diastolic volume, DT: deceleration time.

* $p<0.01$ for comparison between patients with and without CRT-D

**Table 3.** Correlation Coefficients of Echocardiographic Variables with PCWP

| | **All Patients (n = 106)** | **Patients without CRT-D (n = 55)** | **Patients with CRT-D (n = 51)** |
|---|---|---|---|
| LV mass | 0.01 | -0.11 | 0.22 |
| LVEDV (ml) | -0.07 | -0.12 | 0.03 |
| Left atrial volume (ml) | 0.04 | 0.05 | -0.09 |
| E velocity (cm/s) | 0.28* | 0.29* | 0.17 |
| E/A | 0.24 | 0.47* | -0.06 |
| DT (ms) | -0.27* | -0.25* | -0.21 |
| Ea septal annulus (cm/s) | 0.06 | 0.03 | 0.16 |
| E/Ea septal annulus | 0.18 | 0.27 | 0.10 |
| Ea lateral annulus (cm/s) | 0.03 | -0.05 | 0.13 |
| E/Ea lateral annulus | 0.14 | 0.18 | 0.12 |
| Ea average (cm/s) | 0.02 | -0.06 | 0.11 |
| E/Ea average | 0.18 | 0.23 | 0.11 |

*Abbreviations:* CRT-D: cardiac resynchronization therapy with defibrillator, LV: left ventricle, DT: deceleration time. * $p \leq 0.01$

**Figure 1. Relation between mitral E/Ea and pulmonary capillary wedge pressure at baseline (left panel) and relation between changes (baseline-follow-up) in mitral E/Ea and changes (baseline-follow-up) in pulmonary capillary wedge pressure (right panel)**

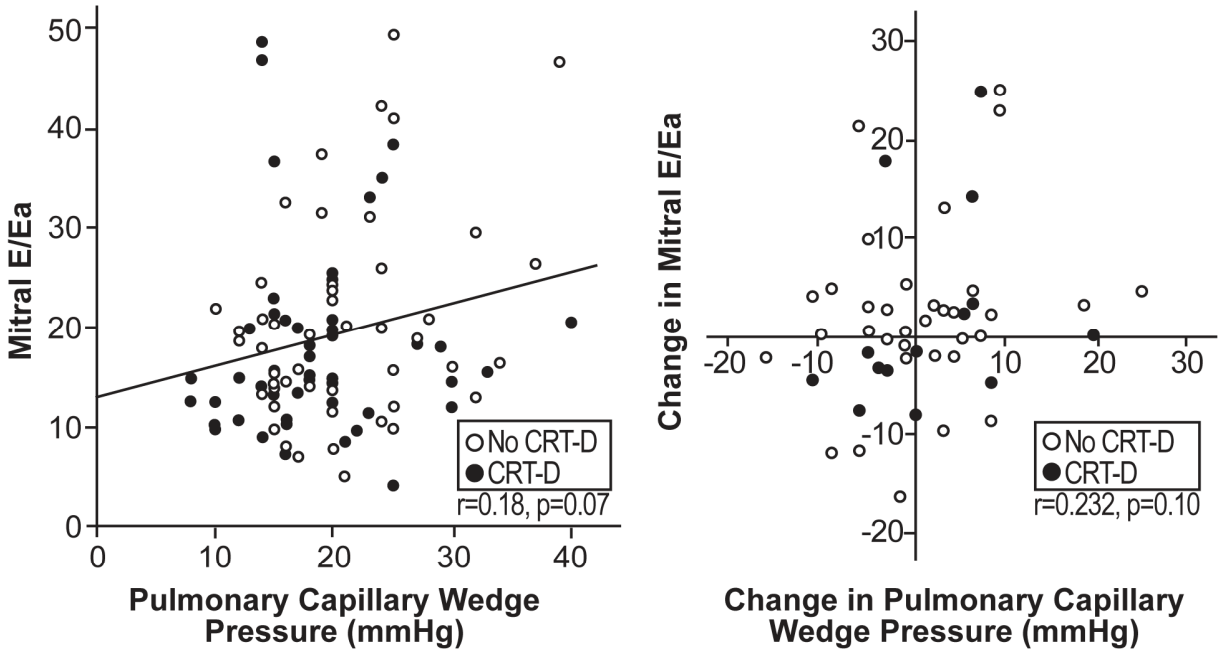


**Figure 2. Mitral E/Ea in all patients and stratified to previous CRT-D implantation or not.**

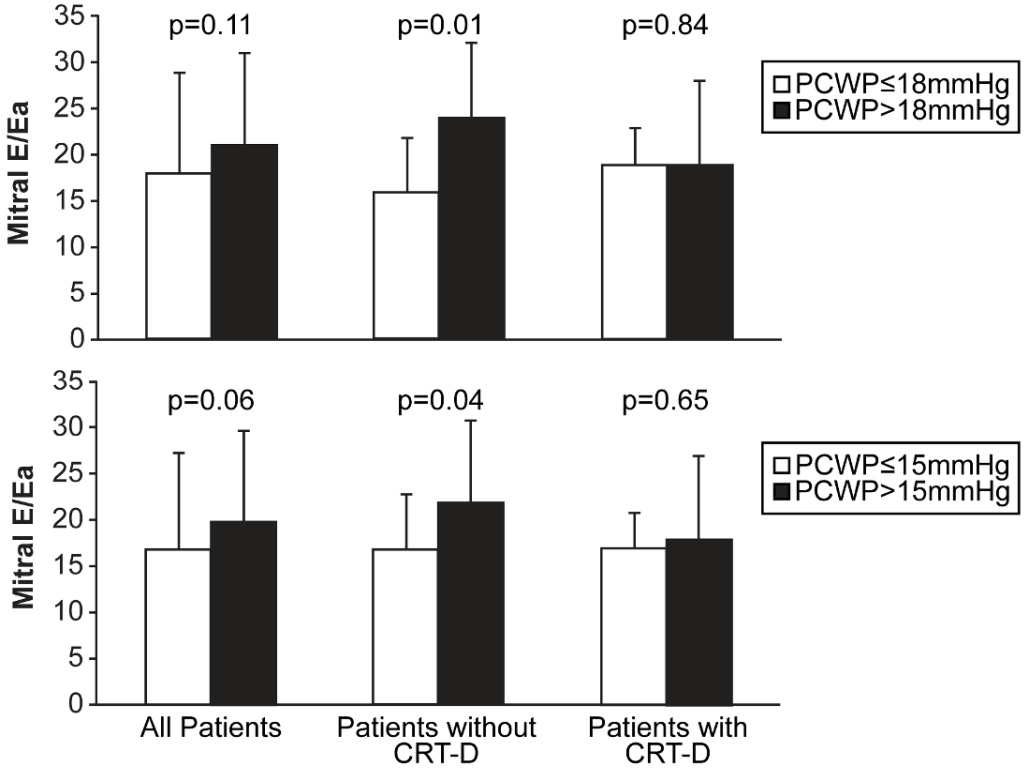


**Figure 3. Receiver operator characteristic curves for the prediction of pulmonary capillary wedge pressure > 18 mmHg (upper panel) and > 15 mmHg (lower panel) for mitral E/Ea.**

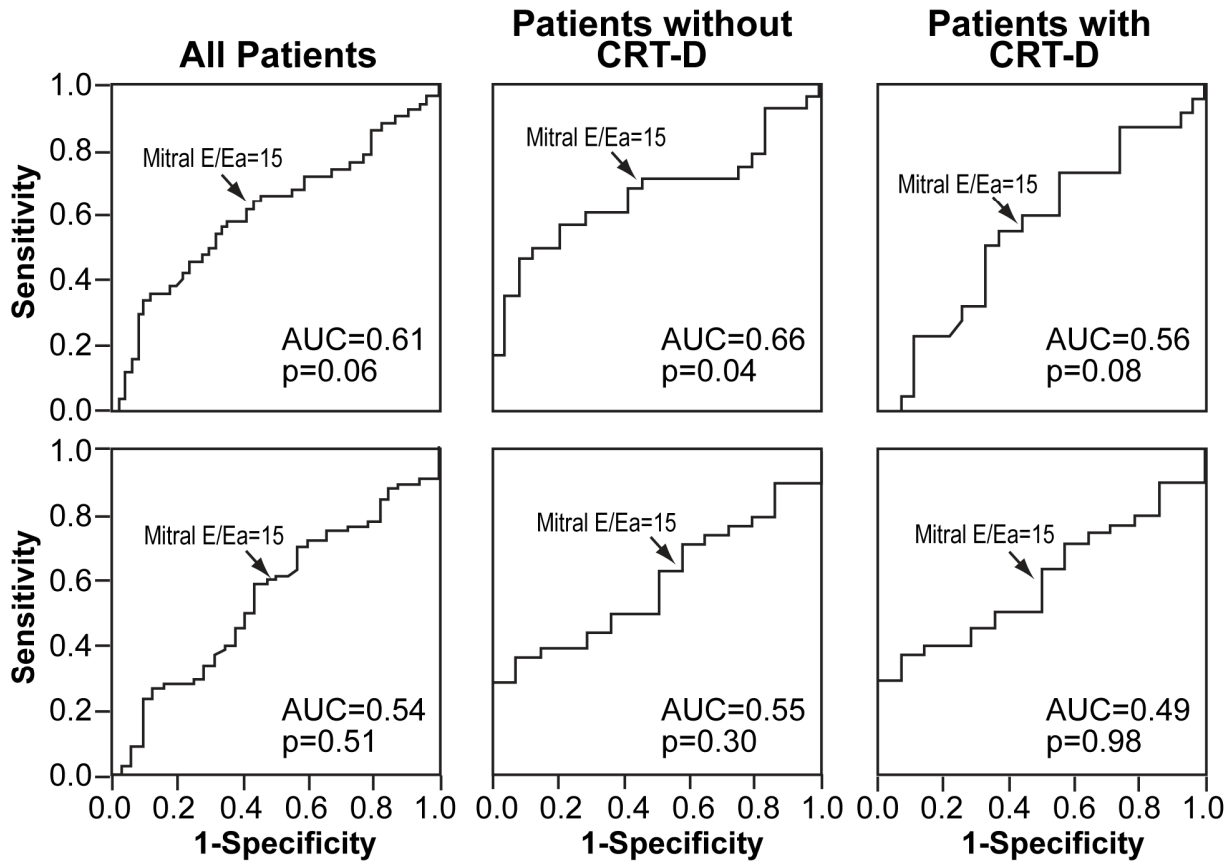


**Figure 4. Relation between mitral E/Ea and pulmonary capillary wedge pressure (PCWP) to LV end-diastolic volume and cardiac index. The p-value represents t-test between concordant and disconcordant PCWP and mitral E/Ea. Error bars represent standard deviation.**

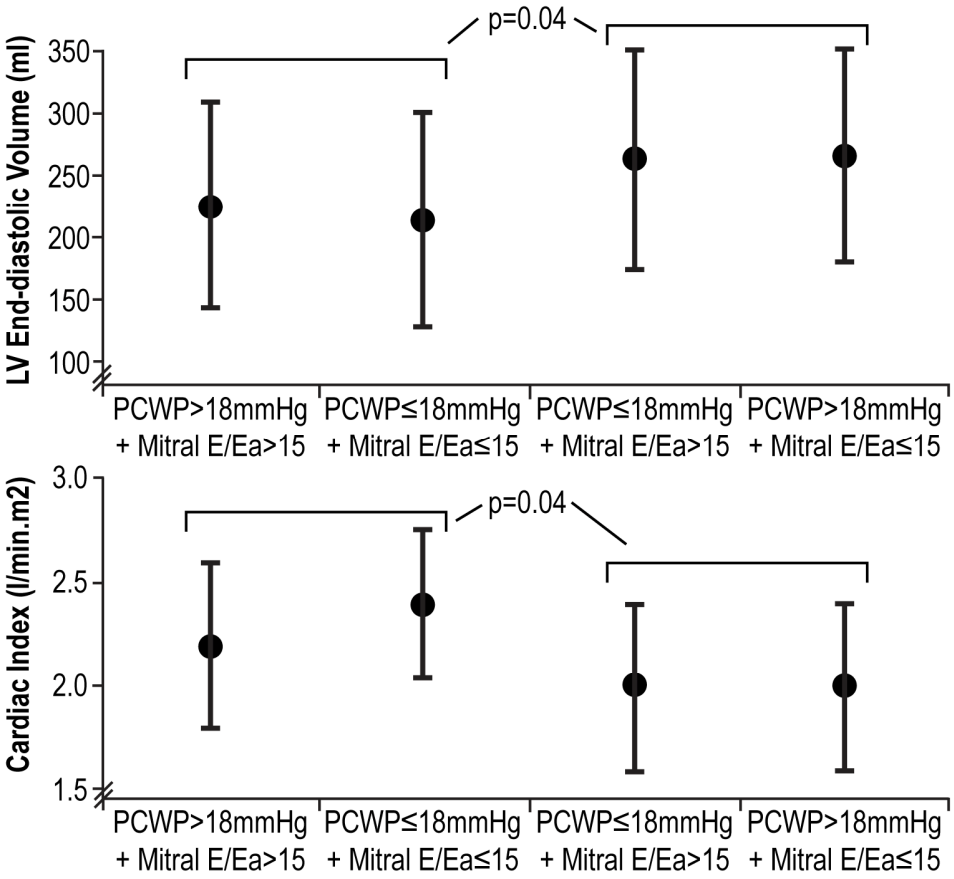


**Figure 5. Example of two patients with discordant pulmonary capillary wedge pressure (PCWP) and mitral E/Ea. Upper panel shows patient with low PCWP and high mitral E/Ea and lower panel shows patient with high PCWP and low mitral E/Ea.**

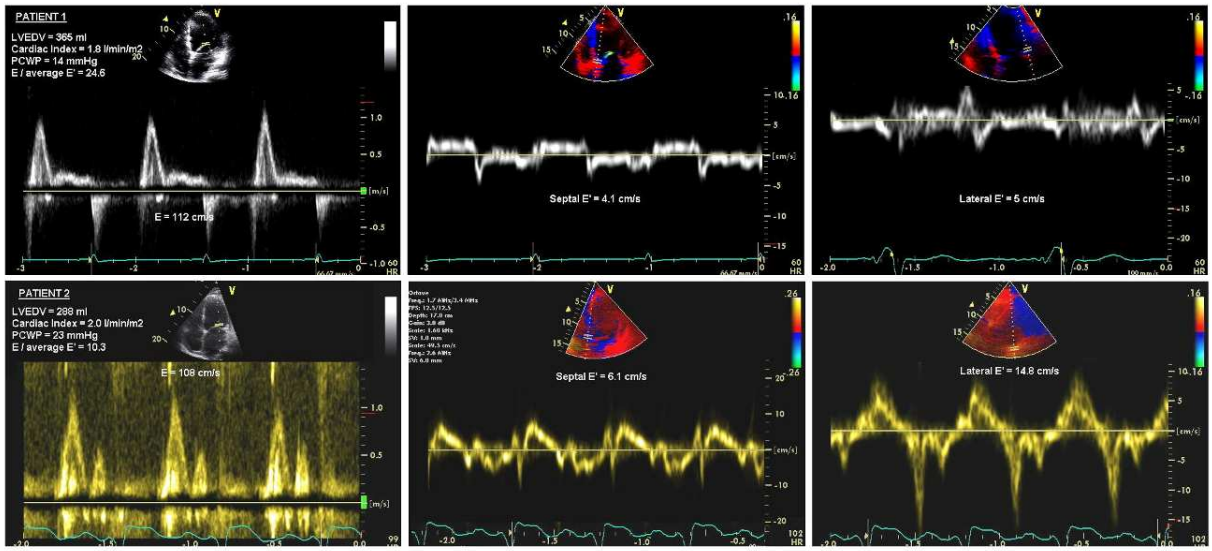
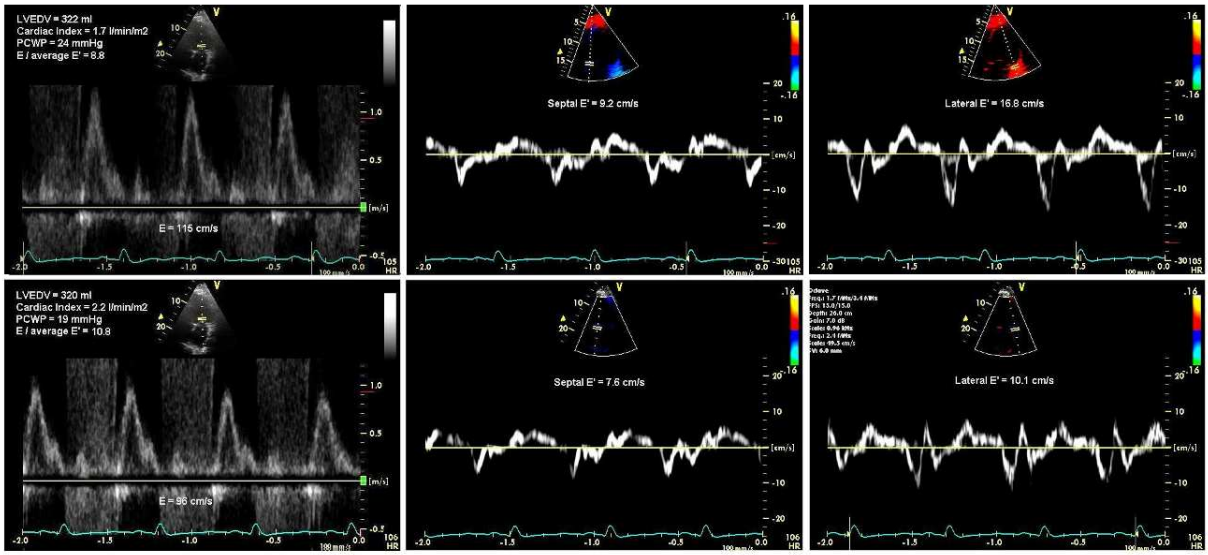


**Figure 6. Example of changes in pulmonary capillary wedge pressure (PCWP) and mitral E/Ea in one patient from baseline (Upper panel) to follow-up (Lower panel). Note the discordant PCWP and mitral E/Ea at baseline and at follow-up, and the reduction in PCWP (-5 mmHg) which is associated with an increase in mitral E/Ea (+ 2).**



# III. New hemodynamic insights into the cardiorenal interactions of advanced heart failure

## III. New hemodynamic insights into the cardiorenal interactions of advanced heart failure

## 1) Importance of venous congestion for worsening of renal function in advanced decompensated heart failure

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### a) Abstract

**Background:** Reduced cardiac output is traditionally believed to be the main determinant of worsening renal function (WRF) in advanced decompensated heart failure (ADHF).

**Objective:** To determine if venous congestion, rather than impairment of cardiac output, is primarily associated with the development of WRF in ADHF.

**Methods:** A total of 145 consecutive patients admitted with ADHF treated with intensive medical therapy guided by pulmonary artery catheter were studied. WRF was defined as an increase of serum creatinine ≥0.3 mg/dl during hospitalization.

**Results:** In the study cohort (age 57 ±14 years, cardiac index 1.9 ±0.6 l/kg.m$^2$, LVEF 20 ±8%, serum creatinine 1.7 ±0.9 mg/dl), 58 patients (40%) developed WRF. 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, and estimated glomerular filtration rates.

**Conclusions:** Venous congestion is the most important hemodynamic factor driving WRF in decompensated patients with advanced heart failure.

### b) Introduction

The pathophysiology of the cardio-renal interaction in the setting of advanced decompensated heart failure (ADHF) is poorly understood. It is commonly observed that coexisting renal dysfunction may complicate the treatment course of heart failure, and the use of intravenous loop diuretics often alleviate congestion at the cost of worsening renal function (WRF) (1,2). WRF during treatment of ADHF typically occurs within days of hospitalization and is a strong independent predictor of adverse outcomes (3,4,5).

Traditionally, WRF has been attributed to hypoperfusion of the kidney due to progressive impairment of cardiac output or intravascular volume depletion secondary to overzealous use of diuretics (6). Although the majority of patients hospitalized with ADHF also present with increased central or peripheral congestion, the presence of venous congestion has been considered a secondary phenomenon due to the "backward failure" caused by impaired cardiac output. Nevertheless, experimental animal data as far back as the 1930's have demonstrated that temporary isolated elevation of central venous pressure (CVP) can be transmitted back to the renal veins, resulting in direct impairment of renal function (7,8). However, human data regarding the differential contributions of venous congestion and cardiac output in the development of WRF during ADHF are lacking.

The primary aim of this study is to test the hypothesis that WRF is more dependent on venous congestion rather than on impairment of cardiac output in patients admitted with ADHF. The secondary aim is to investigate if effective reduction of CVP with intensive medical therapy can prevent the development of WRF.

**c) Methods**

**Subject Population**. We enrolled consecutive subjects, ≥18 year, with ADHF including New York Heart Association class III-IV symptoms, who underwent intensive medical therapy guided by pulmonary artery catheter at the Cleveland Clinic in a dedicated heart failure intensive care unit between January 1, 2006 and June 30, 2007. Subjects who met the following inclusion criteria at the time of admission were enrolled in the study: 1) left ventricular ejection fraction < 30%; 2) cardiac index (CI) ≤ 2.4 l/min/$m^2$; and 3) pulmonary capillary wedge pressure (PCWP) > 18 mmHg and/or central venous pressure (CVP) > 8 mmHg. Exclusion criteria included: 1) mechanical ventilation; 2) renal replacement therapy; 3) intravenous inotropic support on admission; 4) congenital heart disease; 5) recipients of heart transplantation. Institutional

Review Board approval of this research project was obtained, and informed consent was obtained for hospitalization, treatment and documented in the medical records, according to protocol and Cleveland Clinic policy.

**Intensive Medical Therapy.** The hemodynamic goals and pharmacologic approach of intravenous therapy in the dedicated heart failure intensive care unit have been previously described (9). Briefly, optimal hemodynamic response was defined as a decrease in PCWP to ≤ 18 mmHg, decrease in CVP to ≤ 8 mmHg, and improvement in CI to ≥ 2.4 l/min/$m^2$, all while maintaining mean arterial pressure > 65-70 mmHg. In order to achieve these hemodynamic goals, all subjects were treated according to protocols developed in our intensive care unit with intravenous or oral loop diuretics in combination with intravenous vasodilators (and/or inotropic agents), while continuing and optimizing evidence-based therapies (angiotensin-converting enzyme inhibitors, beta-blockers and spironolactone) as tolerated.

**Data Collection and Renal Assessment.** Two experienced heart failure cardiologists manually collected hemodynamic data, demographic characteristics, treatment, and echocardiographical data. Sequential serum creatinine and blood urea nitrogen values were recorded on admission and daily throughout the hospitalization period including the day of discharge. We defined a strict definition on the development of WRF as an increase in serum creatinine of ≥ 0.3 mg/dl during hospitalization, consistent with several previous investigations (4,5,10). It takes into account any significant renal deterioration during the treatment period in the setting of low cardiac output and congestion as defined by the inclusion criteria. Glomerular filtration rate (GFR) in ml/min was estimated daily using the four-variable Modification of Diet in Renal Disease equation (11). Normal or mild renal insufficiency was defined as GFR ≥60 ml/min/1.73$m^2$. Moderate renal insufficiency was defined as GFR 30-59 ml/min/1.73$m^2$ and severe renal insufficiency as GFR <30 ml/min/1.73$m^2$.

**Hemodynamic Assessment.** Complete hemodynamic assessment was collected in all subjects before the start of intensive medical therapy, and again before removing the pulmonary artery catheter. The CVP and PCWP were assessed at end-expiration with a balloon-tipped catheter at steady state with the subject in a supine position. CI was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. The systemic blood pressure was measured non-invasively by an automatic cuff sphygmomanometer. Renal perfusion pressure on

admission was assessed as the difference between mean arterial pressure and central venous pressure.

**Statistical Analysis.** All data were expressed as mean ±standard deviation for continuous data (median and inter-quartile range [IQR] for non-parametric data), and as a ratio for categorical data. Univariate comparisons of these variables were performed between baseline and follow-up variables and between subjects who developed WRF versus those who did not. A paired and unpaired t-test for continuous data and chi-square, Pearson's correlation and Fisher's exact test for categorical data was used for appropriate comparisons. The predictive value of CVP and CI as continuous variables to predict WRF was assessed using a receiver operating characteristic curve analysis. Separate c-statistics for CVP and CI from logistic regression models were calculated and a set of 300 bootstrapped (with replacement) samples were generated to compute the difference and standard error. The difference between the c-statistics was bias corrected, and a one-sample t-test was performed to determine if the difference was equal to zero. Stepwise multivariate linear regression analysis was used to determine the independent relationships between hemodynamic variables, baseline renal function and hemoglobin with WRF. Statistical significance was set at a two-tailed probability level $< 0.05$. Statistical analyses were performed using SPSS for Windows, release 13.0 (SPSS Inc., Chicago IL) and SAS version 8.2 (Cary, NC). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**d) Results**

**Subject characteristics.** A total of 145 subjects, mean LVEF 20 ±8%, were included in this observational prospective study. Patient characteristics on admission are listed in Table 1, which were comparable between subjects who developed WRF versus those who did not (except for serum creatinine, blood urea nitrogen, and hemoglobin at admission). The percentage of patients with moderate to severe right ventricular dysfunction (60%) was similar between the two groups. Plasma B-type natriuretic peptide measurements on admission were available in 40% of subjects, and were comparable between patients with and without incident WRF (median [IQR]: 1,100 [497, 1,921] versus 874 [333, 1,430] pg/ml, p=ns).

The mean time to develop WRF was 1.0 ±1.5 day. Mean duration of pulmonary artery catheter guided therapy was 3.5 ±1.5 days, and mean total length of stay was 9 ±9 days, similar

between those with or without incident WRF. On admission, 19% of the study population had severe renal insufficiency, 45% had moderate renal insufficiency, and 36% had normal or mild renal insufficiency. Overall, 53% of patients who developed WRF during admission demonstrated serum creatinine level at discharge to be less than the peak serum creatinine level

A statistically significant correlation was observed between baseline CI and baseline renal function expressed by serum creatinine ($r = 0.32$, $p=0.001$) or GFR ($r = -0.3$, $p=0.002$). However, there was no correlation between baseline CI and baseline CVP. Finally, no correlation between baseline CVP and baseline renal function could be found.

**Incidence and renal predictors of worsening renal function.** Overall, 58 subjects (40%) developed WRF during their hospitalization, predominantly within the first 5 days of hospitalization. The development of WRF was associated with a higher peak of serum creatinine (2.5 ±1.1 versus 1.5 ±0.8 mg/dL, $p<0.001$) during hospitalization. Subjects who developed WRF were more likely to have severe renal insufficiency at baseline ($p=0.05$), and had higher serum creatinine both at baseline (1.9 ±0.9 versus 1.5±0.8 mg/dL, $p=0.007$) and at discharge (2.2 ±1.1 versus 1.4 ±0.7 mg/dL, $p<0.001$).

**Impact of medication on development of worsening renal function.** Subjects who developed WRF versus those who did not had comparable baseline medication use on admission, with the exception of lower spironolactone utilization (Table 1). Overall, no statistically significant differences in medication use during pulmonary artery catheter guided therapy were observed. Mean dose of furosemide during intensive medical therapy guided by pulmonary artery catheter was similar among patients who developed WRF or not (117±130 mg/day and 116±81 mg/day, p=ns). Half of the patients in both groups received furosemide through continuous parental infusion.

**Baseline hemodynamic predictors of incident worsening renal function.** Table 2 illustrates the baseline hemodynamic measurements, stratified by the presence or absence of incident WRF. All subjects showed signs of impaired hemodynamics with impaired CI and elevated right- and left-sided filling pressures at baseline. Heart rate, systolic arterial blood pressure, PCWP, and systolic pulmonary artery pressure at baseline were comparable (p=ns) between the two cohorts and were not predictive for WRF.

There was an incremental risk in WRF with increasing categories of baseline CVP, with 75% of subjects presenting with a baseline CVP >24 mmHg developing WRF (Figure 1).

Furthermore, the mean baseline CVP was statistically higher in subjects who developed WRF versus those with did not (18 ±7 versus 12 ±6 mmHg, p<0.001). In addition, a significant correlation between admission CVP and severity of WRF was found (r = 0.4, p<0.0001). Estimated renal perfusion pressure on admission was similar among patients who did and did not develop WRF (63±15 vs 65±12 mmHg, p = 0.2).

The mean baseline CI was significantly higher (rather than lower) in subjects who developed WRF versus those who did not (2.0 ±0.8 versus 1.8 ±0.4 l/min/$m^2$, p=0.008). However, the pattern of change in GFR during hospitalization was similar between those with CI above and below mean admission CI, indicating that changes in GFR were not related to baseline CI. In addition, using ROC curve analysis, we observed that baseline CVP (0.734, p < 0.0001) but not baseline CI (0.552, p = 0.6) predicted the development of WRF (Figure 2, difference p = 0.012). In a separate ROC analysis (not shown), baseline CVP remained a predictor of WRF when patients were categorized according to the presence or absence of diabetes mellitus, hypertension or significant baseline renal dysfunction. Finally, another sub-analysis was performed in patients without severe renal insufficiency (GFR >30 ml/min/1.73.$m^2$). In this subset, patients who developed WRF still had higher admission CVP (17 ±4 versus 12 ±5 mmHg, p=0.007) but similar admission CI (1.9 ±0.4 versus 1.8 ±0.5 l/min/$m^2$, p=ns).

**Impact of hemodynamic changes on incident worsening renal function.** Table 2 also compares the hemodynamic measurements from baseline to follow-up, stratified by the presence or absence of incident WRF. All hemodynamic alterations demonstrated significant improvements following intensive medical therapy as expected (all p<0.001). Heart rate, systolic arterial blood pressure, PCWP, and systolic pulmonary artery pressure at the time of pulmonary artery catheter removal remained comparable (p=ns) between the two cohorts.

**Follow-up hemodynamic predictors of incident worsening renal function.** At follow-up, the mean CI remained significantly higher (2.7 ±0.7 versus 2.4 ±0.5 l/min/$m^2$, p=0.01) and the CVP significantly higher (11 ±8 versus 8 ±5 mmHg, p=0.04) in subjects who developed WRF versus those who did not. In particular, a persistently elevated CVP >8 mmHg at the time of PAC removal was associated with greater incidence of WRF (51% versus 18 %, p=0.01). Overall discharge CVP also correlated with the severity of WRF (r = 0.3, p=0.007). Finally, discharge CVP rather than discharge CI was associated with renal impairment (lower GFR) as illustrated in Figure 3.

The ability of CVP on admission (p=0.01) or at time of PAC removal (p=0.03) to stratify risk to develop WRF was apparent across the spectrum of heart rate, PCWP, systolic blood pressure, systolic pulmonary artery pressure, CI, serum creatinine, and hemoglobin in multivariable analysis.

**e) Discussion**

There have been numerous contemporary reports describing the natural history of the development of WRF in the setting of decompensated heart failure. However, the majority lacked careful cardiac and hemodynamic profiling during the clinical course of WRF. Based on early work, WRF is often attributed to hypoperfusion of the kidney due to progressive impairment of cardiac output or intravascular volume depletion secondary to overzealous use of diuretics (6). We observed in our patient population with low-output decompensated heart failure that besides the presence of intrinsic renal insufficiency, venous congestion (both with elevated CVP on admission as well as insufficient reduction of CVP during hospitalization) was the strongest hemodynamic determinant for the development of WRF. In contrast, impaired CI on admission and improvement in CI following intensive medical therapy had limited contribution to WRF. These observations provide important clinical confirmation of experimental data that preservation of cardiac output without relieving venous congestion may not necessarily avert the development of WRF. While many of these findings may seem intuitive to the experienced clinician, the concept of "congestive kidney failure" is of high clinical value with the contemporary epidemic proportions of ADHF where cardiac insufficiency (rather than venous congestion) is often considered the core lesion.

The pathophysiology of WRF in the setting of ADHF is complex and multifactorial. The term "cardio-renal syndrome" is often used to describe progressive renal deterioration with heart failure therapy in an aggressive attempt to relieve congestive signs and symptoms. We chose to use the term "worsening renal function", as there remains much uncertainty regarding the precise definition of the cardio-renal syndrome. Using a clinical surrogate of rise in serum creatinine levels, previous reports have suggested that WRF occurs in one third of patients admitted with ADHF (4,5,12). We found this incidence to be even higher (approaching 40%) in a "cold and wet" patient population. While the initiation or maintenance of certain classes of drugs like angiotensin-converting enzyme inhibitors and loop diuretics have been linked to WRF, we did

not find any difference in their usage at admission or during hospitalization to account for the occurrence of worsening renal function (2,13,14). The lower rates of spironolactone use in those developing WRF is likely due to the relative contraindication of the drug in patients with intrinsic renal diseases.

In patients with severe renal insufficiency at baseline, almost 60% developed WRF. Indeed, the highest quartile of baseline CVP and CI both had the highest mean serum creatinine and corresponding highest rates of WRF. This indicates that the underlying intrinsic kidney disease remains an important determinant of the "reserve" available for the kidneys to relieve congestion and to respond to the insult posed by ADHF and the aggressive diuresis and natriuresis necessary during treatment of ADHF. Naturally, this raises the question as to whether treatment primarily directed with the aim of "renal preservation" should be administered prophylatically, especially in this extraordinary high-risk group.

WRF occurs during the initial days following treatment for ADHF during hospitalization. As a result, the most commonly assumed cause of worsening renal function has been hypoperfusion of the kidney secondary to low-output or hypotension (leading to pre-renal hypoperfusion or impaired renal "preload") (6). In our patient population, we observed that systemic blood pressures were similar between those with versus without WRF, consistent with previous reports (2). Also during intensive medical therapy, systolic blood pressures were carefully monitored and targeted as drugs were being titrated to prevent overzealous hypotension. Although we did not directly assessed regional renal perfusion, the persistently elevated intracardiac pressures in our patient population (with a mean PCWP in the range of 18-19 mmHg) suggested that the overall vasculature was unlikely to be "under-filled." In particular, estimated renal perfusion pressures were similar between those with versus without WRF. Clearly, judicious lowering of filling pressures is still of utmost importance to prevent hypoperfusion and pre-renal azotemia, and there are still indicators that careful monitoring can be helpful in vulnerable patients. For example, the ESCAPE trial demonstrated that renal function did not worsen when treatment was directed at lowering invasively measured CVP and PCWP, while it did worsen in the treatment arm guided by clinical assessment alone (15).

Our data also demonstrate that progressive or persistent impairment of cardiac output may not be the primary culprit in the development of WRF during the treatment for ADHF. Patients who developed WRF did not have a lower CI on admission and at discharge when

compared to those without WRF. Furthermore, the patterns of change in GFR were similar between those with a different degree of CI impairment, independent of inotropic usage. However, this is not to imply that impairment of CI itself does not contribute to WRF, as we acknowledge that patients with progressive pump failure or cardiogenic shock may progress to renal impairment as a result of impaired organ perfusion or indirectly through "backward failure" and venous congestion. Instead, our data indicate that in the setting of hemodynamic alterations of ADHF on admission and following treatment, the relative contributions of CI may be less apparent than historically assumed. Thus, even in this advanced heart failure population with relatively low-output cardiac failure and marginal blood pressures, routine use of inotropic therapy may not necessarily relieve or prevent WRF.

Our observation suggests that the strongest hemodynamic determinant of development of WRF is the presence of venous congestion as measured by elevated CVP, both on admission and at follow-up. There appears to be a near-linear relationship since if the baseline CVP reached >16 or >24 mmHg, we observed a sharp rise in the incidence of WRF approaching 59% and 75%, respectively. During treatment for ADHF, persistent venous congestion also posed a very high risk for the development of WRF. Clearly, this could simply be interpreted as a "sicker" patient population with more advanced disease states that were reflected by higher CVP. However, common cardiovascular measures of disease severity (including systolic blood pressure, serum sodium, plasma B-type natriuretic peptide, PCWP, systolic pulmonary arterial pressure, and dosage of loop diuretics) were similar between those with versus without WRF.

The concept of venous congestion being transmitted to the renal veins and kidneys leading to renal dysfunction is supported by a substantial amount of literature as early as in the 1930s. In an experimental model that iatrogenically induced hypervolemia, an increase in renal vein pressure directly led to renal insufficiency independent of cardiac output or renal blood flow (7,8). Importantly, this was also shown to be a reversible phenomenon as lowering of renal vein pressure immediately improved urine output and GFR (7,8). Other studies indicated that temporary renal vein compression resulted in reduced sodium excretion, reduced GFR and reduced renal blood flow (16-18). Increased CVP also causes an increase in renal interstitial pressure, which might lead to a hypoxic state of the renal parenchyma similar to the mechanism by which hepatic congestion leads to liver dysfunction in heart failure (19-25). In addition, our group recently provided some mechanistic data to suggest the contributions of raised intra-

abdominal pressure caused by visceral edema or ascites in this pathophysiology (26). On the other hand, prolonged increases in plasma volume or CVP will attenuate several vascular reflexes leading to an impaired arterial responsiveness, thereby further impairing the effective renal blood flow (27-32). Increased CVP has also been associated with reduced GFR in patients with primary pulmonary hypertension and relatively preserved cardiac outputs (33). Finally, a recent sub-analysis of the ESCAPE trial also suggested that incident WRF was related to CVP (34).

It is conceivable that in the setting of ADHF, the development of "congestive kidney failure" led by elevated renal venous pressure from venous congestion (increased renal afterload) and increased renal interstitial pressure (intrinsic renal compromise) might be under-appreciated mechanisms by which WRF develops. These findings may therefore help to explain why extra-renal strategies primarily aim to relieve venous congestion (such as ultrafiltration) may be effective in alleviating "congestive kidney failure" in selected cases of heart failure rather than those augmenting cardiac output or forward perfusion. We believe that this is an important conceptual shift with broad implications, implying that the search for future ADHF therapies should focus on strategies that allow safe and optimal reduction of venous congestion to prevent such a devastating complication.

**Study Limitations.** There are several limitations in our study, including the lack of serial weight assessments and direct measurements on glomerular filtration. There were no direct physiological measurements of renal hemodynamics or regional intravascular volume to fully explain the complex underlying pathophysiology, although CI has been considered a reasonable surrogate for renal blood flow under the circumstances. To analyze CI, a standard resting metabolic rate was assumed but overall CI assessed by Fick was comparable with those assessed by thermodilution. Although differences in hemoglobin concentration might have also contributed to differences in absolute oxygen delivery to the kidney, arterio-venous oxygen differences on admission could be retrieved in 50% of patients, and were found to be similar between patients with and without WRF. The relatively low admission rates of neurohormonal antagonists and difference in spironolactone use were probably secondary to the underlying kidney disease, severity of the heart failure, and the withholding of medications due to intolerance related to their "cold and wet" conditions. Finally, though invasive measurements

were used in our protocol, it is not the intention of these data to imply the need for invasive monitoring, but solely to understand the hemodynamic contributors of WRF in ADHF.

**e) Conclusion**

In our cohort of patients with advanced heart failure admitted for decompensation, WRF is commonly observed despite hemodynamic improvements with intensive medical therapy. Our data imply that apart from intrinsic renal insufficiency, the presence of venous congestion, rather than reduced cardiac output, may be the primary hemodynamic factor driving WRF in this patient population.

