Hemodynamic and neurochemical determinates of renal function in chronic heart failure

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1Division of Cardiology and Nephrology, Mount Sinai Hospital and University Health Network Hospital, Toronto, Canada; 2Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada; and 3Division of Cardiology, Saint Michael’s Hospital, Toronto, Canada

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Gilbert C, Cherney DZ, Parker AB, Mak S, Al-Hesayen JS, Parker JD. Hemodynamic and neurochemical determinates of renal function in chronic heart failure. Am J Physiol Regul Integr Comp Physiol 310: R167–R175, 2016. First published November 11, 2015; doi:10.1152/ajpregu.00190.2015.—Abnormal renal function is common in acute and chronic congestive heart failure (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 (ejection fraction: 23 ± 8%) underwent right heart catheterization, measurements of glomerular filtration rate (GFR; inulin) and renal plasma flow (RPF; para-aminohippurate), and radiotracer estimates of renal sympathetic activity. A subset (26 without, 36 with CHF) underwent acute pharmacological 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 among right atrial mean pressure (RAM) pressure, RPF, and GFR. By contrast, mean arterial pressure (MAP), cardiac index (CI), and measures of renal sympathetic activity were not significant predictors. In those with CHF there was also an inverse relationship among the drug-induced changes in RAM as well as pulmonary artery mean 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 among 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.

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 pathophysiological 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 (CI) 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 (34).

The current paper describes the relationship among direct measurements of GFR (inulin) and renal plasma flow (RPF; para-aminobipurrate), invasive hemodynamics, and measures of renal sympathetic activity (radiotracer methodology) in a group of patients without CHF [and preserved left ventricular (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 were 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 procedures.
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 yr) 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 before 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 yr) had a history of stable, chronic CHF secondary to LV 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 [New York Heart Association (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), β-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 of 59) while 46 of 59 were on stable doses of β-adrenergic blockers. In those taking furosemide (57 of 59), the dose ranged from 20 to 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 in the no CHF group and 22 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 catheterization 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, TX) 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 LV peak +dP/dt were acquired with 15 cardiac cycles averaged for the final value. The CI was measured by the Fick method and estimates of body surface area. From the left femoral vein, a Judkins JLA 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, MA) 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:

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

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

\[
\text{RNESP} = \left[ C_r - C_{ar} \right] + C_{ar} \times (\text{NE}_{ex}) / \times \text{RPF}
\]

where \(C_r\) is the NE concentration in the renal vein, \(C_{ar}\) is the NE concentration in the artery, and \(\text{NE}_{ex}\) is the extraction of radiolabeled 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 vs. renal vein concentrations of para-aminohippurate and inulin were determined to measure RPF and GFR using established methods in our laboratory (2). Values for GFR and RPF (in ml/min) were normalized to body surface area (in m²/1.73).

Pharmacological 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⁻¹·min⁻¹, following baseline hemodynamic 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 min 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 min after this reduction in mean arterial pressure had been achieved (2).

