Hemodynamic and neurochemical determinates of renal function in chronic heart failure

Cameron Gilbert, David Z. I. Cherney, Andrea B. Parker, Susanna Mak, John S. Floras
Abdul Al-Hesayen* and John D. Parker

From the Divisions of Cardiology and Nephrology, Mount Sinai and University Health Network and Saint Michael’s Hospitals* and the Department of Pharmacology and Toxicology, University of Toronto, Canada

Running Title: Renal function in heart failure

For correspondence:
John D. Parker MD
Division of Cardiology, Mount Sinai and University Health Network Hospitals
600 University Avenue, Suite 1609
Toronto, Canada, M5G 1X5
Tel: 1-416-586-4794
Fax: 1-416-586-8413
Email: john.parker@uhn.ca
Abstract

Abnormal renal function is common in acute and chronic CHF and is related to the severity of congestion. However, treatment of congestion often leads to worsening renal function. Our objective was to explore basal determinants of renal function and their response to hemodynamic interventions. Thirty-seven patients without CHF and 59 patients with chronic CHF (EF, 23±8%) underwent right heart catheterization, measurements of glomerular GFR (inulin), RPF (para-aminohippurate), and radiotracer estimates of renal sympathetic activity. A subset (26 without, 36 with CHF) underwent acute pharmacologic intervention with dobutamine or nitroprusside. We explored the relationship between baseline and drug-induced hemodynamic changes and changes in renal function. In CHF, there was an inverse relationship between RAM pressure, RPF and GFR. By contrast, MAP, CI and measures of renal sympathetic activity were not significant predictors. In those with CHF there was also an inverse relationship between the drug-induced changes in RAM as well as PAM pressure and the change in GFR. Changes in MAP and CI did not predict the change in GFR in those with CHF. Baseline values and changes in RAM pressure did not correlate with GFR in those without CHF. In the CHF group there was a positive correlation between RAM pressure and renal sympathetic activity. There was also an inverse relationship between RAM pressure, GFR and RPF in patients with chronic CHF. The observation that acute reductions in RAM pressure is associated with an increase in GFR in patients with CHF has important clinical implications.

Key words. heart failure, renal function, hemodynamics, sympathetic nervous system
Introduction

Although some patients with congestive heart failure (CHF) have concomitant primary renal disease, many have abnormalities of renal function with no identified cause, a phenomenon now referred to as the cardiorenal syndrome. Renal insufficiency, most commonly assessed by creatinine-based estimates of glomerular filtration rate (GFR), is now recognized as a powerful independent predictor of mortality in patients with both chronic and acute decompensated CHF. (19, 20) Other investigations have confirmed the importance of baseline renal function, and its response to therapy, as a determinant of clinical outcome. (6)

The pathophysiologic mechanisms underlying the interactions between the heart and kidney that lead to abnormal renal function in CHF are poorly understood. Earlier reports (7) found that cardiac output was an important determinant of GFR, however these patients had very severe CHF with markedly depressed cardiac output. More recently, invasive studies have suggested that systemic blood pressure and cardiac index are not independently related to estimates of GFR. (35) In contrast, venous congestion with high right-sided filling pressures has been reported as independent predictor of estimated GFR, as well as mortality. (10, 35) This observation stands in contrast to a number of earlier reports that found little impact of venous renal pressure on renal blood flow and GFR. (23, 25, 38) However, these reports examined the impact of an increase in renal venous pressure in animals without CHF, and were isolated to the renal vascular bed in the absence of increases in systemic venous pressure. Although increased venous pressure appears to be a predictor of estimated GFR and clinical outcome, therapy of venous congestion does not consistently lead to improvement in these endpoints. Some
patients with severe congestion respond well to therapy with relief of congestion and an
improvement in GFR, while in others congestion persists and renal function worsens.

The current paper describes the relationship between direct measurements of GFR
(inulin) and renal plasma flow (RPF, para-aminohippurate), invasive hemodynamics and
measures of renal sympathetic activity (radiotracer methodology) in a group of patients
without CHF (and preserved LV systolic function) and a group with chronic CHF
secondary to LV systolic dysfunction. Based on previous animal observations and some
human studies we hypothesized that there would be an inverse relationship between
cardiac filling pressures and measures of renal function. In addition, we examined the
impact of acute changes in hemodynamics on these variables. Our aim was to explore the
hemodynamic and neurochemical determinates of renal function and its response to
hemodynamic intervention in patients with CHF.
Methods

Study Population

Data was obtained from 96 patients undergoing an elective diagnostic catheterization in our research cardiac catheterization laboratory. All patients had agreed to participate in a research study to be carried out at the end of the diagnostic cardiac catheterization and in all cases written, informed consent was obtained.