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**Table 1. Baseline patient characteristics and medication use.**

| | Patients with worsening renal function (n=58) | Patients without worsening renal function (n=87) | p value |
|---|---|---|---|
| **Age** | 59 ±14 | 56 ±14 | ns |
| **NYHA class III / IV (%)** | 9/91 | 10/90 | ns |
| **Ischemic Etiology (%)** | 54 | 50 | ns |
| **Body mass index (kg/m$^2$)** | 28 ±3 | 29 ±4 | ns |
| **Male Gender (%)** | 74 | 73 | ns |
| **Caucasian Race (%)** | 78 | 76 | ns |
| **Medical history (%)** | | | |
| Smoking history | 49 | 51 | ns |
| Diabetes | 44 | 34 | ns |
| Hypertension | 48 | 40 | ns |
| Hyperlipidemia | 60 | 59 | ns |
| ICD / CRT-D | 38 / 29 | 42 / 27 | ns |
| **Labs on admission** | | | |
| Hemoglobin (g/dl) | 11.5 ±.2.5 | 13.0 ±1.5 | 0.05 |
| Creatinine (mg/dl) | 1.9 ±0.9 | 1.5 ±0.8 | 0.007 |
| GFR (ml/min/1.73.m$^2$) | 48 ±19 | 56 ±25 | 0.05 |
| BUN (mg/dl) | 58 ±25 | 36 ±20 | <0.001 |
| Sodium (mmol/l) | 134 ±6 | 134 ±5 | ns |
| BNP (pg/ml) | 1,559 ±1340 | 1,157 ±1073 | ns |
| **Oral Medication on Admission (%)** | | | |
| Aspirin / coumadin | 44 | 48 | ns |
| ACE-inhibitor / ARB | 49 | 50 | ns |
| Digoxin | 38 | 43 | ns |
| Beta-blockers | 56 | 62 | ns |
| Spironolactone | 27 | 47 | 0.03 |

| | | | |
|---|---|---|---|
| Loop diuretics | 80 | 86 | ns |
| Hydralazine | 23 | 17 | ns |
| Isosorbide dinitrate | 27 | 22 | ns |
| Statin | 57 | 54 | ns |
| Amiodarone | 22 | 19 | ns |
| **Medication During PAC-Guided Therapy (%)** | | | |
| IV or PO furosemide | 85 | 86 | ns |
| IV vasodilators | 51 | 56 | ns |
| Milrinone | 34 | 30 | ns |
| Dobutamine | 30 | 27 | ns |

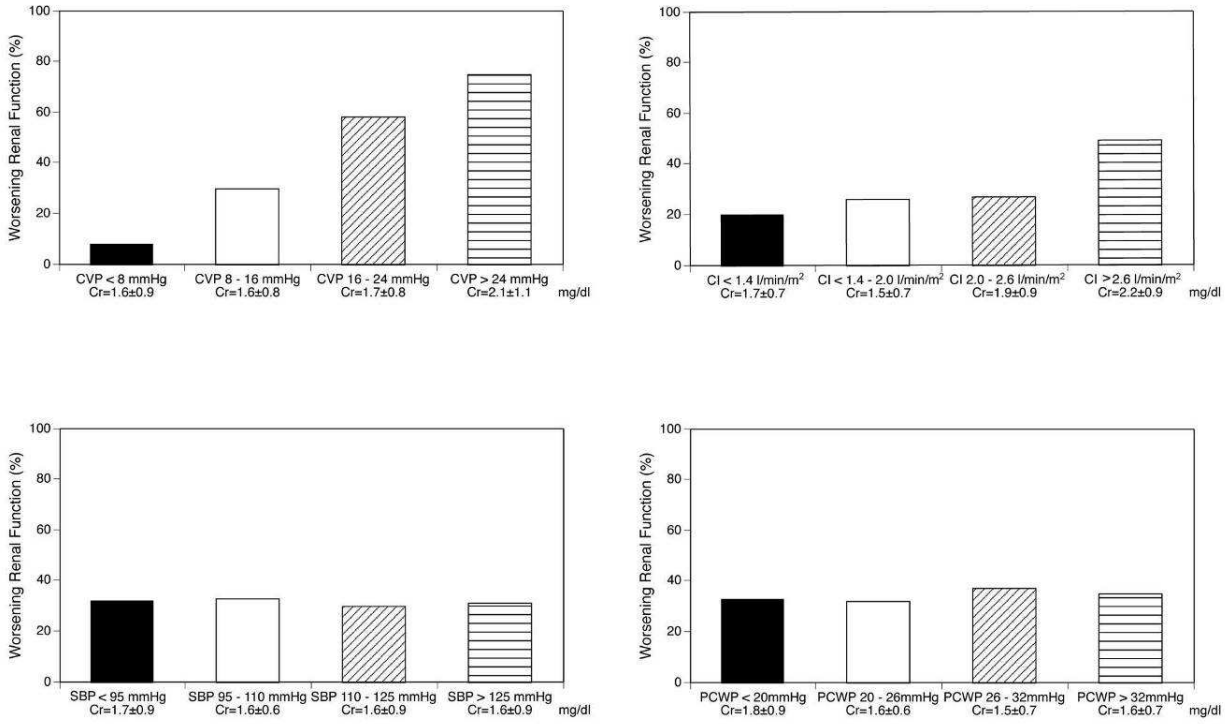
NYHA indicates New York Heart Association functional class, ICD: implantable cardiac defibrillator, CRT-D: cardiac resynchronization therapy with defibrillator, GFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker. Values are mean ± SD or n (%).

**Table 2. Hemodynamic variables on admission and time of pulmonary artery catheter removal in all patients and stratified according to those who developed worsening renal function (n=58) and those who did not (n=87).**

| | **All patients** (n=145) | | | **Patients with worsening renal function** (n=58) | | | **Patients without worsening renal function** (n=87) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **Follow-up** | **p-value** | **Baseline** | **Follow-up** | **p-value** | **Baseline** | **Follow-up** | **p-value** |
| **HR** (bpm) | 88 ±40 | 89 ±18 | ns | 86 ±22' | 90 ±16' | ns | 89 ±46 | 88 ±19 | ns |
| **SBP** (mmHg) | 109 ±18 | 109 ±18 | ns | 111 ±21' | 110 ±25' | ns | 108 ±15 | 109 ±15 | ns |
| **CVP** (mmHg) | 14 ±7 | 9 ±6 | < 0.001 | 18 ±7* | 11 ±8** | < 0.001 | 12 ±6 | 8 ±5 | < 0.001 |
| **SPA** (mmHg) | 55 ±15 | 46 ±7 | < 0.001 | 57 ±13' | 49 ±15' | < 0.001 | 54 ±16 | 46 ±12 | < 0.001 |
| **PCWP** (mmHg) | 24 ±7 | 18 ±5 | < 0.001 | 25 ±7' | 19 ±5' | < 0.001 | 24 ±7 | 18 ±5 | < 0.001 |
| **CI** (l/min/m$^2$) | 1.9 ±0.6 | 2.5 ±0.6 | < 0.001 | 2.0±0.8† | 2.7±0.7‡ | < 0.001 | 1.8 ±0.4 | 2.4 ±0.5 | < 0.001 |

HR: heart rate, SBP: systolic arterial blood pressure, CVP: central venous pressure, SPA: systolic pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac index. ' p = ns, * p < 0.001, ** p = 0.01, † p = 0.008, ‡ p = 0.01 between patients who did and did not develop worsening renal function at same moment in time.

**Figure 1. Prevalence of worsening renal function during hospitalization according to categories of admission central venous pressure, cardiac index, systolic blood pressure and pulmonary capillary wedge pressure.**




CVP = central venous pressure, Cr = serum creatinine, CI = cardiac index, SBP = systolic blood pressure, PCWP = pulmonary capillary wedge pressure.

**Figure 2. ROC curves for central venous pressure (CVP) and cardiac index (CI) on admission for worsening renal function development.**

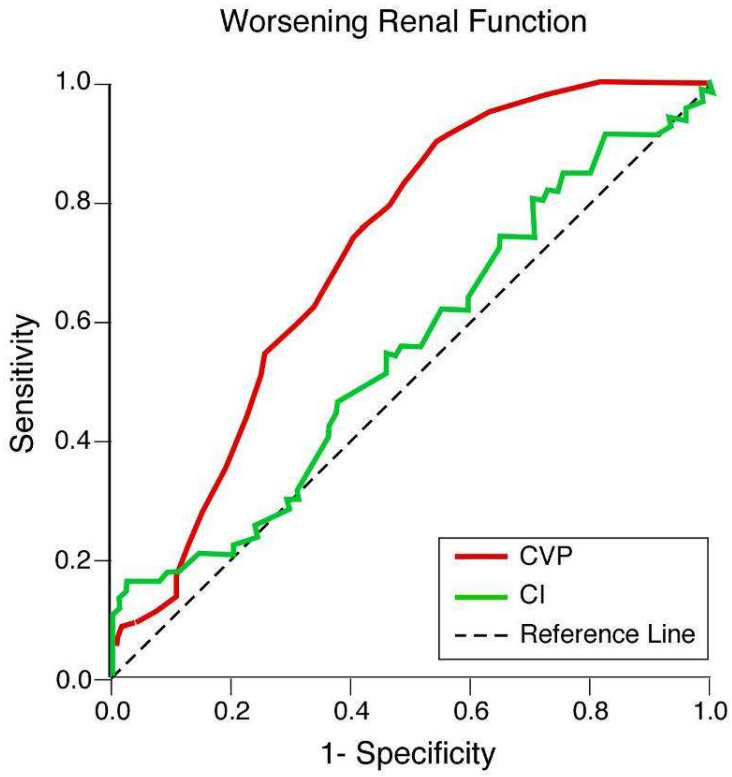
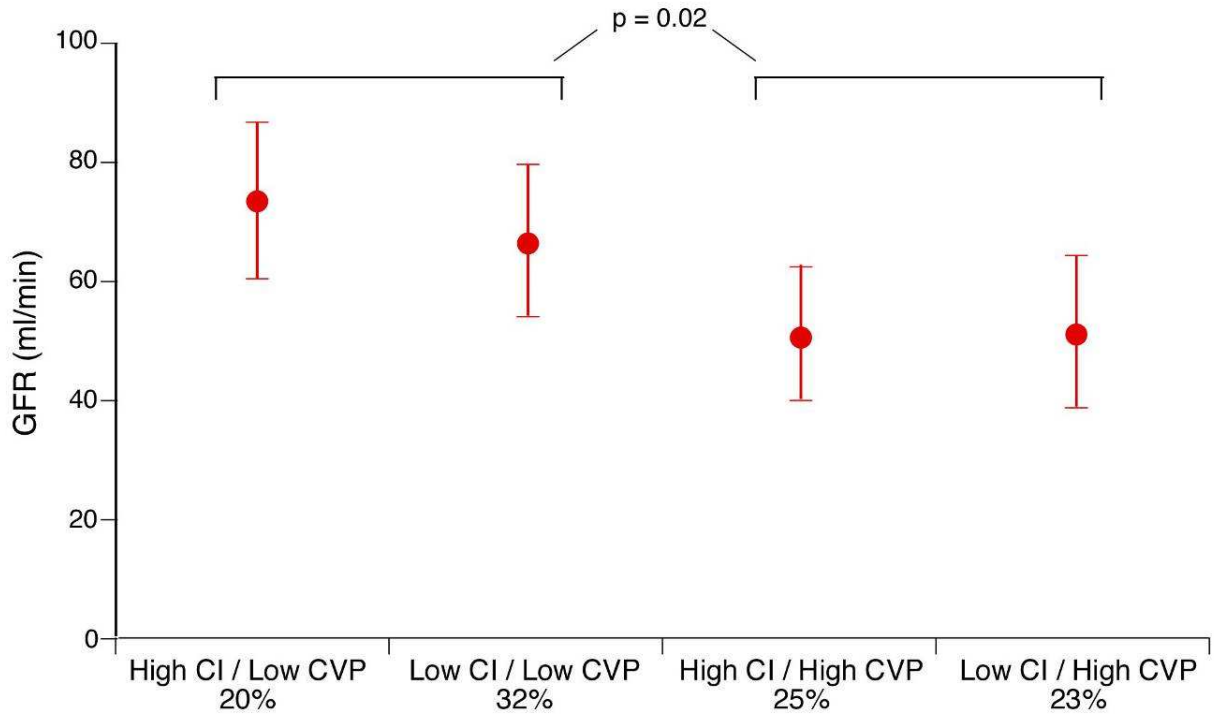


**Figure 3. Relative contributions of central venous pressure (CVP) and cardiac index (CI) to glomerular filtration rate (GFR) at time of pulmonary artery catheter removal.**




Error bars represent 95% confidence interval. Cut-off values for CI = 2.4 l/min.m2 and CVP = 8 mmHg.

## 2) Elevated intra-abdominal pressure: a potential contributor to worsening renal function?

Mullens W, Abrahams Z, Skouri H, Taylor D, Starling R, Young J, Francis G, Tang W. Elevated Intra-Abdominal Pressure in Acute Decompensated Heart Failure: A Potential Contributor to Worsening Renal Function? J Am Coll Card 2008;51:300-306.

### a) Abstract

**Background:** Elevated intra-abdominal pressure (IAP, ≥8mmHg) and intra-abdominal hypertension (IAH = IAP ≥12mmHg) are associated with intra-abdominal organ dysfunction. With the potential of ascites and visceral edema causing elevated IAP in patients with acute decompensated heart failure (ADHF), we hypothesized that changes in IAP with aggressive diuretic or vasodilator therapy would be associated with improvement in renal function.

**Methods:** Forty consecutive patients admitted to a specialized heart failure intensive care unit for management of ADHF with invasive hemodynamically-guided therapy were studied. The IAP was measured using the transvesical technique at time of admission and before removal of the pulmonary artery catheter.

**Results:** In our study cohort (age 59 ±13 years, mean LVEF 19 ±9%, baseline serum creatinine 2.0 ±0.9 mg/dl), the mean baseline IAP was 8 ±4 mmHg, with 24 (60%) patients having elevated IAP and 4 (10%) having IAH. Elevated IAP was associated with worse renal function (p=0.009). Hemodynamically-guided therapy resulted in improvement in both hemodynamic measurements and IAP. A strong correlation ($r = 0.77$, $p < 0.001$) was observed between reduction in IAP and improved renal function in patients with elevated IAP and IAH. However, changes in IAP or renal function did not correlate with changes in any hemodynamic variable.

**Conclusion:** Elevated IAP is prevalent in patients with ADHF and is associated with impaired renal function. In the setting of hemodynamically-guided therapy for ADHF, easily measured changes in IAP were more closely correlated with changes in renal function than any hemodynamic variable.

**b) Introduction**

Despite recent medical advances, the pathophysiology of acute decompensated heart failure (ADHF), in particular the cardio-renal interactions, remain poorly understood. In many cases of heart failure, coexisting renal dysfunction may complicate the treatment course. In addition, therapies that alleviate congestion such as loop diuretics that remain a mainstay of the therapeutic armament against HF, can worsen renal insufficiency and may even increase mortality (1,2).

There has been increasing interest in measuring intra-abdominal pressure (IAP) in critically ill patients as elevated IAP has been associated with intra-abdominal organ dysfunction (3,4). The compliance of the abdominal wall generally limits the rise in IAP as abdominal girth increases. However, once a critical volume is reached, compliance of the abdominal wall decreases abruptly. Further distention beyond this "critical IAP" results in a rapid rise in abdominal pressure and resultant organ dysfunction (5,6). Recently, during the second World Congress on Abdominal Compartment Syndrome, medical critical care specialists defined a normal IAP to be between 5–7 mmHg in critically ill adults, an elevated IAP to be $\geq$ 8 mmHg and intra-abdominal hypertension (IAH) to be $\geq$12 mmHg (7).

It has been recognized over the past century that elevated IAP can directly lead to renal compromise in the setting of abdominal compartment syndrome or other surgical conditions involving visceral edema (4,5,6). However, data regarding measurements of IAP in patients admitted with ADHF are lacking despite the potential for a substantial part of ADHF patients to present with ascites, visceral edema and impaired renal function. The primary aim of our study was to test the hypothesis that IAP is commonly elevated in patients admitted with ADHF. The secondary aim was to investigate if hemodynamically-guided therapy can reduce IAP, and whether reduction in IAP leads to corresponding improvement in renal function.

**c) Methods**

**Patient Population**. We prospectively enrolled consecutive patients, aged 18 years or older, with symptomatic HF (New York Heart Association class III-IV), who underwent a right heart catheterization (RHC) for hemodynamically-guided therapy of ADHF at the Cleveland Clinic heart failure intensive care unit between November 1, 2006 and May 31, 2007. Subjects who met the following inclusion criteria were enrolled in the study: 1) markedly impaired

systolic left ventricular function defined by left ventricular ejection fraction (LVEF) ≤30%; and 2) elevated filling pressures, as defined by pulmonary capillary wedge pressure (PCWP) ≥18 mmHg and right atrial pressure (RAP) ≥8 mmHg. Following are the exclusion criteria: 1) patients on artificial ventilation; 2) patients who underwent abdominal or thoracic surgery within the last three months; 3) patients without Foley catheter; 4) patients on renal replacement therapy. Institutional Review Board approval of this research project was obtained, and informed consent was obtained for hospitalization, treatment and all invasive procedures and documented in the patient charts, according to protocol and Cleveland Clinic policy.

**Hemodynamically-Guided Therapy.** The hemodynamic goals and pharmacologic approach to intravenous therapy in the specialized heart failure intensive care unit have been previously described (8). Briefly, optimal hemodynamic response was defined as a decrease in PCWP to ≤18 mmHg, decrease in central venous pressure (CVP) to ≤8 mmHg and improvement in cardiac index (CI) to ≥2.2 l/min/$m^2$, all while maintaining mean arterial pressure (MAP) >65 mmHg. In order to achieve the hemodynamic goals, most patients were treated according to standardized protocols developed in our intensive care unit with intravenous loop diuretics in combination with vasodilators (i.e. nitroprusside) and/or inotropic agents while continuing previous therapies with ACE-inhibitors, beta-blockers and spironolactone as tolerated. Loop diuretics were always given as a continuous infusion with or without an initial bolus at the discretion of the attending physician. Intermittent bolus therapy was never used.

**Intra-Abdominal Pressure Measurement.** Clinical examination of the abdomen and/or the abdominal perimeter is an inaccurate indicator of IAP (9,10). To obtain a precise IAP value, the pressure was measured with the transvesical method (11,12). Briefly, IAP was measured via a standard Foley catheter, which was connected with a pressure transducer placed in-line with the iliac crest at the mid-axillary line (figure 1). The Foley catheter was flushed with a maximal instillation volume of 50 ml sterile saline via the aspiration port of the Foley catheter with the drainage tube clamped to allow a fluid filled column to develop up into the bladder. Installation of more volume could lead to bladder distention, which can be uncomfortable to the patient and lead to increased intravesical pressure. This could thus give rise to a falsely high IAP measurement. A pressure transducer was then inserted in the aspiration port, and the pressure was measured. The IAP was expressed in mmHg and measured at end-expiration in the supine position, ensuring that abdominal muscle contractions were absent. The IAP reported was

measured on admission prior to drug initiation and prior to removal of the pulmonary artery catheter (36 ±12 hours later). As mentioned before, a normal IAP was considered to be <8 mmHg, an elevated IAP to be ≥8 mmHg and IAH to be ≥12mmHg.

**Data Collection and Variable Definitions.** Subject hemodynamic data were collected by three experienced heart failure cardiologists. The following additional data were recorded: demographic characteristics, medical history, medical treatment, implanted pacemaker and ICD device information, and echocardiographic data. In all patients, creatinine levels on admission and prior to removal of the pulmonary artery catheter were recorded. Estimated glomerular filtration rate (GFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula: GFR for men = 186 x [serum creatinine (µmol/L) x 0.0113]-1.154 x age (years)-0.203. For women the result was multiplied by 0.742 and for African Americans by 1.210.

**Hemodynamic Assessment.** Complete hemodynamic assessment was performed in all patients before the start of hemodynamically-guided therapy, and again before removing the pulmonary artery catheter. The CVP and PCWP were assessed at end-expiration with a balloon-tipped catheter at steady state with the patient in a supine position. CI was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. The MAP was calculated as (systolic blood pressure + 2 x diastolic blood pressure)/3. The abdominal perfusion pressure (APP) was determined by following equation: MAP – IAP (12). The renal filtration gradient (FG) is the mechanical force across the glomeruli, and can be estimated as: glomerular filtration pressure (GFP) - proximal tubular pressure (PTP) (12). In the presence of elevated IAP, PTP may be assumed to equal IAP and thus GFP can be estimated as: MAP - IAP. The FG therefore was therefore calculated as: MAP – 2 x IAP.

**Statistical Analysis.** All data are expressed as mean ± SD for continuous data and as a ratio for categorical data. Univariate comparisons of these variables were performed between baseline and follow-up variables and between patients with normal versus elevated IAP using SPSS for Windows, release 11.5 (SPSS Inc., Chicago, Illinois). A paired and unpaired t-test for continuous data and a Pearson correlation coefficient were used for appropriate comparisons. Statistical significance was set at a two-tailed probability level of <0.05.

**d) Results**

**Baseline characteristics and medical treatment.** A total of 40 patients met eligibility criteria and were enrolled in the study. Baseline characteristics and treatment during admission of the patients stratified according to IAP ≥8 mmHg (n=24) and IAP <8 mmHg (n=16) are summarized in Table 1. All patients were classified as NYHA class III or IV. Mean LV EF was similar between two patient groups as was the percentage of patients with moderate to severe RV dysfunction (38% in both groups). There were no statistically significant differences in medical therapy on admission or during hemodynamically-guided therapy between the two patient groups.

No patient complained of abdominal discomfort on admission or during treatment. The median length of treatment (from baseline to follow-up, defined as "change" in all measurements) was 36±10 hours and 36±14 hours in the patients with normal IAP and elevated IAP respectively (p=0.9).

**Intra-abdominal pressure measurements.** In the overall cohort, the mean IAP at baseline was 7±4 mmHg, which improved to a mean of 5 ±3 mmHg following medical therapy (p<0.001). The mean IAP in the cohort of patients with elevated IAP (n=24) on admission was 10 ±2 mmHg, which was also significantly reduced at follow-up to 6 ±3 mmHg (p<0.001) (figure 2). Four (10%) patients presented with IAH on admission, and they too had a significant drop in IAP at follow-up (15 ±3 mmHg to 7 ±2 mmHg, p<0.001). Only three patients who presented with elevated IAP had an increase of IAP at follow-up. No urinary tract infection or abdominal discomfort was seen in any patient. The inter- and intra-observer variabilities of IAP measurements were compared in 30 consecutive IAP measurements, and were found to be 5% and 4%, respectively.

**Hemodynamic and renal variables at baseline and follow-up.** Table 2 illustrates the hemodynamic measurements on admission and following hemodynamically-guided therapy in all patients, as well as for the subgroup of patients with elevated IAP and normal IAP. Overall MAP, CI, PCWP, CVP and APP were comparable between the two cohorts at baseline and at follow-up. All patients had signs of impaired hemodynamics with elevated right- and left-sided filling pressures, which significantly improved after parenteral administration of vasodilators, diuretics and/or inotropic therapy.

Patients with elevated baseline IAP or IAH had higher serum creatinine at baseline (2.3 ±1.0 versus 1.5±0.8 mg/dL, p=0.009) and at follow-up (1.8 ±0.8 versus 1.3 ±0.9 mg/dL, p=0.04) compared with those who had a normal IAP at baseline. As shown in figure 3, IAP was related to impaired renal function. The renal filtration gradient was statistically lower at baseline in the patients with elevated IAP versus those with normal IAP (56 ±14 versus 65 ±10 mmHg, p = 0.03). Furthermore, in those with elevated IAP at baseline, there was an average increase of renal filtration gradient from 56±14 mmHg to 64 ±12 mmHg (p=0.01) that paralleled with an improvement in mean GFR (40 ±21 to 49 ±23 ml/min, p=0.003) as well as in serum creatinine (2.3 ±1.0 to 1.8 ±0.8 mg/dL, p=0.01).

**Relation between changes in IAP, hemodynamic variables and renal function.** Table 3 illustrates the relationship between changes in hemodynamic variables and renal function changes in all patients and those with elevated IAP. Although there was a significant reduction in right- and left-sided filling pressures together with an improved cardiac index, these hemodynamic improvements did not correlate with improvements in renal function or IAP. Changes in IAP (either an increase or a decrease) following hemodynamically-guided therapy correlated to changes in renal function ($r = 0.77$, $p < 0.001$), and this only in patients with elevated IAP (figure 4A). Patients who had an increase in IAP at follow-up also had a deterioration of their renal function. The one patient who initially presented with a normal IAP and had an increase of IAP at follow-up (from 3 to 8 mmHg) also demonstrated a corresponding worsening of renal function from baseline to follow up. No differences in hemodynamic profile or therapeutic regimen were noticed between patients in whom IAP went up during treatment compared to those who did not. There was a significant negative correlation between changes in FG and changes in creatinine ($r = -0.65$, $p = 0.001$, figure 4B).

**e) Discussion**

There are several key findings in this hypothesis-generating study. First, patients with advanced heart failure presenting with ADHF have a high prevalence of elevated IAP despite the absence of overt abdominal symptoms. Second, elevated IAP is associated with more impaired renal function. Third, improvement in renal function following medical therapy is associated with a reduction of IAP, yet bears no relationship with changes in hemodynamic measurements. Fourth, measurement of IAP is simple, safe, inexpensive, and reproducible. Our clinical

observations raise the possibility that increased IAP might contribute, in part, to the renal dysfunction commonly observed in patients with ADHF. Although the mechanism is unclear, both reduced renal perfusion and increased renal vein pressure (and thus increased renal pressure) might be a consequence of increased IAP.

Elevated IAP among critically ill patients has predominantly been described in the surgical and critical care literature in scenarios involving abdominal catastrophes (3,4,13). As the pathophysiology of IAP becomes better understood, the importance of IAP measurements in the diagnosis and management of elevated IAP and IAH has evolved. The abdomen can be considered a closed box with both rigid (costal arch, spine, and pelvis) and flexible (abdominal wall and diaphragm) walls, thus the IAP measured at one point may be assumed to represent the IAP throughout the abdomen (14,15). However, it is important to remember that clinical judgment and physical examination are far from accurate in estimating IAP (9,16). The transvesical IAP pressure measurement depends on the wall of the bladder functioning as a transducing membrane without imparting any additional pressure from its own musculature, allowing it to act as a passive reservoir (17,18). Although a substantial number of ADHF patients present with ascites and visceral edema, both potential causes of elevated IAP, no reports in the literature have studied the prevalence and potential role of elevated IAP in ADHF patients. As demonstrated by our study, elevated IAP in patients presenting with ADHF is common (60%) with a smaller proportion (10%) demonstrating IAH, which was not detected on routine history and physical exam. None of the patients in this study presented with abdominal discomfort as a subjective sign of elevated IAP, which shows that this phenomenon is often, if not always, asymptomatic in ADHF patients. One explanation might be that the fluid build up in these patients is often gradual over weeks, and thus, the rise in IAP may also be slow and insidious. Lowering of the IAP was likely due to mobilization of fluid from the ‘third space’ through a combination of aggressive diuretic, vasodilator, and/or inotropic therapy. Successful hemodynamically-guided therapy, as evidenced by a reduction in right- and left-sided filling pressures together with improved cardiac output, coincided with the observed reduction in IAP in most patients. However, no correlation between changes in any hemodynamic variable or alterations in IAP was observed. This potentially explains why patients with improved hemodynamics may subsequently develop worsening renal function, following aggressive therapy during ADHF admission, if there is no reduction in IAP. Our data corroborate this

hypothesis since all patients whose renal function deteriorated during treatment had an increase in IAP at follow-up, however with improved hemodynamics.

An inadequate renal filtration gradient (FG) has been identified as a key factor in the development of renal dysfunction (19,20). Patients with an acute exacerbation of advanced heart failure often present with a low systemic blood pressure and impaired cardiac index (21). Both factors may substantially reduce renal blood flow: the most important variable of the FG in patients presenting with congestive heart failure (22,23). Consequently, even small elevations in IAP lead to significant reductions in FG. Indeed, a statistically significant reduction of the FG was noticed in the patients who presented with elevated IAP compared to the patients with normal IAP, though both groups had a comparable reduction in cardiac index and mean systemic arterial blood pressure. Moreover, changes in FG were closely correlated with changes in renal function, thereby emphasizing the importance of an adequate FG. Impaired cardiac index and increased filling pressures seen in advanced heart failure patients with ADHF will further activate the renin-angiotensin and sympathetic nervous system, reduce nitric oxide in the endothelium, and induce inflammatory mediators, thus aggravating the hypo-perfusion state of the glomeruli (24).

Another important finding was that although the degree of renal dysfunction was correlated with the degree of elevated IAP, there was a wide range of IAP in relation to creatinine on presentation. Moreover, changes in IAP in the patient population with elevated IAP were correlated with changes in renal function. These findings corroborate the hypothesis that the response of IAP to treatment rather than the absolute level of IAP on admission is contributing to improved or worsening renal function.

Elevated IAP also leads to renal vein and ureter compression, further impairing renal function (4,25,26). Though impairment of venous return probably plays a role, it cannot by itself completely explain the manifestations of renal function improvement after normalizing the IAP, since the reduction of right- and left-sided filling pressures was not correlated to improved renal function.

Elevated IAP is trans-diaphragmatically transmitted and gives rise to an elevation of intra-thoracic pressures (4,27). This may result in elevated pulmonary pressure, central venous pressure, and capillary wedge pressure readings from the pulmonary artery catheter. In addition, increased IAP decreases venous return by obstructing the inferior vena cava blood flow in the

abdomen, decreasing cardiac output, and increasing the risk for peripheral edema and venous thrombosis (28,29,30). As a result elevated IAP in ADHF patients makes preload assessment difficult and further compromises the already impaired left ventricle. Furthermore, measured intravascular pressures are not reflective of intravascular volumes and inappropriate diuretic admission might increase the risk of renal function worsening.

**Study Limitations.** There are several limitations in our observational series, including the relatively small sample size, the lack of any outcomes data on renal function following hospital discharge, the lack of any urine analysis, the adoption of the technique of IAP measurement used in the surgical literature, and the lack of physiological measurements (such as direct assessment of intraparenchymal renal pressures and renal blood flow) to fully explain the complex underlying pathophysiology. Our observations are however unique, as the prevalence of raised IAP in patients without obvious abdominal symptoms in ADHF has not been previously reported. Animal data have suggested that raised intraparenchymal pressure may not contribute to renal dysfunction (5). Although clinically not apparent, we did not routinely perform an abdominal ultrasound to confirm ascites as a contributing factor to the elevated IAP. Additionally, serial measurements of abdominal girth as a potential indicator of reduction in IAP during therapy were not done. Further studies are necessary to better understand the exact pathophysiology underlying this 'cardio-abdominal' interaction, and whether there is a cause-and-effect relationship between IAP and worsening renal function. The extent to which elevated IAP contributes to the observed renal dysfunction in our ADHF population requires further investigation.

## f) Conclusion

In patients admitted to hospital with advanced decompensated heart failure, we observed a high prevalence of elevated intra-abdominal pressure, which is associated with impaired renal function. A strong correlation between reduction in IAP and improvement in renal function was observed, although independent of hemodynamic changes. Measurement of IAP in patients with ADHF should be considered to assist in the management of these patients, as changes in IAP with therapy are predictive of changes in renal function.

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**Table 1. Baseline patient characteristics and medical therapy. In patients with IAP ≥8 mmHg (n=24) and IAP <8 mmHg (n=16).**

| | **Patients with IAP ≥8 mmHg** (n=24) | **Patients with IAP <8 mmHg** (n=16) | **p value** |
|---|---|---|---|
| **Demographics and vital statistics** | | | |
| Age (y) | 58±11 | 61±14 | Ns |
| Men (%) | 67 | 62 | Ns |
| Weight (kg) | 94±23 | 82±17 | Ns |
| Height (cm) | 177±10 | 172±7 | Ns |
| Hypertension (%) | 70 | 47 | 0.04 |
| Hyperlipidemia (%) | 46 | 53 | Ns |
| Diabetes (%) | 37 | 34 | Ns |
| Smoking (%) | 30 | 20 | 0.05 |
| Previous CABG (%) | 35 | 33 | Ns |
| ICD / CRT-D (%) | 63 | 60 | Ns |
| Idiopathic-Dilated(%) | 62 | 68 | Ns |
| Ischemic (%) | 38 | 32 | Ns |
| Ejection Fraction (%) | 19±8 | 21±12 | Ns |
| Hemoglobin (g/dl) | 11±2 | 11±2 | Ns |
| **Medication on admission (%)** | | | |
| Beta Blockers | 62 | 56 | Ns |
| ACE inh / ARB | 62 | 62 | Ns |
| Spironolactone | 46 | 44 | Ns |
| Loop Diuretic | 96 | 100 | Ns |
| **Parenteral medication during admission (%)** | | | |
| Loop Diuretics | 82 | 86 | Ns |
| Nitroprusside | 45 | 46 | Ns |
| Dobutamine | 24 | 26 | Ns |

| | | | |
|---|---|---|---|
| Milrinone | 31 | 27 | Ns |

Values are mean ± SD or n (%). *Abbreviations:* CABG indicates coronary by-pass surgery; ICD: implantable cardioverter defibrillator, CRT-D: cardiac resynchronization therapy with defibrillator, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker

**Table 2. Hemodynamic variables on admission and time of pulmonary artery catheter removal in all patients and stratified according to IAP ≥8 mmHg (n=24) and IAP <8 mmHg (n=16).**

| | **All patients** (n=40) | | | **Patients with IAP ≥8 mmHg** (n=24) | | | **Patients with IAP <8 mmHg** (n=16) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **Follow-up** | **p-value** | **Baseline** | **Follow-up** | **p-value** | **Baseline** | **Follow-up** | **p-value** |
| **MAP** (mmHg) | 75 ±13 | 73 ±11 | ns | 78 ±14 | 75 ±11 | ns | 72 ±11 | 72 ±11 | ns |
| **CVP** (mmHg) | 15 ±7 | 11 ±6 | < 0.001 | 16 ±7 | 13 ±7 | < 0.001 | 13 ±6 | 9 ±5 | 0.05 |
| **PCWP** (mmHg) | 22 ±6 | 17 ±4 | < 0.001 | 22 ±5 | 17 ±3 | < 0.001 | 23 ±8 | 18 ±5 | 0.03 |
| **CI** (l/min/$m^2$) | 2.1 ±0.9 | 2.6 ±0.7 | < 0.001 | 2.1 ±0.7 | 2.7±0.7 | < 0.001 | 2.2 ±1.0 | 2.5±0.6 | 0.05 |
| **IAP** (mmHg) | 7 ±4 | 5 ±3 | < 0.001 | 10 ±2 | 6 ±3 | < 0.001 | 3 ±1 | 3 ±1 | ns |
| **APP** (mmHg) | 68 ±12 | 69 ±11 | ns | 68 ±13 | 69 ±11 | ns | 68 ±11 | 69 ±11 | ns |
| **FG** (mmHg) | 61 ±13 | 64 ±11 | ns | 56 ±14 | 64 ±12 | 0.01 | 65 ±10 | 66 ±11 | ns |
| **Creatinine** (mg/dL) | 2.0 ±0.9 | 1.6 ±0.9 | 0.002 | 2.3 ±1.0 | 1.8±0.8 | 0.01 | 1.5 ±0.8 | 1.3±0.9 | ns |
| **GFR** (ml/min) | 50 ±35 | 61 ±44 | < 0.001 | 40 ±21 | 49 ±23 | 0.003 | 63 ±46 | 77 ±58 | ns |

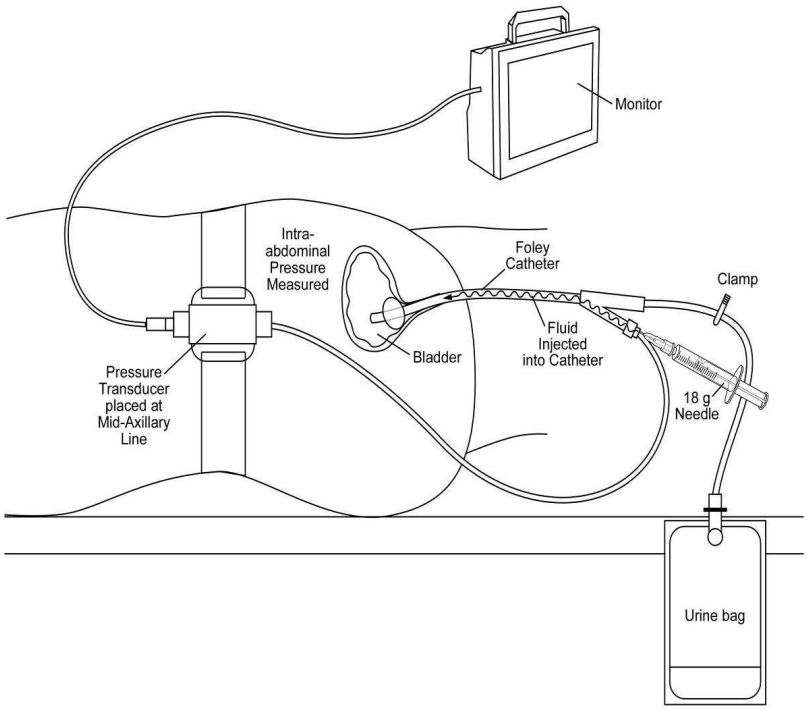
*Abbreviations:* MAP: mean arterial pressure, CVP: central venous pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac index, IAP: intra-abdominal pressure, APP: abdominal perfusion pressure, FG: renal filtration gradient.

**Table 3. Correlation between changes in IAP or serum creatinine and other hemodynamic variables in all patients and in patients with IAP ≥ 8 mmHg**.

| | | | **Delta MAP** | **Delta CVP** | **Delta PCWP** | **Delta CI** |
|---|---|---|---|---|---|---|
| **All Patients** (n = 40) | **Delta IAP** | r | 0.17 | 0.05 | -0.01 | 0.01 |
| | | p value | Ns | ns | ns | ns |
| | **Delta Creat** | r | -0.26 | -0.23 | -0.23 | 0.08 |
| | | p value | Ns | ns | ns | ns |
| **Patients with IAP ≥8 mmHg** (n = 24) | **Delta IAP** | r | 0.02 | 0.16 | 0.01 | -0.03 |
| | | p value | Ns | ns | ns | ns |
| | **Delta Creat** | r | -0.37 | -0.09 | -0.17 | 0.11 |
| | | p value | Ns | ns | ns | ns |

"Delta" refers to changes from follow-up to baseline. *Abbreviations*: r: correlation coefficient; ns: non significant, Creat: serum creatinine, MAP: mean arterial pressure, CVP: central venous pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac index, IAP: intra-abdominal pressure.

**Figure 1. Transvesical method for measuring IAP**.




A standard Foley catheter is connected with a pressure transducer, placed in-line with the iliac crest at the mid-axillary line. The Foley catheter is flushed with an instillation volume of 50 ml sterile saline via the aspiration port of the Foley catheter with the drainage tube clamped to allow a fluid filled column to develop up into the bladder. Installation of more volume could lead to bladder distention, which can be uncomfortable to the patient and lead to increased intravesical pressure. A pressure transducer is then inserted in the aspiration port, and the pressure is measured. The IAP is expressed in mmHg and measured at end-expiration in the supine position, ensuring that abdominal muscle contractions are absent.

**Figure 2. Change in IAP in patients with elevated IAP mmHg at baseline**.

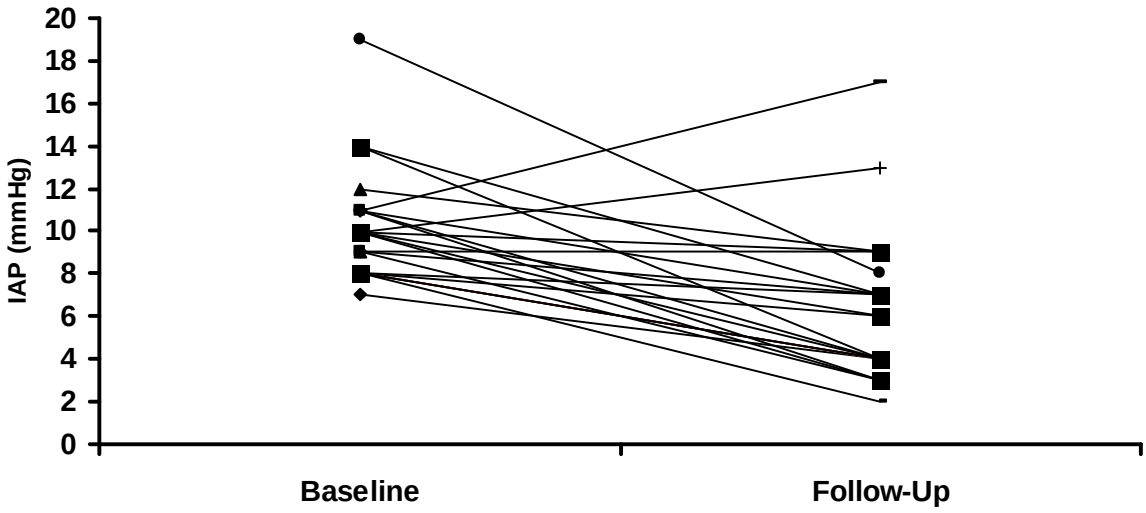


**Figure 3. Box and Whisker plot with median, quartiles and extremes for serum creatinine for all patients with IAP < 8 and ≥ 8 mmHg at baseline**.