The peak change in hemodynamic, neurochemical, and renal functional parameters was calculated (drug vs. control), and regression analyses were 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, VA). Comparison of baseline characteristics, hemodynamics, and neurochemical variables between the no CHF and CHF groups were determined using either Student t-tests or a \(t^2\)-test. \(P < 0.05\) 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 \(P < 0.15\) in the univariate analysis was used for entry into the multivariate analysis. With the use of this threshold, no more than four 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 \(P < 0.05\). Data are presented as means ± 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.
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, yr</td>
<td>67 ± 9</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Diabetes (Type 2)</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>51/89</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>0.40 ± 0.048*</td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>80 ± 16</td>
<td>113 ± 45*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>65 ± 9</td>
<td>73 ± 14*</td>
</tr>
<tr>
<td>EF, %</td>
<td>59 ± 6</td>
<td>28 ± 3*</td>
</tr>
<tr>
<td>RAM, mmHg</td>
<td>2 ± 2</td>
<td>6 ± 5*</td>
</tr>
<tr>
<td>PM, mmHg</td>
<td>13 ± 6</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 ± 14*</td>
</tr>
<tr>
<td>RPP, mmHg</td>
<td>96 ± 15</td>
<td>76 ± 17</td>
</tr>
<tr>
<td>CI, l/min⁻¹·m⁻²</td>
<td>2.5 ± 0.4</td>
<td>2.3 ± 0.5*</td>
</tr>
<tr>
<td>GFR, ml/min⁻¹·1.73 m²</td>
<td>107 ± 33</td>
<td>91 ± 26*</td>
</tr>
<tr>
<td>RPF, ml/min⁻¹·1.73 m²</td>
<td>508 ± 115</td>
<td>408 ± 125*</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>21.5 ± 5.0</td>
<td>23.6 ± 6.9</td>
</tr>
<tr>
<td>NEart, nmol/l</td>
<td>1.6 ± 1.1</td>
<td>2.1 ± 3*</td>
</tr>
<tr>
<td>NEven, nmol/l</td>
<td>2.1 ± 1.1</td>
<td>3.1 ± 1.7*</td>
</tr>
<tr>
<td>TBNESP, amol/min</td>
<td>4.8 ± 3.7</td>
<td>7.1 ± 4.0*</td>
</tr>
<tr>
<td>RNESP, pmol/min</td>
<td>707 ± 404</td>
<td>926 ± 509*</td>
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</table>

Data are means ± SD. CHF, congestive heart failure; BSA, body surface area; BMI, body mass index; 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; NEart, arterial norepinephrine; NEven, renal vein norepinephrine; TBNESP, total body norepinephrine spillover; RNESP, renal norepinephrine spillover. *P < 0.05 vs. no CHF group; †P = 0.053 vs. no CHF group.

GFR: variables contributing to the model. 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 (Fig. 1; Table 2). 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 RPP (P < 0.0001 and 0.04, respectively). Furthermore, there was a significant inverse univariate relationship between GFR and RAM pressure (Fig. 1; P < 0.001). In the multivariate analysis, RPF and RPP both made independent contributions to the model of GFR (Table 2). If RPF 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 with lower values of GFR.

RPF: variables contributing to the model. 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).

Renal sympathetic activity: variables contributing to the model. 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.

Pharmacological intervention. 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. 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; Table 4; Fig. 2). 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 (all P < 0.01; Table 4; Fig. 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 CI by either the univariate or multivariate regression analysis.

As can be seen in Fig. 2B, 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 vs. the change in MAP were separated into the subjects that received nitroprusside vs. those that received dobutamine (Fig. 2C).

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

Change in renal sympathetic activity: variables contributing to the model. 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; Table 4). There was also a positive univariate relation-
ship 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% 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 compared with 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 GFR 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 direct 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 the 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 pharmacological 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 finding

### Table 2. Stepwise regression: baseline variables

<table>
<thead>
<tr>
<th>Predictors of GFR</th>
<th>Adjusted R²</th>
<th>( p )</th>
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</thead>
<tbody>
<tr>
<td>No CHF group</td>
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<tr>
<td>Multivariate model</td>
<td>0.445</td>
<td>&lt;0.0001</td>
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<td>Contributing variables</td>
<td>RPF</td>
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<td>CHF group</td>
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<td>&lt;0.0001</td>
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<tr>
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<td>RPF</td>
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<tr>
<td>CHF group</td>
<td>0.536</td>
<td>&lt;0.0001</td>
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<tr>
<td>Multivariate model (MAP and RAM)</td>
<td>Contributing variables</td>
<td>RPF</td>
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### Predictors of RPF

<table>
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<th>( p )</th>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate model</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CHF group</td>
<td>0.143</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Multivariate model</td>
<td>Contributing variables</td>
<td>RAM (w cox)</td>
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### Predictors of RNESP