The no CHF group consisted of 37 patients (26 men, 11 women; age 67±9 years) with preserved LV systolic function (ejection fraction > 50%) who had no current or prior symptoms of CHF. These patients had been referred for assessment of chest pain and were found to have normal coronary arteries (n = 14) or stable coronary artery disease (n = 23) at the time of coronary angiography. Those with normal coronary arteries were felt to have atypical chest pain. In those with coronary artery disease 19 were felt to have angina while the remaining 4 patients were felt to have atypical chest pain. The no CHF group had normal cardiac filling pressures and cardiac output during the right heart catheterization performed prior to research study procedures. Patients with significant valvular disease or evidence of an acute coronary syndrome were excluded. The remaining 59 patients (51 men, 8 women, age 69±12 years) had a history of stable, chronic CHF secondary to left ventricular systolic dysfunction with an ejection fraction ≤40%. They had been referred for cardiac catheterization as part of their diagnostic assessment. Of this group, 49 patients had significant coronary artery disease. Patients in the CHF group had stable symptoms (NYHA class II/III). Patients with CHF due to valvular heart disease or acute ischemia were specifically excluded. For both groups,
evidence of renal parenchymal disease (active urine sediment or significant proteinuria) or known renal artery disease were exclusions.

Patients in the no CHF group were taking various medications. These drugs include long-acting nitrates \((n = 6)\), beta-adrenergic receptor blockers \((n = 12)\), calcium channel antagonists \((n = 7)\) and/or inhibitors of the renin angiotensin system \((n = 21)\). Patients with CHF were taking angiotensin converting enzyme inhibitors or angiotensin II antagonists \((54 \text{ of } 59)\) while 46 of 59 were on stable doses of beta-adrenergic blockers. In those taking furosemide \((57 \text{ of } 59)\) the dose ranged from 20-160 mg daily. Only 20 patients in the CHF group were taking spironolactone and 6 were on a concomitant thiazide.

Some of the patients presented here \((11 \text{ in the no CHF group and } 22 \text{ with CHF})\) participated in prior reports of the effect of nitroprusside and dobutamine on renal sympathetic activity. \((1, 2)\)

**Cardiac Catheterization Protocol**

Hemodynamic, neurochemical and renal function data presented here were obtained from a series of investigations examining the control and regulation of renal sympathetic activity. The Mount Sinai Hospital Ethics Review Committee for experimentation involving human subjects approved the study protocols and all patients gave written informed consent.

All medications were held on the morning of the catheterization procedure. A right heart catheterisation was performed in all patients and arterial pressures were obtained from the femoral arterial sheath. A subset of patients \((n = 29)\) had a high-
fidelity catheter (Millar industries, Houston, Texas) placed in the LV for measurement of peak + dP/dt. Measurements of heart rate (HR), mean arterial pressure (MAP), right atrial mean (RAM), pulmonary artery mean (PAM), Pulmonary capillary wedge pressure (PCWP) and left ventricular (LV) peak +dP/dt were acquired with 15 cardiac cycles averaged for the final value. Cardiac index (CI) was measured by the Fick method and estimates of body surface area. From the left femoral vein, a Judkins JL4 catheter was placed in the right renal vein.

**Neurochemical measurements**

Cardiac and total body sympathetic activity was estimated using radiotracer methodology. For these measurements, tritiated norepinephrine (NE; New England Nuclear, Boston, Massachusetts) was infused into a peripheral vein to steady state concentration in plasma. TBNESP, an index of the total amount of NE presenting to the plasma compartment over time was calculated as:

\[
TBNESP = \frac{[\text{^3H}] \text{ infusion rate}}{\text{Plasma NE specific activity}}
\]

Renal NE production was estimated by calculating renal NE spillover (RNESP):

\[
RNESP = \left( (C_{rv} - C_{art}) + C_{art} \times (NE_{extr}) \right) \times \text{RPF}
\]

where \(C_{rv}\) is the NE concentration in the renal vein, \(C_{art}\) is the NE concentration in the artery and \(NE_{extr}\) is the extraction of radiolabelled NE across the kidney. Our laboratory has experience with all of the techniques described and details of the methodology can be found in previous publications. (4, 36)
Measures of Renal Function

RPF was measured by use of the para-aminohippurate clearance technique. GFR was measured by use of inulin clearance. Arterial versus renal vein concentrations of p-aminohippurate and inulin were determined to measure RPF and GFR using established methods in our laboratory. (2) Values for GFR and RPF in mls/min were normalized to body surface area in m²/1.73.

Pharmacologic Intervention

A subgroup of patients received a drug intervention after control measurements were completed. One group (n = 29, 14 in the no CHF group and 15 with CHF) had an intravenous infusion of dobutamine, starting at 2.5 μg/kg/min, following baseline haemodynamic measurements. The dobutamine infusion rate was increased until the LV +dP/dt had increased by 20%. Hemodynamic, renal function and neurochemical responses were measured 30 minutes later.(1) A separate group (n = 33, 12 in the no CHF group and 21 with CHF) had an intravenous infusion of sodium nitroprusside, starting at 10 μg/min. The nitroprusside infusion rate was increased until MAP had decreased by 10%. Hemodynamic, renal function and neurochemical responses were reassessed 30 minutes after this reduction in mean arterial pressure had been achieved.(2)

The peak change in hemodynamic, neurochemical and renal functional parameters was calculated (drug versus control) and regression analyses carried out to explore the relationship between changes in renal function and the changes in hemodynamic and neurochemical variables. The responses to dobutamine and nitroprusside were combined.
so that the effect of a broad spectrum of hemodynamic changes and renal function parameters could be observed.