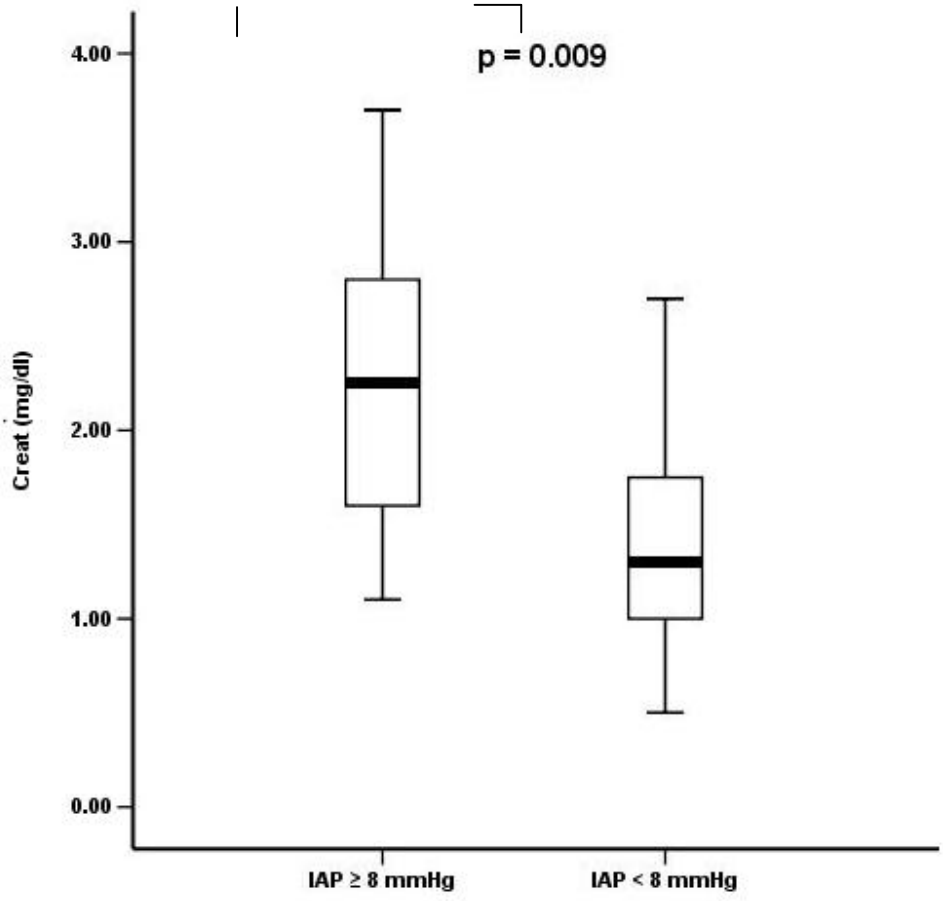
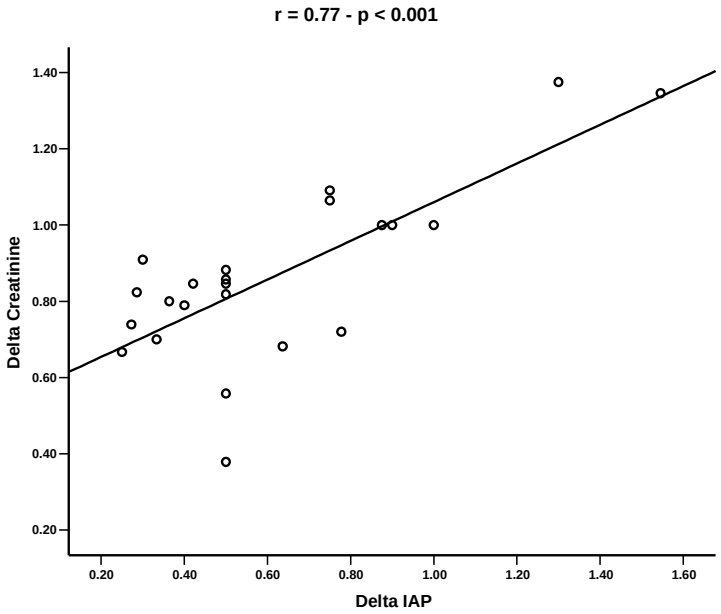
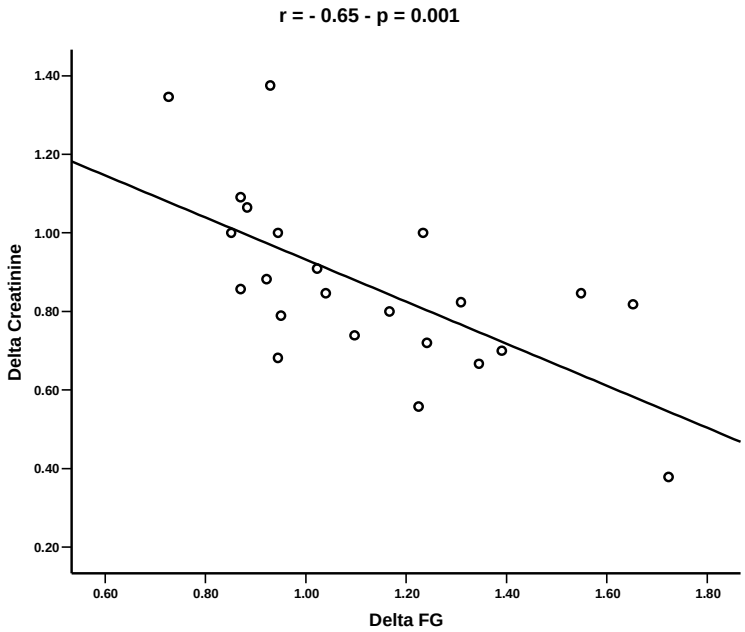


**Figure 4. Relationship between changes in renal function and changes in intra-abdominal pressure (Figure 4A) and renal filtration gradient (Figure 4B) in patients with IAP ≥ 8 mmHg at baseline.**

**4A**




**4B**



## 3) Prompt reduction in intra-abdominal pressure following large volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure

Mullens W, Abrahams Z, Francis G, Taylor D, Starling R, Tang W. Prompt Reduction in Intra-Abdominal Pressure Following Large-Volume Mechanical Fluid Removal Improves Renal Insufficiency in Refractory Decompensated Heart Failure. J Card Fail 2008;6:508-514.


### a) Abstract

**Background:** Our group recently reported that elevated intra-abdominal pressure (IAP ≥ 8mmHg) can be associated with renal dysfunction in patients with advanced decompensated heart failure (ADHF). We hypothesize that in the setting of persistently elevated IAP and progressive renal insufficiency refractory to intensive medical therapy, mechanical fluid removal can be associated with improvements in IAP and renal function.

**Methods and Results:** Renal and hemodynamic profiles of 9 consecutive, volume-overloaded subjects with ADHF and elevated IAP refractory to intensive medical therapy were prospectively collected. All subjects experienced progressive elevation of serum creatinine and IAP in response to intravenous loop diuretics. Within 12 hours following mechanical fluid removal via paracentesis (n=5, mean volume removed 3,187 ±1,772 mL) or ultrafiltration (n=4, mean volume removed 1,800 ±690 mL), there was a significant reduction in IAP (from 13 ±4 to 7 ±2 mmHg, p=0.001), with corresponding improvement in renal function (serum creatinine from 3.4 ±1.4 to 2.4 ±1.1 mg/dl, p=0.01) without significantly altering any hemodynamic measurement.

**Conclusion:** In volume-overloaded patients admitted with ADHF refractory to intensive medical therapy, we observed a reduction of otherwise persistently elevated IAP with corresponding improvement in renal function following mechanical fluid removal.


### b) Introduction

In the setting of advanced decompensated heart failure (ADHF), primary therapies that alleviate congestion (such as intravenous loop diuretics) can worsen renal insufficiency and may

even increase mortality (1,2). The underlying pathophysiology of this so-called "cardio-renal syndrome" remains poorly understood and ill defined, in part because our understanding of this concept has been hindered by the lack of clinically available surrogate markers other than the end-result of the process (i.e. rising serum creatinine).

There has been long-standing recognition in the surgical literature that elevated intra-abdominal pressures (IAP, defined as ≥8 mmHg) can be associated with progressive intra-abdominal organ dysfunction (3,4,5,6). Recently, our group has demonstrated that a substantial number of volume-overloaded patients admitted to the hospital with ADHF have detectable increases in IAP in the absence of overt abdominal symptoms (7). We have further demonstrated the association between elevated IAP and impaired renal function, as well as between reduction of IAP and improvement in renal function with successful intravenous diuretic therapy, both independent of hemodynamic changes (8). However, we have also observed that if IAP could not be lowered by intensive medical therapy, renal function can be further compromised or renal insufficiency unresolved. These findings suggest that persistently elevated IAP might be one of many potential contributors to cardio-renal compromise, particularly when worsening renal insufficiency may occur despite optimal medical therapy. With the recent interest in the role of mechanical fluid removal as a mean to alleviate congestion in ADHF, we hypothesize that in selected patients with volume overload admitted with ADHF refractory to intensive medical therapy, large-volume mechanical fluid removal can lead to resolution of otherwise elevated IAP. We further hypothesize that the reduction in IAP by mechanical fluid removal might lead to corresponding improvements in renal function without hemodynamic compromise.

**c) Methods**

**Patient Population**. We prospectively enrolled consecutive subjects, aged 18 years or older, with symptomatic heart failure (New York Heart Association class III-IV), who underwent a right heart catheterization for intensive medical therapy of ADHF at the Cleveland Clinic heart failure intensive care unit between March 1, 2006 and June 30, 2007. Subjects who met the following inclusion criteria were enrolled in the study: 1) markedly impaired systolic left ventricular function defined by left ventricular ejection fraction ≤30%; 2) elevated intracardiac filling pressures, as defined by pulmonary capillary wedge pressure (PCWP) ≥18 mmHg and central venous pressure (CVP) ≥8 mmHg; 3) scheduled to undergo mechanical removal of fluid

by either paracentesis or ultrafiltration due to clinically apparent abdominal ascites or overt extracellular fluid refractory to intravenous diuretic therapy. Exclusion criteria included: 1) subjects on mechanical ventilation; 2) subjects who underwent abdominal or thoracic surgery within three months; and 3) subjects without Foley catheter. Institutional Review Board approval of this research project was obtained, and informed consent was obtained for hospitalization, treatment and all invasive procedures and documented in the patient charts, according to protocol and hospital policy.

**Treatment Protocol for Intensive Medical Therapy.** All subjects were admitted to the heart failure intensive care unit for intensive medical therapy with continuous hemodynamic monitoring via pulmonary artery catheter. The hemodynamic goals and pharmacologic approaches to intensive medical therapy (including intravenous diuretic and vasoactive therapies) using standardized treatment protocols have been previously described (9). Continuous intravenous diuretic therapy was always used and carefully titrated.

The decision to initiate mechanical fluid removal was determined by the attending heart failure specialist, always after observing a lack of clinical improvement with intensive medical therapy after 12 hours of treatment. Patients with clinical and ultrasonic evidence of abdominal ascites underwent paracentesis of at least 1,000 ml of fluid, within a 30-minute time period. In the absence of clinical evidence of ascites, continuous veno-venous ultrafiltration was initiated through a central venous line (internal jugular of subclavian) at a rate of 100-200 ml per hour and continued for a minimum of 12 hours.

**Intra-Abdominal Pressure and Hemodynamic Measurement.** The IAP was measured with the transvesical method as illustrated and explained in Figure 1(6,8,10,11,12). The PCWP and CVP were assessed at end-expiration with a balloon-tipped catheter at steady state with the patient in a supine position. Cardiac index was estimated by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates.

**Data Collection and Variable Definitions.** Hemodynamic data were collected by two experienced heart failure cardiologists. The following additional data were recorded: demographic data, medical history, medical treatment, implanted device information, and echocardiographic data. In all subjects, hemodynamic data, serum creatinine levels and IAP were measured at three time points: 1) on admission to the intensive care unit at the time of

initiating intensive medical therapy; 2) immediately preceding ultrafiltration or paracentesis (= on average 12 hours later); and 3) 12 hours after initiating ultrafiltration or paracentesis.

**Statistical Analysis.** All data are expressed as mean ± standard deviation for continuous data and as a ratio for categorical data. Univariate comparisons of these variables by a paired T-test were performed between admission, start of mechanical fluid removal and follow-up variables using SPSS for Windows, release 11.5 (SPSS Inc., Chicago, Illinois). Statistical significance was set at a two-tailed probability level of <0.05.

**d) Results**

**Baseline characteristics and medical treatment.** A total of nine subjects met eligibility criteria for the study, with 5 of the group receiving paracentesis and 4 of the group receiving ultrafiltration. Baseline characteristics and medical treatment during admission of the subjects are summarized in Table 1. All subjects underwent intensive medical therapy for an average of 12 hours prior to commencing mechanical fluid removal. As expected, subjects who underwent large-volume paracentesis had extensive abdominal ascites documented by ultrasound. The 4 subjects who underwent ultrafiltration did not have overt clinical signs of ascites or clinical abdominal symptoms documented, and therefore did not undergo an ultrasound evaluation.

**Intra-abdominal pressure measurements in refractory heart failure.** In the overall cohort, the mean IAP on admission was 11 ±4 mmHg, with majority of subjects fulfilling criteria of elevated IAP (67% with IAP ≥8 mmHg, including 4 subjects with intra-abdominal hypertension with IAP >12 mmHg). Upon intensive medical therapy following admission to the intensive care unit, an average of 878 ±355 mL of net fluid loss by intensive medical therapy was documented. In this subject population, we observed an increase (rather than decrease) in mean IAP to 13 ±4 mmHg prior to initiation of mechanical fluid removal (statistically significant difference from baseline, p=0.01).

Twelve hours after initiating mechanical fluid removal, the measured IAPs had significantly dropped in all subjects to a mean IAP of 7 ±2 mmHg (p=0.001), with an average absolute reduction in IAP by -6 ±3.5 mmHg (or 47% relative reduction). Mean plasma B-type natriuretic peptide levels fall within 12 hours after starting ultrafiltration or paracentesis but did not reach statistical significance (1,577 ±1,254 vs 1,228 ±720, p=ns).

**Relation of IAP with hemodynamic and renal variables.** An average of 1,800 ±690 ml and 3,187 ±1,772 ml of total fluid were removed by ultrafiltration or paracentesis, respectively, within the first 12 hours of therapy. In addition, 2,670 ±1,520mL of net fluid loss by diuresis was documented over the following day with the maintenance of intensive medical therapy, which was significantly greater than that prior to mechanical fluid removal (p=0.03). Table 2 illustrates the hemodynamic measurements on 1) admission when intensive medical therapy was initiated; 2) when mechanical fluid removal was initiated; and 3) 12 hours after mechanical fluid removal. All subjects had evidence of impaired hemodynamics with elevated right- and left-sided filling pressures on admission. Overall systolic blood pressure, PCWP, and cardiac index, were comparable on admission, start of mechanical fluid removal, and at follow-up in all subjects. The only significant hemodynamic change was an expected drop in CVP following mechanical fluid removal, demonstrating effective relief of venous congestion. Serum sodium levels on admission, within the first 12 hours of therapy and at follow-up were comparable (133±7, 133±6 and 134±4 mmol/l, p=ns).

As expected, the mean IAP was higher in the subjects who underwent paracentesis compared to those who underwent ultrafiltration (Figure 2). Also, patients who underwent paracentesis had higher mean serum creatinine levels during the entire follow-up period (Figure 3). There was an increase in serum creatinine levels during the first 12 hours of the admission while the subjects were managed with intensive medical therapy alone (which corresponded to increased IAP), and it was only after initiating ultrafiltration or paracentesis that both IAP and serum creatinine improved (Table 2). As illustrated in Figure 3, reduction in IAP was directly associated with improvement in serum creatinine levels in both ultrafiltration and paracentesis treatment groups.

**e) Discussion**

There are several key findings in our hypothesis-generating study. First, we identified the association between the presence of refractory, volume-overloaded ADHF and further increase in IAP. Furthermore, this pathophysiologic link probably is associated with the presence of worsening renal function despite intensive medical therapy. Second, we identified the effectiveness of large volume mechanical fluid removal (either by paracentesis or ultrafiltration, whenever applicable) in achieving effective resolution of elevated IAP that was

not achievable by intensive medical therapy. Third, we illustrated with the subjects as their own control that the reduction of IAP following large volume mechanical fluid removal can be directly associated with prompt improvement in venous congestion and renal function in the absence of direct hemodynamic contribution or compromise. Taken together, we believe that our observations further support the hypothesis that an increase in IAP can directly contribute to the cardio-renal compromise commonly observed in patients with ADHF. Furthermore, our data provide provocative implications that the mode of fluid removal may differentially affect this cardio-renal pathophysiology. Our data confirm the concept that in the setting of volume overload (with persistently elevated IAP), mechanical fluid removal can provide effective resolution of renal insufficiency in selected patients refractory to intensive medical therapy.

It has been well recognized that during intensive medical therapy with intravenous loop diuretics some patients may progress to worsening renal function. Often elusively described as "diuretic resistance" or "cardio-renal syndrome," such conditions are difficult to define, largely because the underlying pathophysiology is heterogeneous and often unclear. While renal azotemia due to low cardiac output and venous congestion have been the two main explanations, in some cases aggressive fluid removal via glomerular filtration may alter the delicate balance between intra- and extra-renal hemodynamics, leading to progressive renal insufficiency (13,14,15,16). Our previous data suggested that in some cases this might be the result of sustained elevated IAP (8). As demonstrated by this study, patients with clinically apparent abdominal ascites or overt extracellular fluid that were unresponsive to intensive medical therapy may present with elevated IAP. Contrary to those responsive to intensive medical therapy including intravenous loop diuretic and vasoactive therapies, we observed that these "refractory" patients demonstrated a significant and progressive increase in IAP during intensive medical therapy, with those having overt abdominal ascites showing the highest IAP and serum creatinine levels. One potential explanation might be that the fluid build-up within the abdominal compartment with concomitant rise in IAP was so extensive that renal function was significantly compromised, resulting in renal tubular dysfunction and ischemia and refractoriness to loop diuretics and vasoactive therapies. The significantly higher serum creatinine levels seen in these patients compared with our previous study, as well as the initial rise in serum creatinine with coinciding progressive elevation in IAP during intensive medical therapy support this hypothesis (8). It is important to emphasize that there is a wide range of IAP in relation to serum creatinine

on presentation, with higher IAP observed in the patients with abdominal ascites. Differences in underlying intrinsic kidney disease might be an important determinant of the "reserve" available for the kidneys to respond to the insult posed by ADHF, aggressive diuretic treatment and elevated intra-abdominal pressures.

Our new observations highlighted that the choice of mode of fluid removal might have to be based on the underlying pathophysiology of the renal dysfunction. Reduction of IAP was found to be a direct result from mechanical removal of fluid out of the intra-abdominal space in patients undergoing paracentesis, and likely due to mobilization of fluid from the "third space" including the abdomen in the ultrafiltration group (17). In the case of elevated IAP where renal compromise is commonly observed, relief of the "renal tamponade" by mechanical removal of ascites or extra-renal volume may therefore preserve rather than compromise renal hemodynamics. Indeed, successful mechanical removal of fluid, independent of any hemodynamic alteration, coincided with the observed reduction in IAP and increase in urine output in all patients. Elevated IAP in these patients probably contributed to the observed renal dysfunction, and only when a reduction in IAP was achieved did renal function improve. Therefore, this approach of mechanical fluid removal may not only provide symptomatic relief but may also directly alter the underlying pathophysiology of the cardio-renal syndrome.

Although mechanical fluid removal is an invasive approach to treat ADHF patients with volume overload, our data suggest that this strategy may have significant advantages over standard medical therapy in selected cases. The ability of IAP to provide insight into the underlying pathophysiologic target also provides an opportunity to test the hypothesis of an IAP-guided approach to the management of refractory heart failure. The advantage of measuring IAP includes the utilization of existing equipment commonly available and the relatively low cost of the procedure, both allowing easy clinical adoption. The simplicity of measuring IAP via the transvesical approach may allow early identification of elevated IAP, and efforts to quickly lower IAP through mechanical fluid removal when not responding to intensive medical therapy might substantially reduce the risk for subsequent renal failure. It is therefore conceivable that in this setting, IAP can be used to identify those who may benefit from mechanical fluid removal as an option in the management of volume overload. Raising IAP in patients with ADHF may alert the clinician that cardio-renal syndrome may be worsening before a rise in serum creatinine is seen, especially if laboratory values are only obtained once a day. Large studies are needed to

confirm the advantages of mechanical fluid removal over intensive medical therapy in the management of volume overloaded patients with refractory heart failure and elevated IAP.

Finally, elevated IAP is trans-diaphragmatically transmitted and gives rise to an elevation of intra-thoracic pressures (4,6). This may result in elevated right- and left sided filling pressure readings from the pulmonary artery catheter. Measured intravascular pressures are therefore not reflective of intravascular volumes and inappropriate diuretic admission might increase the risk of renal function worsening. In addition, venous return will be decreased by obstructing the inferior vena cava blood flow in the abdomen, which will increase the risk for peripheral edema and venous thrombosis (18,19,20).

**Study Limitations.** There are several limitations to our study, including the small sample size, the lack of any outcomes data on renal function following hospital discharge, the lack of any urine analysis, the adoption of the technique of IAP measurement from the surgical literature, and the lack of physiological measurements (such as direct assessment of renal vein-, renal artery- and renal intra-parenchymal pressures together with renal blood flow) to fully explain the complex underlying pathophysiology. It is important to recognize that intrinsic renal diseases, diabetes, hypertension and obesity may be present in some patients presenting with ADHF refractory to intensive medical therapy, and we emphasize that elevated IAP is not the *sole* mechanism explaining worsening renal function or the "cardio-renal syndrome". The substantial venous congestion seen in our patient population probably also contributed to worsening renal function (15,21). We already indicated in our prior observations that effective lowering of IAP with intensive medical therapy can directly lead to improvement in renal function in a majority of ADHF patients presenting with renal insufficiency ("responders" to intensive medical therapy). Our data also did not imply that mechanical fluid removal is not effective in situations without elevated IAP. Our observations are, however, unique and we strongly believe that our findings support further investigations into the role of IAP in the management of cardio-renal syndrome.

## f) Conclusion

Large volume mechanical fluid removal can achieve a reduction of otherwise persistently elevated IAP with corresponding improvement in renal function, in selected volume-overloaded patients admitted with ADHF, refractory to intensive medical therapy. Further studies are

warranted to determine the clinical utility of IAP measurements in this challenging patient population.

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**Table 1. Baseline patient characteristics and medical therapy**

| | | |
|---|---|---|
| Age (y) | | 53±15 |
| Men (%) | | 67 |
| Weight (kg) | | 99±24 |
| Height (cm) | | 174±12 |
| Medical History (%) | | |
| | Hypertension | 77 |
| | Hyperlipidemia | 77 |
| | Diabetes | 34 |
| | Smoking | 34 |
| | Previous CABG | 23 |
| | AICD / CRTD | 77 |
| Etiology Heart Failure (%) Idiopathic / Ischemic | | 77 / 23 |
| Ejection Fraction (%) | | 18±7 |
| Medication on admission (%) | | |
| | Beta Blockers | 67 |
| | ACE inhibitors / ARB | 44 |
| | Spironolactone | 44 |
| | Loop Diuretic | 100 |
| Medication during admission | | |
| | Loop Diuretics | 100 |
| | Nitroprusside | 44 |
| | Dobutamine | 44 |
| | Milrinone | 22 |
| BNP (pg/ml) | | 1163 ±939 |

Values are mean ± SD or n (%). *Abbreviations:* CABG indicates coronary by-pass surgery; ICD: implantable cardioverter defibrillator, CRT-D: cardiac resynchronization therapy with defibrillator, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, BNP: brain natriuretic peptide

**Table 2. Hemodynamic variables on admission, at moment of start ultrafiltration / paracentesis and at follow-up**

| **Patient** | **Sys Bp (mmHg)** | | | **CVP (mmHg)** | | | **PCWP (mmHg)** | | | **CI (l/min.m2)** | | | **IAP (mmHg)** | | | **Serum Creatinine (mg/dl)** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Adm | Start | FU | Adm | Start | FU | Adm | Start | FU | Adm | Start | FU | Adm | Start | FU | Adm | Start | FU |
| PC 1 | 95 | 130 | 128 | 10 | 9 | 5 | 22 | 24 | 20 | 2.4 | 2.43 | 3.8 | 14 | 15 | 5 | 4.5 | 5.2 | 2.9 |
| PC 2 | 100 | 121 | 110 | 14 | 13 | 10 | 20 | 16 | 16 | 2.4 | 2.34 | 1.45 | 18 | 19 | 8 | 2.6 | 2.8 | 1.1 |
| PC 3 | 91 | 91 | 93 | 22 | 22 | 23 | 26 | 14 | 14 | 2.55 | 2.55 | 2.55 | 9 | 11 | 8 | 2.5 | 2.9 | 1.8 |
| PC 4 | 117 | 110 | 104 | 11 | 11 | 14 | 19 | 22 | 18 | 2.4 | 2 | 2.2 | 12 | 15 | 10 | 0.9 | 1 | 0.8 |
| PC 5 | 100 | 116 | 117 | 18 | 20 | 12 | 20 | 25 | 18 | 2.2 | 2.5 | 2.7 | 13 | 16 | 9 | 4 | 4.1 | 3.6 |
| UF 1 | 99 | 90 | 95 | 28 | 24 | 20 | 31 | 27 | 24 | 2 | 2.7 | 2.3 | 6 | 9 | 4 | 3 | 3.3 | 3.1 |
| UF 2 | 138 | 132 | 127 | 19 | 20 | 12 | 23 | 21 | 20 | 2.2 | 2.4 | 2.5 | 5 | 9 | 7 | 2.6 | 2.7 | 2.2 |
| UF 3 | 117 | 106 | 105 | 20 | 22 | 11 | 17 | 16 | 18 | 1.45 | 1.44 | 2.29 | 8 | 10 | 4 | 2.2 | 2.5 | 2.5 |
| UF 4 | 102 | 96 | 102 | 27 | 30 | 25 | 28 | 28 | 30 | 2.3 | 3.35 | 2.8 | 6 | 11 | 9 | 5.6 | 5.5 | 4.3 |
| **Overall** | **107±14** | **110±16** | **109±13** | **19±6** | **19±7** | **15±7** | **23±5** | **22±6** | **21±5** | **2.3±0.4** | **2.4±0.6** | **2.5±0.7** | **11±4** | **13±3** | **7±2** | **3.1±1.5** | **3.4±1.4** | **2.4±1.1** |
| **p value** | | **ns** | **ns** | | **ns** | **0.01** | | **ns** | **ns** | | **ns** | **ns** | | **0.01** | **0.001** | | **0.02** | **0.01** |

**Figure 1. Transvesical method for measuring intra-abdominal pressure**.

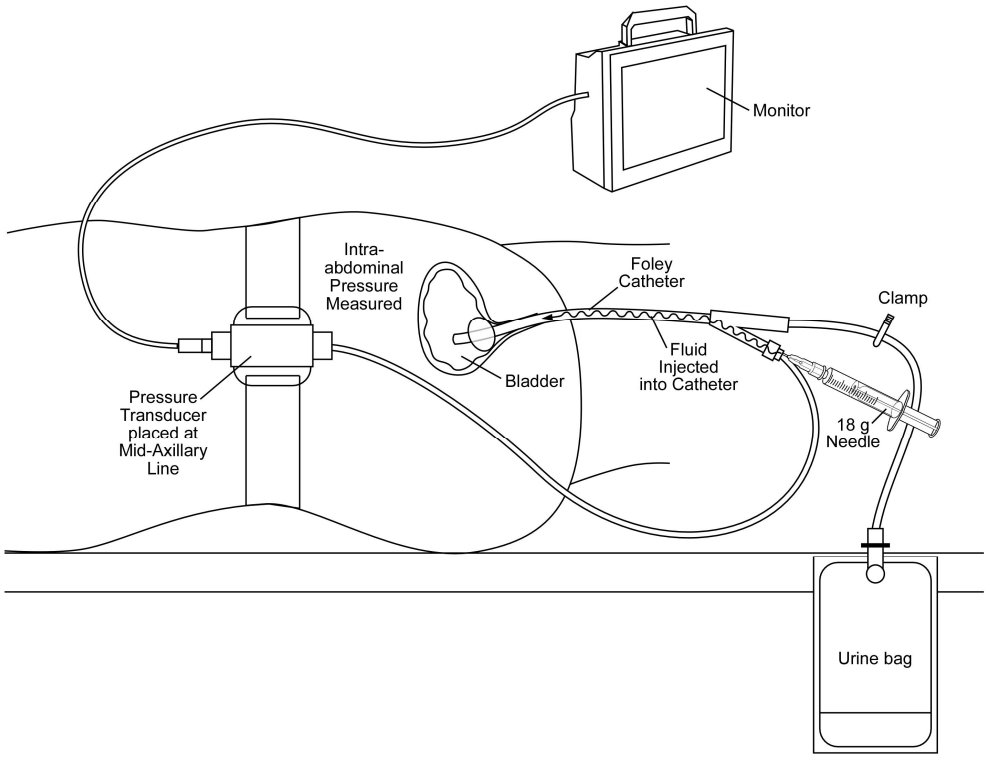


**Figure 2. Change in intra-abdominal pressure (IAP) in individual patients who underwent paracentesis or ultrafiltration.**

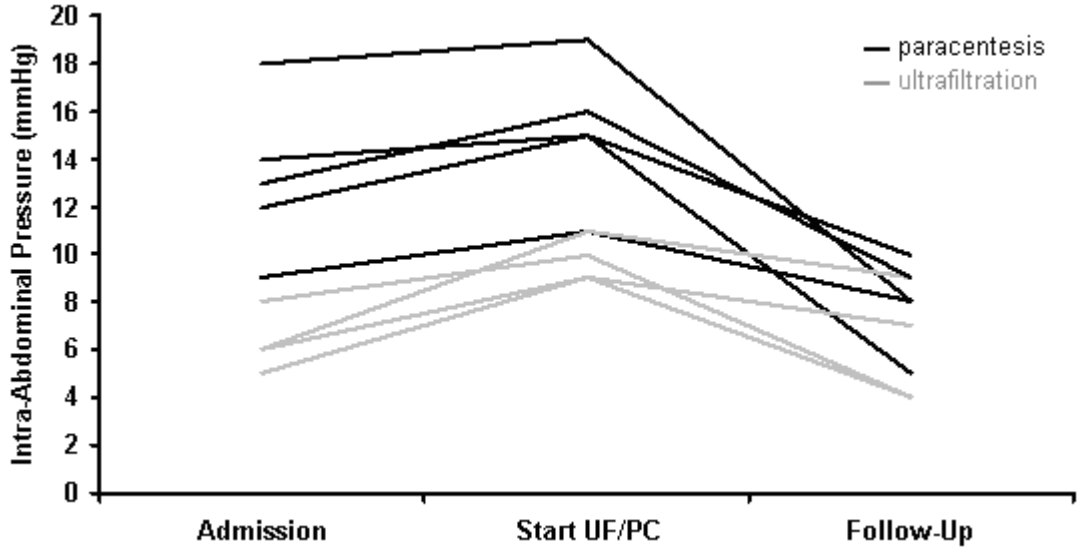
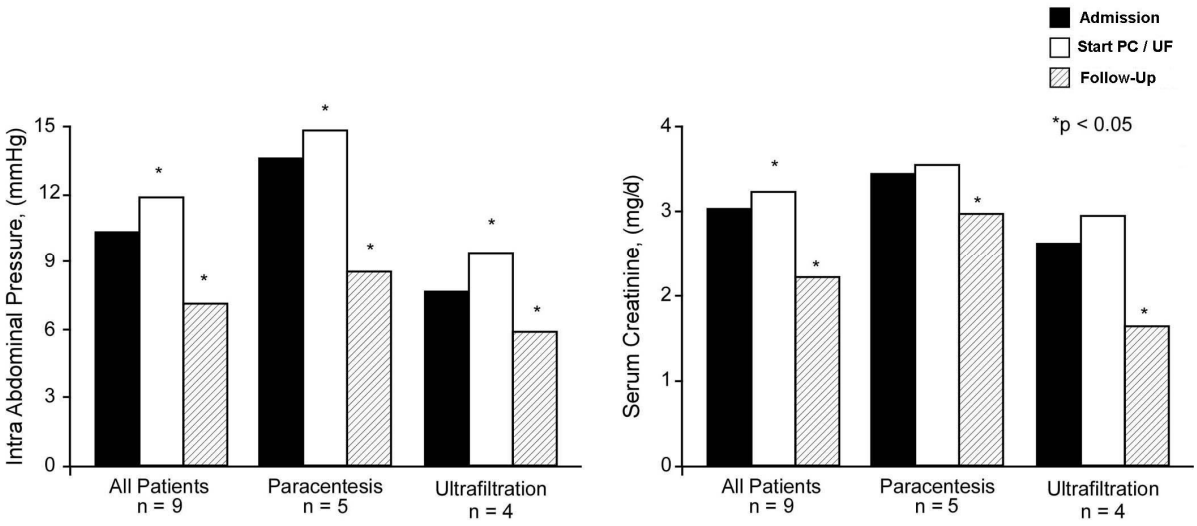


**Figure 3. Change in intra-abdominal pressure (IAP) and serum creatinine in patients who underwent paracentesis or ultrafiltration.**



# IV. Unraveling the response to cardiac resynchronization therapy in advanced heart failure: effects on cardiac hemodynamics and molecular gene expression

# IV. Unraveling the response to cardiac resynchronization therapy in advanced heart failure: effects on cardiac hemodynamics and molecular gene expression

## 1) Early and late effects of cardiac resynchronization therapy upon force frequency relation and contractility regulating gene expression in heart failure patients

Mullens W, Bartunek J, Tang W, Delrue L, Herbots L, Willems R, De Bruyne B Goethals M, Verstreken S, Vanderheyden M. Early and Late Effects of Cardiac Resynchronization Therapy upon Force-Frequency Relation and Contractility Regulating Gene Expression in Heart Failure Patients. Heart Rhythm 2008;5:52-9.

### a) Abstract

**Background:** Heart failure is associated with a reduction in left ventricular contractility as evidenced by a blunted force-frequency response (FFR) and downregulation of contractility regulating genes.

**Objective:** To investigate if cardiac resynchronization therapy (CRT) is capable of reversing the blunted FFR and the downregulation of contractility regulating genes.

**Methods:** Twenty heart failure patients underwent echocardiographic examination during incremental AAI and DDD-CRT pacing at 70, 90 and 110 bpm, immediately after and 4 months following CRT implantation. The FFR was determined from the ratio of the left ventricle (LV) systolic pressure/end systolic volume index at given heart rate. In a subgroup of six patients with idiopathic dilated cardiomyopathy, serial LV dP/dtmax was invasively measured during both pacing modes and serial LV endomyocardial biopsies were taken to measure sarcoplasmatic reticulum calcium ATPase 2 (SERCA2), phospholamban (PLN), sarcolemal sodium calcium exchanger (NCX), β1- adrenoreceptor (β1-AR) and apelin (APL) gene expression using rt-PCR.

**Results:** Acutely, DDD-CRT pacing was associated with a decrease in dyssynchrony($p<0.01$) and increase in diastolic filling time($p<0.01$) at all heart rates paralleled by an upward shift of the FFR($p<0.01$) without force-frequency amplification. A greater upward shift of the FFR

was noticed during DDD-CRT as compared to AAI($p<0.01$) after four months. In addition, CRT was associated with a significant force-frequency amplification at follow-up as evidenced from the steeper slope of the FFR relationship($p=0.039$). This was associated with a significant upregulation of SERCA2 ($p=0.01$), PLN($p=0.01$), their ratio($p=0.01$), ratio of SERCA/NCX($p=0.02$), β1-AR($p=0.03$) and APL($p=0.01$) m-RNA levels.

**Conclusion:** CRT is associated with an acute upward shift in the FFR without force-frequency amplification related to restored synchronicity and increased filling time of the LV. Only chronic CRT is associated with force-frequency amplification in parallel to upregulation of contractility regulating genes.

**b) Introduction**

Cardiac resynchronization therapy (CRT) improves cardiac function and exercise capacity leading to a better survival in patients with advanced heart failure and ventricular conduction delay (1). The underlying mechanisms of these beneficial effects are not fully elucidated but appear to be related to a restored coordination of the left ventricular (LV) contraction and relaxation and an improvement in functional mitral regurgitation (2,3). These effects may directly lead to augmented contractile function and reduction of LV filling pressures at resting heart rates (4,5).

In the intact normal heart, the force of contraction is augmented by an increase in heart rate (6). This stepwise increase in tension seen at faster rates, known as the positive staircase or Treppe phenomenon, is one of the hallmarks of LV contractility and is greatly attenuated or absent in patients with heart failure. Attenuation of this force-frequency relationship (FFR) can directly lead to impairment in exercise tolerance (7,8). A recent study has shown that compared to univentricular pacing, LV contractile function may acutely improve with increasing heart rates during biventricular pacing (9). This suggests that restoration of a positive FFR may contribute to functional improvement after CRT. However, the underlying mechanisms for the acute improvement of LV contractile function at higher heart rates have not been explained and long-term effects of CRT on FFR, comparing atrial and biventricular pacing, have not been examined. Furthermore, it remains unclear whether long-term CRT can modulate the molecular underpinnings of myocardial contractility. Recently, a noninvasive assessment of the FFR using the ratio of the systolic blood pressure and end-systolic volume index has been validated (10,11). This method is based upon the proven assumption that positive inotropic interventions are mirrored by smaller end-systolic

volumes and higher end-sytolic pressures. Accordingly, the present study investigates acute and chronic effects of CRT on FFR during atrial and biventricular pacing. Furthermore, we postulate that improvements in FFR are directly related to changes in the expression of various contractility regulatory genes.

**c) Methods**

**Patients:** Between August 2005 and January 2006 twenty consecutive patients (16 men) referred for CRT were included. All patients were in New York Heart Association (NYHA) Functional Class III or IV, had severe LV dysfunction with LV ejection fraction < 35 % and a QRS complex >120 ms with a LBBB morphology. All patients were on optimal medical therapy including beta-blockers, angiotensin converting enzyme inhibitors (ACE-I), loop diuretics and spironolactone. Moreover, they all had to have significant mechanical inter- and intraventricular dyssynchrony, with a sum of dyssynchrony >102 ms, a resting heart rate of less than 70 beats per minute, and a preserved AV conduction at heart rates up to 110 beats per minute(bpm) (12). Patients with ischemic cardiomyopathy underwent a coronary angiogram 1 month prior to the CRT-implantation to exclude the need for revascularisation. An extensive echocardiogram was performed to rule out the presence of extensive scar in the posterolateral region. If any of the aforementioned conditions was present the patient was not eligible for the study. All patients underwent echocardiographic examination within 1 day after CRT implantation (baseline, BL) and at 4 months follow-up (FU). A subset of six patients, all with idiopathic dilated cardiomyopathy, consented to undergo invasive high fidelity tip micromanometer measurement of LV dP/dtmax and serial LV biopsy procurement at BL and at FU. Twelve patients received a CRT-Defibrillator (CRT-D) because of episodes of sustained ventricular tachycardia or inducible ventricular arrhythmias during diagnostic electrophysiological examination. All patients gave oral and written informed consent and the study was approved by the institutional ethics committee.

**CRT system and pacing protocol:** All CRT or CRT-D devices (InSync III, Medtronic, Minneapolis, USA or Contac Renewal, Guidant, Indianapolis, USA) were implanted as previously described, with the LV pacing electrode positioned by a transvenous approach into the lateral or posterolateral vein (13). Position of this localization was confirmed by conventional fluoroscopy 1 day and 4 months after implant in every patient. The device was programmed into a non-functional pacing mode (VVI, backup 40 bpm) until the first baseline echocardiographic evaluation. The pacing protocol at pre-defined heart rates

was performed in 2 basic modes: AAI (atrial) and DDD-CRT (biventricular). First, pacing was initiated in the AAI-mode at 70 bpm with a stepwise increase by 20 beats every 4 minutes until the target heart rate of 110 bpm was reached. After 4 minutes of recovery in VVI back-up mode 40 bpm, DDD-CRT mode was initiated after optimization of the AV and VV interval starting at 70 beats per minute with 20 beats increments every 4 minutes until a heart rate of 110 bpm (14,15). Heart rate increase was achieved through incremental pacing without adrenergic stimulation, which could have influenced the inotropic response through a mechanism different from the Treppe effect. During each step three blood pressure measurements (right arm) were recorded using a cuff sphygmomanometer and the diaphragm of a standard stethoscope by a technician who also changed the pacemaker settings. After the protocol was completed, the device was re-programmed in DDD-CRT mode 50-140 bpm with a fixed optimized AV and VV interval with scheduled follow-ups and device checks. The pacing protocol was performed in an identical manner four months later.

**Echocardiography protocol:** Two-dimensional echocardiography was performed with commercially available systems (Acuson Sequioa, C512, USA and Vingmed, System Seven, General Electric, USA). Images were acquired in the left lateral decubitus position using a 3,5-MHz transducer in the standard parasternal and apical views during each pacing step. Standard two-dimensional and Doppler data, triggered to the QRS complex, were digitally stored in a cine-loop format and analysed off-line by two independent experienced echocardiographers unaware of the study design and pacing mode. Measurements were averaged from three consecutive cycles. The left ventricular volumes were calculated from the apical four-chamber view using the Simpson's formula and the LV end-systolic volume index (LVESVI) was calculated as the LVESV divided by the body surface area (16). To build the FFR, the contractility index (CI) at each step was determined as the ratio of the systolic blood pressure (average of three measurements) over LVESVI (10,11). In addition, following analyses were performed: 1) diastolic function was evaluated using E, diastolic filling time (DFT) and myocardial performance index (MPI) (17); 2) the degree of mitral valve regurgitation was assessed semi-quantitatively using color flow Doppler images in the apical four-chamber view (18); 3) the total amount of dyssynchrony was calculated as the sum of inter- and intraventricular dyssynchrony (12). LV dyssynchrony was assessed from regional time intervals between the onset of the QRS complex to the peak of the systolic myocardial velocity in the six basal segments of the left ventricle using pulsed-wave Doppler imaging. LV intraventricular dyssynchrony was defined as the maximum time delay between

basal LV segments. Interventricular dyssynchrony was assessed by comparison of the time delay between onset of QRS complex and opening of pulmonary and aortic valve measured by continuous Doppler imaging in the RV and LV outflow tract.

**Invasive protocol:** Left ventricular endomyocardial biopsies were obtained at BL and at FU in a subgroup of six patients with idiopathic dilated cardiomyopathy using a long guiding sheath and a disposable transfemoral bioptome (Cordis Corporation, USA) at the level of the distal interventricular septum. They were snap frozen in liquid nitrogen and stored at -80$^0$C for subsequent m-RNA analyses. Subsequently a 0,014-inch pressure high fidelity sensor-tipped guide wire (Radi Medical Systems, Upsula, Sweden) with a 500-Hz frequency response was advanced through a 6-F multipurpose catheter into the left ventricle for the measurement of LV dP/dtmax. The high-fidelity LV pressure signal was computed online. The ECG and LV dP/dtmax were recorded simultaneously, digitized to a personal computer and analysed off-line by an experienced cardiologist unaware of the study design. Each reported measurement represents the mean of at least 40 consecutive beats excluding any post-systolic beats.