<table>
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<td>No CHF group</td>
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<td>Multivariate model</td>
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<tr>
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<td>MAP</td>
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<tr>
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<td>&lt;0.03</td>
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<tr>
<td>Multivariate model</td>
<td></td>
<td></td>
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<tr>
<td>Contributing variables</td>
<td>TBNESP</td>
<td>&lt;0.03</td>
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</table>

### Table 3. Pharmacological intervention: hemodynamic changes

<table>
<thead>
<tr>
<th></th>
<th>No CHF Group (n = 26)</th>
<th>CHF (n = 36)</th>
</tr>
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<tbody>
<tr>
<td>ΔHR, beats/min</td>
<td>8 ± 10% (−3; 21)</td>
<td>3 ± 11% (−13; 20)</td>
</tr>
<tr>
<td>ΔRAM, mmHg</td>
<td>−43 ± 91% (−6; 2)</td>
<td>−70 ± 71% (−8; 2)</td>
</tr>
<tr>
<td>ΔPAM, mmHg</td>
<td>−20 ± 28% (−5; 3)</td>
<td>−23 ± 24% (−20; 5)</td>
</tr>
<tr>
<td>ΔPCWP, mmHg</td>
<td>−38 ± 46% (−10; 7)</td>
<td>−24 ± 65% (−25; 5)</td>
</tr>
<tr>
<td>ΔMAP, mmHg</td>
<td>−3 ± 10% (−17; 13)</td>
<td>−6 ± 13% (−22; 22)</td>
</tr>
<tr>
<td>ΔRPP</td>
<td>−1 ± 11% (−22; 18)</td>
<td>−1 ± 15% (−22; 20)</td>
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<tr>
<td>ΔCI, l/min⁻¹ m⁻²</td>
<td>2 ± 17% (−0.8; 0.7)</td>
<td>14 ± 22% (−1.0; 1.4)</td>
</tr>
<tr>
<td>ΔGFR, ml/min⁻¹ 1.73 m⁻²</td>
<td>3 ± 9% (−12; 21)</td>
<td>8 ± 17% (−12; 36)</td>
</tr>
<tr>
<td>ΔRPF, ml/min⁻¹ 1.73 m⁻²</td>
<td>5 ± 36% (−24; 136)</td>
<td>8 ± 10% (−92; 161)</td>
</tr>
<tr>
<td>ΔRenal filtration fraction, %</td>
<td>−1 ± 8% (−0.02; 0.021)</td>
<td>3 ± 24 (−0.122; 0.137)</td>
</tr>
<tr>
<td>ΔTBNESP, pmol/min</td>
<td>14 ± 99% (−2.6; 2.0)</td>
<td>1 ± 78% (−5.4; 2.4)</td>
</tr>
<tr>
<td>ΔTBNESP, mmol/min</td>
<td>35 ± 74% (−0.84; 5.77)</td>
<td>0.04 (−2.78; 3.044)</td>
</tr>
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</table>

Values are presented as %change ± SD (range), control vs. drug.
ings 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 and GFR was essentially identical in patients with CHF and 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 min) 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 necessarily 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 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...

<table>
<thead>
<tr>
<th>Predictors of the change in GFR</th>
<th>Adjusted $R^2$</th>
<th>$P$</th>
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<tr>
<td>Multivariate model (RPP)</td>
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<tr>
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<td>Multivariate model</td>
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<tr>
<td>Predictors of the change in RNESP</td>
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<td>$\Delta$CI</td>
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Fig. 2. Univariate relationship between the change in GFR and the change in mean right atrial pressure in the group without CHF (A) and those with chronic CHF (B). Univariate relationship between the change in GFR and the change in renal perfusion pressure in the group without CHF (C) and those with chronic CHF (D). Univariate relationship between the change in GFR and the change in mean arterial pressure in the group without CHF (E) and those with chronic CHF (F).
effects and their impact on renal functional responses may well be different compared with other pharmacological and non-pharmacological 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 pharmacological 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.

**REFERENCES**