Statistical Methods

Data were analyzed using the Stagraphics, version 1.1.2; Warrenton, Virginia. Comparison of baseline characteristics, haemodynamics and neurochemical variables between the no CHF and CHF groups were determined using either Student t-tests or a chi-square test. A p-value of <0.05 was considered significant. Baseline hemodynamic and neurochemical correlates of GFR, RPF, and RNESP were determined by univariate, followed by stepwise linear regression. Independent variables included age, HR, MAP, RAM, PAM, PCWP, CI, RNESP, TBNESP, RPF and renal pressure (RPP). Similar univariate and multiple regression analyses were carried out examining the relationships between changes in hemodynamic and neurochemical variables with changes in renal function using the same independent and dependent variables described above. A threshold of $P \leq 0.15$ in the univariate analysis was used for entry into the multivariate analysis. Using this threshold, no more than 4 independent variables were entered into any of the multivariate models. Independent variables were only considered to make an independent contribution to the model if they remained in the model with a $P$ value of $\leq 0.05$. Data are presented as mean ± SD.
Results

Baseline patient characteristics are presented in Table 1. The groups with and without CHF were similar in age. Those with CHF had lower systemic arterial pressures, CI, GFR as well as RPF. They also manifest increased central filling pressures and measures of systemic and renal-specific sympathetic activity.

GFR - Variables contributing to the model (Figure 1, Table 2)

In the group without CHF, the univariate analysis revealed a significant positive relationship between GFR and RPF (P < 0.0001) but no relationship between GFR and other variables. In the multivariate regression model, the only variable making a significant contribution to the model with GFR as the dependent variable was RPF.

In those with CHF, there was also a positive univariate relationship between GFR and RPF as well as with RPP (P < 0.0001 and 0.04 respectively). Further, there was a significant inverse univariate relationship between GFR and RAM pressure (Figure 1, P < 0.001). In the multivariate analysis, RPF and (RPP) both made independent contributions to the model of GFR (Table 2). If RPP was not entered in the model, the multivariate model again revealed an independent contribution from RPF but also significant contributions from the components of RPP, namely RAM and MAP (Table 2). Of note, as with the univariate analysis, in the multivariate model, RAM showed a negative relationship with GFR, with higher right atrial pressures being associated lower values of GFR.
In the group without CHF, the univariate analysis revealed an inverse relationship between RPF and both PAM and RAM ($P = 0.008$ and $0.03$ respectively, Table 2). In the multiple regression analysis, no independent variable made a significant contribution to the model with RPF as the dependent variable in the group without CHF. In the CHF group there was a negative correlation between RAM and RPF in both the univariate and multivariate analysis; no other variable had a significant relationship to RPF (Table 2).

In the group without CHF there was a significant inverse relationship between RNESP and MAP ($P < 0.04$), a relationship that the multivariate stepwise procedure confirmed was independent of other variables (Table 2). In those with CHF only TBNESP (a measure of total body sympathetic activity) had a significant relationship to RNESP in both the univariate analysis ($P < 0.02$) and in the multivariate analysis (Table 2). No hemodynamic variable was associated with renal sympathetic activity in those with CHF.

The administration of nitroprusside and dobutamine was associated with a significant range of change in hemodynamics in both groups. The percent change and range of change for each variable are presented in Table 3.
Change in GFR - Variables contributing to the model (Table 4, Figure 2)

In the group without CHF, the univariate analysis revealed a significant positive correlation between the change in GFR and the change in RPF (P < 0.0001). There was also a significant positive univariate relationship between the change in GFR and the change in both MAP (P = 0.02) and RPP (P < 0.01). In this group, the multivariate regression analysis revealed that the change in RPF and RPP both made independent contributions to the model where the change in GFR was the dependent variable. If the components of RPP (RAM and MAP) were included in the analysis the result was very similar in that both the change in RPF and MAP made independent contributions to the model.

In the CHF group there was an inverse relationship between the change in RAM, PAM as well as PCWP and the change in GFR (P all < 0.01, Table 4, Figure 2). In the multivariate regression model RAM and PAM pressures both made independent contributions to the model of the change in GFR, demonstrating that decreases in cardiac filling and pulmonary pressures were associated with increases in GFR. In contrast, there was no relationship between the change in GFR and the change in RPP or the change in cardiac index by either the univariate or multivariate regression analysis.

As can be seen in figure 2 (panel B), the slopes of the regression lines depicting the relationship between the change in GFR and the change in RAM pressure in the CHF group were essentially identical when the effects of nitroprusside and dobutamine were examined separately. Similar findings were found in the group without heart failure when the relationship between the change in GFR versus the change in MAP were separated
into the subjects that received nitroprusside versus those that received dobutamine (Figure 2, panel C).

Change in RPF - Variables contributing to the model (Table 4)
No variable was associated with the change of RPF in the univariate or multivariate regression analysis in either group.