**Quantitative Real-time Reverse Transcriptase PCR (RT-PCR):** Highly sensitive RT-PCR was used for m-RNA quantifications as previously described (19). Briefly, total RNA was isolated from left ventricular endomyocardial biopsies using the RNeasy Fibrous Tissue Mini Kit (Qiagen) and DNase digested. RNA was reverse transcribed with random primers using the High-Capacity cDNA Archive Kit (Applied Biosystems). RT-PCR was performed in 96-well plates on the ABI Prism 7000 Sequence Detection System (ABI) using TaqMan Universal PCR Master Mix and Assays-On-Demand, with a final reaction volume of 25µl. PCR primers and FAM probes for all of the target genes were purchased as Assays-On-Demand (Applied Biosystems). The assay numbers for the target genes were Hs01564008_m1, Hs00160179_m1, Hs00411899_m1, Hs02330048_s1 and Hs00175572_m1 for SERCA2a, PLN, NCX, β1-AR and APELIN respectively. Human GAPDH gene was used as endogenous control (Applied Biosystems). All samples were performed in triplicate. The relative expression of the target genes was normalized to the level of GAPDH in the same cDNA

**Brain natriuretic peptide:** Plasma venous levels of NT-proBNP (Elecsys 2010 – Roche diagnostics, PmbH, 68298 Mannheim, Germany) were determined from blood samples collected the day prior to CRT implantation and 4 months later just before starting the echocardiography protocol.

**Statistics:** All data are expressed as mean ± SD for continuous data and as a ratio for categorical data. Gaussian distribution of data was tested by Kolmogorov-Smirnov test. A paired t-test for continuous data, Fisher's exact test for categorical data and a Spearman correlation coefficient were used for appropriate comparisons. Comparison of hemodynamic data measured during AAI, and DDD-CRT pacing at various heart rates was performed by use of a 2-way repeated-measures ANOVA followed by Tukey test. Statistical significance was set at a two-tailed probability level of less than 0.05.

**d) Results**

Baseline characteristics of the 20 patients enrolled in the study are summarized in Table 1. One patient was lost during FU because of worsening heart failure requiring urgent cardiac transplantation one month after CRT implantation. In the remaining 19 patients, the pacing protocol was performed within one day after CRT implantation and repeated at 4 months follow-up. Medical treatment with beta-blockers, ACE-I and spironolactone remained unchanged at follow-up. Heart failure was due to ischemic disease in 11 patients and idiopathic dilated cardiomyopathy in 9 patients. No patient complained of angina during the pacing protocol and no evolutive ECG changes compatible with ischemia could be detected on ECG.

**Clinical and Echocardiographic Follow-up.** Serial changes in echocardiographic indices during baseline AAI and follow-up DDD-CRT pacing at 70 bpm are summarized in Table 2. At follow-up, a significant reduction in dyssynchrony and MPI was observed in parallel with an improvement in LV ejection fraction and a decrease in LV volumes as well as severity of mitral regurgitation. This was accompanied by a significant improvement in NYHA functional class, with 95% of the patients improving to class I or II and a significant decrease in plasma NT-proBNP levels. One patient experienced an appropriate shock by the ICD because of sustained ventricular tachycardia. The inter-observer and intra-observer variabilities have been compared in 100 consecutive dyssynchrony measurements and were 3.5 and 3.2% respectively. The intra-patient variability for the systolic blood pressure and diastolic blood pressure at each step was 5.2 and 4.7%.

**Impact of Early and Late Rate-dependent Effects of CRT on Contractile Performance, Diastolic Filling Time and Dyssynchrony.** Figure 1 illustrates non-invasive assessment of baseline and follow-up left ventricular FFR during different modes of stimulation In a subset of 6 patients FFR was assessed invasively. Baseline AAI-pacing was

associated with a blunted FFR at baseline. DDD-CRT was associated with an acute upward shift in FFR ($p<0.01$) in the absence of any significant change in the slope of the FFR. At FU, AAI mode demonstrated an upward shift in FFR ($p<0.01$), the slope of the relationship was similar as compared to BL. In contrast, during DDD-CRT at FU, an upward shift of FFR ($p<0.01$) with force-frequency amplification ($p=0.039$ for echo- and $p=0.030$ for invasive protocol) was observed. There was an excellent correlation between the echo- and invasive protocol since the relative changes in LV dP/dtmax measured invasively correlated significantly with the relative changes in contractility index measured non-invasively during the different pacing modes ($r = 0.99$, $p = 0.035$).

Figure 2 illustrates BL and FU dyssynchrony and diastolic filling time measurements during different modes of stimulation. The better contractile performance during DDD-CRT as compared to AAI at baseline was associated with a rate-independent decrease in sum of dyssynchrony ($p<0.01$) and a prolongation of the diastolic filling time ($p<0.01$) that was unchanged at follow-up. However at follow-up, the dyssynchrony during AAI pacing was significantly reduced as compared to baseline ($p<0.01$).

**LV Endomyocardial Gene Expression.** Figure 3 and table 3 illustrate the changes in gene expression of several contractile-regulating proteins from BL to FU. Chronic resynchronization therapy was associated with a significant upregulation of gene expressions of SERCA2 ($p=0.01$), PLN ($p=0.01$), β1-AR ($p=0.03$) and APL ($p=0.01$). A trend towards increase in sodium-calcium exchange (NCX) gene expression was also noted ($0.85 \pm 0.2$ versus $1.09 \pm 0.3$, $p=0.06$). Furthermore, a significant increase in the ratio of SERCA2α to PLB ($p=0.01$) and SERCA2α to NCX ($p=0.02$) was observed (Figure 4). The improvement in contractile function, expressed as the increase in LV dP/dtmax between BL and FU DDD-CRT pacing at a heart rate of 70bpm correlated significantly with the change in gene expression between BL and FU of SERCA2α ($r=0.98$, $p=0.01$), SERCA2α /PLB ($r=0.97$, $p=0.025$), NCX ($r=0.94$, $p=0.05$) ,SERCA2α /NCX ($r=0.9$, $p=0.004$) and β1-AR ($r=0.92$, $p=0.01$).

**e) Discussion**

Careful elucidation of the hemodynamic and molecular underpinnings of the beneficial effects of CRT in improving myocardial contractility may hold an important key to understand the acute and chronic contributions of restoring ventricular synchrony in the failing heart. By performing force-frequency relationship assessment in both atrial (AAI) and

biventricular (DDD-CRT) pacing modes, we illustrated the contributions of restoring ventricular synchrony in improvement of myocardial performance at baseline and at long-term follow-up. Furthermore, we demonstrated the at least partial restoration of contractility following long-term CRT, both overall and specifically at increased heart rates. Moreover, the key finding of this mechanistic study implies the presence of a molecular remodeling process with long-term CRT that is directly contributing to the improvement in myocardial contractility.

**Acute effects of CRT on the FFR, Dyssynchrony and Diastolic Filling Time.** In a normal heart, augmentation of LV contraction at increased heart rates modulates cardiac performance (6). Attenuation of this response contributes to the impaired exercise performance observed in heart failure (7). This supports the hypothesis that improved exercise capacity and functional status of patients treated with CRT may reflect a partial restoration of the blunted force-frequency relation. Our findings corroborate this by demonstrating at least an upward shift of the contractility index at each pacing step during DDD-CRT pacing as compared to that of AAI-pacing. In addition, we demonstrated for the first time that this upward shift of the FFR curve is related to beneficial effects of CRT upon dyssynchrony and diastolic filling time which are sustained at higher heart rates. These observations suggest that in the acute (baseline) setting, improvement of the myocardial contractile performance following CRT results primarily from a more synchronous activation rather than from intrinsic alteration of the contractile apparatus of the individual myocyte.

Recently, Vollman et al demonstrated that during acute biventricular pacing, contractile function improves with increasing heart rates (9). In contrast, we failed to observe force-frequency amplification at higher heart rates at this time point. It is likely that differences in study design may account for these different findings. While Vollman compared biventricular versus right and left ventricular pacing up to heart rates of 140 bpm, we compared AAI and DDD-CRT stimulation with the rationale that AAI pacing allows normal atrioventricular conduction and more closely reflects normal conduction of the dyssynchronous heart. In the study of Vollman et al, force-frequency amplification was noted only during biventricular-pacing at heart rates ≥120 bpm (9). They speculated that the prolongation of the diastolic filling period induced by biventricular stimulation might play an important role especially at high heart rates when ventricular filling is shortened. Although we were unable to pace our patients at heart rates >110bpm (most of them developed atrioventricular block at this pacing

frequency) we noticed a significantly longer diastolic filling time at each heart rate up to 110 bpm during CRT as compared to AAI, in part supporting Vollman's hypothesis.

**FFR and LV Remodeling: Chronic Effects and Potential Mechanisms.** First, we observed a significant upward shift of the FFR from baseline to follow-up during AAI. This "unexpected" observation may be attributed to the improvement in myocardial structure with reversed LV remodeling induced by four months of BiV-pacing thereby reducing LV volumina and mitral regurgitation. Moreover, a statistically significant reduction of dyssynchrony was observed in AAI suggesting that four months of CRT partially restored ventricular synchrony, which can also be related to reversal of LV structural remodeling.
Second, in contrast to the AAI mode, CRT not only shifted the FFR curve upwards but also induced force-frequency amplification. Our data suggest a phenotype-genotype correlation between this improved contractile reserve and global LV remodeling. Of note the blunted force-frequency relation of the failing human myocardium has been attributed to disturbed excitation-contraction coupling due to decreased calcium cycling with a reduction in $Ca^{2+}$ uptake capacity into the sarcoplasmatic reticulum secondary to decreased levels of SERCA2α relatively to PLB (20,21,22). Calcium cycling in heart failure patients can further be disturbed by a reduction in SERCA2α levels relatively to NCX (23). The latter will result in enhanced $Ca^{2+}$ extrusion from the myocardial cells through a NCX mediated increased inward $Na^{+}$ current which might be arrhythmogenic in heart failure patients (24). In this regard it has been demonstrated that the upregulation of SERCA2□ m-RNA levels following prolonged unloading by LV assist devices or beta-blocker therapy is associated with improved LV contractility (25,26,27,28). Therefore, our findings of upregulation of SERCA2□ gene expression, higher SERCA2□/PLN ratio and higher SERCA2□/NCX ratio suggest that chronic CRT leads to a better calcium handling. Moreover, we also observed increased expression of APL, a potent endogenous inotropic protein, which has also been proven to be upregulated after prolonged LV assist device therapy (29,30).

Congestive heart failure is also associated with a chronic increase in sympathetic activity which leads to a downregulation and an uncoupling of β1-AR resulting in a decrease of intracellular c-AMP levels and diminished functional responsiveness of cardiac β-receptors (31,32). These changes may be beneficial by protecting the heart from adrenergic overdrive. However at long term, donwregulation of receptors will incapacitate the ability of the heart to meet chronotropic demands at higher heart rates and may be responsible for lower exercise performance. Our data corroborate this postulate by our observation of upregulation of β1-

AR levels and by recent findings indicating reduced muscle sympathetic nerve activity coinciding with reduced levels of catecholamines in responders to CRT (33).

The more pronounced reduction of dyssynchrony as well as the additional prolongation of diastolic filling times in CRT vs AAI pacing at the various pacing rates might explain why at 4 months follow-up despite a similar expression of contractile regulatory genes, amplification of the force-frequency relationship is only observed during DDD-CRT and not during AAI pacing.

To which extent the restoration of synchrony, LV remodeling and reduced neurohormonal activation contribute to the observed molecular remodeling requires further investigation. Hence, it is clear that improvements in calcium cycling and inotropic response of the individual myocyte may in part contribute to the improvement in global LV contractility as a result of long-term CRT. Further studies are necessary to better understand the determinants of this “molecular remodeling” process and also to see if changes in gene expression after CRT are induced by the resynchronization therapy itself or the result of modifying electrical impulse propagation in general.

**Study limitations.** First, we could only collect data up to a heart rate of 110 bpm in all patients as the majority of our patients developed atrioventricular block at heart rates above 110 bpm. This could be explained by optimal medical therapy including maximally tolerated dose of beta-blockers. Second, the FFR was assessed in all patients from the non-invasive ratio of systolic blood pressure / end-sytolic volume index (apical four chamber view). Although the blood pressure was always measured at the right arm no right and left arm blood pressure differences were checked. Nevertheless, previous non-invasive and invasive studies demonstrated that this index is a reliable and reproducible parameter of left ventricular contractility (10,11,34,35,36). Moreover, we were able to confirm the accuracy of the echocardiographic data for FFR assessment in a subgroup of 6 patients invasively by measuring LV dP/dtmax at various heart rates and pacing modes. Third, only one patient was qualified as a clinical non-responder requiring an urgent cardiac transplantation making the success rate of responders clearly higher than typically reported in a similar cohort of patients referred for CRT. It is likely that use of rigorous selection criteria based upon severe electrical and mechanical dyssynchrony, and the absence of extensive posterolateral scar tissue has limited the proportion of non-responders (12). Fourth, we used atrial pacing, which could have introduced a rate-dependent and pacing mode dependent delay time between atrial excitation and contraction. Though recent data suggest that LV function is better with VDD

rather than with DDD stimulation, the mechanistic design of our study urged for a compromise between optimizing atrioventricular filling and systole. Fifth, LV gene expression could be potentially heterogeneous in various part of the left ventricle and no real control group was used. To limit the impact of regional differences, serial LV biopsies were obtained only from dilated cardiomyopathy patients from the apicoseptal regions in all patients. Only RNA analysis and no protein analyses or functional activity studies of contractile handling genes were possible due to the small size of the LV biopsies. Nevertheless, an increase in contractile gene expression was clearly correlated with the observed improvement in contractile function and was concomitant with the observed functional improvement suggesting that the increase in contractile gene expression was functionally meaningful. Finally, though we clearly demonstrated improved expression of the most established molecular markers of heart failure it is likely that many other relevant genes are participating in the complex process of tissue remodeling that need to be identified in studies using microarray analysis.

**f) Conclusions**

In heart failure patients with mechanical dyssynchrony and on optimal medical therapy, CRT leads to an acute upward shift in the FFR without force-frequency amplification. Amplification of the FFR occurs following long-term CRT in parallel to LV remodeling and upregulation of contractility regulating genes.

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**Table 1 Baseline patient characteristics (n = 20)**

| | |
|---|---|
| **Age** (years) | 66 ± 14 |
| **Gender** (Male/Female) | 16/4 |
| **Body Surface Area** (kg/m2) | 1.83 ± 0.24 |
| **NYHA Functional Class** (%) | |
| III | 12 (60) |
| IV | 8 (40) |
| **Etiology** (%) | |
| Ischemic | 11 (55) |
| Idiopathic Dilated Cardiomyopathy | 9 (45) |
| **Medication** (%) | |
| ACE-I inhibitor | 20 (100) |
| Beta-blocker | 19 (95) |
| Loop diuretic | 20 (100) |
| Spironolactone | 17 (85) |
| **CRT-D** (%) | 12 (60) |
| **Electrocardiography** | |
| Heart rate (bpm) | 63 ± 6 |
| PR interval (msec) | 180 ± 42 |
| QRS width (msec) | 177 ± 12 |

NYHA indicates New York Heart Association functional class, Htx heart transplantation, ACE-I angiotensin converting enzyme. Values are mean ± SD or n (%).

**Table 2 Resting echocardiography and clinical parameters at baseline and at follow-up**

| | Baseline | Follow-up | p-value |
|---|---|---|---|
| **Echocardiography** | | | |
| SBP (mm Hg) | 111 ± 16 | 131 ± 16 | < 0.001 |
| LVEDV (ml) | 331 ± 114 | 241 ± 79 | 0.002 |
| LVESV (ml) | 259 ± 76 | 164 ± 47 | < 0.001 |
| LVEF (%) | 21 ± 5 | 34 ± 8 | < 0.001 |
| CI (mm $Hg.m^2.ml^{-1}$) | 0.898 ± 0.329 | 1.860 ± 1.083 | 0.001 |
| MR grade | 2.4 ± 1.1 | 0.6 ± 0.8 | < 0.001 |
| DFT (msec) | 339 ± 74 | 425 ± 97 | 0.003 |
| E (m/s) | 0.89 ± 0.17 | 0.61 ± 0.15 | 0.009 |
| MPI | 0.87 ± 0.43 | 0.47 ± 0.27 | < 0.001 |
| InterV Dyssynch (msec) | 60 ± 33 | 13 ± 9 | < 0.001 |
| IntraV Dyssynch (msec) | 91 ± 54 | 32 ± 14 | < 0.001 |
| Sum of Dyssynch (msec) | 152 ± 47 | 45 ± 19 | < 0.001 |
| **Clinical Characteristics** | | | |
| BNP (pg/ml) | 8524 ± 1560 | 975 ± 703 | 0.001 |
| NYHA ≥ III (%) | 20 (100 %) | 1 (5%) | 0.002 |

SBP: systolic blood pressure, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, CI: contractility index, MR: mitral regurgitation, DFT: diastolic filling time, E: transmital peak early diastolic filling velocity, MPI: myocardial performance index, NYHA: New York Heart Association functional class.

**Table 3 Gene expression levels at baseline and at follow-up (n=6)**

| Gene Expression (relative units) | Baseline | Follow-Up | p – value |
|---|---|---|---|
| **SERCA** | 1.24 ± 0.23 | 1.72 ± 0.30 | 0.01 |
| **(median, 25%-75%)** | (1.11; 1.06-1.49) | (1.66; 1.52-1.96) | |
| **PLN** | 5.74 ± 1.14 | 7.00 ± 1.32 | 0.01 |
| **(median, 25%-75%)** | (6.06; 4.63-6.69) | (6.15; 6.06-8.36) | |
| **NCX** | 0.85 ± 0.21 | 1.08 ± 0.29 | 0.06 |
| **(median, 25%-75%)** | (0.89; 0.63-1.06) | (1.05; 0.80-1.39) | |
| **Apelin** | 0.03 ± 0.01 | 0.05 ± 0.01 | 0.01 |
| **(median, 25%-75%)** | (0.04; 0.02-0.05) | (0.05;0.03-0.06) | |
| **β-1 AR** | 0.06± 0.01 | 0.10 ± 0.03 | 0.03 |
| **(median, 25%-75%)** | (0.06; 0.05-0.06) | (0.10; 0.07-0.14) | |

SERCA: sarcoplasmatic reticulum calcium ATPase 2□, PLN: phospholamban, NCX: sarcolemmal sodium calcium exchanger, APL: apelin, β1-AR: β1-adrenoreceptor.

**Figure legend**

**Figure 1 Time-dependent changes in force-frequency relation during AAI and CRT pacing**

Force-frequency relation during different pacing modes at baseline and at follow-up measured by the contractility index (Figure 1a) and by LV dP/dtmax (Figure 1b). Upper panel left represents AAI baseline vs AAI follow-up, upper panel right CRT baseline vs CRT follow-up, middle and lower panel left baseline AAI vs baseline CRT, middle and lower panel right follow-up AAI vs follow-up CRT.

At follow-up a significant upward shift in FFR is noted in both pacing modes compared to baseline. Increasing stimulation frequencies augmented contractile function only during DDD-CRT follow-up (**; p=0.039 for echo- and p=0.030 for invasive protocol).

***** indicates $p < 0.01$ compared to similar heart rate. ns: no significant rate dependent change in FFR.

**Figure 2 Dyssynchrony and diastolic filling time at incremental heart rates**

Relationship between the sum of intra- and interventricular dyssynchrony (upper and middle panel) and diastolic filling time (lower panel) and increasing heart rate during AAI and CRT. Increasing stimulation frequencies showed a trend towards an increase in sum of dyssynchrony during baseline AAI (p=0.06). Diastolic filling time was increased during CRT at all heart rates.

* indicates $p < 0.01$ compared to similar heart rate, ns indicates non-significant.

**Figure 3 Gene expression levels at baseline and at follow-up (n=6)**

SERCA: sarcoplasmatic reticulum calcium ATPase 2□, PLN: phospholamban, NCX: sarcolemmal sodium calcium exchanger, APL: apelin, β1-AR: β1-adrenoreceptor.

* indicates $p = 0.01$ compared to BL. ** indicates $p = 0.06$ compared to BL *** indicates $p = 0.03$ compared to BL.

**Figure 4 Ratio of SERCA/PLN and SERCA/NCX at baseline and at follow-up (n=6)**

SERCA: sarcoplasmatic reticulum calcium ATPase 2□, PLN: phospholamban, NCX: sarcolemmal sodium calcium exchanger.

* indicates $p = 0.01$ compared to BL, ** indicates $p = 0.02$ compared to BL.

# Figure 1a: Non-Invasive Measurements (n = 19 pts)

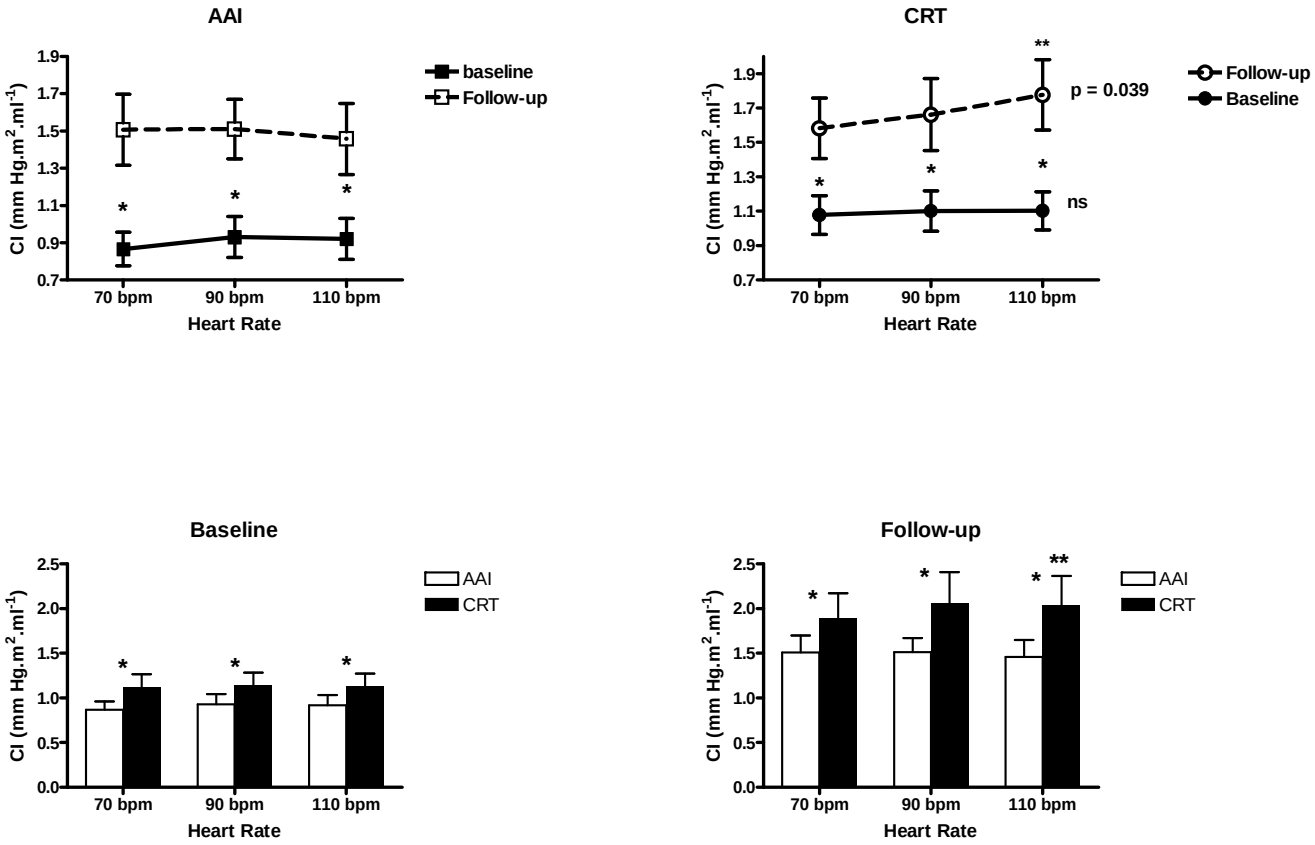
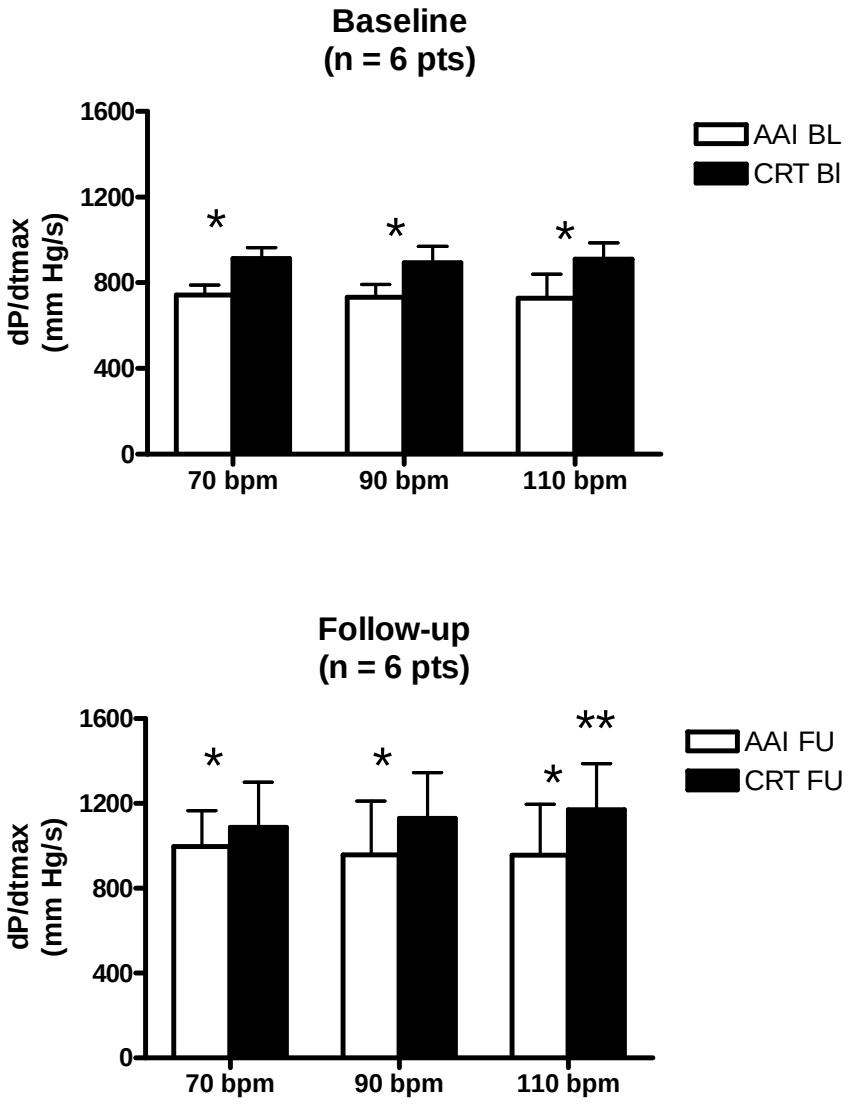
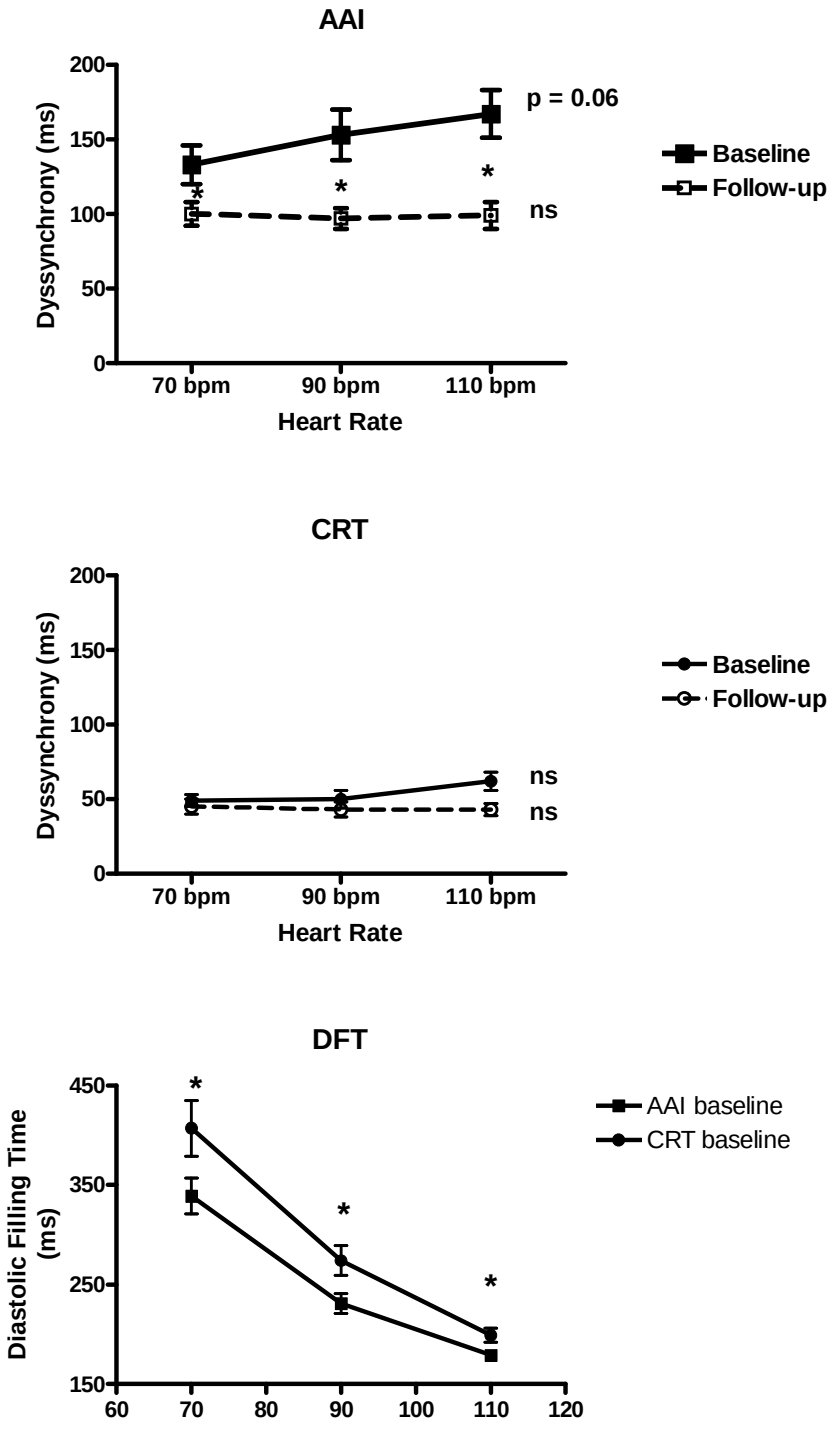


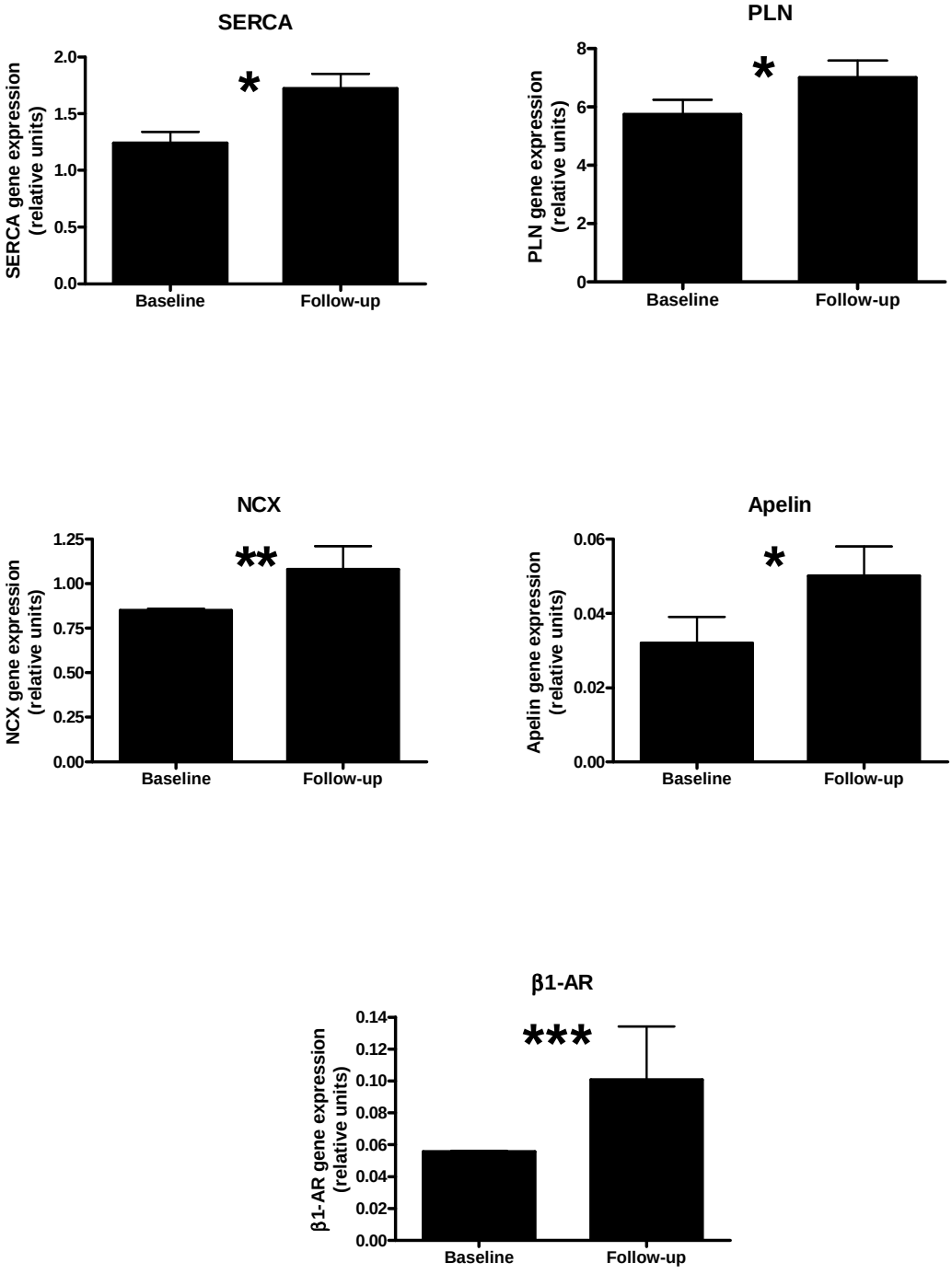
**Figure 1b: Invasive Measurements**
**(n = 6 pts)**



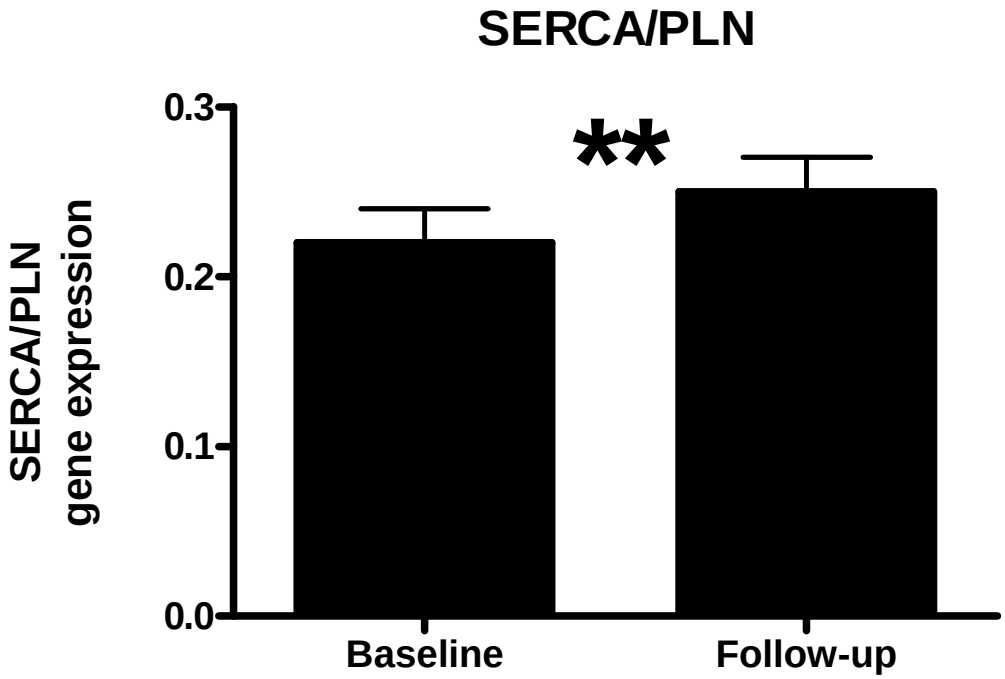
# Figure 2

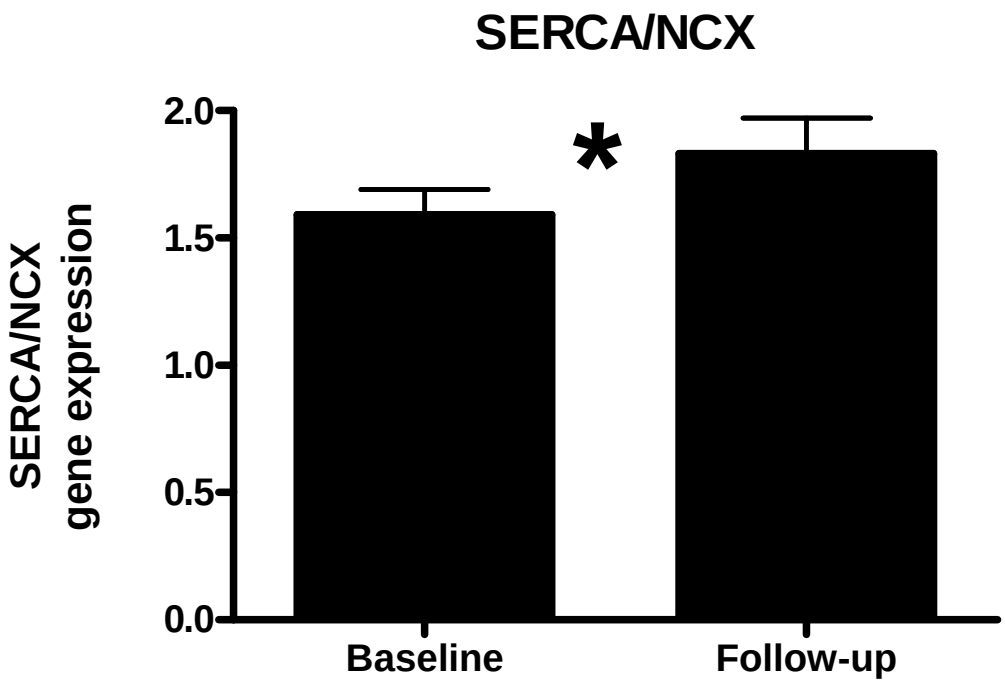

AAI
Dyssynchrony (ms)
200
150
100
50
0
p = 0.06
*
*
*
ns
Baseline
Follow-up
70 bpm
90 bpm
110 bpm
Heart Rate
CRT
Dyssynchrony (ms)
200
150
100
50
0
ns
ns
Baseline
Follow-up
70 bpm
90 bpm
110 bpm
Heart Rate
DFT
Diastolic Filling Time (ms)
450
350
250
150
60
70
80
90
100
110
120
*
*
*
AAI baseline
CRT baseline

# Figure 3


SERCA
SERCA gene expression (relative units)
2.0
1.5
1.0
0.5
0.0
*
Baseline
Follow-up
PLN
PLN gene expression (relative units)
8
6
4
2
0
*
Baseline
Follow-up
NCX
NCX gene expression (relative units)
1.25
1.00
0.75
0.50
0.25
0.00
**
Baseline
Follow-up
Apelin
Apelin gene expression (relative units)
0.06
0.04
0.02
0.00
*
Baseline
Follow-up
β1-AR
β1-AR gene expression (relative units)
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
***
Baseline
Follow-up

## Figure 4


SERCA/PLN
SERCA/PLN gene expression
0.3
0.2
0.1
0.0
**
Baseline
Follow-up


SERCA/NCX
SERCA/NCX gene expression
2.0
1.5
1.0
0.5
0.0
*
Baseline
Follow-up

## 2) Endomyocardial upregulation of β1-adrenoreceptor gene expression and myocardial contractile reserve following cardiac resynchronization therapy

Mullens W, Vanderheyden M, Delrue L, Goethals M, Verstreken S, Geelen P, De Bruyne B, Wijns W, Bartunek J. Endomyocardial Upregulation of β1-Adrenoreceptor Gene Expression and Myocardial Contractile Reserve Following Cardiac Resynchronization Therapy. J Card Fail 2008;14:172-178.


**a) Abstract**

**Background:**

Congestive Heart Failure (CHF) is associated with a blunted force-frequency relation (FFR) and myocardial contractile reserve (MCR) partially due to a downregulation of β1-adrenoreceptors (β1-AR). We investigated whether acute and chronic cardiac resynchronization therapy (CRT) was capable of reversing the blunted FFR and MCR and if this was associated with upregulation of β1-AR.

**Methods:**

Left ventricle dP/dtmax was invasively measured in 10 CHF patients (NYHA class ≥ 3; EF < 25%) during incremental DDD-CRT pacing at 70,90,110 and 130 bpm, with and without continuous infusion of intravenous dobutamine, immediately after CRT implantation (BL) and four months later (FU). In a subgroup of 5 patients serial left ventricle β1 and β2-AR gene expression was measured using rt-PCR.

**Results:**

Four months after the initiation of resynchronization therapy, DDD-CRT pacing results in a significant upward shift of the heart rate vs LV dPdtmax relationship ($p<0.01$) with force frequency amplification as evidenced by the steeper slope of the force frequency response ($p=0.04$). Infusion of dobutamine recruits myocardial contractile reserve, increases the heart rate vs LV dPdtmax relationship at BL as well as at FU (both $p<0.05$). However only at follow-up an additional force frequency amplification was noticed ($p<0.05$) during dobutamine infusion. This observation was paralleled by a significant upregulation of β1-AR gene expression ($p=0.02$).

**Conclusions:**

Chronic CRT is associated with a partial restoration of the force frequency relation and with a recruitment in myocardial contractile reserve which is paralleled by upregulation of β1-AR.

**b) Introduction**

Cardiac resynchronization therapy (CRT) improves cardiac function and exercise capacity leading to a better survival in patients with advanced heart failure and ventricular conduction delay (1,2). The underlying mechanisms of these beneficial effects are not fully elucidated but appear to be related to a restored coordination of the left ventricular (LV) contraction and relaxation and an improvement in functional mitral regurgitation (3,4). These effects may directly lead to augmented contractility and reduction of LV filling pressures at resting heart rates (5,6).

In contrast to normal myocardium, frequency related increase in tension, or Treppe positive staircase is greatly attenuated or absent in patients with heart failure (7,8,9). In addition, congestive heart failure is characterized by abnormal □-adrenergic receptor and post-receptor mechanisms which diminish the adrenergically mediated contractile reserve during inotropic stimulation with dobutamine infusion (10,11).

The present study was designed to evaluate acute and chronic effects of CRT on cardiac hemodynamic function at incremental heart rates by invasive measures. Furthermore, our goal was to evaluate any change in the contractile respons to exogenous catecholamines by comparing the LV dP/dtmax response to a dobutamine infusion at incremental heart rates during acute and long term DDD-CRT pacing. Furthermore, we postulate that improvements in myocardial contractile reserve are related to changes in the expression of β1- and β2-adrenergic receptor gene expression.

**c) Methods**

**Patients and CRT implantation.** The study population consisted of 10 consecutive NYHA III-IV pts undergoing CRT implantation. All patients were in sinus rhythm, on optimal medical therapy for at least 3 months, had an LV ejection fraction < 25 %, left bundle branch block with QRS duration > 140 ms, severe mechanical dyssynchrony with a total sum of dyssynchrony > 102 ms on tissue Doppler echocardiography and a resting heart rate < 70 bpm (12). Patients were studied immediately after CRT implantation(BL) and at 4 months(FU). Cardiovascular medications, comprising ACE-I, beta-blockers either carvedilol or bisoprolol, aldosterone antagonists and diuretics were continued during the study period and their dose remained unchanged. Patients with heart rate > 70 bpm, atrial fibrillation, primary valvular heart disease, recent myocardial infarction (< 12 months) or under intravenous inotropic support were excluded. Patients with ischemic cardiomyopathy had a

coronary angiogram within a month before the CRT-implantation to exclude the need for revascularisation. Five patients with idiopathic dilated cardiomyopathy consented to undergo serial left ventricular endomyocardial biopsy sampling at BL and at FU. Eight patients received a CRT-Defibrillator (CRT-D) because of episodes of sustained ventricular tachycardia or inducible ventricular arrhythmias during diagnostic electrophysiological examination. All CRT or CRT-D devices (InSync III, Medtronic, Minneapolis, USA or Contac Renewal, Guidant, Indianapolis, USA) were implanted as previously described with the LV pacing electrode positioned by a transvenous approach into the lateral or posterolateral vein (13). The device was programmed into a non-functional pacing mode (VVI, backup 40 bpm) until the first baseline hemodynamic evaluation. All patients gave oral informed consent and the study was approved by the institutional ethics committee.

**Hemodynamics and Pacing Protocol.** All patients underwent left heart catheterization via the femoral approach. A 0,014-inch pressure high fidelity sensor-tipped guide wire (Radi Medical Systems, Upsula, Sweden) with a 500-Hz frequency response was advanced through a 6-F multipurpose catheter into the left ventricle for the measurement of LV pressure (14). The high-fidelity LV pressure signal was computed online and LV contractility was assessed from the maximal positive LV dP/dt. The ECG, LV pressure and LV dP/dtmax were recorded simultaneously, digitized to a personal computer and analysed off-line by an experienced cardiologist unaware of the study design. Each measurement represents the mean of at least 10 consecutive beats, except LV dP/dtmax which was the average of at least 40 consecutive beats, excluding any extrasystolic beats. All patients received their daily dose of beta-blocker 2 to 3 hours before the catheterization. Individual doses of beta-blockers were kept constant during follow-up.

The pacing protocol at pre-defined heart rates was performed one day and four months after CRT implantation without and under adrenergic stimulation as follows: First, pacing was initiated in the AAI-mode at 70 bpm with a stepwise increase by 20 beats every 4 minutes until the target heart rate of 130 bpm. After 4 minutes of recovery in VVI back-up mode 40 bpm, the DDD-CRT mode with an optimized AV interval was initiated at 70 beats per minute with 20 beats increments every 4 minutes until a heart rate of 130 bpm. After another 4 minutes of recovery, pacing was repeated under continuous infusion of dobutamine at a dose of 5 µg/kg/min. Once a steady state had been achieved, the DDD-CRT protocol was repeated as described above. At the end, the device was re-programmed in DDD-CRT mode 50-140 bpm with a fixed optimized AV interval and patient was clinical followed. The DDD-CRT

part of the pacing protocol with and without dobutamine was repeated in an identical manner 4 months later.

**Endomyocardial biopsies.** Serial left ventricular endomyocardial biopsies were obtained at BL and at FU in five patients using a long guiding sheath and a disposable transfemoral bioptome (Cordis Corporation, USA) at the level of the distal interventricular septum. Two to three biopsies were acquired from every patient at baseline and at follow-up. They were snap frozen in liquid nitrogen and stored at -80$^0$C for subsequent m-RNA analyses.

**Quantitative Real-time Reverse Transcriptase PCR (RT-PCR).** Highly sensitive RT-PCR was used for mRNA quantifications as previously described (15). Briefly, total RNA was isolated from left ventricular endomyocardial biopsies using the RNeasy Fibrous Tissue Mini Kit (Qiagen) and DNase digested. RNA was reverse transcribed with random primers using the High-Capacity cDNA Archive Kit (Applied Biosystems). RT-PCR was performed in 96-well plates on the ABI Prism 7000 Sequence Detection System (ABI) using TaqMan Universal PCR Master Mix and Assays-On-Demand, with a final reaction volume of 25µl. PCR primers and FAM probes for all of the target genes were purchased as Assays-On-Demand (Applied Biosystems). The assay number for the target genes were Hs02330048_s1, Hs00240532_s1 and Hs00173590_m1 for β1-, □2- adrenoreceptor and BNP. Human GAPDH gene was used as endogenous control (Applied Biosystems). All samples were performed in triplicate. The relative expression of the target gene was normalized to the level of GAPDH in the same cDNA

**Brain natriuretic peptide.** Plasma venous levels of Nt-proBNP (Elecsys 2010 – Roche diagnostics, PmbH, 68298 Mannheim, Germany) were determined from blood samples collected the day before CRT implantation and 4 months later just before starting the pacing protocol.

**Statistics.** All data are expressed as mean ± SD for continuous data and as a ratio for categorical data. Gaussian distribution of data was tested by Kolmogorov-Smirnov test. A t-test for continuous data and Fisher's exact test for categorical data were used as appropriate. ANOVA for multiple comparisons and for repeated measurements followed by Neuman-Keuls post hoc test was used for appropriate multiple comparisons. Statistical significance was set at a two-tailed probability level of less than 0.05.

**d) Results**

**Baseline Characteristics and Clinical Follow-up.** Baseline characteristics together with serial clinical and hemodynamic data are summarized in table 1. All patients had severe

LV dysfunction with mean EF of 19±4 %, significant left intra- and interventricular dyssynchrony and severe LV dilatation. All were in NYHA class ≥ 3 heart failure. Heart failure was due to ischemic heart disease in 4 patients and idiopathic dilated cardiomyopathy in 6 patients. One patient was lost during the FU because of worsening heart failure requiring urgent cardiac transplantation early after CRT implantation. Medical treatment remained unchanged at FU except the dose of loop diuretics which was reduced in 5 patients. At follow-up, a significant reduction in electrical-, mechanical dyssynchrony and mitral regurgitation was observed in parallel with an improvement in LV ejection fraction, an increase in diastolic filling time and a decrease in LV end-diastolic volume. This was associated with a significant improvement in NYHA functional class and a decrease in plasma NT-proBNP levels. One patient experienced an appropriate shock by the ICD because of sustained ventricular tachycardia. None of the subjects reported chest pain as a potential indicator for myocardial ischemia and no arrhythmias were observed during pacing tachycardia and dobutamine infusion.

**Force Frequency Response and Contractile Reserve: Acute Effects.** Upper panels of Figure 1 show the relationship between LV dP/dtmax, heart rate and dobutamine infusion at baseline, immediately after CRT implantation. At baseline, AAI-pacing (left upper panel) was associated with a blunted FFR with a decrease in force at heart rate of 130 bpm. In contrast, DDD-CRT pacing was associated with an upward shift in LV dP/dtmax at all heart rates ($p<0.01$ vs AAI) without change in the slope of the FFR. In addition, under continuous dobutamine infusion at baseline (upper right panel), a further upward shift of the LV dP/dt at all heart rates was noticed ($p<0.05$) with a trend toward a steeper slope of the heart rate vs LV dP/dtmax relationship.

**Force Frequency Response and Contractile Reserve: Late Effects.** Lower panels of Figure 1 show the relationship between LV dP/dtmax, heart rate and dobutamine infusion 4 months after CRT implantation. At 4 months, an upward shift of the heart rate versus LV dP/dtmax relationship ($p<0.05$) with force-frequency amplification ($p=0.04$) was observed as compared to baseline DDD-CRT pacing (lower left panel). Furthermore, as shown in lower right panel, dobutamine infusion resulted in further increase in the LV dP/dtmax at corresponding heart rates ($p<0.05$) with additional force amplification at increasing heart rates as evidenced by the steeper slope of the FFR ($p<0.05$). Figure 2 shows the relationship between the heart rate and change (Δ) in LV dP/dtmax during dobutamine infusion and DDD-CRT pacing at baseline and follow-up. At follow-up, force increasement at all heart rates was higher compared to baseline ($p<0.05$) consistent with improved recruitable contractile reserve.

Moreover, the slope of the heart rate-LV dP/dt max relationship at follow-up was significantly steeper as compared to baseline (p=0.04).

**Relationship between biventricular pacing, dobutamine and LV end-diastolic pressure (show also BL heart rate and LV SP).** Table 2 shows LV end diastolic pressures during DDD-CRT pacing at different heart rates before and during dobutamine infusion. Overall, there was no statistically significant difference between baseline and follow-up before and during dobutamine infusion at corresponding heart rates.

**LV endomyocardial gene expression.** None of the patients had complications of the endomyocardial biopsy procurement and no infiltrative or inflammatory processes were identified at histopathological analysis. Figure 3 illustrates the changes in gene expression of the β1-adrenoreceptor gene expression from BL to FU. Chronic resynchronization therapy was associated with a significant upregulation of β1-adrenoreceptor gene expression (0.04±0.01 vs 0.10±0.04, p=0.02) without any significant change in the β2-adrenoreceptor gene expression (0.08±0.03 vs 0.10±0.07, p=0.12). In addition, a downregulation of BNP gene expression was also noted (21.43±13 vs 7.53±7, p=0.04).

**e) Discussion**

This study describes detailed hemodynamics of congestive heart failure patients at different heart rates after CRT implantation. The main findings are that CRT improves the force-frequency relationship and amplifies the contractile reserve in response to inotropic stimulation. This effect appears to be associated with an upregulation of the β1-adrenoreceptor gene expression

**Potential mechanisms of the improved force-frequency relation during chronic CRT**. In normal myocardium, increasing heart rate augments ventricular contractility (7,8). This phenomenon, also known as the positive FFR, is an important mechanism for the heart to meets its hemodynamic demands during exercise. Failing myocardium is characterized by a reduction in contractile force at increasing heart rate and a loss of force-frequency amplification (9). Vollman et al recently reported a partial restoration of the blunted FFR already during acute Bi-V pacing not during acute RV or LV pacing (16). In our study, we could only demonstrate an upward shift of the LV dP/dtmax vs heart rate relationship early after the CRT implant during DDD-CRT pacing compared with AAI pacing and force frequency amplification only to occur at follow-up, four months after CRT implantation. Differences in patient population - patients appeared to be sicker and had a lower EF compared to the Vollman study population - or differences in pacing protocol could account

for this observation. While Vollman compared biventricular versus right and left ventricular pacing, we acutely compared AAI and DDD-CRT stimulation with the rationale that AAI pacing allows normal atrio-ventricular conduction and more closely reflects normal conduction of the dyssynchronous heart. In addition, we recently demonstrated that the acute beneficial hemodynamic effects of BiV pacing at incremental heart rates are modulated primarily by a prolongation of the diastolic filling time together with a more synchronous interaction of diseased myocytes whereas late after CRT the reverse remodeling and changes in the contractile apparatus of the individual myocyte itself might contribute to the force frequency amplification (*article in press*).

**Myocardial Contractile Reserve.** In the human heart, β1 adrenergic receptors represent ~ 80% of β-adrenergic receptors being the main regulator of cardiac inotropy and chronotropy (10). Control of the FFR by β-adrenergic stimulation is primarily mediated by protein kinase A-mediated phosphorlyation of L-type calcium channels and phospholamban (17,18,19). Congestive heart failure is associated with a chronic increase in sympathetic activity which leads to a downregulation of β1-adrenergic receptors and an uncoupling of β-adrenergic receptors resulting in a decrease of intracellular c-AMP levels and diminshed functional responsiveness of cardiac β-receptors (20,21). Our data confirm that especially the β1 adrenergic receptors are downregulated which might explain the more equal expression of β1- and β2 receptors. These changes may be beneficial by protecting the heart from adrenergic overdrive. However at long term, donwregulation of receptors will incapacitate the ability of the heart to meet chronotropic demands at higher heart rates and may be responsible for lower exercise performance. Our data corroborate this postulate by demonstrating a blunted force-frequency relationship in patients referred to CRT. Though, adrenergic stimulation was associated with an acute upward shift of the LV dP/dtmax vs heart rate relationship early after the CRT implant, amplification of the force-frequency relation by β-adrenergic stimulation only occurred after four months CRT besides reverse LV remodeling. We hypothesize that the better contractile response to dobutamine may reflect the restored catecholamine sensitivity and adrenergic signaling due to reduction of the adrenergic drive after CRT. This hypothesis is supported by our observation of upregulation of gene expression of β1-adrenergic receptors levels and by recent findings indicating reduced muscle sympathetic nerve activity coinciding with reduced levels of catecholamines in responders to CRT (23). Finaly, the reduced wall stress induced by LV remodeling after chronic CRT

reduces the stretch-induced upregulation of BNP which beneficially affects LV remodeling. The downregulation of BNP gene expression further corroborates this hypothesis.

**Limitations.** First, the number of patients included in our study was relatively small but the effects of β-adrenergic stimulation at baseline and follow-up were consistent and each patient served as its own control. In addition, changes in hemodynamics were consistent with a uniform increase in β1-adrenergic receptor gene expression. Second, the number of non-responders was very low with only one patient finally needing a heart transplantation four weeks after CRT implantation. The high success rate of responders might be due to stringent selection criteria based upon the presence of significant mechanical dyssynchrony. Our group already reported that the degree of intra- and interventricular dyssynchrony are highly accurate to predict the functional response and reversed remodeling after cardiac resynchronization therapy (12). Third, concomitant therapy might have modified the hemodynamic effect. However, all patients were on optimal medical therapy for at least 4 months priort to CRT and except of lowering of diuretics, doses of ACE inhibitors and betablockers remained unchanged during the follow-up Fourth, LV dP/dtmax is also preload and afterload dependent. However, the reduction in LV volumes and increase in systolic blood pressure was uniform in all patients. In addition, no significant changes in LVEDP were noted during the incremental pacing protocol and rise in contractility at follow-up is therefore unlikely to be related to changes in preload (24). Fifth, though we clearly demonstrated improved expression of β1-adrenoreceptor and BNP, it is likely that many other established molecular markers of heart failure are participating in the complex process of tissue remodeling that need to be identified in studies using microarray analysis. Finally, only RNA analysis and no protein analyses were possible due to the small size of the LV biopsies. Nevertheless, an increase in β1-AR gene expression was clearly correlated with the observed improvement in contractile function and was concomitant with the observed functional improvement.

**f) Clinical Implications**

Congestive heart failure is associated with a variety of abnormalities of β-adrenergic receptors leading to chronotropic impairment as well as diminished myocardial contractility reserve during exercise. This study provides evidence that CRT is associated with a restoration of the FFR and upregulation of β1-adrenoreceptors together with improved

myocardial contractile reserve. These changes may contribute to improved exercise tolerance after four months of CRT

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**Table 1 A. Baseline patient characteristics**

| Patient | Bx | Age | Male Gender | Ischemic Etiology | ACE-i | BB | Loop Diur | Spiron | LVEF | LV dP/dtmax (mmHg/sec) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | y | 60 | n | n | y | y | y | y | 17 | 947 |
| 2 | n | 60 | y | y | y | y | y | y | 17 | 1460 |
| 3 | y | 74 | y | n | y | y | y | y | 22 | 865 |
| 4 | n | 67 | y | y | y | y | y | y | 17 | 880 |
| 5 | y | 54 | n | n | y | y | y | y | 19 | 996 |
| 6 | y | 64 | y | y | y | y | y | y | 23 | 860 |
| 7 | n | 53 | y | y | y | y | y | y | 14 | 910 |
| 8 | y | 75 | y | y | y | y | y | y | 27 | 874 |
| 9 | n | 53 | y | n | y | y | y | n | 21 | 909 |
| 10 | n | 75 | y | y | n | y | y | y | 20 | 1100 |
| **Overall** | **50%** | **64±10y** | **80%** | **60%** | **90%** | **100%** | **100%** | **90%** | **19±4%** | **980±184** |

**Table 1 B Baseline clinical and hemodynamic baseline and follow-up data.**

| | Baseline | Follow-up | p-value |
|---|---|---|---|
| **Electrocardiography** | | | |
| Heart rate (bpm) | 64 ±6 | 63 ±7 | ns |
| PR interval (msec) | 182 ±39 | 130 ±20 | 0.001 |
| QRS width (msec) | 179 ±11 | 146 ±19 | 0.01 |
| **Echocardiography** | | | |
| SBP (mm Hg) | 113 ± 15 | 133 ± 16 | 0.001 |
| LVEDV (ml) | 343 ± 81 | 228 ± 65 | 0.02 |
| LVEF (%) | 19 ± 4 | 34 ± 8 | 0.002 |
| Diastolic Filling Time (msec) | 329 ± 78 | 426 ± 103 | 0.05 |
| Mitral Regurgitation | 1.9 ± 1.1 | 0.4 ± 0.7 | < 0.001 |
| InterV Dyssynchrony (msec) | 68 ± 42 | 15 ± 12 | 0.02 |
| IntraV Dyssynchrony (msec) | 67 ± 30 | 32 ± 13 | 0.04 |
| Sum of Dyssynchrony (msec) | 136 ± 27 | 46 ± 22 | < 0.001 |
| **Clinical Characteristics** | | | |
| NT-ProBNP (pg/ml) | 6532 ± 1876 | 757 ± 320 | 0.001 |
| NYHA ≥ III (%) | 10 (100 %) | 1 (10%) | 0.002 |

**Table 2. LV end diastolic pressures during DDD-CRT pacing at baseline and follow-up before and during dobutamine infusion.**

| | Dobutamine - | | Dobutamine + | |
|---|---|---|---|---|
| **HR/LVEDP** | **BL-CRT** | **FU-CRT** | **BL-CRT** | **FU-CRT** |
| **70 bpm** | 13 ± 8 | 11 ± 6 | 16 ± 7 | 11 ± 6 |
| **90 bpm** | 14 ± 8 | 14 ± 8 | 16 ± 8 | 11 ± 8 |
| **110 bpm** | 18 ± 7 | 17 ± 8 | 21 ± 7 | 11 ± 5 |
| **130 bpm** | 19 ± 6 | 20 ± 4 | 21 ± 9 | 16 ± 6 |

**Figure 1. Force-frequency relationship during different pacing modes before and during dobutamine infusion at baseline and follow-up.**

Upper left panel indicates AAI BL vs CRT BL: significant increase in LV dP/dtmax for each heart rate during CRT BL ($p<0.01$) without any change in slope of the FFR.

Upper right panel indicates CRT BL before vs during dobutamine: significant increase in LV dP/dtmax for each heart rate during dobutamine infusion ($p<0.05$) with a trend toward a steeper slope of the FFR.

Lower left panel indicates CRT BL vs FU: significant increase in LV dP/dtmax for each heart rate during CRT FU ($p<0.05$) with an increase in slope of the FFR ($p=0.04$).

Lower right panel indicates CRT FU before vs during dobutamine infusion: significant increase in LV dP/dtmax for each heart rate during dobutamine infusion ($p<0.05$) with an increase in slope of the FFR ($p<0.05$).

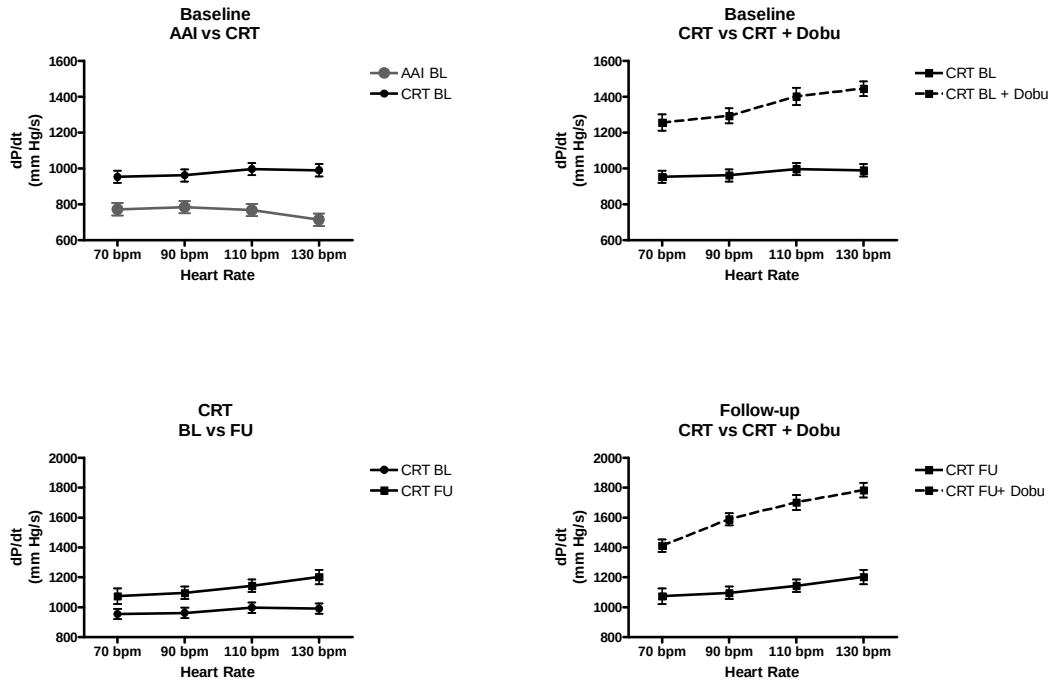


**Figure 2. Change (Δ) in LV dP/dtmax during dobutamine infusion at BL vs FU .**

Note the significantly more pronounced increase in Δ dP/dt at FU compared to BL at increasing heart rates indicated by the abcense of a significant slope at BL (ns) in contrast to FU (p=0.04).

There also is a significant difference in ΔLV dP/dtmax at each heart rate between BL and FU (* = p <0.05).

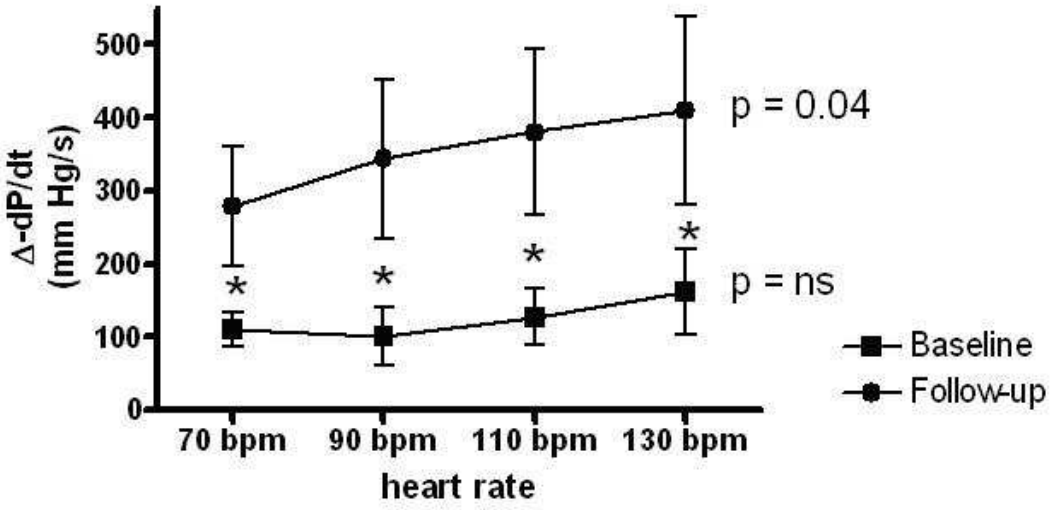
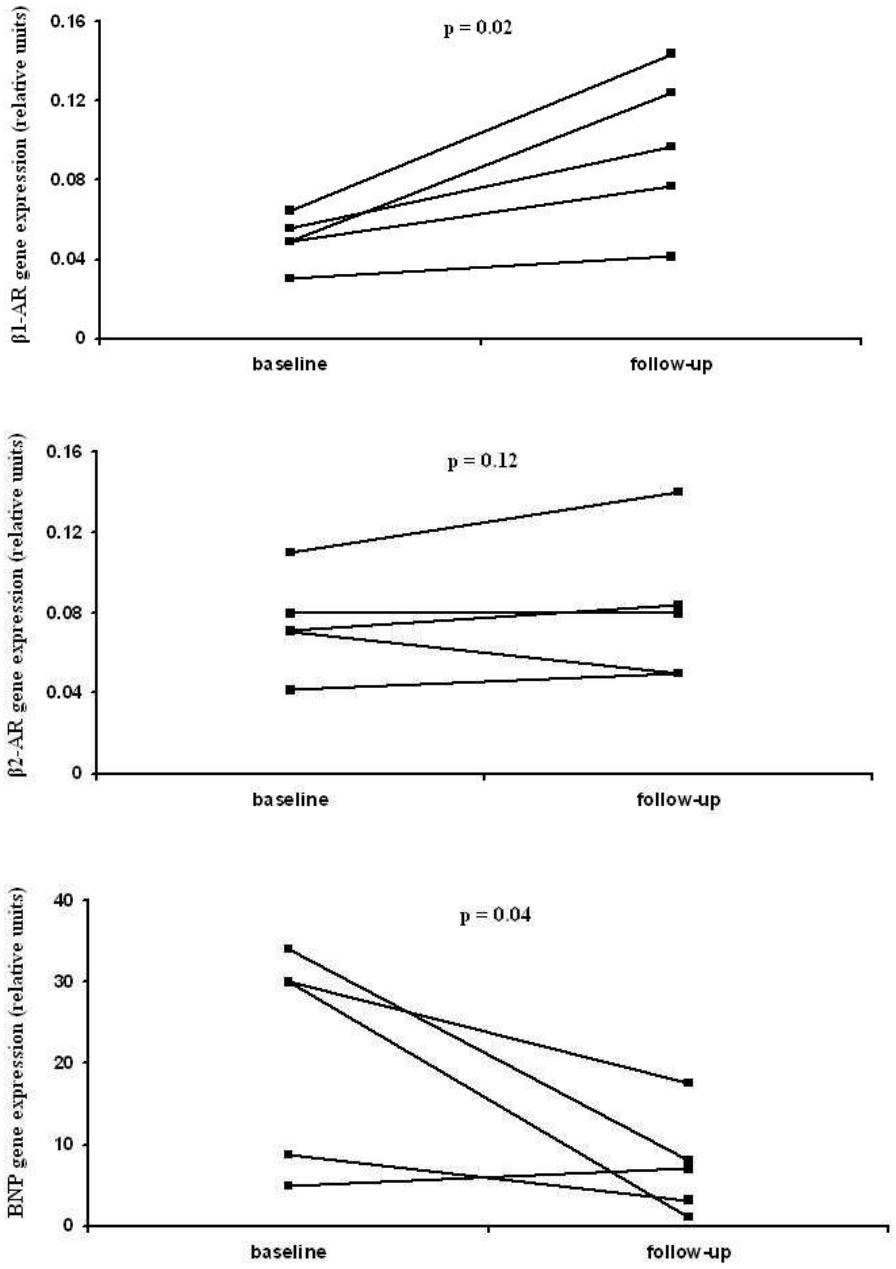


**Figure 3. Serial β1-, β2-adrenoreceptor and BNP gene expression levels (n=5).**

Note the significant changes in β1-adrenoreceptor and BNP gene expression.



## 3) Myocardial gene expression in heart failure patients treated with cardiac resynchronization therapy: responders versus non-responders

Vanderheyden M, Mullens W, Delrue L, Goethals M, De Bruyne B, Wijns W, Geelen P, Verstreken S, Wellens F, Bartunek J. Myocardial Gene Expression in Heart Failure Patients treated with Cardiac Resynchronization Therapy: Responders versus Non-responders. J Am Coll Card 2008;51:129-136.

### a) Abstract

**Introduction:** Cardiac resynchronization therapy (CRT) improves exercise tolerance and survival in patients with advanced congestive heart failure (CHF) and dyssynchrony. We studied whether functional improvement following CRT is associated with reversal of the heart failure gene program.

**Methods**: Twenty-four patients referred for CRT underwent left ventricular (LV) endomyocardial biopsies immediately before CRT implantation(BL). In addition, 17 out of them underwent LV endomyocardial biopsy procurement 4 months later(FU). In 6 control(C) patients with normal LV function, LV biopsies were obtained at the time of CABG. LV mRNA levels of contractile and calcium regulatory genes were measured by quantitative rt-PCR and normalized for GADPH. Heart failure patients showing an improvement in NYHA class by > 1 score and a relative increase in LV EF $\geq$ 25 % at 4 months after CRT were considered as responders.

**Results**: Heart failure patients were characterized by lower LV mRNA levels of $\alpha$-myosin heavy chain($\alpha$-MHC), $\beta$-myosin heavy chain($\beta$-MHC), sarcoplasmic reticulum calcium ATPase 2$\alpha$ (SERCA), phospholamban(PLN) and higher BNP mRNA levels as compared to C. Responders to CRT (n=11) showed an increase in LV ejection fraction($p<0.001$), a decrease in LVEDD($p=0.003$) and NYHA class($p=0.002$) and a reduction in Nt-proBNP levels($p=0.032$) as compared to BL. This was associated with an increase in mRNA levels of $\alpha$-MHC($p=0.035$), SERCA($p=0.032$), a decrease in BNP mRNA levels($p=0.002$) and an increase in the ratio of $\alpha$–/$\beta$-MHC($p=0.018$) and

SERCA/PLN(p=0.012). No significant changes in molecular profile were observed in non-responders.

**Conclusion:** In heart failure patients with electromechanical cardiac dyssynchrony, functional improvement related to cardiac resynchronization therapy is associated with favorable changes in established molecular markers of heart failure including genes that regulate contractile function and pathologic hypertrophy.

**b) Introduction**

The adverse left ventricular (LV) remodeling and the reduced contractile function observed in heart failure is associated with altered gene expression profile. One of the hallmarks of the altered molecular response is the activation of the "fetal" gene program including isoform switch in myosin heavy chain gene expression with downregulation of the fast α–myosin isoform(1,2,3) and upregulation of natriuretic peptides. Other molecular changes include alterations in expression of genes encoding excitation-contraction coupling such as sarcoplasmic reticulum calcium ATPase 2α (SERCA) and phospholamban (PLN). End-stage heart failure is associated with decreased levels of SERCA relative to PLN as well as reduced activity, resulting in impaired calcium cycling thereby accounting for the contractile deficit of the failing heart(4). These changes appear to represent basic molecular mechanisms underlying LV dysfunction and heart failure. Accordingly, it was postulated that clinical strategies should be designed to target these adverse molecular changes in order to effectively improve contractile performance of the failing myocardium(5).

Few clinical studies have addressed the reversibility of adverse molecular profile in human heart failure. In terminal heart failure, unloading with LV assist devices resulted in a decrease in cellular hypertrophy and fibrosis in parallel with de-activation of the "fetal" gene program and improvements in myocyte contractile properties and β-adrenergic responsiveness(6-9). In addition, in idiopathic dilated cardiomyopathy, functional improvement related to beta-blocker therapy was associated with an increase in SERCA and α-myosin heavy chain (α–MHC) mRNA together with a decrease in β-myosin heavy chain (β-MHC) mRNA (10).

Cardiac resynchronization therapy (CRT) acutely improves cardiac performance by restoring the coordination between left and right ventricles leading to improved mechanical efficiency in parallel with improved contraction and relaxation(11). These effects appear to be persistent over time and translate into a reversal of LV remodeling and improved clinical prognosis(12,13,14). However, alterations in the molecular fingerprint associated with this reversed remodeling have not been elucidated. Accordingly, we investigated whether functional improvement following CRT was associated with favorable changes in expression of established molecular structural and calcium regulatory markers of heart failure.

**c) Methods**

**Study Population:** The study population consisted of 24 consecutive NYHA III-IV patients undergoing CRT. Patients were studied the day before and 4 months after CRT implantation. All patients had to be on optimal stable medical therapy for at least three months and all cardiovascular medications, comprising ACE-I (n = 24), beta-blockers (n = 23), aldosterone antagonists (n = 20) and diuretics (n = 24) were continued during the study period. Only the dose of the loop diuretics was changed during FU. All patients were in sinus rhythm, had an LV ejection fraction < 35 %, left bundle branch block with QRS duration > 140 ms and significant mechanical dyssynchrony assessed by tissue Doppler echocardiography(15). All patients underwent LV endomyocardial biopsy sampling at baseline before CRT implantation. In 17 patients, LV endomyocardial biopsies were obtained at baseline and 4 months after CRT. The control group consisted of 6 patients with normal LV systolic and diastolic function undergoing elective CABG due to stable coronary artery disease. All patients gave informed consent and the study was approved by the institutional ethics committee.

**Biventricular Pacemaker Implantation:** Biventricular pacing (BVP) devices were implanted as previously described(16). The LV pacing electrode was positioned using a transvenous approach through the coronary sinus into the lateral or posterolateral cardiac vein**.** The device was programmed in biventricular-DDD mode with a fixed atrioventricular delay (115 ± 24 ms) optimized by echocardiography(17).

**Doppler Echocardiography.** Two-dimensional and Doppler echocardiography was performed (Acuson Sequoia C512, USA). Images were acquired in semi-supine position at rest by two experienced echocardiographers blinded by the moment of study examination. The following morphological and functional analyses were performed off-line from digitally-stored images: mitral regurgitation was assessed semi-quantitatively on a scale of 1 to 4(18), LV end-diastolic and end-systolic volumes, diameters and LV ejection fraction (EF) using the Simpson's formula(19).

In addition, pulsed-wave tissue Doppler imaging was used to assess interventricular and LV intraventricular dyssynchrony from regional time intervals between the onset of QRS complex and the onset of systolic myocardial velocity in basal segments of the left and right ventricle. LV dyssynchrony was defined as the maximum delay between basal LV segments. Interventricular dyssynchrony was assessed by comparison of the most delayed basal segment of the left ventricle with the right ventricle free wall delay(15,17).

**Endomyocardial biopsies:** LV endomyocardial biopsies were obtained using a long guiding sheath and a disposable transfemoral bioptome (Cordis Corporation, USA) at the level of the distal interventricular septum. Seventeen patients consented at the time of enrollment to undergo repeat biopsies after four months. Control LV endomyocardial biopsies (n=6) were obtained from the free LV wall at the time of CABG in patients with normal LV function prior to initiation of extracorporeal circulation. In all patients, biopsies were snap frozen in liquid nitrogen and stored at -80 $^{0}$C for subsequent RNA analyses.

**Brain natriuretic peptide:** Venous levels of NT-pro-BNP (Elecsys 2010 – Roche diagnostics, PmbH, 68298 Mannheim, Germany) were determined from blood samples collected the day before CRT implantation and 4 months later.

**Data analysis:** Four months after CRT, patients were divided into 2 groups according to their response to CRT. Responders were identified by a relative increase in EF of ≥ 25 % together with an improvement in NYHA class score > 1(15,20). LV gene expression of established molecular markers of heart failure was determined: among contractile/structural genes, LV mRNA levels of α–MHC, β-MHC and BNP and among calcium regulatory genes, SERCA and phospholamban were analyzed.

**Quantitative Real-time Reverse Transcriptase PCR (RT-PCR):** Highly sensitive RT-PCR was used for RNA quantifications as previously described(21). Briefly, total RNA was isolated from left ventricular endomyocardial biopsies using the RNeasy Fibrous Tissue Mini Kit (Qiagen) and DNase digested. RNA was reverse transcribed with random primers using the High-Capacity cDNA Archive Kit (Applied Biosystems). RT-PCR was performed in 96-well plates on the ABI Prism 7000 Sequence Detection System (ABI) using TaqMan Universal PCR Master Mix and Assays-On-Demand, with a final reaction volume of 25µl. PCR primers and FAM probes for all of the target genes were purchased as Assays-On-Demand (Applied Biosystems). The assay numbers for the target genes were Hs01564008_m1, Hs00160179_m1, Hs00411899_m1, Hs01110632_m1 and Hs00173590_m1 for SERCA, PLN, α–MHC, β-MHC and BNP respectively. Human GAPDH gene was used as endogenous control (Applied Biosystems). All samples were performed in triplicate. The relative expression of the target genes was normalized to the level of GAPDH in the same cDNA

**Statistical Analysis:** Data are expressed as mean ± SEM or as median. An exact Wilcoxon signed-rank test, a Mann-Whitney test and a Spearman correlation coefficient were used for appropriate comparisons. A p value of $< 0.05$ was considered significant for comparisons and correlations.

**d) Results**

**Baseline Characteristics.** Table 1 shows baseline clinical characteristics. All patients had severe LV dysfunction,, significant intra- and interventricular dyssynchrony and severe LV dilatation. All were in NYHA class $\geq 3$ heart failure. Heart failure was due to ischemic heart disease in 13 patients and idiopathic dilated cardiomyopathy in 11 patients. All patients were on optimal medical therapy that remained unchanged at follow-up. All control patients had normal LV function with stable coronary artery disease, none of them had a history of acute coronary syndrome.

**Baseline LV Endomyocardial Gene Expression: Heart Failure Patients vs Control Population.** Table 2 shows LV gene expression of the entire study population. No infiltrative or inflammatory processes were identified at diagnostic histopathological analysis. As expected, heart failure patients showed lower levels of mRNA for SERCA,

phospholamban, α-myosin and β-myosin heavy chain and higher levels of BNP mRNA compared to controls. The ratio of SERCA to phospholamban was significantly lower in the heart failure patients compared to the control group. No differences in myocardial gene expression were noted between patients with ischemic and non-ischemic dilated cardiomyopathy (data not shown). In the entire study population, LV EF was inversely related to BNP mRNA ($r = -0.615$; $p = 0.003$) and directly related to SERCA mRNA ($r = 0.660$; $p = 0.001$).

**Effects of CRT on Ventricular Function and Myocardial Gene Expression.** Table 3 shows serial changes in echocardiographic indices and myocardial gene expression in 17 heart failure patients undergoing serial LV biopsies. CRT overall resulted in a significant increase in LV EF together with a decrease in LV dimensions and volumes. This was associated with a reduction in mitral regurgitation, cardiac dyssynchrony and serum Nt-proBNP levels. Consequently, NYHA class decreased in all but 4 patients. In the entire patient population, LV BNP mRNA levels significantly decreased 4 months after CRT, while no significant changes were observed in the expression of contractile or $Ca^{2+}$ regulating genes.

**Myocardial Gene Expression in Responders vs Non-responders to CRT.** Table 4 and figure 1 summarize the effects of CRT upon LV function and gene expression in responders vs. non-responders. By definition responders were identified by a relative increase in EF of ≥ 25 % together with an improvement in NYHA class score > 1(15,20). At baseline, responders and non-responders had similar LV EF and volumes. Non-responders tended to have lower LV dyssynchrony and mitral regurgitation but more significant interventricular dyssynchrony and larger LV volumes compared to responders. At follow-up, responders showed a greater increase in LV ejection fraction and a greater reduction in LV end-diastolic dimensions and volume whereas LV and interventricular dyssynchrony were reduced to a similar extent in both groups. Serum Nt-proBNP levels decreased significantly in responders and remained unchanged in non-responders.