Change in Renal Sympathetic Activity - Variables contributing to the model (Table 4)
In those without CHF, the univariate analysis revealed that the change in the RNESP was inversely related to the change in both MAP and CI (P < 0.04 and 0.02 respectively). There was also a positive univariate relationship between the change in TBNESP and this measure of renal-specific sympathetic activity (P < 0.0001). In the multivariate regression only the change in TBNESP was significantly related to the change in the RNESP (Table 4). In the group with CHF, there was also an inverse relationship between the change in both MAP and RPP and the change in the RNESP (P < 0.04 and 0.01 respectively). In the multivariate regression model the change in TBNESP, CI and RAM made independent contributions to the model of the change in the RNESP (Table 4).
Discussion

Renal insufficiency is very common in the setting of both chronic and acute decompensated CHF, with 30-35 percent of patients having a moderate reduction in GFR. (33, 39) Traditionally, it was believed that renal insufficiency in CHF was secondary to a reduction in cardiac output and effective circulating blood volume. Early studies documented that severe CHF, with very low cardiac output, is associated with reductions in both RPF and GFR. (7, 31) However, in patients with moderate reductions in cardiac output, GFR can be maintained in the face of moderate reductions in RPF, as filtration fraction increases to compensate for the reduction of filtered volume. This is mediated by an increase in glomerular filtration pressure secondary to constriction of efferent glomerular arterioles. Despite this ability to maintain GFR, the majority of patients with CHF are not hypotensive and do not have evidence of low cardiac output. However, despite the presence of normal blood pressure they often have significant renal dysfunction with reduced GFR. In such patients, the cause of renal insufficiency remains ambiguous, with multiple suggested mechanisms, but no consensus. The data presented here, explore differences in the control of renal function in a group of patients with normal hemodynamics and no history of CHF as compared to patients with chronic CHF secondary to LV systolic dysfunction.

Analysis of baseline variables confirms that RPF is the only independent determinant of GFR in the group without CHF. In the CHF group there was also a strong univariate correlation between RPF and GFR, as has been previously described. (7) In the multivariate analysis, RPF made the strongest contribution to the model predicting GFR, however in this group RPP was also an important determinant – with lower pressures
associated with lower GFR. If the components of RPP (RAM and MAP) were entered into the model, instead of RPP, both made significant contributions, with higher RAM pressures predicting lower GFR. In the group without CHF, there was no independent predictor of RPF, while in those with CHF, only RAM pressure was an independent predictor of RPF. Overall, these observations point to an interaction between right atrial pressure and renal function in patients with CHF. This is consistent with a number of prior observations that venous congestion/elevated central venous pressure is associated with reduced renal function as assessed by estimated GFR in patients with CHF (3, 35) and those with pulmonary hypertension. (10) In fact, this inverse relationship between right atrial pressure and GRF has been demonstrated across a broad spectrum of patients with cardiovascular disease. (11) Previously, only one small study has examined the relationship between cardiac filling pressures and directly measured GFR. (26) These studies all examined the relationship between baseline right-sided filling pressures and renal function in patients with CHF, and did not describe the response to a hemodynamic intervention. As will be discussed below, the interaction between right atrial pressure and renal function is further supported by our observations concerning effect of acute, drug-induced changes in hemodynamics and measures of both RPF and GFR.

The current analysis also provides unique information concerning the response of renal function to acute hemodynamic interventions. A number of studies have examined the impact of vasodilators and positive inotropes on renal blood flow, (27-30, 32) but remarkably few have made use of direct measures of GFR. (8, 16, 21, 37). These studies reported hemodynamic and GFR responses to a pharmacologic intervention as the mean change of each variable but did not examine the relationship between individual
hemodynamic and GFR responses. In this regard, our observations make a significant contribution to our knowledge in this area. The findings demonstrate that in the setting of CHF, reductions in right atrial and pulmonary pressures are associated with increases in GFR. Importantly, this inverse relationship is similar to the (paradoxical) relationship found between RAM and GFR at baseline. Of note, the relationship between the change in RAM pressure and the change in GFR was essentially identical whether the hemodynamic effect was mediated by dobutamine or nitroprusside, suggesting that the GFR response was not mediated by a specific pharmacodynamic effect of either drug. Importantly, changes in systemic arterial blood pressure and cardiac output in patients with CHF were not related to changes in GFR. This is consistent with prior observations that therapy with vasodilators or positive inotropic agents is not associated with significant changes in GFR. (8, 30) By contrast, in the group without CHF, the predictors of a change in GFR were quite different, with independent contributions from changes in RPF and MAP. These contrasting responses emphasize that the impact of hemodynamic changes on renal function in patients with CHF cannot be predicted by what is anticipated from normal physiology.