At baseline, LV mRNA levels PLN and β-MHC were similar between responders and non-responders. There was a non significant trend towards lower SERCA and α–MHC gene expression and higher BNP gene expression in responders vs. non-responders. At follow-up a significant increase in mRNA of α-myosin and in the ratio of

α/β-myosin heavy chain was noted in responders in parallel to a reduction in mRNA levels of BNP. The α/β-myosin heavy chain ratio was significantly higher in responders vs. non-responders ($p<0.05$). In responders, LV SERCA message levels increased together with the SERCA/PLN ratio. In contrast, no significant changes in gene expression were noted in non-responders.

**Variability of gene expression.** In 3 patients biopsy samples from different sites of the left ventricular were used. In these patients the variability of SERCA, PLN, BNP, β-MHC and α-MHC mRNA concentrations were 10 ± 4 %, 12 ± 3 %, 33 ± 6 %, 12 ± 5 % and 18 ± 5 % respectively.

**e) Discussion**

The present study is the first to investigate the effects of CRT on established molecular structural and calcium regulatory markers of heart failure in human subjects. Our findings demonstrate that the beneficial effects of CRT on LV function and remodeling are associated with "reversed molecular remodeling" characterized by an increase in expression of genes regulating excitation-contraction coupling and a reversal of the isoform switching of the contractile genes. These data suggest that gene expression profile in human heart failure patients, on optimal medical therapy with ACE-I, BB and spironolactone, is at least partially reversible and that molecular changes in structural and functional proteins may contribute to favorable effects of CRT on myocardial performance.

**Heart failure and myocardial gene expression.** Activation of so-called "fetal gene program" is the best described myocardial molecular alteration relevant to the pathophysiology of heart failure. It is characterized by isoform switching in the expression of genes regulating contractile proteins and the down-regulation of genes regulating excitation-contraction coupling(22,23). Though an altered molecular profile is part of an adaptive response to persistent mechanical overload, changes in contractile proteins are responsible for depressed performance and contribute to further negative LV remodeling and failure. This is corroborated by single cardiac myocytes or isolated heart experiments showing negative inotropic effects secondary to increased expression of the slow β-myosin heavy chain isoform(24,25). Accordingly, it was postulated that only

those therapeutic strategies that interfere with or reverse these molecular changes will result in an effective functional improvement and survival benefit in congestive heart failure patients (5, 26). This postulate is supported by experimental studies demonstrating improved contractility after adenoviral gene transfer of SERCA in animal models of heart failure or failing human cardiac myocytes(27,28). Likewise, increased SERCA levels relative to PLN mRNA levels were associated with improved SERCA mediated $Ca^{2+}$ sequestration and enhanced systolic function(4,29).

**CRT and myocardial gene expression.** CRT is associated with improved performance and survival in patients with advanced heart failure and electromechanical dyssynchrony(11,13,30). Nevertheless, ~ 1/3 of these patients do not exhibit any benefit from this therapy. We hypothesized that reversed LV remodeling and improved myocardial performance in patients undergoing resynchronization therapy was associated with changes in established molecular structural and calcium regulatory markers of heart failure. As expected, prior to CRT, heart failure patients showed altered expression of genes that regulate $Ca^{2+}$ handling and contractile proteins as compared to controls. Of note, in the entire population, CRT was not associated with changes in gene expression of these proteins. Only the subgroup of patients with improved LV function, reversed LV remodeling and reduction in NYHA class, categorized as responders to CRT, did demonstrate an increase in expression of the fast α-myosin heavy chain and an increase of the α-myosin to β-myosin heavy chain mRNA ratio. Moreover, in these responders, improved myocardial performance was associated with a significant increase in LV SERCA mRNA levels and in the SERCA/PLN ratio as compared to baseline. In contrast, the absence of LV remodeling and functional beneficial effects of CRT in non-responders was associated with no changes in the gene profile of the structural or calcium regulatory proteins. Furthermore, the significant reduction of serum Nt-proBNP levels in all patients was paralleled by a significant down-regulation of myocardial BNP gene expression only in the responders. Our observations are consistent with experimental studies demonstrating beneficial effects of molecular intervention on myocardial performance(27,28). In addition, they corroborate previous observations demonstrating increased expression of fast α-myosin isoform or calcium handling proteins following beta-blocker therapy or LV unloading with assist devices(6,10). Taken together, these

observations support the postulate that interventional therapies in heart failure could lead to sustained functional and clinical improvement only if they will efficiently alter adverse molecular remodeling.

Interestingly, we noticed a trend towards higher mRNA expression of α-MHC and SERCA in the non-responders at baseline as compared to responders indicating that despite a similar degree of LV dysfunction, dyssynchrony or clinical heart failure class, non-responders had paradoxically a better, “more favourable”, molecular profile of established structural and calcium regulatory markers at baseline as compared to responders. This seems to implicate that these patients were less sick in terms of “the molecular remodeling”, and therefore, less prone to improve after CRT. In addition, this indirectly suggests that the current selection criteria based on clinical, electrocardiograhic and echocardiographic derived parameters are not sufficient enough to predict the individual response to CRT. We speculate that baseline gene expression profiling might be a new and more accurate tool in predicting the response to CRT therapy. Further studies using large scale microarray profiling are needed to address this hypothesis and identify novel molecular markers predictive of reversed remodeling after CRT.

Our study, similar to previous clinical reports on the effects of beta-blocker therapy(10), does not allow to address causative or mechanistic relationship between LV remodeling after CRT and molecular changes. Nevertheless, LV dyssynchrony and increased neurohormonal activation are associated with downregulation of contractile regulating genes (31,32,33,34). A more synchronous contraction together with the reduction of muscle sympathetic nerve activity coinciding with reduced levels of catecholamines in responders to CRT(35) may thus account for the observed molecular changes. Alternatively, the reduced wall stress induced by LV remodeling after chronic CRT reduces the stretch-induced upregulation of BNP which beneficially affects LV remodeling. This hypothesis is supported by our observation of inverse relationship between BNP and EF and positive correlation between SERCA and EF and previous report on BNP-mediated reduction in SERCA gene expression indirectly supports this hypothesis(31). To which extent the restoration of synchrony, LV remodeling and reduced neurohormonal activation contribute to the observed molecular remodeling requires further investigation. Experimental studies with serial endomyocardial biopsies

could unravel the time- and spatial-myocardial relationship of relevant molecular changes and further elucidate causative mechanisms underlying CRT-induced molecular changes.

**Limitations.** First, LV dyssynchrony generates alterations in transmural and transchamber protein expression, which are most prominent in the late-activated high stress lateral endocardium(32) and may cause differences in regional gene expression(33). To limit the impact of regional differences, LV biopsies were obtained from the apicoseptal regions in all patients at baseline and at follow-up. Furthermore, multiple biopsies were procured from various LV sites in 3 patients. In these patients, the variability in SERCA, PLN, α-myosin heavy chain, β-myosin heavy chain and BNP mRNA levels in the different biopsies were minimal. Thus, in the current study, gene expression data appear to reflect global rather than local changes related to LV remodeling. Second, the underlying etiology of heart failure may affect the molecular response to CRT. Though our study may be underpowered to compare smaller subgroups, no difference in gene expression was noted between heart failure patients with ischemic versus idiopathic dilated cardiomyopathy**.** In addition, the variability was limited by performing paired comparisons in samples from the same individuals. Third, as being the case in a typical CRT study, the dose of diuretics was different before and during CRT. On the other hand, the dose of beta-blocker and angiotensin converting enzyme inhibitor therapy remained unchanged and there were no differences in heart failure medication between responders and non-responders excluding potential drug effects on remodeling. Fourth, only RNA analysis and no protein analyses or functional activity studies of calcium handling genes were possible due to the small size of the LV biopsies. In this regard, it should be noted that the relationship between transcriptional and translational changes in SERCA expression is controversial. Nevertheless, an increase in SERCA gene expression was concomitant with the functional improvement in responders suggesting that the increase in SERCA message was functionally meaningful. Fifth, although GADPH is generally accepted as a very reliable housekeeping gene, we do admit that doing the whole procedure again with another housekeeping gene could add some incremental value to the study and compensate for variability in the gene expression of the housekeeping itself. However lack of tissue samples made this impossible. Finally, though we clearly demonstrated improved expression of the most established molecular

markers of heart failure it is likely that many other relevant genes are participating in the complext tissue remodeling and need to be identified in studies using microarray analysis.

**e) Conclusions**

In congestive heart failure patients responding to CRT, an improvement in LV function and reduction in NYHA class are associated with "reversed molecular remodeling", characterized by increased expression of contractile and calcium regulatory proteins. This suggests that reversed "molecular remodeling" might be the key mechanism contributing to sustained improvement in LV function and survival after CRT.

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**Legends**

**Figure 1**

**LV endomyocardial expression of functional and contractile genes at baseline (white bar) and at 4 month follow-up (black bar) in responders and non-responders.**

Data are normalized for GADPH and expressed as relative units. SERCA - sarcoplasmic reticulum calcium ATPase 2α, PLN – Phospholamban, α-MHC – α-myosin heavy chain, β-MHC – β-myosin heavy chain, BNP – brain natriuretic peptide

**Figure 2**

**LV endomyocardial gene expression of BNP gene at baseline (white bar) and at 4 month follow-up (black bar) in responders and non-responders.**

Data are normalized for GADPH and expressed as relative units. BNP – brain natriuretic peptide

**Table 1. Baseline characteristics of the control and heart failure patients**

| VARIABLE | CONTROL (n = 6) | CRT (n = 24) | p- value |
|---|---|---|---|
| **Clinical Characteristics** | | | |
| Age (years) | 61 ± 5 | 68 ± 2 | ns |
| Sex (% Male) | 6(100) | 21(87) | ns |
| Etiology (% Ischemic CMP) | 6 (100) | 13 (55) | |
| NYHA functional class (no of pts) | | | |
| NYHA III | n.a | 8 | < 0.001 |
| NYHA IV | n.a | 16 | < 0.001 |
| ICD implantation (%) | n.a | 6 (25) | |
| **Hemodynamic Parameters** | | | |
| LVEDD (mm) | 51 ± 3 | 66 ± 3 | 0.004 |
| LVEDV (ml) | 158 ± 27 | 315 ± 29 | 0.018 |
| EF (%) | 72 ± 4 | 25 ± 2 | < 0.001 |
| LV dyssyn (ms) | n.a. | 55 ± 7 | |
| InterV dyssyn (ms) | n.a. | 57 ± 7 | |
| **Medical Therapy (%)** | | | |
| Beta-blockers | 3 (50) | 23 (95) | < 0.001 |
| ACEI | 0 (0) | 24 (100) | < 0.001 |
| Loop Diuretics | 0 (0) | 24 (100) | < 0.001 |
| Spironolactone | 0 (0) | 20 (85) | < 0.001 |

LVEDD - left ventricular end diastolic diameter, LVEDV - left ventricular end diastolic volume, EF - ejection fraction, LV Dyssyn - left intraventricular dyssynchrony, InterV Dyssyn - interventricular dyssynchrony, ACEI - angiotensin-converting enzyme inhibitors, CABG - coronary artery bypass grafting, CAD - coronary artery disease, ICD - implantable cardioverter-defibrillator, ns – not significant, n.a - not applicable

**Table 2: Baseline mRNA expression of the control and heart failure patients. Data are normalized for GADPH and expressed as relative units.**

| **Gene Expression (relative units)** | **Controls (n = 6)** | **Heart Failure (n = 24)** | **p – value** |
|---|---|---|---|
| **SERCA (median, 25%-75%)** | 4.08 ± 1.34 (2.76; 1.83-7.63) | 1.47 ± 0.15 (1.27; 0.97-1.57) | 0.002 |
| **PLN (median, 25%-75%)** | 11.65 ± 2.02 (10.87; 7.29-16.99) | 6.47 ± 0.53 (6.06; 4.69-7.94) | 0.002 |
| **α-MHC (median, 25%-75%)** | 2.22 ± 0.51 (2.17; 0.99-3.48) | 1.12 ± 0.21 (0.73; 0.40-1.50) | 0.037 |
| **β-MHC (median, 25%-75%)** | 66.02 ± 16.69 (57.90; 37.66-108.50) | 32.58 ± 3.46 (29.24;22.78-40.93) | 0.005 |
| **BNP (median, 25%-75%)** | 0.13 ± 0.06 (0.08; 0.01-0.30) | 13.18 ± 2.60 (8.75; 2.39-22.16) | 0.014 |

SERCA - sarcoplasmic reticulum calcium ATPase 2α, PLN - Phospholamban, α-MHC - α-myosin heavy chain, β-MHC - β-myosin heavy chain, BNP - brain natriuretic peptide

**Table 3. Serial LV endomyocardial mRNA expression, echocardiographic and functional characteristics at baseline and at 4 months follow-up in the CRT population (responders + non-responders).** Data are normalized for GADPH and expressed as relative units.

| | **Baseline (n = 17)** | **Follow-up (n = 17)** | **p – value FU vs BL** |
|---|---|---|---|
| **Hemodynamics** | | | |
| EF | 24 ± 1 | 39 ± 2 | < 0.001 |
| LVEDD (mm) | 68 ± 3 | 63 ± 4 | 0.014 |
| LVEDV (ml) | 291 ± 24 | 183 ± 17 | < 0.001 |
| LV dyssyn (ms) | 53 ± 6 | 27 ± 3 | 0.001 |
| InterV dyssyn (ms) | 64 ± 9 | 17 ± 3 | < 0.001 |
| MR grade > 2 (%) | 75 | 25 | < 0.001 |
| **Functional** | | | |
| NYHA class | 3.4 ± 0.1 | 2.6 ± 0.1 | 0.001 |
| Nt-proBNP (pg/ml) | 2897 ± 495 | 1480 ± 303 | 0.003 |
| **Gene expression** | | | |
| **SERCA (units)** | 1.392 ± 0.16 | 1.54 ± 0.12 | Ns |
| **PLN (units)** | 6.56 ± 0.38 | 6.75 ± 0.40 | Ns |
| **SERCA/PLN** | 0.21 ± 0.02 | 0.23 ± 0.02 | Ns |
| **α-MHC (units)** | 1.01 ± 0.21 | 1.28 ± 0.4 | Ns |
| **β-MHC (units)** | 33.60 ± 2.33 | 31.72 ± 2.99 | Ns |
| **α/β-MHC** | 0.03 ± 0.01 | 0.04 ± 0.01 | Ns |
| **BNP (units)** | 16.77 ± 3.07 | 6.09 ± 1.27 | 0.005 |

SERCA - sarcoplasmic reticulum calcium ATPase 2α, PLN - Phospholamban, α-MHC - α-myosin heavy chain, β-MHC - β-myosin heavy chain, BNP - brain natriuretic peptide, EF - ejection fraction, LVEDD - left ventricular enddiastolic diameter, LVEDV - left ventricular enddiastolic volume, LV Dyssyn - left intraventricular dyssynchrony, InterV Dyssyn - interventricular dyssynchrony, MR - mitral regurgitation, ns = not significant

**Table 4. Serial LV endomyocardial mRNA expression, echocardiographic and functional characteristics at baseline and at 4 months follow-up in responders and non-responders to CRT.** Gene expression data are normalized for GADPH and expressed as relative units.

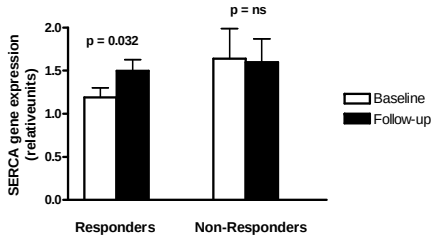
| | **Responders (n =11)** | | | **Non-responders (n = 6)** | | |
|---|---|---|---|---|---|---|
| | **Baseline (BL)** | **Follow-up (FU)** | **p-value BL vs FU** | **Baseline (BL)** | **Follow-up (FU)** | **p-value BL vs FU** |
| **Hemodynamics** | | | | | | |
| EF (%) | 23 ± 1 | 35 ± 3 | < 0.001 | 20 ± 3 | 23 ± 1[#] | 0.004 |
| LVEDD (mm) | 68 ± 4 | 61 ± 4 | 0.003 | 71 ± 4 | 69 ± 4 | 0.056 |
| LVEDV (ml) | 290 ± 26 | 191 ± 21 | < 0.001 | 343 ± 69 | 304 ± 56[#] | 0.070 |
| LV dyssyn (ms) | 69 ± 9 | 28 ± 3 | 0.002 | 40 ± 4 | 27 ± 6 | 0.154 |
| InterV dyssyn (ms) | 61 ± 10 | 18 ± 5 | 0.003 | 79 ± 17 | 14 ± 4 | 0.013 |
| MR grade > 2 (%) | 36 | 0 | 0.010 | 14 | 1 | 0.034 |
| **Functional** | | | | | | |
| NYHA class | 3.4 ± .5 | 2.3 ± 0.5 | 0.00210 | 3.4 ± 0.5 | 3.1 ± 0.4[$$] | ns |
| Nt-proBNP (pg/ml) | 3334 ± 692 | 1634 ± 322 | 0.032 | 2230 ± 703 | 1153 ± 1012 | ns |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Gene Expression** | | | | | | |
| SERCA (units) | 1.19 ± 0.11 | 1.50 ± 0.13 | 0.032 | 1.64 ± 0.35 | 1.60 ± 0.27 | ns |
| PLN (units) | 6.28 ± 0.46 | 6.4 ± 0.56 | ns | 6.70 ± 0.68 | 7.41 ± 0.46[#] | ns |
| SERCA/PLN | 0.19 ± 0.01 | 0.24 ± 0.02 | 0.012 | 0.23 ± 0.03 | 0.22 ± 0.04 | ns |
| α-MHC (units) | 0.69 ± 0.10 | 1.14 ± 0.26 | 0.035 | 1.40 ± 0.48 | 1.52 ± 1.13 | ns |
| β-MHC (units) | 32.29 ± 2.99 | 28.67 ± 3.80 | ns | 32.55 ± 4.73 | 37.32 ± 4.26 | ns |
| α– /β–MHC | 0.021 ± 0.005 | 0.044 ± 0.008 | 0.018 | 0.041 ± 0.010[$] | 0.040 ± 0.030[#] | ns |
| BNP (units) | 19.76 ± 3.33 | 6.79 ± 1.27 | 0.002 | 10.65 ± 5.08 | 4.79 ± 2.86 | ns |

SERCA - sarcoplasmic reticulum calcium ATPase 2α, PLN – Phospholamban, α-MHC – α-myosin heavy chain, β-MHC – β-myosin heavy chain, BNP – brain natriuretic peptide, EF – ejection fraction, LVEDD – left ventricular enddiastolic diameter, LVEDV – left ventricular enddiastolic volume, LV Dyssyn – left intraventricular dyssynchrony, InterV Dyssyn – interventricular dyssynchrony, MR – mitral regurgitation

[#] = $p < 0.05$ FU non-responders vs responders, [$] = $p < 0.05$ BL non responders vs responders, [$$] = $p < 0.01$ FU non responders vs responders, ns = not significant. The relative expression of the individual genes is normalized to the level of GADPH

# Figure 1


SERCA gene expression (relativeunits)
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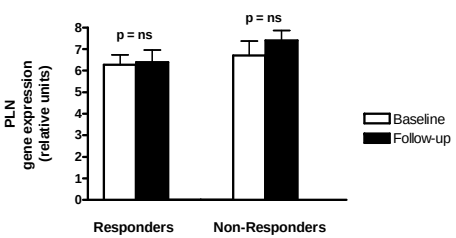
1.5
1.0
0.5
0.0
p = 0.032
p = ns
Responders
Non-Responders
Baseline
Follow-up


PLN gene expression (relative units)
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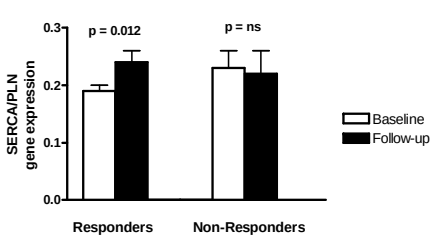
7
6
5
4
3
2
1
0
p = ns
p = ns
Responders
Non-Responders
Baseline
Follow-up


SERCA/PLN gene expression
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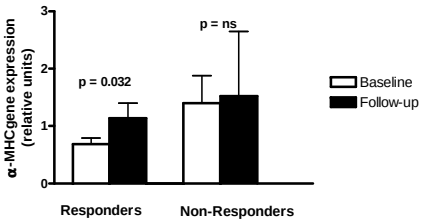
0.2
0.1
0.0
p = 0.012
p = ns
Responders
Non-Responders
Baseline
Follow-up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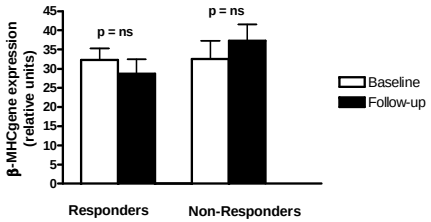
2
1
0
p = 0.032
p = ns
Responders
Non-Responders
Baseline
Follow-up


β-MHCgene expression (relative units)
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35
30
25
20
15
10
5
0
p = ns
p = ns
Responders
Non-Responders
Baseline
Follow-up

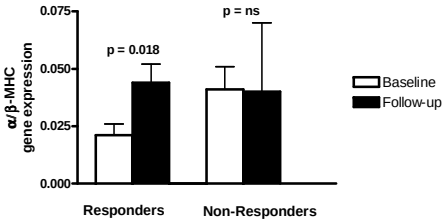
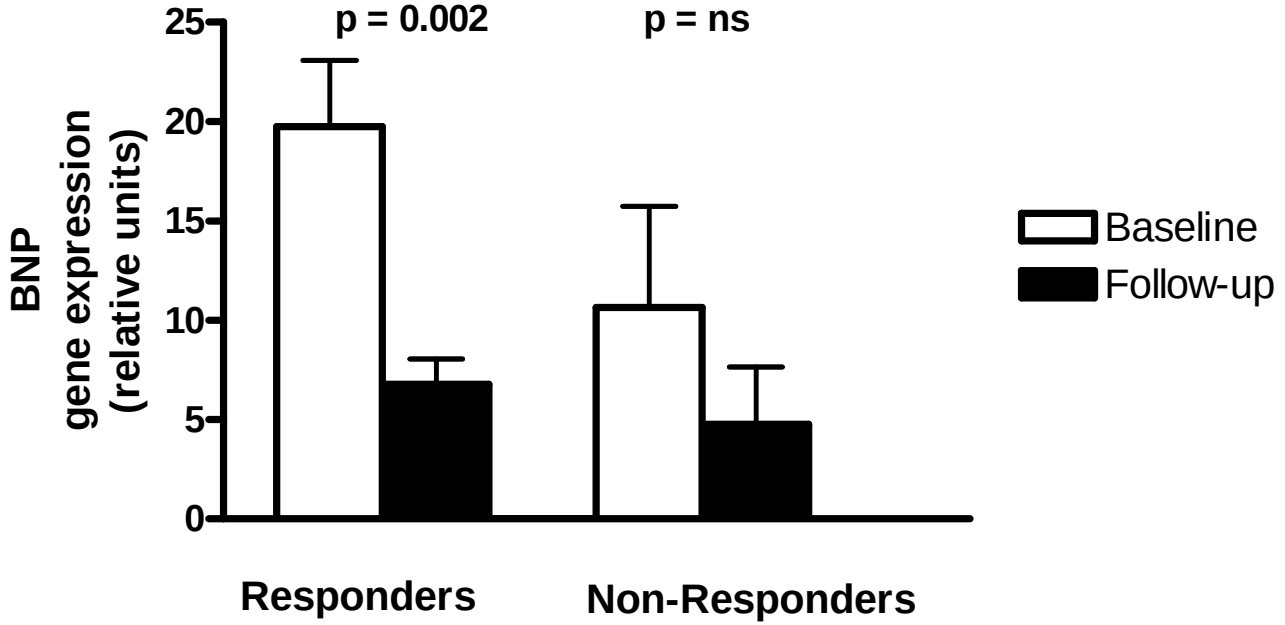

α/β-MHC gene expression
0.075
0.050
0.025
0.000
p = 0.018
p = ns
Responders
Non-Responders
Baseline
Follow-up

**Figure 2**


p = 0.002
p = ns
25
20
15
10
5
0
BNP
gene expression
(relative units)
Baseline
Follow-up
Responders
Non-Responders

## 4) Persistent hemodynamic benefits of cardiac resynchronization therapy with disease progression in advanced heart failure

Mullens W, Verga T, Grimm R, Starling R, B Wilkoff, Tang W. Persistent Hemodynamic Benefits of Cardiac Resynchronization Therapy with Disease Progression in Advanced Heart Failure. J Am Coll Card 2009;53:589-596.

### a) Abstract

**Background**: Cardiac resynchronization therapy (CRT) restores synchrony of the heart resulting in hemodynamic support that can facilitate the reversal of left ventricular (LV) remodeling. However, as with any effective therapy for patients responses are often heterogeneous and ventricular function may not improve or even deteriorate after intervention.

**Objectives:** To determine the potential hemodynamic contributions of CRT in patients admitted for advanced decompensated heart failure (ADHF).

**Methods:** A total of 40 consecutive patients admitted with ADHF and CRT implanted >3 months, admitted due to hemodynamic derangements, underwent simultaneous comprehensive echocardiographic and invasive hemodynamic evaluation under different CRT settings.

**Results:** All patients (mean LV ejection fraction 22±7%, LV end-diastolic volume 323±140 ml, 40% ischemic) had experienced progressive cardiac remodeling despite adequate LV lead positions and continuous biventricular pacing. A significant worsening of hemodynamics was observed immediately when CRT was programmed OFF in the majority (92%) of patients (systolic blood pressure: 105±12 to 98±13 mmHg; pulmonary capillary wedge pressure: 17±6 to 21±7 mmHg; cardiac output: 4.6±1.4 to 4.0±1.1 l/min.$m^2$; all $p<0.001$). Worsening of hemodynamics coincided with re-appearance of significant electrical (QRS width 161±29 to 202±39 ms, $p<0.001$) and intra-ventricular mechanical dyssynchrony (15±26 to 57±41 ms, $p<0.001$), together with a significant reduction in diastolic filling time (377±138 to 300±118 ms, $p<0.001$).

**Conclusion:** Despite progressive cardiac remodeling and decompensation, chronic CRT continues to provide hemodynamic augmentation in the failing heart in most patients.

Our data suggest that disease progression may not be explained by diminished beneficial hemodynamic contributions of successful resynchronization.

**b) Introduction**

Cardiac resynchronization therapy (CRT) restores the coordination of contraction and relaxation among cardiac chambers, leading to a better survival in patients with advanced heart failure and evidence of ventricular conduction delay (1-3). The primary contribution of CRT is thought to be the restoration of hemodynamic support from a coordinated heart that might facilitate the reversal of pathophysiologic processes. While the extent of hemodynamic improvement is only an indicator of early response, reversal of basal dyssynchrony by CRT has proven to be a better indicator of chronic response and cardiac remodeling (reduction in left ventricular [LV] volumes, and improvement in LV ejection fraction) (4-9). However, as with any effective therapy for patients responses are often heterogeneous and patients may not see any improvement in clinical status and/or reversal of cardiac remodeling after 3-6 months of CRT (2,10-13). Therefore, one might postulate that "non-responders" may experience a diminished hemodynamic benefit by CRT over time. Although discordance between clinical and echocardiographic response to CRT has been observed in prior studies, the degree of hemodynamic response in the absence of a robust echocardiographic remodeling to long-term CRT have not been explored (14). Herein, we aim to examine the contributions of biventricular pacing to the clinical, hemodynamic, and echocardiographic profiles of patients admitted with advanced heart failure and evidence of disease progression despite long-term CRT therapy.

**c) Methods**

**Study population.** We prospectively enrolled forty consecutive patients who had received a CRT plus defibrillator device for at least 3 months, and were subsequently admitted to the Cleveland Clinic heart failure intensive care unit between October 1, 2007, and February 20, 2008, due to hemodynamic compromise. The CRT-device was always implanted because of stable but advanced heart failure (New York Heart Association class III or IV) despite optimal medical therapy, including angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker, beta-blocking agent and spironolactone for at

least three months, a depressed left ventricular ejection fraction (≦35%), and prolonged QRS duration (≧120 ms). Exclusion criteria included: 1) patients on artificial ventilation; and 2) status post cardiac transplantation or congenital heart disease. The Cleveland Clinic Institutional Review Board approved this research project, which is part of the standard clinical evaluation tailored for patients admitted to our heart failure intensive care unit.

**CRT optimization protocol.** Data reported were collected during a CRT optimization protocol as part of standard evaluation within 24 hours of admission to the heart failure intensive care unit. Briefly, an electrocardiogram and anterior-posterior and lateral chest X-ray were performed to ensure biventricular pacing and adequate positions of the right atrial, right ventricular and left ventricular leads (basal or mid lateral / posterior position). A comprehensive device interrogation was then performed including assessment of battery status, lead impedances and thresholds, heart rate and activity histograms, percentage of atrial and ventricular pacing, and presence of atrial and ventricular tachyarrhythmias.

Hemodynamic and echocardiographic data were then simultaneously collected with nominal settings of the CRT device ("CRT-ON"). Next, the CRT device was programmed into a non-functional pacing mode (VVI, backup 40 bpm) for 10 minutes, after which collection of hemodynamic and echocardiographic data were repeated ("CRT-OFF"). No changes in intensive medical therapy were made during the entire pacing protocol. If the patient had no underlying atrial rhythm or a total atrio-ventricular nodal block, the pacemaker could be programmed in an AAI or DDD mode respectively, at similar heart rates as the nominal settings (only 2 patients of study population, one in AAI and one in DDD). After completion, the device was re-programmed in a CRT mode and the AV-interval was optimized using conventional Doppler echocardiography (15,16). The optimal AV-interval was assessed by pulsed wave Doppler at the mitral valve leaflet tips and corresponded to the shortest AV-interval that dissociated the E and A wave but did not interrupt the end of the A wave (15,16). Afterwards, patients were scheduled for long-term clinical follow-ups and device checks. Appropriate actions would be taken, such as identifying cases of inadequate lead position, inappropriate device programming, arrhythmias, or improvement of hemodynamics in those with CRT-OFF.

**Hemodynamic evaluation.** Hemodynamic data, including systemic blood pressure, central venous pressure (CVP), pulmonary artery pressures, and pulmonary capillary wedge pressure (PCWP, wedge position was verified by fluoroscopy and phasic changes in pressure waveforms), represent the average of 5 cycles, and with balanced transducers (0 level at the mid-axillary line). The CVP, pulmonary artery pressures and PCWP were assessed at end-expiration with a balloon-tipped catheter at steady state with the patient in a supine position by an investigator unaware of the echocardiographic measurements. Cardiac output (CO) was determined using the Fick equation through averaging of two samples of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. Systemic blood pressures were measured non-invasively by an automatic cuff sphygmomanometer at scheduled intervals.

**Transthoracic echocardiography.** A comprehensive two-dimensional echocardiographic exam was performed with a commercially available system (Vingmed, System VII, General Electric, USA) by a cardiologist highly experienced in echocardiography. Images were acquired in the left lateral decubitus position using a phased array transducer in the standard parasternal and apical views. Standard two-dimensional and Doppler data, triggered to the QRS complex, were digitally stored in a cine-loop format. Individuals experienced with echocardiographic measurements without prior knowledge of clinical or hemodynamic data performed the analysis off-line.

All reported echocardiographic measurements were averaged from at least three consecutive cycles. LV volumes, LV ejection fraction, diastolic filling parameters (mitral E, deceleration time, diastolic filling time, Q-A time), trans-mitral, and LV outflow velocity time integral were assessed as recommended by the American Society of Echocardiography (17). Inter-ventricular mechanical dyssynchrony was assessed as the difference between the pre-ejection intervals from QRS onset to the beginning of ventricular ejection at the pulmonary and aortic valve levels using pulsed-wave Doppler (1,2). Intra-ventricular mechanical dyssynchrony was assessed from regional time intervals between the onset of the QRS complex to the peak of the systolic myocardial velocity (Ts) in four basal segments of the left ventricle (septal, lateral, antero-septal, posterior) using color Tissue-Doppler Imaging (7).

**Statistical Analysis.** All data were expressed as mean ±SD for continuous data (median and inter-quartile range for non-parametric data), and as a ratio for categorical data. Univariate comparisons of these variables were performed between the same patients with CRT-ON and CRT-OFF, using SPSS for Windows, release 13.0 (SPSS Inc., Chicago, Illinois). A paired t-test for continuous data was used for appropriate comparisons. Statistical significance was set at a two-tailed probability level of less than 0.05. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**d) Results**

**Patient characteristics.** Baseline characteristics and treatment during admission of the 40 patients are summarized in Table 1. All patients were classified as NYHA class III (14%) or IV (86%), with a mean LV ejection fraction of 22 ±7% and mean LV end-diastolic volume of 323 ±140 ml. Device and lead implantation were successful in all patients without major complications, on average 574 ±410 days before enrollment into the study. Seventy-five percent of patients had experienced a subjective improvement in ≥1 NYHA class at three months post-implant. However, at the time of study enrollment 1.2 hospitalizations for heart failure exacerbation per patient had occurred. Reliable serial LV end-diastolic volumes [and diameters] could be retrieved in 29 (72.5%) patients, and were found to be 266 ±128 ml [6.8 ±1.2 cm] pre-implant, 272 ±141 ml [6.8 ±1.3 cm] at 3 months post-implant ($p=0.2$ vs pre-implant), and 309 ±133 ml [7.1 ±1.2 cm] ($p<0.01$ vs pre-implant and 3 months) at time of study enrollment.

Device interrogation was successful in all patients (Table 2). All patients had a lead in the right atrium, right ventricle and coronary sinus, including 14% of patients that were in atrial fibrillation at enrollment. No lead dislodgement was detected, and in 35 (87.5%) patients, the LV lead was deemed to be in a satisfactory lateral or posterolateral position. Patients were being paced in a biventricular mode 96% of the time, predominantly in an atrial sensing–ventricular pacing mode. Heart rates at time of study enrollment, with CRT-ON and CRT-OFF, were also similar (69±34 vs. 67±38 bpm, p=ns).

**Impact of biventricular pacing on echocardiographic variables.** Acute changes in echocardiographic indices in different settings of CRT programming are illustrated in

Figure 1 and Table 3. Overall, compared to CRT-ON, native conduction (i.e. CRT-OFF) was associated with acute worsening of LV diastolic filling, as evidenced by a significant reduction in diastolic filling time, mitral valve deceleration time and time between onset QRS and end of A wave. Also, acutely, the mitral valve velocity time integral (as a surrogate of the total volume of blood that entered the LV) and corresponding estimated LV stroke volume was reduced with CRT-OFF compared to CRT-ON. Furthermore, the amplitude of mitral E wave and severity of mitral regurgitation increased. There was also evidence of increased electrical dyssynchrony (i.e. QRS width), as well as inter-, and intra-ventricular mechanical dyssynchrony with CRT-OFF compared to CRT-ON.

**Impact of biventricular pacing on hemodynamic variables.** CRT-OFF was associated with acute worsening of LV contractile performance, indicated by a statistically significant drop in CO (-13%) and systemic systolic blood pressure (-7%), as well as a statistically significant increase in CVP (+22%), systolic- (+12%) and diastolic (+14%) pulmonary artery pressure, and PCWP (+24%, all $p<0.001$) (Figure 2, Table 3). Figure 3 shows a typical example of the detrimental hemodynamic changes assessed by echocardiography and invasive hemodynamic measurement when CRT was programmed from ON to OFF.

Sub-analysis of patients implanted with a CRT device for more than 6 months (n=26) versus between 3-6 months (n=14) revealed similar detrimental effects of hemodynamic measurements when CRT was programmed OFF, regardless of implant duration. Also, the magnitude of deterioration of hemodynamic parameters during CRT off was also similar in patients with LV end-diastolic volumes above or below the mean (assessed at moment of CRT implant or at study enrollment), and between patients with ischemic or non-ischemic etiology (data not shown).

Three patients had a significant and sustained improvement of their hemodynamic (systolic blood pressure [+8%], CVP [-17%], PCWP [-17%], and CO [+15%]) and echocardiographic measurements in CRT-OFF, rather than in CRT-ON. In all three patients, the CRT was programmed in a permanent VVI back-up mode. Two patients had an inadequate anterolateral LV lead position and were scheduled for revision of their LV lead. The other patient had a QRS complex of 114 ms, and it was decided to keep the CRT device in a back-up pacing mode.

**e) Discussion**

This mechanistic observational study provides detailed echocardiographic and invasive hemodynamic measurements to determine the relative contributions of biventricular pacing in patients with decompensation of their advanced heart failure despite chronic CRT therapy. The key finding is that long-term CRT continues to provide hemodynamic augmentation in a patient population typically categorized as clinical and echocardiographic "non-responders" to CRT. These observations challenge the prevailing belief that patients with symptomatic disease progression have not derived benefit from CRT and are "non-responders." In a subset of patients with serial measurements of LV volumes we observed that improvement of hemodynamic derangements through successful resynchronization therapy itself is not always sufficient to avert progressive left ventricular remodeling.

The present study is the first to investigate the effects of chronic CRT on invasive hemodynamics in patients who did not exhibit beneficial reverse remodeling at a time period long after implantation. Importantly, invasive hemodynamic and echocardiographic assessments were performed with CRT ON and OFF in close temporal proximity, providing a more accurate measure of the extent of acute hemodynamic deterioration in the absence of biventricular pacing support, with a minimized likelihood for time-dependent changes in factors such as pre-load or heart rate to confound the analysis. The improvement in diastolic filling is largely dependent on the restoration of a more physiologic atrio-ventricular interval. Additionally, improvement in cardiac output can be achieved through restoration of contractile coordination, which subsequently leads to reduction in LV filling pressures. These benefits were lost acutely when CRT was programmed OFF. This relative "inotropic" effect can be achieved at reduced oxygen demand (18), and the hemodynamic benefits appear to be consistent with previous reports from patients shortly after their device implantation (4,5).

The focus on achieving reversal of LV remodeling with CRT stems from the wide acceptance that "resynchronized" electrical-mechanical coupling results in changes in cardiac structure and performance, which are primarily responsible for changing the disease course in patients with heart failure. Indeed, prevention of cardiac remodeling

improves prognosis in heart failure, and numerous studies have shown chronic CRT to be linked with reverse remodeling (2,3,10,19-21). Though the clinical and echocardiographic responses to CRT may vary significantly among individuals and heart failure etiology, this does not always appear to translate into a greater effect on clinical outcomes . Also, patients with non-ischemic heart disease derive more improvement in ventricular function and seem to exhibit a greater improvement in survival after CRT (22,23,24,25). Therefore, it is important to recognize that like any effective drug or device therapy for patients with heart failure, response to therapy can be heterogeneous. In the case of CRT, various factors that may affect the efficiency of resynchronization include (but are not limited to) extent and location of scar tissue and viable myocardium, the appropriateness of lead positioning, inadequate delivery of LV pacing, the presence of concomitant rhythm abnormalities, sub-optimal device programming, or absence of myocardial contractile reserve (4,16,26,27). While many of these factors may directly influence the ability of CRT to provide beneficial hemodynamic effects, patients in our study population had fulfilled standard inclusion criteria including significant electrical dyssynchrony (QRS duration) for CRT at time of implantation, and the aforementioned standard reasons for lack of response could not account for the lack of reverse remodeling.

It is therefore likely that unrecognized contributors of disease progression (e.g. progressive myocyte dysfunction, apoptosis, chamber size and geometry) that may be independent of hemodynamic derangements may directly influence the clinical and echocardiographic response to CRT. Such contributors may also affect responses to any therapeutic intervention. Hence, lack of clinical or echocardiographic responses despite successful resynchronization should not directly imply lack of acute or chronic hemodynamic benefits from CRT. Instead, the appropriate interpretation for our "non-responder" population should consider the possibility that the hemodynamic augmentation following successful resynchronization by CRT may not be sufficient to warrant a persistent meaningful change in the natural history of heart failure disease progression but rather may slow down the disease progression. In fact, our group and others have suggested the presence of alterations in molecular expression of myocardial contractile genes following CRT being more predictive of clinical and echocardiographic responses than effective reduction in baseline dyssynchrony or contractile reserve (20,28). In addition,

lead position and its incumbent role in any evaluation for suboptimal responses to CRT remains an unknown until precise mechanisms of CRT are elucidated.

**Study Limitations.** It is important to recognize that this is not a randomized comparison, even though echocardiographic analyses were made independent of any knowledge of clinical or hemodynamic data. Our observations do not exclude the possibility of improving response by lead repositioning, although >87% of LV leads were deemed to be in an appropriate position and significant reduction in electrical and mechanical dyssynchrony were observed in our population. We also cannot exclude the possibility that early hemodynamic changes during CRT-OFF might not reflect more long-term ones and that optimization of atrio-ventricular and ventriculo-ventricular timings at the time of implantation may have provided better clinical and echocardiographic responses leading to fewer patients with disease progression, although that strategy has yet to be proven. No acute post-implant hemodynamic data were gathered though early clinical improvement in NYHA class and stabilization of LV volumes suggests at least some early benefits of CRT. However, despite continuous hemodynamic support, patients had experienced progressive LV remodeling at the time of study enrollment. Despite the goal to reach maximally-tolerated, guideline-recommend medical therapy as specified in the methods section, the challenge of up-titration in this patient population with advanced heart failure (32% inotropic agents during hospitalization) is apparent to most practicing physicians. However, at the time of CRT implant all patients were on optimal, stable medical therapies. Although the echocardiographic techniques used in this study have been widely considered as relatively robust measures, the gold standard for defining and quantifying dyssynchrony is still being debated and currently undergoing prospective validation,

**f) Conclusion**

Despite adverse cardiac remodeling and heart failure decompensation, CRT continues to provide persistent hemodynamic augmentation in the failing heart. Our data show that detrimental disease progression may not be explained solely by diminishing beneficial hemodynamic contributions of successful resynchronization. Our data also illustrate that a lack of clinical and/or echocardiographic response should not be interpreted

as a failure to deliver hemodynamic benefits from successful cardiac resynchronization therapy.

**g) References**


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**Table 1. Subject Characteristics (n=40)**

| | |
|---|---|
| Demographics | |
| Age (y) | 62 (53-67) |
| Men (%) | 71 |
| Weight (kg) | 88 (70-103) |
| Co-morbidities | |
| Hypertension (%) | 68 |
| Hyperlipidemia (%) | 71 |
| Diabetes (%) | 24 |
| Heart failure etiology | |
| Idiopathic Dilated (%) | 60 |
| Ischemic (%) | 40 |
| Medications | |
| ACE inhibitors / ARB (%) | 60 |
| Beta Blockers (%) | 72 |
| Spironolactone (%) | 60 |
| Loop Diuretic (%) | 92 |
| Digoxin (%) | 36 |
| Hydralazine (%) | 42 |
| Isosorbide dinitrate (%) | 44 |
| Sodium nitroprusside (%) | 50 |
| Inotropic Drugs (%) | 32 |
| Laboratory Data | |
| Hemoglobin (g/dl) | 11.6 (10.4-13.6) |
| Creatinine (mg/dl) | 1.4 (1.0-2.2) |
| B-type natriuretic peptide (pg/ml) | 580 (269-1469) |

**Table 2. Biventricular pacemaker diagnostics (n=40)**

| | |
|---|---|
| Sinus Rhythm (%) | 86 |
| DDD configuration (%) | 94 |
| VVIR configuration (%) | 6 |
| Lower rate (bpm) | 60±10 |
| Upper rate (bpm) | 125±15 |
| Biventricular pacing (%) | 96 |
| ASVS (%) | 4 |
| ASVP (%) | 66 |
| APVS (%) | 0 |
| APVP (%) | 30 |
| Paced AV interval (ms) | 130 (120-160) |
| Sensed AV interval (ms) | 120 (100-130) |
| VV timing (ms) | 0 (0-4) |

Values are mean ±SD, median (inter-quartile range) or %. Abbreviations: DDD: atrial and ventricular pacing and sensing, VVIR: ventricular pacing and sensing only, bpm: beats per minute, ASVS: atrial sensing ventricular sensing, ASVP: atrial sensing ventricular pacing, APVS: atrial pacing ventricular sensing, APVP: atrial pacing ventricular pacing, AV: atrio-ventricular, VV timing: interventricular timing interval

**Table 3. Hemodynamic and echocardiographic changes in patients with CRT-ON and CRT-OFF (n=40).**

| Variable | CRT-ON | CRT-OFF | p value |
|---|---|---|---|
| Heart Rate (bpm) | 69±34 | 67±38 | ns |
| Systolic blood pressure (mmHg) | 105 ±12 | 98 ±13 | < 0.001 |
| Central venous pressure(mmHg) | 9 ±7 | 11 ±7 | < 0.001 |
| Systolic pulmonary artery pressure (mmHg) | 44 ±13 | 49 ±15 | < 0.001 |
| Diastolic pulmonary artery pressure (mmHg) | 22 ±8 | 25 ±9 | < 0.001 |
| Pulmonary capillary wedge pressure (mmHg) | 17 ±6 | 21 ±7 | < 0.001 |
| Cardiac output (l/min) | 4.6 ±1.4 | 4.0 ±1.1 | < 0.001 |
| QRS width (ms) | 161 ±29 | 202 ±39 | < 0.001 |
| Mitral valve regurgitation (scale 0-4/4) | 1.9 ±0.8 | 2.1 ±1 | < 0.001 |
| Mitral valve E velocity (cm/s) | 96 ±26 | 108 ±37 | < 0.001 |
| Mitral valve E deceleration time (ms) | 178 ±63 | 159 ±59 | < 0.001 |
| LV diastolic filling time (ms) | 377 ±138 | 300 ±118 | < 0.001 |
| Onset QRS till end of A wave time (ms) | 69 ±47 | 19 ±31 | < 0.001 |
| LV inflow velocity time integral | 19 ±6 | 16 ±5 | < 0.001 |
| LV outflow velocity time integral | 14 ±5 | 11 ±4 | < 0.001 |
| Inter-ventricular mechanical dyssynchrony (ms) | 22 ±15 | 45 ±25 | < 0.001 |
| Intra-ventricular mechanical dyssynchrony (ms) | 15 ±26 | 57 ±41 | < 0.001 |

Values are mean ±SD. Abbreviations: LV: left ventricle.

**Table 4. Selected hemodynamic changes in patients who improved with CRT OFF.**

| | Systolic Blood Pressure (mmHg) | | Central Venous Pressure (mmHg) | | Pulmonary Capillary Wedge Pressure (mmHg) | | Cardiac Output (l/min) | |
|---|---|---|---|---|---|---|---|---|
| | CRT ON | CRT OFF | CRT ON | CRT OFF | CRT ON | CRT OFF | CRT ON | CRT OFF |
| Patient 1 | 86 | 92 | 13 | 11 | 13 | 11 | 4.5 | 5.0 |
| Patient 2 | 93 | 95 | 16 | 13 | 16 | 13 | 3.6 | 4.8 |
| Patient 3 | 106 | 123 | 11 | 9 | 11 | 9 | 3.9 | 4.0 |

**Figure 1. Echocardiographic changes in patients with CRT-ON and CRT-OFF.**

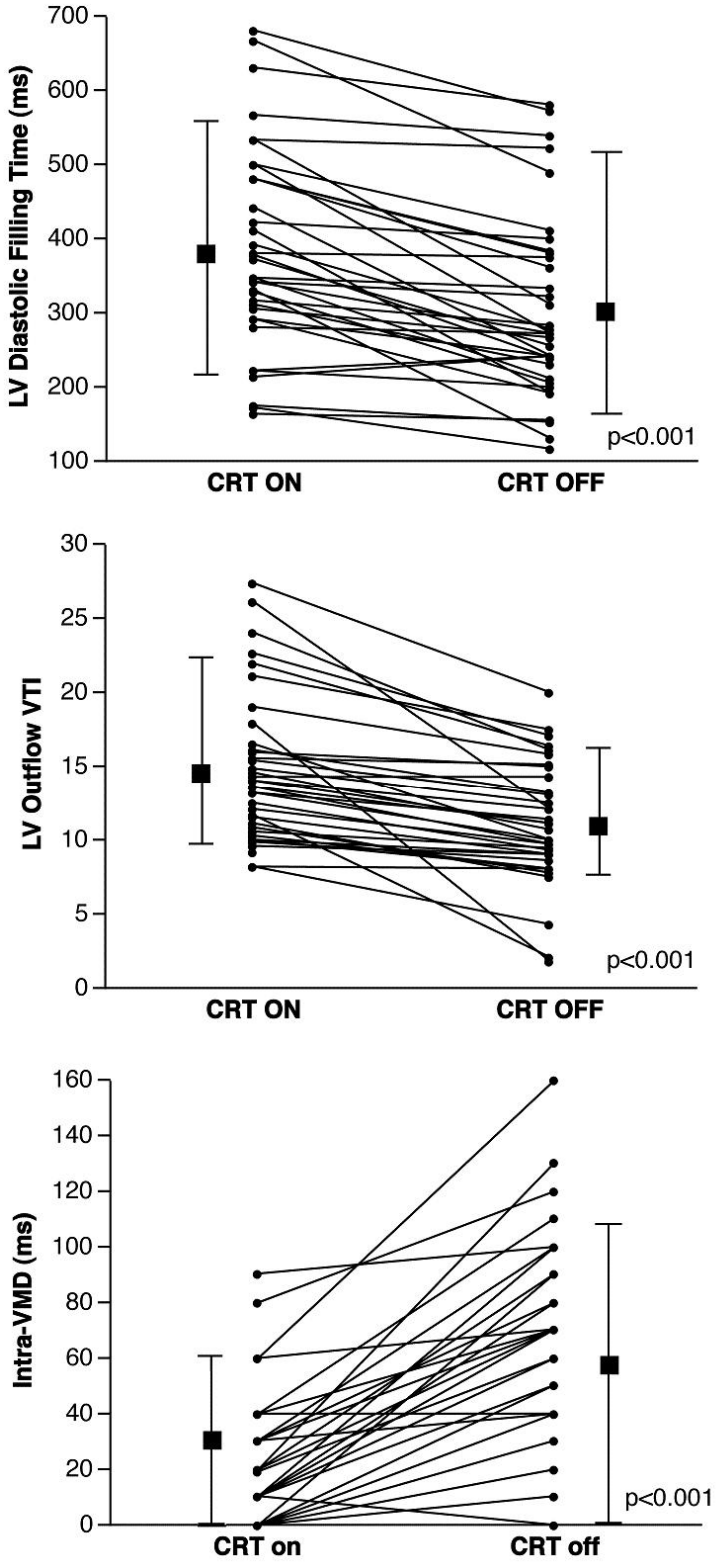


**Figure 2. Hemodynamic changes in patients with CRT-ON and CRT-OFF.**

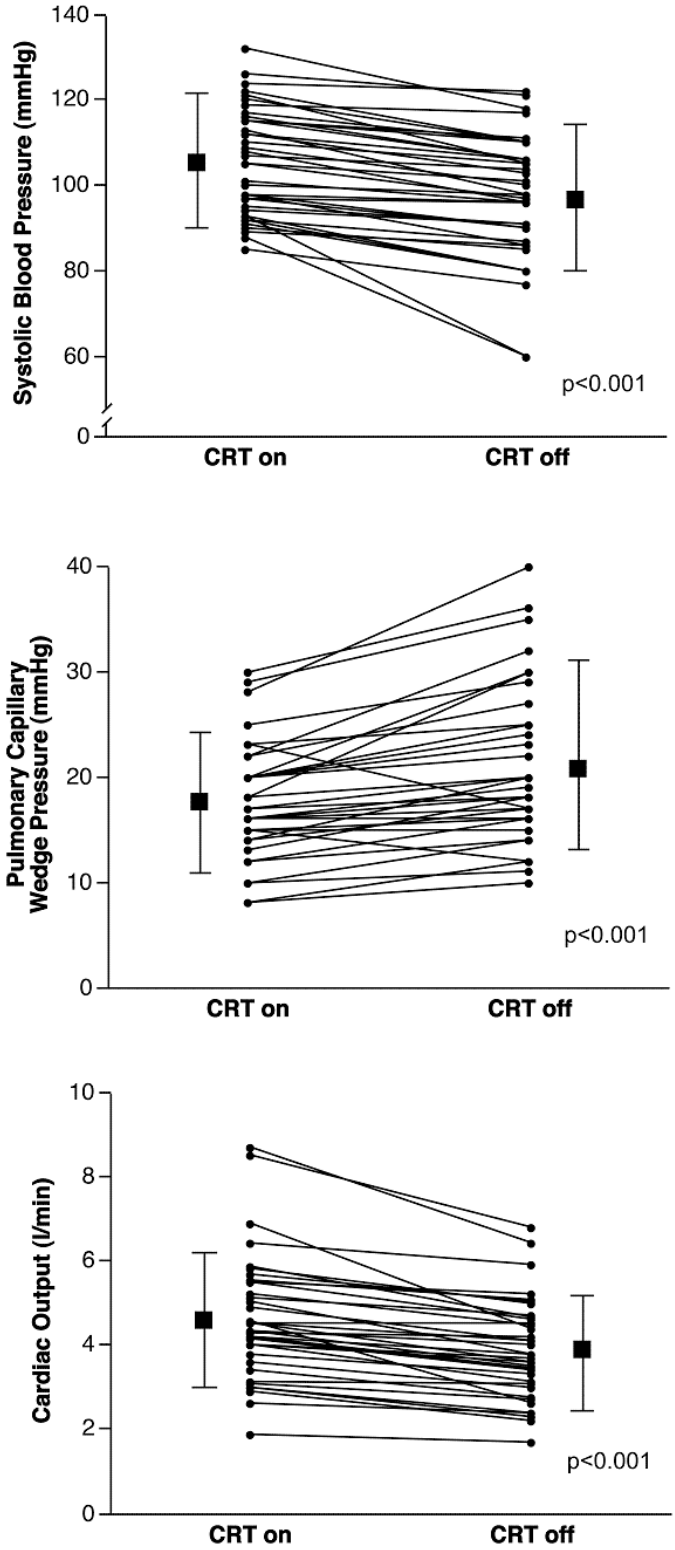
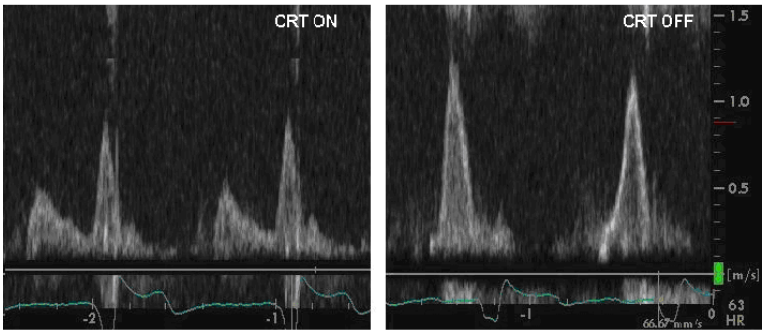


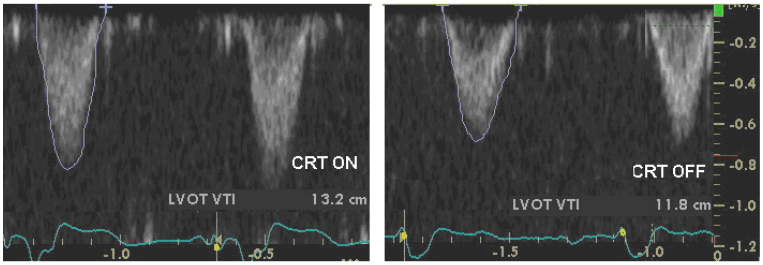
**Figure 3. Example of hemodynamic changes during CRT-ON and CRT-OFF.**

- **Left ventricular inflow using pulsed wave Doppler at the mitral valve leaflet tips.** Programming CRT-OFF leads to fusion of early (E-wave) and late (A-wave) filling, shortens left ventricular diastolic filling time, deceleration time and time between onset of QRS and end of A wave (QA-time), and reduces mitral valve velocity time integral; all indicative of worse diastolic function.
- **Left ventricular outflow using pulsed wave Doppler at left ventricular outflow tract.** Programming CRT-OFF leads to increased left ventricular pre-ejection times (onset QRS to start of LV ejection) and reduces the left ventricular outflow tract velocity time integral; indicative of worse left ventricular contractile performance.
- **Intra-ventricular dyssynchrony using color tissue Doppler echocardiography.** Color tissue Doppler sample placed at basal part of the septum (yellow) and lateral wall (green) in an apical 4-chamber view. Septal to lateral wall motion delay is measured as the maximal time difference between onset of QRS and peak of regional velocities of myocardial systolic shortening between different walls. Note the appearance of a septal to lateral wall motion delay as an indicator of intra-ventricular mechanical dyssynchrony when CRT-OFF (AVO = aortic valve opening, AVC = aortic valve closing).
- **Pulmonary artery catheter tracings in pulmonary artery and pulmonary capillary wedge position.** Note the increase in pulmonary artery pressure and pulmonary capillary wedge pressure when CRT is programmed OFF.

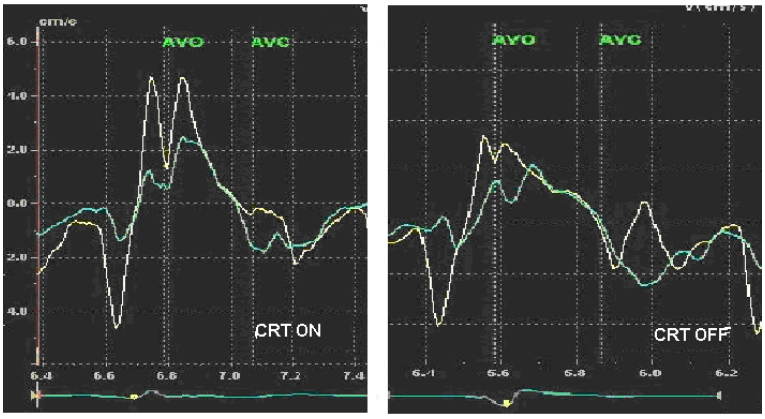
Left Ventricular Inflow



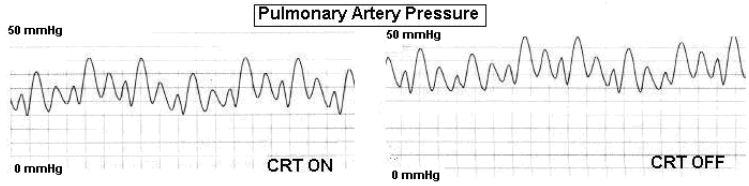

Left Ventricular Outflow



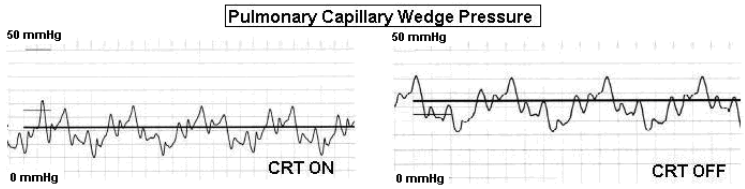

Intra-Ventricular Mechanical Dyssynchrony




Pulmonary Artery Pressure




Pulmonary Capillary Wedge Pressure



## 5) Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program

Mullens W, Grimm R, Verga T, Dresing T, Starling R, Wilkoff B, Tang W. Insights from a Cardiac Resynchronization Optimization Clinic as Part of a Heart Failure Disease Management Program. J Am Coll Card 2009;53:765-73.

### a) Abstract

**Objectives:** To prospectively determine the feasibility and value of a protocol-driven approach to ambulatory CRT patients who did not exhibit a positive response long after implant.

**Background**: Although response to CRT is heterogeneous, one-third of advanced heart failure patients do not exhibit a positive response.

**Methods:** A total of 75 consecutive ambulatory patients with persistent advanced heart failure symptoms, adverse reverse remodeling and CRT implanted >6 months, underwent a comprehensive protocol-driven evaluation to determine potential reasons for suboptimal response. Afterwards, recommendations were made in order to maximize the potential of CRT, and adverse events were recorded.

**Results:** All patients (mean LV ejection fraction 23±9%, LV end-diastolic volume 275±127 ml) underwent successful evaluation, with mean clinic visit duration of 75 minutes with involvement of a designated nurse and cardiologist. Though 88% of patients had significantly better echocardiographic indices of LV filling and ejection with CRT compared to no CRT, most patients had identifiable reasons for suboptimal response including inadequate device settings (47%), suboptimal medical treatment (32%), arrhythmias (32%), inappropriate lead position (21%), or lack of baseline dyssynchrony (9%). Multi-disciplinary recommendations lead to changes in device settings and/or other therapy modifications in 74% of patients resulting in a reduction in adverse events (13 vs 50%, OR 0.2 [0.07-0.56], p = 0.002) compared to patients in which no recommendation could be made.

**Conclusion:** Routine protocol-driven approach of ambulatory CRT patients who did not exhibit a positive response is feasible without significant time commitment, and often

leads to changes in device settings and/or other therapies which may result in reduced adverse events.

**b) Introduction**

Cardiac resynchronization therapy (CRT) restores the coordination of contraction and relaxation among cardiac chambers, leading to improved exercise tolerance, cardiac remodeling (reduction in left ventricular [LV] volumes, and improvement in LV ejection fraction) and a better survival in patients with advanced heart failure and evidence of ventricular conduction delay (1-3). However, up to one-third of patients may not experience any improvement in clinical status and/or reversal of cardiac remodeling after CRT based on current selection criteria (2,4-7).

The literature regarding post-implantation management of CRT is sparse, particularly long after device implantation. While the extent of the response can be heterogeneous, most studies have focused primarily on refining pre-implantation patient selection to predict favorable response (such as detecting evidence of basal dyssynchrony) (8-13). However, a variety of post-implant issues besides patient selection can also contribute to suboptimal responses, although less is known about their prevalence and impact. There has been a paucity of data to systematically evaluate how to best manage patients with CRT following their implantation, and to troubleshoot their settings post-implant in order to maximize the potential of the resynchronization therapy. In particular, the feasibility and value of a systematic protocol-driven multi-disciplinary approach to diagnose potential contributors for a suboptimal response and to optimize or titrate CRT in these patients is unknown.

The aim of this pilot study is to describe the feasibility of a multi-disciplinary protocol-driven approach of ambulatory CRT patients who did not experience clinical or echocardiographic improvement (or improved only transiently) following CRT implantation. We aim to identify potential clinical- or device related contributors associated with suboptimal response, and to estimate the time and personnel commitment required if such a strategy would be incorporated in a heart failure disease management program. Finally, the impact of multidisciplinary tailoring of CRT individually will be evaluated.

**c) Methods**

**Study population.** We evaluated 75 consecutive ambulatory patients between April 1, 2007, and April 1, 2008, who were referred to the CRT optimization clinic for comprehensive evaluation. All had received a CRT plus defibrillator device for at least 6 months (54% implanted in the Cleveland Clinic) but experienced persistent advanced heart failure symptoms (New York Heart Association class III or IV symptoms), and/or continuation (or lack of reversal) of adverse cardiac remodeling. The CRT-device was implanted because of stable but advanced heart failure despite optimal medical therapy, a depressed left ventricular ejection fraction ($\leq$35%), and prolonged QRS duration ($\geq$120 ms). The Cleveland Clinic Institutional Review Board approved this research project.

**CRT optimization clinic protocol.** The CRT optimization clinic protocol has been established as part of a multi-disciplinary approach incorporated in a heart failure disease management program accessible to any referring cardiologist (Figure 1). Briefly, on the day of the clinic visit, a heart failure nurse recorded an electrocardiogram with and without CRT pacing to ensure biventricular pacing, and the patient performed a 6-min walk test to objectively assess his/her exercise tolerance. An anterior-posterior and lateral chest X-ray was performed to ensure adequate positions of the right atrial, right ventricular and left ventricular lead (basal or mid lateral and posterior position), and routine lab tests were obtained (including standard electrolyte and renal panel, complete blood count, and B-type natriuretic peptide) to detect occult anemia and metabolic derangements. Afterwards a physician performed a careful clinical evaluation and data review, and a comprehensive device interrogation was performed including assessment of battery status, lead impedances and thresholds, heart rate and activity histograms, percentage of atrial and ventricular pacing, and presence of atrial and ventricular tachyarrhythmias.

Next, a comprehensive two-dimensional echocardiographic exam was performed (Vingmed, System VII, General Electric, USA) with nominal settings of the CRT device. All reported echocardiographic measurements were averaged from at least three consecutive cycles as recommended by the American Society of Echocardiography (14). Inter-ventricular mechanical dyssynchrony (VMD) was assessed as the difference between the pre-ejection intervals from QRS onset to the beginning of ventricular ejection at the pulmonic and aortic valve levels using pulsed-wave Doppler (1,2). Intra-VMD was assessed from regional time intervals between the onset of the QRS complex to the peak of

the systolic myocardial velocity (Ts) in four basal segments of the left ventricle (septal, lateral, antero-septal, posterior) using color Tissue-Doppler Imaging (11). Then, an effort was always made to optimize the LV diastolic filling (if other than stage I) by altering atrio-ventricular(AV)-timing using conventional Doppler echocardiography. The optimal AV interval was determined by sampling mitral inflow with pulsed wave Doppler and corresponded to the shortest AV interval that dissociated the E and A wave but did not interrupt the end of the A wave (15,16,17). Next, the CRT device was programmed into a non-functional pacing mode (VVI, backup 40 bpm) for 10 minutes, after which collection of echocardiographic data was repeated to ensure that CRT pacing itself was not detrimental. If the patient had no underlying atrial rhythm or a total atrio-ventricular nodal block, the pacemaker was programmed in an AAI or DDD mode respectively, at similar heart rates as the nominal settings.

**Multi-disciplinary hypothesis and recommendations.** Based upon the findings of the CRT optimization clinic, a working hypothesis for the lack of optimal response was formulated, and a multi-disciplinary recommendation was proposed based on consensus of a designated electrophysiologist, cardiac imaging, and heart failure specialist, to the patient and referring cardiologist in order to maximize or improve the potential of the CRT. These recommendations were not mutually exclusive, and such changes were made only upon agreement by the patient and referring cardiologist following a discussion of risks, benefits, and alternatives of the interventions. Appropriate actions can be categorized as repositioning of the LV lead in case of inappropriate lead position, change in device programming in case of suboptimal device programming (mostly AV timing), treat arrhythmias either medically or invasively, adding and up-titrating of medical therapy, as well as non-pharmacologic interventions (such as recommendations of diet and fluid restriction). The option of programming the CRT device to a back-up mode (VVI 40 bpm) was considered in case of absence of underlying electrical dyssnchrony and improvement of hemodynamics without CRT as assessed by echocardiographic parameters of global LV function. Finally, patients were scheduled for long-term clinical follow-up and device checks.

**End-points.** We pre-specified the primary end-point for this analysis as time to first occurrence of any of the following outcomes followed up to July 31, 2008: all-cause

mortality, cardiac transplantation, ventricular assist device implantation, and/or first readmission for heart failure following the CRT optimization clinic visit. Death was determined using data documented in the medical record and confirmed by the Social Security Death Index. Since interventions performed can vary widely, we also established a dichotomous grading scheme ("favorable" versus "neutral" intervention) to capture and qualitatively assess the subjective impression of the multidisciplinary team with regards to the propensity of subsequent clinical improvement based on the implemented recommendation. This data was documented at the conclusion of the CRT optimization session after the recommendation was made and implemented.

**Statistical Analysis.** All data were expressed as mean ±SD for continuous data, and as a ratio for categorical data. Univariate comparisons of these variables were performed between patients with "Favorable Intervention" versus those with "Neutral Intervention". The Cox Proportional hazards regression model was used to determine if patients with a "Favorable Intervention" had in a reduction in the combined endpoint during the follow-up period compared to patients with "Neutral Intervention". Kaplan-Meier survival curves were constructed for the combined end-point for patients with and without "Favorable Intervention". Statistical significance was set at a two-tailed probability level of less than 0.05. All statistical analyses were performed using SPSS for Windows, release 13.0 (SPSS Inc., Chicago, Illinois). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**d) Results**

**Patient characteristics.** Tables 1 and 2 summarized the baseline characteristics of the study population. All patients were classified as experiencing NYHA class III or IV symptoms, with a mean LV ejection fraction of 23 ±9% and mean LV end-diastolic volume of 275 ±127 ml. Device and lead implantation were successful in all patients without major complications, on average 24 ±22 months before enrollment into the study.

**Potential clinical contributors to suboptimal response (Figure 2).** Patients presented with low normal systemic blood pressures and mildly elevated jugular venous pressure (Table 2). Up to 24% of patients were not prescribed an angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker, beta-blocking agent and/or

spironolactone, despite having no noticeable contraindications. Another 8% of patients were identified to be non-compliant with regards to medication or fluid / diet intake. In addition, 41% of patients had a body mass index of $\geq$ 30 kg/m$^2$, and 16% even qualified as being morbidly obese (body mass index $\geq$ 40 kg/m$^2$). Finally, 30% of patients experienced anemia (defined as hemoglobin < 11 g/dl for females / < 12 g/dl for males), although only 3 patients (4%) had hemoglobin < 10 g/dl. One patient had primary RV dysfunction without LV dysfunction.

**Potential electro-mechanical related issues to suboptimal response (Figure 2).** All patients had a lead in the right atrium, right ventricle and on the left ventricle, either via the coronary sinus (95%) or epicardially (5%). No lead dislodgement was detected but 21% of patients had their LV lead placed in an inappropriate position (Figure 4, patient 1), mostly anteriorly. The mean QRS width was 152 ±44 ms for the overall patient cohort at the time of evaluation at the CRT optimization clinic. An underlying narrow QRS (<130 ms) was detected in 9% of patients and another 16% of patients had persistent significant mechanical dyssynchrony with biventricular pacing (11% inter-VMD and 9% intra-VMD). Finally, inefficient LV filling due to suboptimal programming of AV-timings was found in 47% of patients.

**Potential electrophysiological and device related issues to suboptimal response (Figure 2).** Device interrogation was successful in all patients. All were being paced in a biventricular mode on average 90% of the time, predominantly in an atrial sensing–ventricular pacing mode (Table 3). No battery depletion, lead threshold / impedance problem, or lack of rate response was noted (all but 2 patients were programmed in DDDR / VVIR mode with adequate heart rate histograms). Underlying arrhythmias were common, with 15% of patients being in permanent atrial fibrillation and another 17% of patients demonstrating a significant amount of supraventricular- and ventricular ectopy (Figure 4, patient 3), contributing to an insufficient percentage of biventricular pacing (< 90% of time).

**Multi-disciplinary recommendation and actions (Table 4).** All patients and referring physicians agreed to follow the outlined recommendations (average 1.6/patient) with the exception of LV lead replacement. In 53% of the patients, appropriate clinical measures could be taken to improve patient compliance to diet, fluid restriction and

medication adherence including initiation and uptitration of neurohormonol blockade to guideline recommended doses whenever possible. Patients with obesity were scheduled to see a nutritional therapist as well. All patients with inappropriate LV lead positions were advised to replace their LV leads. However, only 7 out of 16 patients (9% of total) opted to do so because they either felt better with other instituted measures (5 out of 16), or were deemed too sick by their referral cardiologist to undergo the procedure (4 out of 16). AV-timings could be optimized (stepwise changes by ≥30 ms), resulting in improved LV filling, in 45% of patients with conventional Doppler echocardiography (Figure 4, patient 2). Arrhythmia burden was successfully reduced leading to Biv pacing in >90% of time in all patients with institution of medical therapy, though 3 patients also underwent invasive electrophysiological procedures.

Eighty-eight % patients had significantly better echocardiographic indices of LV filling and LV ejection with optimal setting of their CRT compared to no CRT. However, 9 patients (12%) had an immediate improvement in their hemodynamics when the CRT was turned off. Overall, baseline characteristics were similar between patients who improved or deteriorated when CRT was temporarily withold. In 7 patients, the CRT was programmed in a permanent VVI back-up mode. Five out of the 7 had underlying narrow QRS complex (< 130 ms) without any mechanical significant dyssynchrony. One other patient had an inadequate antero-lateral LV lead position and was scheduled for revision of the LV lead and the other patient had an AV nodal tachycardia, which was successfully ablated after which CRT pacing was resumed. The two remaining patients had a QRS width between 120-130 ms and the CRT was kept ON.

**Feasibility and outcomes.** Mean clinic visit duration was 75 minutes with involvement of a designated nurse (75 minutes) and cardiologist (60 minutes). At the end of the follow-up period (mean follow-up duration 6.1 months), 23% of the patients had either died, undergone cardiac transplantation, were hospitalized for decompensated heart failure or underwent implantation of a left ventricular assist device. As shown in Table 4, patients categorized in the “Favorable Intervention” group (n=55, 73%) had more changes in device settings including AV-timing reprogramming (20 vs 69%, $p < 0.001$) and LV lead repositioning (0 vs 9%, $p = 0.006$) compared to those in the “Neutral Intervention” group (n=20, 27%). Baseline characteristics between the two groups were similar besides from a

more impaired LV ejection fraction (19 ±8 vs 24 ±10%, p=0.03) in the Neutral Intervention group. However, even corrected for LV ejection fraction, the Favorable Intervention group was associated with a lower adverse event rate during follow-up (13 vs 50%, OR 0.2 [0.07-0.56], p = 0.002, Figure 3). Importantly, within the Favorable Intervention group, the potential to optimize AV-timings indicated a group with fewer adverse events during follow-up (Figure 3).

**e) Discussion**

We present our clinical experience in a multi-disciplinary, protocol-driven CRT optimization clinic as part of a heart failure disease management program for ambulatory patients with persistent symptoms and/or disease progression long after their implantation. Using an algorithm with standard equipment and testing that can be reproduced in any outpatient cardiology clinic, we identified suboptimal medical treatment, LV lead-position, and uncontrolled arrhythmias to be associated most often with a suboptimal response. The remaining changes that resulted from a perceived favorable intervention by the multidisciplinary team commonly involved optimization of AV timing interval titrating to the best LV filling efficiency based on easy-to-obtain transmitral Doppler flow. Although hypothesis-generating, our data suggest that a multidisciplinary, individually tailored approach is feasible, and might be associated with lower adverse clinical events at long-term follow-up, irrespective of the extent of underlying cardiac remodeling. These data also underscore the complexicity of this patient population and the importance of maximizing the potential of CRT in patients with advanced heart failure without optimal responses.

The design of our CRT optimization clinic protocol in ambulatory patients who did not exhibit a beneficial clinical response and/or reverse remodeling at a time period long after implantation, is unique in several aspects. First, it utilized a combination of a comprehensive clinical and device-based evaluation, as well as an echocardiographic examination embedded in a single centralized multidisciplinary outpatient evaluation without additional appointments for the patient to visit. Thus, allowing a comprehensive evaluation of the impact of CRT on cardiac structure, function and hemodynamics as well as on electromechanical events that is universally available to all physicians. Second, the multi-disciplinary approach including input of electrophysiological and cardiac imaging

expertise, coupled with a heart failure disease management strategy, allowed the CRT optimization clinic to provide insights into reasons for a suboptimal response to long-term CRT above and beyond the standard of care. Third, by classifying these cases individually, a management strategy of titrating resynchronization therapy could be prospectively validated.

The clinical and echocardiographic responses to CRT may vary significantly among individuals, and it is important to recognize that like any effective drug or device therapy for patients with heart failure, response to therapy can be heterogeneous. This report is the first to explore the potential reasons for suboptimal response to CRT in patients with ongoing disease progression and/or persistent (or returning) symptoms at a time period long after implantation. Although various reversible device-related issues that may affect the efficacy of resynchronization therapy were anticipated, the prevalence in which they occurred was higher than expected. Issues including inappropriate lead positioning (21%), the presence of rhythm abnormalities (32%) with concomitant inadequate delivery of biventricular pacing and suboptimal device programming (47%) were surprisingly high, especially since these patients were implanted on average 2 years before enrollment into the study. These observations highlight the notion that current post-implant approaches to longitudinal monitoring may overlook treatable problems. Finally, a subset of patients clearly demonstrated an improvement of their hemodynamics without biventricular pacing, either secondary to lack of underlying dyssynchrony or inappropriate lead positioning.

Importantly, the multi-disciplinary design of the clinic also allowed to potentially impact on the clinical condition in more than two-thirds of the patients. Despite the challenge of up-titration guideline-recommend medical therapy in this patient population with advanced heart failure, we were able to modify their medical regimen in more than half of the cases, in addition to providing standard patient education materials by a heart failure disease management clinic. Device-related issues such as replacement of the LV lead or device reprogramming of the AV-interval based on a simple echocardiographic protocol were also very prevalent. Moreover, the CRT optimization clinic protocol resulted in an individualized titration of an optimal amount of resynchronization therapy that might even have resulted in a reduction of adverse events during follow-up. The fact that this benefit was mostly observed in patients without mechanical ventricular dyssynchrony but

with symptomatic disease progression lends credence to the suggestion that the institution of clinical measures and especially optimization of the AV-interval may have been exerting a beneficial effect via mechanisms incremental to resynchronization of the ventricular activation only. Indeed AV-optimization has shown to be safe, feasible and associated with reduced filling pressures and improved cardiac output thereby creating a more favorable hemodynamic profile which might be associated with reduced adverse events (18-21).

There might be a reluctance of physicians to use a dedicated CRT optimization clinic protocol as part of their routine follow-up of patients with CRT who experience ongoing disease progression. The lack of data to illustrate the incremental benefit (in the form of clinical outcomes), the lack of resources to support such an ambitious venture, or the impression that one might be able to also detect subtle inefficiencies of CRT programming without a dedicated protocol may all contribute to physicians lack of enthusiasm in establishing such a process. In addition, there might be realistic concerns that such an approach might lead to an increased workload, unnecessary treatments based on inaccurate information, and even incurring costs due to excessive investigations and/or procedures. It is therefore reassuring to observe in our "real-life" experience that a routine protocol-driven approach, without using complex expensive additional testing or invasive procedures, resulted in the identification of mostly clear-cut easily correctable reasons for suboptimal response in more than two-thirds of patients. Importantly, by combining the imaging, heart failure, and electrophysiology evaluation within one centralized outpatient visit total cost could be contained. The amount of time commitment is likely acceptable as part of any heart failure disease management program, and these data illustrate the inadequacy of management regarding current approaches to post-implant care that warrant further investigations.

**Study Limitations.** It is important to recognize that this is not a randomized comparison between optimization and no optimization, and that referral of patients was based on the referring physicians' impression of "non-response" which might have introduced some bias towards referral of patients who were less sick and therefore more prone to be successfully optimized. However, in the second part of the study, patients were also seen as part of their cardiac transplantation work-up and patients that could be

optimized demonstrated significantly better outcomes than those who could not. Although some patients might have experienced an immediate or short (3-6 months) term response to CRT, the design of our protocol focused on long-term (> 6 months) response, being more representative of the true clinical impact of the therapy. Though optimal AV intervals were assessed at rest and not during exercise, we were still able to demonstrate a significant benefit from AV-optimization based on a simple, easy-to-obtain echocardiographic approach. Moreover, improved LV filling (as illustrated in Figure 3B) surely lead to improved hemodynamics in certain cases. We did not optimize ventriculo-ventricular timings since there is no reliable methodology to do so, and we cannot exclude the possibility that optimization of ventriculo-ventricular timings may have provided better clinical and echocardiographic responses, although that strategy has yet to be proven. Finally, patients were not routinely scheduled for a follow-up CRT optimization clinic visit, so any effect on reverse remodeling or weight loss could not be detected. Recognizing all the aforementioned limitations we believe that the information provided in this manuscript is a well-balanced description of our overall remarkable positive experience with the use of a multi-disciplinary protocol-driven approach of ambulatory CRT patients who did not exhibit a positive response long after implant. Moreover, our concept of the Optimization Clinic has recently been implemented in several other national and international centers with the ultimate goal to provide guidelines, upon verification of our pivotal findings, how to approach this immer growing patient population.

**f) Conclusion**

A multi-disciplinary protocol-driven approach of ambulatory CRT patients who did not exhibit a positive response long after implant, may uncover potential contributors to a suboptimal response, potentially maximize the potential of CRT, and may be associated with a reduction in adverse events.