The mechanism of the association between elevated central venous pressure and reduced GFR, to date, remains speculative. Normal physiology defines a positive relationship between central venous pressure and GFR whereby increased filling pressures increases filtration and natriuresis. In animal models, elevation of renal venous pressure, even to values as high as 30-50 mmHg are not associated with significant changes in either renal blood flow or GFR. However, these animals did not have heart failure and the increase in venous pressure was isolated to the renal vein. (23, 25, 38)
the setting of CHF, however, the renal response to increased atrial pressure appears to be
abnormal. Elegant work by Zucker and colleagues demonstrated that increases in atrial
pressure and dimensions lead to a brisk natriuresis in normal dogs, but not in those with
CHF. (43) Other studies demonstrated that atrial distension in the setting of heart failure
is associated with a paradoxical increase in renal sympathetic nerve activity, as compared
to a sympatholytic effect in normal animals. (12, 42) These observations are relevant to
the findings presented here, since they suggest a mechanism by which increased atrial
pressures in the setting of CHF can lead to increases in sympathetic activity with
subsequent adverse effects on renal function. Increased renal sympathetic activity can
modify glomerular filtration pressure, is associated with increased sodium absorption and
with augmented renin release. (13) Renal sympathetic activity was elevated in the current
CHF population, when compared to the group without CHF; however, this measure was
not an independent determinant of GFR. Importantly, this does not mean that renal
sympathetic activity has no impact on renal filtration in CHF, but rather that it is not an
independent determinant.

The current observations suggest that therapy aimed at reducing filling pressures
would be an obvious therapeutic aim. We acknowledge that the current interventions
were short (30-40 minutes) and did not involve the use of diuretics. Clinical experience
makes it clear that the response to therapy directed at relieving congestion has variable
effects, and, unfortunately, is often associated with deterioration in renal function.
Although we did not find that changes in blood pressure (or cardiac output) were
independently related to the changes in renal function in patients with CHF, this does not
imply that such systemic effects have no impact on GFR or renal blood flow. Renal
function is at most risk when interventions aimed at reducing congestion are associated
with significant reductions in systemic arterial blood pressure, a finding that has been
clearly documented when such interventions are sustained over several days. (15, 40)
Furthermore, it must be emphasized that increases in cardiac filling pressure are not
always representative of an increase in total body volume. Recent commentaries have
served to remind us of this fact, pointing out that in some patients, intra-thoracic
congestion can result from a shift in volume from the intra-abdominal capacitance veins.
(17) Similarly, changes in cardiac filling pressure are not necessarily dependent on
changes in venous blood volume as, in some cases, they may be mediated by changes in
the compliance or distensibility of venous capacitance system. As such, changes in
cardiac filling pressures during therapy may not correlate with changes in volume or
weight loss, a finding that has recently been convincingly reported. (3) Making matters
more complicated is the fact that patients with CHF routinely receive multiple different
drugs that can have direct and indirect effects on renal function. The summative effects of
such different lines of therapy on intracardiac pressures, intravascular volume and renal
function can, in the individual patient, be very difficult to predict. These complex
relationships are becoming increasingly recognized and have been nicely summarized in
recent publications. (17, 41)

Diuretic therapy, particularly loop diuretic therapy, plays a central role in the
therapy of congestion. However, diuretics have multiple effects that can modify renal
function. They can impact intravascular volume and sodium balance, with secondary
effects on systemic blood pressure and cardiac output as well as neurohormonal
responses. They also have vasoactive effects (both systemic and intrarenal) that are time-
dependent. (14, 18) Less obvious to the practitioner, is the fact that diuretics can have important direct effects on renal function modifying GFR both through both their vasoactive effects and their ability to alter distal tubular sodium delivery, via the tubuloglomerular feedback mechanism.

The observation that elevated cardiac filling pressures are associated with reduced GFR, combined with the finding that lowering filling pressure appears to improve renal filtration, serves to emphasize that relief of congestion remains a priority not only for the management of symptoms but also, potentially, because it may improve renal function. However, the recognition that diuretics can have deleterious effects on renal function, even in the absence of volume contraction or systemic hypotension, serves to emphasize that better strategies to manage congestion and lower cardiac filling pressures without having adverse effects on renal function are urgently required. To date, other approaches to reducing intravascular volume have focussed on the use of ultrafiltration, but here too adverse effects of such volume reduction on renal function are well documented. (5, 9)

The data presented here provide unique information concerning the relationship between baseline hemodynamic parameters and renal sympathetic activity. Along with the heart, the kidney is subject to increased renal sympathetic activity in patients with chronic CHF.(22) Cardiac filling pressures and pulmonary artery pressures are closely correlated with increased cardiac sympathetic activity; (24) a positive correlation that is not predicted by normal physiology. In the current data set, there was no systematic relationship between filling pressures and renal sympathetic activity at baseline, which to our knowledge, has not been reported previously in humans. It is of interest that during a hemodynamic intervention, a reduction in right atrial pressure did predict a decrease in
renal sympathetic activity. The response was similar to that observed for cardiac sympathetic activity in patients with CHF where acute reductions of cardiac filling pressures, in the absence of systemic blood pressure reduction, have a sympathoinhibitory effect. (4) It is also consistent with prior observations in animal models of CHF in which increase in right atrial pressure were associated with paradoxical increases in sodium avidity and renal sympathetic activity. (12, 42)

This study provides novel information relating detailed hemodynamic and neurochemical parameters to direct measures of GFR and RPF. However, it is important to emphasize a number of limitations. First, the CHF population studied had severe left ventricular systolic dysfunction but were stable and well compensated at the time of the study. As such, their responses may not be symmetric with what would be observed in a population with acute decompensated CHF. Second, as mentioned above, the hemodynamic interventions were brief and, although they provide unique insight into the apparent salutary effects of lowering cardiac filling pressures in those with CHF, their short duration cannot be used to predict longer-term responses and the superimposed effect of concurrent diuretic therapy. Third, the drugs used here have complex pharmacodynamic actions that include direct renal, systemic vascular and central effects and their impact on renal functional responses may well be different as compared to other pharmacologic and non-pharmacologic interventions. Fourth, the background medical therapy of these patients may well have an impact on the observed responses. Finally, although we have documented a relationship between drug-induced changes in filling pressure and GFR it is clear other factors play a role in mediating the GFR response to these interventions. Future studies should expand the current observations to longer time
periods and evaluate the impact of diuretic therapy and/or ultrafiltration on these direct
measures of RPF and glomerular filtration while exploring the impact of therapy on renal
tubular handling of sodium in an effort to better understand the impact of
tubuloglomerular feedback on renal vascular resistance and GFR.

Perspectives and Significance

Venous congestion is an important determinant of GFR and RPF in patients with CHF. The current findings confirm that increased cardiac filling pressures have an impact on
baseline GFR and that acute reduction in these pressures is associated with an increase in
GFR. In contrast, RPP and CI did not play a significant role in the regulation of renal
function at baseline or in response to pharmacologic interventions in this CHF
population. An improved mechanistic understanding of the renal functional responses to
therapies designed to relieve congestion is required, and should help devise therapeutic
approaches that allow relief of congestion without the adverse effects on renal that are so
commonly seen today.
Acknowledgements

Supported, in part, by an operating grant from the Canadian Institute for Health Research (RN136292 – 260133)
Figure Legends

Figure 1
Univariate relationship between glomerular filtration rate (GFR) and right atrial mean pressure in the group without CHF (panel A) and those with chronic CHF (panel B). Univariate relationship between GFR and renal perfusion pressure in the group without CHF (panel C) and those with chronic CHF (panel D). Univariate relationship between GFR and mean arterial pressure in the group without CHF (panel E) and those with chronic CHF (panel F).

Figure 2
Univariate relationship between the change in GFR and the change in mean right atrial pressure in the group without CHF (panel A) and those with chronic CHF (panel B). Univariate relationship between the change in GFR and the change in renal perfusion pressure in the group without CHF (panel C) and those with chronic CHF (panel D). Univariate relationship between the change in GFR and the change in mean arterial pressure in the group without CHF (panel E) and those with chronic CHF (panel F)
**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>No CHF Group (n = 37)</th>
<th>CHF (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67 ± 9</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Diabetes (type 11)</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Male/Female</td>
<td>26/11</td>
<td>51/8†</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78±10</td>
<td>83±8</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9±0.2</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8±3.1</td>
<td>29.5±2.7</td>
</tr>
<tr>
<td>Hct</td>
<td>0.430 ± 0.033</td>
<td>0.409 ± 0.048*</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>80 ± 16</td>
<td>113±45*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>65 ± 9</td>
<td>73 ± 14*</td>
</tr>
<tr>
<td>EF, percent</td>
<td>59 ± 8</td>
<td>23 ± 8*</td>
</tr>
<tr>
<td>RAM, mmHg</td>
<td>2 ± 2</td>
<td>6 ± 5*</td>
</tr>
<tr>
<td>PAM, mmHg</td>
<td>13 ± 4</td>
<td>27 ± 11*</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>6 ± 3</td>
<td>15 ± 9*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>99 ± 15</td>
<td>82 ± 15*</td>
</tr>
<tr>
<td>RPP, mmHg</td>
<td>96 ± 15</td>
<td>76 ± 17</td>
</tr>
<tr>
<td>Cl, L/min/m²</td>
<td>2.5 ± 0.4</td>
<td>2.3 ± 0.5*</td>
</tr>
<tr>
<td>GFR, ml/min/1.73m²</td>
<td>107 ± 33</td>
<td>91 ± 26*</td>
</tr>
<tr>
<td>RPF, ml/min/1.73m²</td>
<td>508 ± 115</td>
<td>408 ± 125*</td>
</tr>
<tr>
<td>Filtration Fraction, percent</td>
<td>21.5 ± 5.0</td>
<td>23.6 ± 6.9</td>
</tr>
<tr>
<td>NE&lt;sub&gt;ar&lt;/sub&gt;, nmol/L</td>
<td>1.6 ± 1.1</td>
<td>2.1 ± 1.3*</td>
</tr>
<tr>
<td>NE&lt;sub&gt;rv&lt;/sub&gt;, nmol/L</td>
<td>2.1 ± 1.1</td>
<td>3.1 ± 1.7*</td>
</tr>
<tr>
<td>TBNESP, nmol/min</td>
<td>4.8 ± 2.7</td>
<td>7.1 ± 4.0*</td>
</tr>
<tr>
<td>RNESP, pmol/min</td>
<td>707 ± 404</td>
<td>926±509*</td>
</tr>
</tbody>
</table>