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**Table 1. Baseline Demographics (n=75)**

| | |
|---|---|
| Age (y) | 62 ±12 |
| Men (%) | 77 |
| Body mass index (kg/m2) | 29 ±8 |
| Hemoglobin (g/dl) | 12.5 ±1.7 |
| Creatinine (mg/dl) | 1.3 ±0.4 |
| Brain natriuretic peptide (pg/ml) | 557 ±574 |
| New York Heart Association functional class III / IV (%) | 75 / 25 |
| Hypertension (%) | 74 |
| Hyperlipidemia (%) | 61 |
| Diabetes (%) | 34 |
| Idiopathic Dilated (%) | 60 |
| Ischemic (%) | 40 |
| Beta Blockers (%) | 89 |
| ACE inhibitors / ARB (%) | 84 |
| Spironolactone (%) | 66 |
| Loop Diuretic (%) | 96 |
| Digoxin (%) | 42 |
| Hydralazine (%) | 19 |
| Isosorbide dinitrate (%) | 24 |
| Dobutamine (%) | 6 |

**Table 2. Clinical and echocardiographic parameters (n=75).**

| | |
|---|---|
| 6-min Walk Test (Feet) | 1022 ±378 |
| Heart Rate (bpm) | 75 ±9 |
| Systolic blood pressure (mmHg) | 110 ±16 |
| Diastolic blood pressure (mmHg) | 68 ±11 |
| Jugular venous pressure(mmHg) | 8 ±4 |
| QRS width (ms) | 152 ±44 |
| LV ejection fraction (%) | 23 ±9 |
| LV end-diastolic volume (ml) | 275 ±127 |
| Diastolic function (scale 1-3) | 1.9 ±0.8 |
| Mitral valve regurgitation (scale 0-4/4) | 2.0 ±0.9 |
| Tricuspid valve regurgitation (scale 0-4/4) | 1.4 ±0.8 |
| Inter-ventricular mechanical dyssynchrony (ms) | 11 ±20 |
| Intra-ventricular mechanical dyssynchrony (ms) | 14 ±26 |

**Table 3. Biventricular pacemaker diagnostics (n=75)**

| | |
|---|---|
| Time after implant (months) | 23.7 ±21.8 |
| Sinus Rhythm (%) | 85 |
| DDDR configuration (%) | 94 |
| VVIR configuration (%) | 6 |
| Lower rate (bpm) | 60 ±10 |
| Upper rate (bpm) | 127 ±10 |
| Biventricular pacing (%) | 90 ±23 |
| ASVS (%) | 8 |
| ASVP (%) | 66 |
| APVS (%) | 2 |
| APVP (%) | 24 |
| Paced AV interval (ms) | 153 ±37 |
| Sensed AV interval (ms) | 123 ±33 |
| VV timing (ms) | 5 ±9 |

**Table 4. Recommendation.**

| Recommendation (%) | All patients (n=75) | Neutral Intervention (n=20) | Favorable Intervention (n=55) | p-value Favorable vs Neutral |
|---|---|---|---|---|
| Better with Biv-ON | 88 | 85 | 89 | ns |
| AV changes (>30ms) | 45 | 20 | 69 | <0.001 |
| Unchanged device settings | 36 | 65 | 25 | 0.003 |
| Arrhytmia Intervention | 31 | 30 | 31 | ns |
| LV lead revision | 9 | 0 | 9 | 0.006 |
| Biv OFF | 9 | 10 | 9 | ns |
| Other (Compliance, medication, diet…) | 53 | 40 | 58 | ns |

**Figure 1. CRT optimization clinic flow-chart.**

**Figure 2. Potential reasons for suboptimal response.**

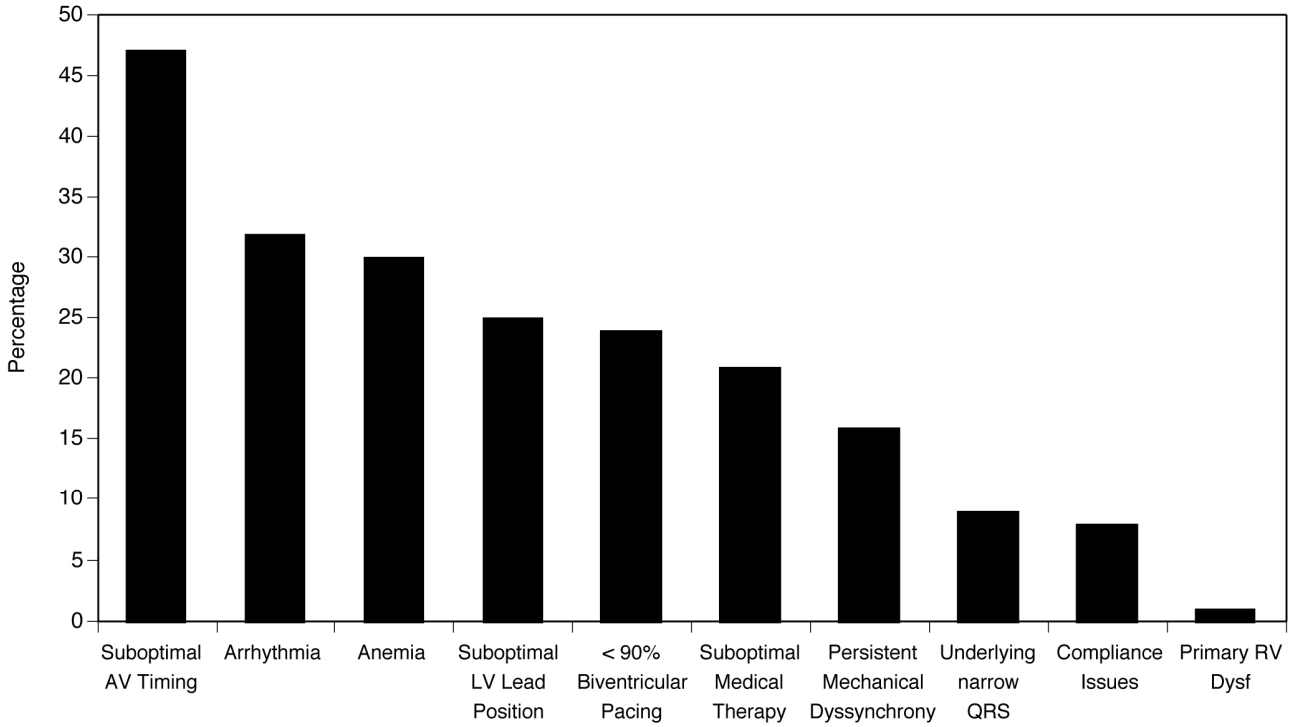


**Figure 3. Kaplan Meier curves for patients deemed to be succesfully optimized (= Favorable Intervention) with / without AV-optimization versus those that could not be significantly optimized (= Neutral Intervention) after the CRT optimization clinic.**

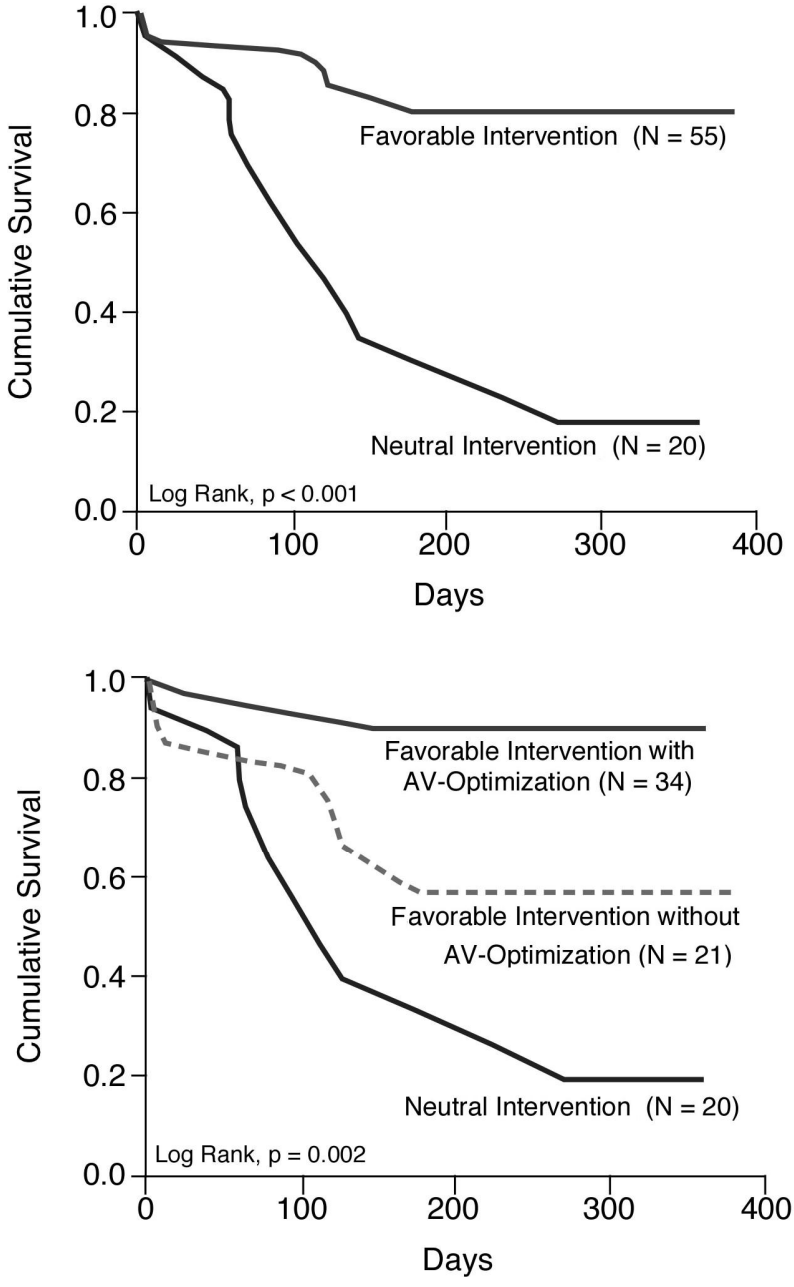
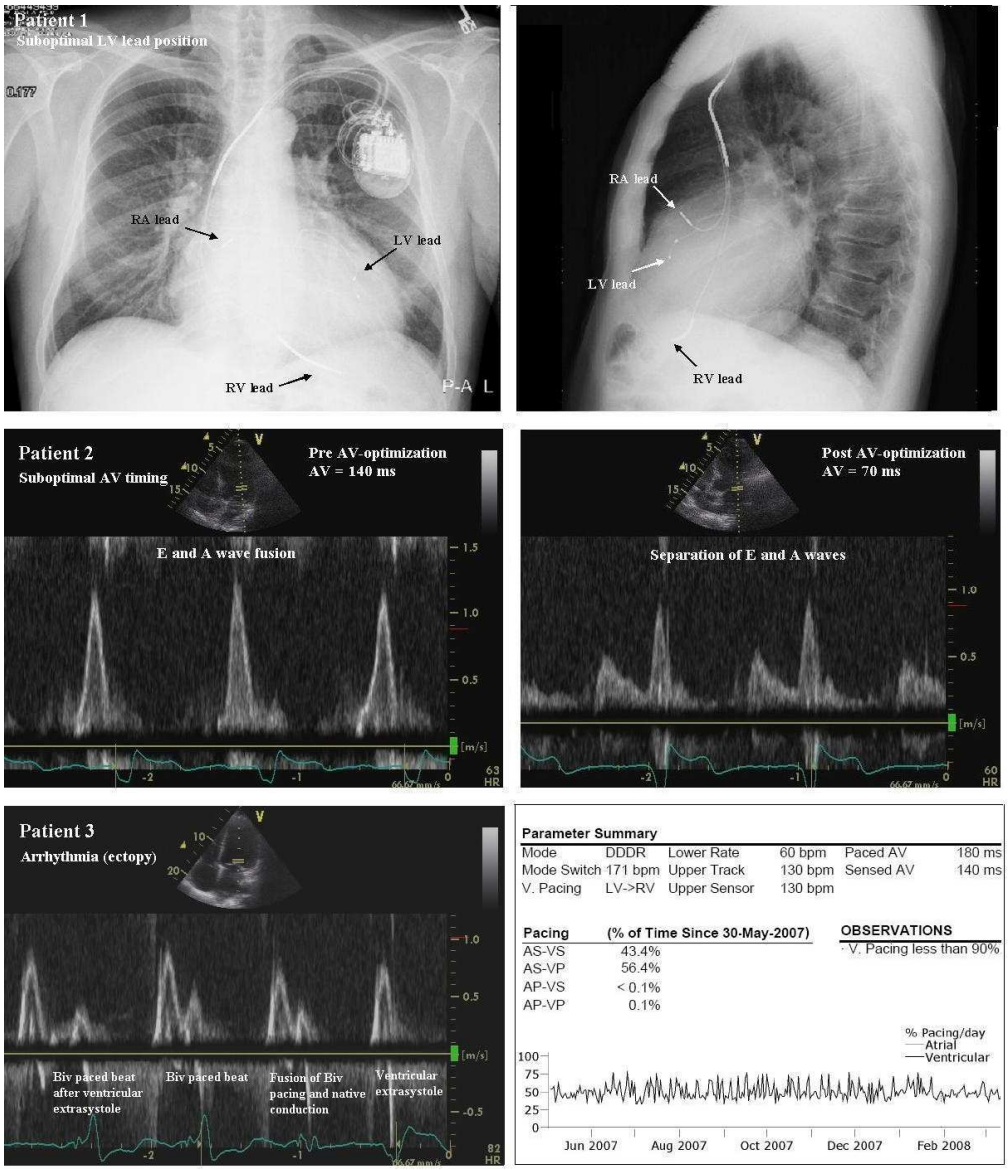


**Figure 4. Patient examples.**



# V. Discussion

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## 1. Prevalence and importance of hemodynamic alterations in advanced heart failure

There has been a longstanding notion that clinical outcomes may improve when hemodynamic targets can be achieved (1,2,3). Therefore, the challenge is to better identify those patients with concerning hemodynamic compromise that might not be clinically apparent in the ambulatory care setting and to optimize their medications when possible (such as incorporating oral vasodilator therapy like hydralazine and nitrate therapy). From a large cohort of ambulatory patients with advanced heart failure who have been treated with contemporary therapies including neurohormonal blockade, we demonstrated that a substantial proportion of patients still presents with predominantly elevated intracardiac filling pressures rather than low cardiac indices (4). This represents a population that despite receiving evidence-based therapies for HF still experiences ongoing disease progression, leading to progressive hemodynamic and renal compromise. In fact, the hemodynamic and clinical profile of this group of patients can be characterized in HF jargon as the "walking wounded", as evidenced by an overall poor prognosis with up to 38% of patients who are subsequently admitted to the hospital for heart failure exacerbation within one year (4).

Recently, several risk stratification models have been constructed using datasets from clinical trials with carefully selected chronic HF populations or, from large registries of hospitalized patients with decompensated HF, all independent of hemodynamic variables (5,6,7). Hence, the use of invasive hemodynamic assessment has been largely confined to evaluation for candidacy for cardiac transplantation (8). However, we demonstrated that invasively assessed hemodynamic alterations and renal function abnormalities are valuable determinants of long-term prognosis (4). Moreover, when a clinical model for Cox multivariate analysis of all-cause mortality was compared with a model that also included cardiac index and filling pressures the chi-square score increased from 45 to 69 ($p < 0.0001$, ref 4). Importantly, the probability of survival was reduced even by minor reductions in renal function or cardiac index, and the relationship between serum creatinine levels or cardiac index and prognosis was sustained over a wide range of values.

## 2. Gender differences in advanced heart failure

Women with heart failure have been reported to have a better age-adjusted survival rate than men with the same condition (9,10,11,12). However, most studies so far interrogated datasets from clinical trials or large natural history databases with carefully selected stable and ambulatory chronic heart failure populations, independent of hemodynamic variables. In addition, potential gender-specific differences in clinical presentation, prognosis and response to treatment in patients admitted with advanced decompensated heart failure (ADHF) are lacking. We reported on our experience in a large population of hospitalized patients with ADHF to examine potential gender-specific differences, especially with regards to invasive hemodynamic measurements as an objective assessment for disease severity, and compared clinical responses to diuretic and vasoactive therapies between males and females. The key clinical implication is that guideline recommended care is well tolerated by females and can be safely administered to achieve significant hemodynamic improvement (13). Crude clinical outcomes do not differ among males and females, though a small survival benefit is seen in females with nonischemic etiology of heart failure (13). Taken together, female patients with ADHF tolerate guideline recommend care as well as their male counterparts leading to overall similar outcomes (13).

## 3. Vasodilator therapy to restore an optimal hemodynamic balance

Advances in medical therapies (such as neurohormonal modulation and pacing/defibrillation strategies) have significantly altered the natural history of heart failure and improved long-term outcomes (14,15,16,17,18). However, the pathophysiology and treatment of advanced decompensated heart failure (ADHF) remains poorly understood, especially in more advanced stages when cardiac output is significantly reduced. Although vasodilators were considered one of the earliest “evidence-based” treatment strategies for systolic heart failure based on the cardio-circulatory model of heart failure (19,20), its current use is eclipsed by the large volume of evidence supporting the use of neurohormonal antagonists such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-adrenergic blockers (beta-blockers), and aldosterone receptor antagonists. Nevertheless, there is a resurgence of interest in the use

of intravenous and oral vasodilators in the management of ADHF, particular with the recognition that a large majority of patients present with elevated rather than low blood pressures (21).

Despite clinical evidence suggesting hemodynamic and concordant clinical improvement, there has been limited scientific data on the impact of continuous infusion of sodium nitroprusside (SNP) on long-term outcomes in ADHF. Furthermore, SNP is infrequently used today for ADHF exacerbations especially when the cardiac output is significantly depressed and blood pressure is marginal. However, the dual arteriolar and venous effects of SNP appear to contribute to the immediate hemodynamic response of the drug. Dilation of the arterial resistance vessels reduces LV afterload and allows the severely compromised LV to eject more blood. The venodilator effect increases venous capacitance and reduces congestion. Both effects lead to an increase in cardiac output in patients with heart failure and often reduce the basal tachycardia. Nevertheless, there is a reluctance of physicians to use SNP in hospitalized ADHF patients with low cardiac output or marginal blood pressure. This stems from the misguided belief that vasodilatation could potentially be risky if systemic vascular resistance is reduced without any compensatory increase in CO, leading to significant hypotension and downward spiraling of detrimental hemodynamic support. This concept, however, is an oversimplification of the usual cardiac hemodynamics observed, typically in patients with severe LV systolic dysfunction with increased ventricular volumes. The substantial improvement in cardiac output more than offsets any fall in blood pressure under most circumstances. As a result, a reduction in afterload or wall stress during SNP administration usually leads to a marked increase in cardiac output, preventing the development of significant hypotension.

We recently reviewed all consecutive patients with ADHF admitted with a cardiac index $\leq 2L/min/m^2$ for intensive medical therapy including vasoactive drugs and compared patients who received SNP with those who did not receive SNP (22). Administration of SNP was administered per protocol under hemodynamic guidance via a pulmonary artery catheter and titrated to a target mean arterial pressure of 65-70 mmHg (22). Our data clearly corroborated the aforementioned beneficial hemodynamic effects of SNP, as we observed that the SNP treated patients had a statistically greater increase in cardiac index without substantial reduction in systemic blood pressure when compared to the non-SNP

treated controls (22). In addition, use of SNP was associated with reduced adverse events, irrespective of the use of inotropic therapy or underlying renal function (22). The early and continuous separation of the mortality curves for the two cohorts was noticed in favor of SNP implying a ongoing and increasing benefit of vasodilator therapy throughout the follow-up period (22,23). We hypothesized this to be secondary to the ability to establish an early optimal hemodynamic balance with SNP, allowing the institution of longer-term oral vasodilator therapy with isosorbide dinitrate and hydralzine bridged by SNP titration. Thus, use of early intravenous and late oral vasodilators exerts an improved short-term hemodynamic benefit and a long-term survival benefit.

By demonstrating the potential advantages of using add-on oral vasodilators over up-titration of standard neurohormonal antagonists, we revisited the concept of "hemodynamic dependence" in the setting of progressive pump failure (22,23). Indeed, the fact that this benefit was observed in patients already treated with neurohormonal antagonism lends credence to the suggestion that the combination of agents may provide benefits beyond blockade of the renin-angiotensin-aldosterone system. Neurohormonal blockers slow the progression of left ventricular dysfunction, retard the structural left ventricular remodeling and reduce the rate of death and complications among patients with heart failure. Impaired bioavailability of nitric oxide, and increased oxidant stress leading to endothelial dysfunction may also contribute to the remodeling process in heart failure. Therefore, it has been postulated that combining the nitric oxide donor (isosorbide dinitrate) with the antioxidant (hydralazine) may provide an alternative or supplemental approach to slow or reverse progressive heart failure. Based on our data, we cannot confirm or exclude the potential benefits of incremental isosorbide dinitrate / hydralazine benefit beyond their role in hemodynamic optimization. Nevertheless our patient characteristics were consistent with the clinical profile of "direct vasodilator responders," particularly in those with dilated ventricles whereby reduction of left ventricular impedance (or enhanced systolic ejection) and reduction in regurgitant volume may lead to wall stress reduction. Therefore, our observations may encourage future studies to better understand the mechanistic underpinnings of such a strategy and further clarify our understanding of the complex role of nitric oxide and oxidative stress in advanced heart failure.

**4. Echocardiography cannot replace an invasive hemodynamic assessment for the estimation of filling pressures**

Numerous advances in imaging techniques like echocardiography have allowed clinicians to visualize different cardiac structural abnormalities and also made it possible to simultaneously assess structural and hemodynamic alterations. Therefore, echocardiography has been advocated to replace an invasive hemodynamic assessment to assess hemodynamic alterations. For example, the early transmitral velocity / tissue Doppler mitral annular early diastolic velocity (E/Ea) has been shown to correlate with pulmonary capillary wedge pressure (PCWP) in a wide range of cardiac patients (23,24,25,26). However, while some smaller studies have included patients with depressed LV systolic function, none has included patients admitted with advanced heart failure and extensive reverse remodeling. Using simultaneously measured echocardiographic and invasive hemodynamic variables, we found the predictive value of baseline mitral E/Ea in estimating PCWP in this population to be less robust than previously reported, especially in patients with cardiac resynchronization therapy (27). Furthermore, we were unable to identify any reliable direct correlation between changes in mitral E/Ea and PCWP (27). With increasing acceptance of mitral E/Ea as a surrogate measure of diastolic function and as a reliable estimate of intracardiac filling pressures, our observations provide an important refinement in the clinical interpretation of the mitral E/Ea ratio as it applies to patient populations where confounders such as alterations in myocardial structure, severity of systolic dysfunction, or the presence of synchronized pacing may influence its predictive value.

**5. New hemodynamic insights into cardiorenal interactions**

**a) Prevalence of worsening renal function during decompensated heart failure**

Worsening of renal function (WRF) during treatment of advanced decompensated heart failure (ADHF) typically occurs within days of hospitalization and is a strong independent predictor of adverse outcomes. We found the incidence of WRF to approach 40% in a “cold and wet” patient population (28). Moreover, in patients with severe renal insufficiency at baseline, almost 60% developed WRF (28). This indicates that the

underlying intrinsic kidney disease remains an important determinant of the "reserve" available for the kidneys to relieve congestion and to respond to the insult posed by ADHF and the aggressive diuresis and natriuresis necessary during treatment of ADHF. Naturally, this raises the question as to whether treatment primarily directed with the aim of "renal preservation" should be administered prophylactically, especially in this extraordinary high-risk group. Importantly, while the initiation or maintenance of certain classes of drugs like angiotensin-converting enzyme inhibitors and loop diuretics have been linked to WRF, we did not find any difference in their usage at admission or during hospitalization to account for the occurrence of worsening renal function (28). In addition, WRF occurs during the initial days following treatment for ADHF during hospitalization, thereby suggesting that hemodynamic factors might contribute as well to the very high incidence of this detrimental complication of ADHF.

**b) The emerging concept of congestive kidney failure**

The pathophysiology of the cardiorenal interaction in the setting of ADHF is complex and poorly understood. The most commonly assumed cause of WRF has been hypoperfusion of the kidney secondary to low-output or hypotension (leading to pre-renal hypoperfusion or impaired renal "preload") (29). However, in a large cohort of patients admitted with ADHF (admission mean cardiac index 1.9 ±0.6 l/min.m2, central venous pressure 14 ±7 mmHg, and pulmonary capillary wedge pressure 24 ±7 mmHg), we observed that systemic blood pressures were similar between those with versus without WRF (28). Also during intensive medical therapy, systolic blood pressures were carefully monitored and targeted as drugs were being titrated to prevent overzealous hypotension. In addition, the persistently elevated intracardiac pressures in our patient population (with a mean PCWP in the range of 18-19 mmHg) suggested that the overall vasculature was unlikely to be "under-filled" (28). Our data also demonstrate that progressive or persistent impairment of cardiac output may not be the primary culprit in the development of WRF during the treatment for ADHF (28). Patients who developed WRF did not have a lower cardiac output on admission or at discharge when compared to those without WRF (28). Thus, even in an advanced heart failure population with low-output cardiac failure and

marginal blood pressures, routine use of inotropic therapy may not necessarily relieve or prevent WRF.

Although the majority of patients hospitalized with ADHF (systolic and diastolic) also present with increased central or peripheral congestion, the presence of venous congestion has been considered a secondary phenomenon due to the "backward failure" caused by impaired cardiac output. Nevertheless, experimental animal data as far back as the 1930's have demonstrated that temporary isolated elevation of central venous pressure (CVP) can be transmitted back to the renal veins, resulting in direct impairment of renal function (30,31). However, human data regarding the differential contributions of venous congestion and cardiac output in the development of WRF during ADHF were lacking. Our observations suggest that the strongest hemodynamic determinant of development of WRF is the presence of venous congestion, measured by elevated CVP, both on admission and at follow-up (28). In addition, there appears to be a near-linear relationship since if the baseline CVP reached >16 or >24 mmHg, we observed a sharp rise in the incidence of WRF approaching 59% and 75%, respectively (28). Clearly, this could simply be interpreted as a "sicker" patient population with more advanced disease states that were reflected by higher CVP. However, common cardiovascular measures of disease severity (including systolic blood pressure, serum sodium, plasma B-type natriuretic peptide, PCWP, systolic pulmonary arterial pressure, and dosage of loop diuretics) were similar between those with versus without WRF (28).

Therefore, it is conceivable that in the setting of ADHF, the development of "congestive kidney failure" led by elevated renal venous pressure from venous congestion (increased renal afterload) and increased renal interstitial pressure (intrinsic renal compromise) might be under-appreciated mechanisms by which WRF develops. These findings may therefore help to explain why extra-renal strategies primarily aimed to relieve venous congestion (such as ultrafiltration) may be effective in alleviating "congestive kidney failure" in selected cases of heart failure rather than those augmenting cardiac output or forward perfusion. This is an important conceptual shift with broad implications, implying that the search for future ADHF therapies should focus on strategies that allow safe and optimal reduction of venous congestion to prevent worsening of renal function.

**c) A novel hemodynamic contributor: intra-abdominal pressure**

There has been increasing interest in measuring intra-abdominal pressure (IAP) in critically ill patients as elevated IAP has been associated with intra-abdominal organ dysfunction. We recently described the prevalence and significance of elevated IAP in consecutive patients admitted with ADHF scheduled to undergo invasive medical therapy guided by a pulmonary artery catheter (32). As demonstrated by our mechanistic observational study, elevated IAP in patients presenting with ADHF is common (60%) with a smaller proportion (10%) demonstrating IAH, which was not detected on routine history and physical exam (32). None of the patients in this study presented with abdominal discomfort as a subjective sign of elevated IAP, which shows that this phenomenon is often, if not always, asymptomatic in ADHF patients (16). One explanation might be that the fluid build up in these patients is often gradual over weeks, and thus, the rise in IAP may also be slow and insidious. Lowering of the IAP at follow-up was likely due to mobilization of fluid from the 'third space' through a combination of aggressive diuretic, vasodilator, and/or inotropic therapy. Indeed, successful hemodynamically-guided therapy, as evidenced by a reduction in right- and left-sided filling pressures together with improved cardiac output, coincided with the observed reduction in IAP in most patients (32). Moreover, a statistically significant impairment of renal function was noticed in the patients who presented with elevated IAP compared to the patients with normal IAP (32).

In addition, an IAP-guided approach aimed to reduce IAP by mechanical fluid removal (paracentesis in case of ascites and ultrafiltration in the absence of ascites) in patients with diuretic resistance, was associated with an impressive reduction in IAP and concomitant improvement in renal function (33). Although mechanical fluid removal is an invasive approach to treat ADHF patients with volume overload, our data suggest that this strategy may have significant advantages over standard medical therapy in selected cases.

The ability of IAP to provide insight into the underlying pathophysiologic target of the cardiorenal syndrome also provides an opportunity to test the hypothesis of an IAP-guided approach to the management of refractory heart failure. The advantage of measuring IAP includes the utilization of existing equipment commonly available and the relatively low cost of the procedure, both allowing easy clinical adoption. The simplicity of measuring IAP via the transvesical approach may allow early identification of elevated

IAP, and efforts to quickly lower IAP might substantially reduce the risk for subsequent renal failure. Indeed, raising IAP in patients with ADHF may alert the clinician that cardio-renal syndrome may be worsening before a rise in serum creatinine is seen, especially if laboratory values are only obtained once a day.

## 6. Cardiac resynchronization therapy, a therapy beyond hemodynamic restoration

### a) Background

There has been a longstanding recognition that an electrical intra-ventricular conduction delay (particularly as a result of left bundle branch block) will lead to improper coordination of timing in pumping function among the different cardiac chambers. This abnormal conduction delay, known as "dyssynchrony," may directly influence the heart's ability to pump efficiently (34,35,36,37,38). Recently, selected patients with advanced heart failure and dyssynchrony have found to benefit from an implanted device to simultaneously activate or pace both ventricles (biventricular or "BiV" pacing) (36). This approach is referred to as cardiac resynchronization therapy (CRT), and is thought to restore a normal coordination of the different atrial and ventricular contraction and relaxation sequences. At present, CRT is recommended in patients with advanced heart failure (New York Heart Association Class III or IV symptoms), severe systolic dysfunction (left ventricular ejection fraction ≤ 35%), on stable optimal medical therapy for at least three months and with electrical intra-ventricular conduction delay (eg, QRS width >120 msec).

### b) Restoring the force frequency relation and myocardial contractile reserve

In the intact normal heart, the force of contraction is augmented by an increase in heart rate or addition of a beta-agonist. This stepwise increase in tension seen at faster rates or during beta-agonist stimulation, known as the force frequency relation (FFR) or myocardial contractile reserve (MCR) are two of the hallmarks of LV contractility and are greatly attenuated or absent in patients with heart failure. However, if CRT would be capable of restoring this blunted FFR and MCR has not been investigated.

By assessing the force-frequency relationship through measuring of LV dP/dt during incremental heart rates in both atrial (AAI) and biventricular (DDD-CRT) pacing modes, with and without dobutamine infusion, we recently illustrated the contributions of restoring ventricular synchrony in the improvement of myocardial performance at baseline and at long-term follow-up (39,40). Acutely aftre CRT implantation, we demonstrated an upward shift of the FFR during DDD-CRT pacing as compared to that of AAI-pacing (39). In addition, we demonstrated for the first time that this upward shift of the FFR curve was related to beneficial effects of CRT upon dyssynchrony and diastolic filling time which were sustained at higher heart rates (39). These observations suggest that in the acute (baseline) setting, improvement of the myocardial contractile performance following CRT results primarily from a more synchronous activation rather than from intrinsic alteration of the contractile apparatus of the individual myocyte.

After three months of biventricular pacing, we observed a significant upward shift of the FFR from baseline to follow-up during AAI. This “unexpected” observation may be attributed to the improvement in myocardial structure with reversed LV remodeling induced by four months of BiV-pacing which lead to a reduction in LV volumina and mitral regurgitation (39). Moreover, a statistically significant reduction of dyssynchrony was observed in AAI illustrating that four months of CRT partially restored ventricular synchrony, which can also be related to reversal of LV structural remodeling (12). Second, in contrast to the AAI mode, CRT not only shifted the FFR curve upwards but also induced force-frequency amplification (39). Finally, chronic CRT also amplified the contractile reserve in response to inotropic stimulation (40). In conclusion, long term CRT pacing restores, at least partially, LV contractility.

**c) Restoring the myocardial contractile gene profile**

The adverse LV remodeling and the reduced contractile function observed in heart failure are associated with an altered gene expression profile. Accordingly, we recently investigated whether functional improvement following CRT would be associated with favorable changes in expression of established molecular structural and calcium regulatory markers of heart failure by taking serial LV endomyocardial biopsies in 24 patients sent for CRT implant (41). Our findings demonstrate that the beneficial effects of CRT on LV

function and remodeling are associated with “reversed molecular remodeling” characterized by an increase in expression of genes regulating excitation-contraction coupling and a reversal of the isoform switching of the contractile genes after three months of CRT (41). These data suggest that the contractile gene expression profile in human heart failure patients, already treated with optimal medical therapy with ACE-I, BB and spironolactone, is at least partially reversible and that molecular changes in structural and functional proteins may contribute to favorable effects of CRT on myocardial performance. Importantly, only the subgroup of patients with improved LV function, reversed LV remodeling and reduction in NYHA class, categorized as responders to CRT, did demonstrate an improvement in molecular remodeling (41).

**d) Restoring hemodynamics even in “non-responders”**

Up to one-third of patients may not see any improvement in clinical status and/or reversal of cardiac remodeling after 3-6 months of CRT (42,43,44,45). Therefore, one might postulate that “non-responders” may experience a diminished hemodynamic benefit by CRT over time. Recently, we investigated the effects of chronic CRT on invasive and echocardiographic hemodynamics in patients who did not exhibit beneficial reverse remodeling at a time period long after implantation. Importantly, invasive hemodynamic and echocardiographic assessments were performed with CRT ON and OFF in close temporal proximity, providing a more accurate measure of the extent of acute hemodynamic deterioration in the absence of biventricular pacing support, with a minimized likelihood for time-dependent changes in factors such as pre-load or heart rate to confound the analysis (46). The key finding is that long-term CRT continues to provide hemodynamic augmentation in a patient population typically categorized as clinical and echocardiographic “non-responders” to CRT (46). Therefore, it is important to recognize that like any effective drug or device therapy for patients with heart failure, response to therapy can be heterogeneous. In addition, lack of clinical or echocardiographic responses despite successful resynchronization should not directly imply lack of acute or chronic hemodynamic benefits from CRT. Instead, the appropriate interpretation from our “non-responder” population should consider the possibility that the hemodynamic augmentation following successful resynchronization by CRT may not be sufficient to warrant a

persistent meaningful change in the natural history of heart failure disease progression yet still may slow down the disease progression.

Moreover, we demonstrated that a routine multi-disciplinary protocol-driven approach of ambulatory CRT patients who did not exhibit a positive response is feasible without significant time commitment, and often leads to changes in device settings and/or other therapies which may result in reduced adverse events (47).

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# VI. Summary: Resurgence of Interest in the Hemodynamic Alterations of Advanced Heart Failure

## VI. Summary: Resurgence of Interest in the Hemodynamic Alterations of Advanced Heart Failure

Historically, cardiac insufficiency has always being allocated to be the culprit lesion of the heart failure syndrome. However, contemporary heart failure pharmacotherapy solely focuses on preservation of neurohormonal homeostasis. The research described in this manuscript is the result of thorough investigation of the hemodynamic alterations of hundreds of patients admitted for advanced decompensated heart failure (ADHF). Firstly, our data suggest that progressive cardiac insufficiency and hemodynamic derangements assessed through invasive hemodynamic monitoring, are still contributing to short- and long-term compromise, and this independent of race or gender. In addition, we demonstrated that restoring an optimal hemodynamic balance with add-on afterload reduction provides incremental intermediate- and long-term benefits over evidence based neurohormonal blockade alone. Indeed parental vasodilator therapy with sodium nitroprusside can be safely administered to achieve more hemodynamic improvement in patients presenting with ADHF. In addition, the institution of a more aggressive oral vasodilator regimen with isosorbide diniatrate / hydralazine over standard neurohormonal antagonists at the time of discharge after an episode of ADHF can safely maintain these hemodynamic improvements leading to improved outcomes. Another novel insight comes from the notice that venous congestion and raised intra-abdominal pressure, more than impaired cardiac output, seem to be related to the development of worsening renal function in patients admitted with ADHF. Treatment strategies with the aim of better renal preservation should therefore focus how to safely reduce this renal venous congestion with diuretic therapy, ultrafiltration or paracentesis whenever indicated. Finally, we demonstrated that cardiac resynchronization therapy (CRT) really acts as a novel “hemodynamic therapy” for advanced heart failure patients even in the patient population previously categorized as “non-responders”. Moreover, we have proven that the phenotypic improvement in heart failure status after prolonged CRT is paralleled by a reversed left ventricualr remodeling and recovery of left ventricular contractility. Thus, prolonged (hemodynamic) unloading of the heart will lead to physiological changes on the myocyte level in hearts once destined to only further deteriorate.

# VII. Conclusions and Future Perspectives

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Historically, cardiac insufficiency has always being allocated to be the culprit lesion of the heart failure syndrome. However, contemporary heart failure pharmacotherapy solely focuses on preservation of neurohormonal homeostasis. The current PhD project suggests that progressive cardiac insufficiency and hemodynamic derangements assessed through invasive hemodynamic monitoring, are still contributing to short- and long-term compromise, and this independent of race or gender. Therefore an invasive hemodynamic assessment should be incorporated in future risk models assessing risk for adverse events in patients with advanced heart failure.

In addition, restoring an optimal hemodynamic balance with add-on afterload reduction provides incremental intermediate- and long-term benefits over evidence based neurohormonal blockade alone. Parental vasodilator therapy can be safely administered to achieve more hemodynamic improvement in patients presenting with advanced decompensated heart failure (ADHF). In addition, the institution of a more aggressive oral vasodilator regimen with isosorbide dinitrate / hydralazine over standard neurohormonal antagonists at the time of discharge after an episode of ADHF can safely maintain these hemodynamic improvements leading to improved outcomes. While this might seem intuitive for the experienced clinician, this is a novel concept for most physicians as they mainly are focusing on instituting maximal neurohormonal blockade and reserve an invasive hemodynamic assessment for candidacy of cardiac transplantation. However, assessing invasive hemodynamics and if needed, restoring an optimal hemodynamic balance with vasodilators on top of neurohormonal blockade is the way to go since this approach improves outcome. These provocative results await verification in a prospective multi-center trial which is currently under design and underscore the importance of extra-cardiac physiology (vasculature) contributing to hemodynamic derangements in ADHF.

Another novel insight comes from the notice that venous congestion and elevated intra-abdominal pressure, more than impaired cardiac output, seem to be related to the development of worsening renal function in patients admitted with ADHF. These data challenge for the first time that low output secondary to cardiac insufficiency would be the core lesion responsible for worsening renal function in patients with ADHF, but advocate more a combination of cardio-circulatory defects leading to “congestive kidney failure”.

Nevertheless, further studies are warranted to determine the clinical utility of intra-abdominal pressure measurements in this challenging patient population. Based on the presented research, several cardiovascular research groups in Europe and the USA are collaborating and systematically collecting data on the incidence and clinical impact of intra-abdominal pressure in patients admitted with ADHF. Future translational cardio-vascular research will have to embrace biomedical engineering technology in order to better monitor and subsequently treat the aforementioned dismal responses related to heart failure. For example, miniature pressure / flow transducers built-in the abdominal cavity, cardio-renal vasculature or cardiac chambers might allow physicians to continuously monitor cardio-circulatory alterations which might provide novel insights into the pathophysiology and treatment options of advanced heart failure. While we anxiously await results from the aforementioned ongoing research protocols, it already became clear that future treatment strategies with the aim of better renal preservation should focus how to safely reduce renal venous congestion with diuretic therapy, ultrafiltration or paracentesis whenever indicated instead of only augmenting cardiac output with inotropic agents.

While cardiac resynchronization therapy (CRT) has expanded the treatment options for advanced heart failure tremendously, its use is eclipsed by high rate of so called "non-responders" with no clear clinical or echocardiographic improvement. However, this PhD project suggests that CRT might still provide hemodynamic augmentation in a patient population typically categorized as clinical and echocardiographic "non-responders" to CRT. These observations challenge the prevailing belief that patients with symptomatic disease progression have not derived benefit from CRT. This also implies that a response to CRT is much more complicated than a yes or no but merely consists of a whole array of echocardiographic, clinical and/or hemodynamic responses. Although a great amount of research has focused on how to predict a positive response, clearly this remains a very complex and challenging field with future work needed and several studies ongoing. Also, advances in our understanding of the pathophysiology of heart failure and associated conduction delays have great potential to impact future clinical practice and improve patient outcomes. For example, a routine protocol-driven approach of ambulatory CRT patients who did not exhibit a positive clinical response will result in reduced adverse events at follow-up. Also, the phenotypic improvement in heart failure status after

prolonged CRT seems to be paralleled by a reversed left ventricular remodeling and recovery of left ventricular contractility. Thus, prolonged (hemodynamic) unloading of the heart will lead to physiological changes on the myocyte level in hearts once destined to only further deteriorate. To which extent the restoration of synchrony and a normal hemodynamic balance, LV remodeling and reduced neurohormonal activation contribute to the observed molecular remodeling requires further investigation. Experimental studies with serial endomyocardial biopsies could unravel the time- and spatial-myocardial relationship of relevant molecular changes and further elucidate causative mechanisms underlying CRT-induced changes.

# VIII. Short Curriculum Vitae and List of Peer Reviewed Publications

## VIII. Short Curriculum Vitae and List of Peer Reviewed Publications

**Medical Degrees and Professional Appointments**

- Degree of Medical Doctor (Summa Cum Laude) at the Katholieke Universiteit Leuven, Belgium (07/1999).
- Degree of Cardiologist at the Katholieke Universiteit Leuven, Belgium (07/2005).
- Advanced Degree in Heart Failure and Cardiac Rehabilitation at the Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium (07/2006).
- Advanced Degree in Heart Failure and Cardiac Transplantation at the Cleveland Clinic Foundation, Cleveland, Ohio, United States of America (08/2007).
- Advanced Degree in Electrical Therapies for Heart Failure at the Cleveland Clinic Foundation, Cleveland, Ohio, United States of America (08/2008).
- Staff Cardiologist, Head of Heart Failure Section at the Ziekenhuis Oost-Limburg Genk, Belgium (09/2008).
- Associate Professor in the Faculties of Medicine and Biomedical Engineering of the Transnational University Limburg, Belgium and the Netherlands and the University of Hasselt, Belgium (09/2008).

**Scientific Work**

- Mentor for several biomedical- and medicine studens, internal medicine residents, and cardiology fellows in Belgium, and Cleveland Clinic, Cleveland, Ohio - USA.
- Invited speaker on numerous international medical / cardiology meetings in Belgium, Poland, the Netherlands, France, Italy, Spain, Finland, Germany and USA.
- Ad Hoc Journal Reviewer for 10 international Tier 1 Medical Journals.
- Principal Investigator in several (>15) medical and biomedical research projects.
- Finalist of Several Research Prizes including Samuel A Levine Young Investigator Award Competition at the American Heart Association Scientific Sessions in 2006.
- First Author of 37 Peer Reviewed Publications including Tier 1 Journals as the Journal of American College of Cardiology, Circulation, European Heart Journal, American Heart Journal, Journal of Cardiac Failure, and Heart Rhythm.

- First Author of 6 Book Chapters including renowned “Braunwald’s Heart Disease”.
- Presenter of 42 Abstracts at International Cardiology Meetings including American Heart Association, American College of Cardiology, European Heart Association….

**List of Peer Reviewed Publications**

1. Mullens W, Dubois C, Gielen F, Janssens S. Diagnosis and Therapy for Massive Pulmonary Embolism. (Diagnostisch en therapeutisch beleid bij massale longembolie. Casus en overzicht van de geactualiseerde richtlijnen.) *Belg Tijdsch Geneesk* 2003,6.
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10. Mullens W, De Keyser J, Herregods MC. Collapse of three cardiac chambers due to a pericardial effusion. *Int J Cardiol* 2008;123:e62-e63.
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13. Skouri H, Mullens W, Young J. Current Trends in Recipients Selection for Heart Transplantation. *Curr Opin Organ Transplant* 2007;12:529-35.
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# IX. Acknowledgements

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