Hgb, haemoglobin; Hct, hematocrit; HR, heart rate; EF, ejection fraction; RAM, right atrial mean pressure; PAM, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial blood pressure; RPP, renal perfusion pressure; CI, cardiac index; GFR, glomerular filtration rate; RPF, renal plasma flow; NE<sub>ar</sub>, arterial norepinephrine; NE<sub>rv</sub>, renal vein norepinephrine; TBNESP, total body norepinephrine spillover; RNESP, renal norepinephrine spillover; * P<0.05 versus no CHF group; † P = 0.053 vs no CHF group
### Table 2: Stepwise Regression: Baseline Variables

#### Predictors of GFR

<table>
<thead>
<tr>
<th>No CHF Group</th>
<th>Adjusted $R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate Model</strong></td>
<td>0.445</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td><strong>Contributing Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPF</td>
<td></td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

| CHF Group | | |
| **Multivariate Model (RPP)** | 0.524 | $<0.0001$ |
| **Contributing Variables** | | |
| RPF | | $<0.0001$ |
| RPP | | $0.001$ |

| CHF Group | | |
| **Multivariate Model (MAP and RAM)** | 0.536 | $<0.0001$ |
| **Contributing Variables** | | |
| RPF | | $<0.0001$ |
| MAP | | $0.006$ |
| RAM [-ve coef] | | $0.006$ |

#### Predictors of RPF

<table>
<thead>
<tr>
<th>No CHF Group</th>
<th>Adjusted $R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate Model</strong></td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

| CHF Group | | |
| **Multivariate Model** | 0.143 | $<0.004$ |
| **Contributing Variables** | | |
| RAM [-ve coef] | | $<0.004$ |

#### Predictors of RNESP

<table>
<thead>
<tr>
<th>No CHF Group</th>
<th>Adjusted $R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate Model</strong></td>
<td>0.1</td>
<td>$&lt;0.009$</td>
</tr>
<tr>
<td><strong>Contributing Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>

| CHF Group | | |
| **Multivariate Model** | 0.095 | $<0.02$ |
| **Contributing Variables** | | |
| TBNESP | | $<0.02$ |

GFR, glomerular filtration rate; CHF, congestive heart failure; RPF, renal plasma flow; RPP, renal perfusion pressure, MAP, mean arterial pressure, RAM, right atrial mean pressure, RNESP, renal norepinephrine spillover.
Table 3: Pharmacologic Intervention: Hemodynamic Changes

<table>
<thead>
<tr>
<th></th>
<th>No CHF Group (n = 26)</th>
<th>CHF (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ HR, bpm</td>
<td>8±10% (-3 ; 21)</td>
<td>3±11% (-13 ; 20)</td>
</tr>
<tr>
<td>Δ RAM, mmHg</td>
<td>-43±91% (-6 ; 2)</td>
<td>-70±71% (-8 ; 2)</td>
</tr>
<tr>
<td>Δ PAM, mmHg</td>
<td>-20±28% (-5 ; 3)</td>
<td>-23±24% (-20 ; 5)</td>
</tr>
<tr>
<td>Δ PCWP, mmHg</td>
<td>-38±46% (-10 ; 7)</td>
<td>-24±65% (-25 ; 5)</td>
</tr>
<tr>
<td>Δ MAP, mmHg</td>
<td>--3±10% (-17 ; 13)</td>
<td>-6±13% (-22 ; 22)</td>
</tr>
<tr>
<td>Δ RPP</td>
<td>-1±11% (-22 ; 18)</td>
<td>-1±15% (-22 ; 20)</td>
</tr>
<tr>
<td>Δ CI, L/min/m²</td>
<td>2±17% (-0.8 ; 0.7)</td>
<td>14±22% (-1.0 ; 1.4)</td>
</tr>
<tr>
<td>Δ GFR, ml/min/1.73m²</td>
<td>3±9% (-12 ; 21)</td>
<td>8±17% (-12 ; 36)</td>
</tr>
<tr>
<td>Δ RPF, ml/min/1.73m²</td>
<td>5±36% (-24 ; 136)</td>
<td>8±10% (-92 ; 161)</td>
</tr>
<tr>
<td>Δ Renal Filtration Fraction, percent</td>
<td>-1±8% (-0.020 ; 0.021)</td>
<td>3±24 (-0.122 ; 0.137)</td>
</tr>
<tr>
<td>Δ RNESP, pmol/min</td>
<td>14±99% (-2.6 ; 2.0)</td>
<td>1±78% (-5.4 ; 2.4)</td>
</tr>
<tr>
<td>Δ TBNESP, nmol/min</td>
<td>35±74% (-0.84 ; 5.77)</td>
<td>0.04 (-2.78 ; 3.044)</td>
</tr>
</tbody>
</table>

Values presented as %change±SD (range), control versus drug; HR, heart rate; RAM, right atrial mean pressure; PAM, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial blood pressure; RPP, renal perfusion pressure; CI, cardiac index; GFR, glomerular filtration rate; RPF, renal plasma flow; NE_{art}, arterial norepinephrine; NE_{rv}, renal vein norepinephrine; TBNESP, total body norepinephrine spillover; RNESP, renal norepinephrine spillover
Table 4. Stepwise Regression: Pharmacologic Intervention

Predictors of the change in GFR

<table>
<thead>
<tr>
<th>No CHF Group</th>
<th>Adjusted $R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate Model (RPP)</strong></td>
<td>0.594</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Contributing Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$ RPF</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>$\Delta$ RPP</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

| No CHF Group                  |                |           |
| **Multivariate Model (MAP and RAM)** | 0.563          | < 0.0001  |
| **Contributing Variables**    |                |           |
| $\Delta$ RPF                 |                | < 0.001   |
| $\Delta$ MAP                 | 0.004          |           |

| CHF Group                     |                |           |
| **Multivariate Model**        | 0.401          | 0.0002    |
| **Contributing Variables**    |                |           |
| $\Delta$ PAM [-ve coef]       | 0.002          |           |
| $\Delta$ RAM [-ve coef]       | < 0.02         |           |

Predictors of the change in RPF

<table>
<thead>
<tr>
<th>No CHF Group</th>
<th>Adjusted $R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate Model</strong></td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

| CHF Group                     |                |           |
| **Multivariate Model**        | ----           | ----      |

Predictors of the change in RNESP

<table>
<thead>
<tr>
<th>No CHF Group</th>
<th>Adjusted $R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivariate Model</strong></td>
<td>0.625</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Contributing Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$ TBNESP</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

| CHF Group                     |                |           |
| **Multivariate Model**        | 0.565          | < 0.001   |
| **Contributing Variables**    |                |           |
| $\Delta$ TBNESP               | 0.0001         |           |
| $\Delta$ CI [-ve coef]        | 0.002          |           |
| $\Delta$ RAM [-ve coef]       | <0.02          |           |

GFR, glomerular filtration rate; CHF, congestive heart failure; RPF, renal plasma flow; RPP, renal perfusion pressure; PAM, pulmonary mean pressure; RAM, right atrial mean pressure; RNESP, renal norepinephrine spillover; TBNESP, Total body norepinephrine spillover; CI, cardiac index
Figure 1.

A  No Heart Failure Group

B  Heart Failure Group

C  No Heart Failure Group

D  Heart Failure Group

E  No Heart Failure Group

F  Heart Failure Group

P = NS

R² = 0.197; P < 0.001

GFR (mls/min/BSA 1.74)

Right Atrial Mean Pressure (mmHg)

Mean Arterial Pressure (mmHg)

Renal Perfusion Pressure (mmHg)

Heart Failure Group B A No Heart Failure Group

Heart Failure Group E F No Heart Failure Group

R² = 0.197; P < 0.001

P = NS

GFR (mls/min/BSA 1.74)
Figure 2

A No Heart Failure Group

B Heart Failure Group

C No Heart Failure Group

D Heart Failure Group

E No Heart Failure Group

F Heart Failure Group

P = NS

Nitroprusside

Dobutamine

R² = 0.218; P = 0.04

R² = 0.266; P = 0.05

R² = 0.422; P = 0.01

R² = 0.357; P = 0.03

R² = 0.314; P = 0.04

P = NS

P = NS

References


**GFR (mls/min/BSA 1.74)**

- **A** No Heart Failure Group
- **B** Heart Failure Group

**Right Atrial Mean Pressure (mmHg)**

- **A**: $P = \text{NS}$
- **B**: $R^2 = 0.197; P < 0.001$

**Renal Perfusion Pressure (mmHg)**

- **C** No Heart Failure Group
- **D** Heart Failure Group

- **C**: $P = \text{NS}$
- **D**: $P = \text{NS}$

**Mean Arterial Pressure (mmHg)**

- **E** No Heart Failure Group
- **F** Heart Failure Group

- **E**: $P = \text{NS}$
- **F**: $P = \text{NS}$
**Heart Failure Group**

A. No Heart Failure Group

- Delta Right Atrial Mean Pressure (mmHg)
- Delta GFR (mls/min/1.74 BSA)

P = NS

B. Heart Failure Group

- Delta Right Atrial Mean Pressure (mmHg)
- Delta GFR (mls/min/1.74 BSA)

Nitroprusside: $R^2 = 0.218; P = 0.04$

Dobutamine: $R^2 = 0.422; P = 0.01$

C. No Heart Failure Group

- Delta Renal Perfusion Pressure (mmHg)
- Delta GFR (mls/min/1.74 BSA)

Nitroprusside: $R^2 = 0.357; P = 0.03$

Dobutamine: $R^2 = 0.314; P = 0.04$

D. Heart Failure Group

- Delta Renal Perfusion Pressure (mmHg)
- Delta GFR (mls/min/1.74 BSA)

P = NS

E. No Heart Failure Group

- Delta Mean Arterial Pressure (mmHg)
- Delta GFR (mls/min/1.74 BSA)

Nitroprusside: $R^2 = 0.415; P = 0.024$

Dobutamine: $R^2 = 0.266; P = 0.05$

F. Heart Failure Group

- Delta Mean Arterial Pressure (mmHg)
- Delta GFR (mls/min/1.74 BSA)

P = NS

- Nitroprusside (○)
- Dobutamine (●)