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ORIGINAL ARTICLE

Association between central haemodynamics and renal function in advanced heart failure: a nationwide study from Sweden

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Abstract

Aims Renal dysfunction in patients with heart failure (HF) has traditionally been attributed to declining cardiac output and renal hypoperfusion. However, other central haemodynamic aberrations may contribute to impaired kidney function. This study assessed the relationship between invasive central haemodynamic measurements from right-heart catheterizations and measured glomerular filtration rate (mGFR) in advanced HF.

Methods and results All patients referred for heart transplantation work-up in Sweden between 1988 and 2019 were identified through the Scandiatransplant organ-exchange organization database. Invasive haemodynamic variables and mGFR were retrieved retrospectively. A total of 1001 subjects (49 ± 13 years; 24% female) were eligible for the study. Analysis of covariance adjusted for age, sex, and centre revealed that higher right atrial pressure (RAP) displayed the strongest relationship with impaired GFR [β coefficient −0.59; 95% confidence interval (CI) –0.69 to −0.48; $P < 0.001$], followed by lower mean arterial pressure (MAP) (β coefficient 0.29; 95% CI 0.14–0.37; $P < 0.001$), and finally reduced cardiac index (β coefficient 3.51; 95% CI 2.14–4.84; $P < 0.003$). A combination of high RAP and low MAP was associated with markedly worse mGFR than any other RAP/MAP profile, and high renal perfusion pressure (RPP, MAP minus RAP) was associated with superior renal function irrespective of the degree of cardiac output.

Conclusions In patients with advanced HF, high RAP contributed more to impaired GFR than low MAP. A higher RPP was more closely related to GFR than was high cardiac index.

Keywords Advanced heart failure; Glomerular filtration rate; Invasive haemodynamics; Right atrial pressure; Renal perfusion pressure

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Introduction

Heart failure (HF) is a significant risk factor for impaired renal function, which in turn leads to further deterioration of cardiac function.[1] Both acute and chronic HF may lead to renal impairment in the absence of primary kidney disease. Worsening renal function is frequently associated with fluid retention, diuretic resistance, and hospital readmission.[2,3] Moreover, in patients with chronic HF, renal insufficiency is independently associated with increased risk for

cardiovascular death and all-cause mortality.[3,4] However, dynamic changes in kidney function should always be interpreted within the present clinical context in order to achieve an adequate risk stratification and to optimize the individual treatment adequately.[5]

Traditionally, impaired renal function in HF has been attributed to hypoperfusion of the kidneys due to either progressive decline of cardiac output (CO) or intravascular volume depletion secondary to excessive use of diuretics.[6] However, other mechanisms may also be of importance,[7,8] including elevated central venous pressure leading to renal congestion.[9]

Several studies have investigated how disturbances in central haemodynamics may affect kidney function,[2,10,11] but those were limited by a single-centre design, a small sample size, and the use of estimated glomerular filtration rate (eGFR) as an outcome measure.[12–14] Various creatinine-based equations have been elaborated for estimating GFR in the general population or in patients with chronic kidney disease, but none of them have been found to be accurate in predicting GFR in HF.[15] Therefore, the gold standard for assessing renal function is the direct measurement of GFR (measured GFR; mGFR) by the plasma clearance of either ^{51}Cr-ethylenediamine tetraacetic acid or iohexol. However, these methods are seldomly applied as they are labour-intensive and costly.[12,13]

To increase our knowledge of how renal function is affected by HF, we assessed the relationship between invasive central haemodynamic variables and measured GFR in patients with advanced HF in a large, multicentre, nationwide study.

Material and methods

Population

Between 1988 and 2019, all patients referred for heart transplantation (HTx) work-up in Sweden were identified through the Scandiatransplant organ-exchange organization (Aarhus University Hospital, Skejby, Denmark), which operates a pre-HTx and post-HTx register of patients from Nordic countries. During that time, three centres in Sweden performed HTx: Sahlgrenska University Hospital, Gothenburg; Lund University, Lund; and Karolinska University Hospital, Stockholm.

Study design

We designed a retrospective cohort study, in which eligible individuals were selected according to pre-specified criteria. Patients were included if they were aged $\geq$ 18 years and if they suffered from advanced HF and had undergone a right-heart catheterization (RHC) as part of their HF work-up at a Swedish HTx centre. Furthermore, it was required that mGFR had been performed within 1 month after the RHC. Exclusion criteria comprised treatment with renal replacement therapy, ongoing mechanical circulatory support, or evaluation for re-transplantation.

The diagnosis of advanced HF was made according to the European Society of Cardiology guidelines,[16] based on the presence of the following features in patients treated with guideline directed optimal therapy: typical signs (fluid retention and/or peripheral hypoperfusion) and symptoms (New York Heart Association class III to IV); evidence of severe cardiac dysfunction [shown by either left-ventricular ejection fraction $<$ 30%, pseudonormal or restrictive mitral inflow pattern at Doppler echocardiography, high left-ventricular and/or right-ventricular filling pressures, or elevated natriuretic peptides]; severely impaired functional capacity (confirmed by either a 6 min walk test distance $<$ 300 m, a peak oxygen uptake $<$ 12–14 mL/kg/min during cardiopulmonary exercise test, or inability to exercise); positive anamnesis for more than one hospitalization for HF in the past 6 months.[16,17] Despite poor cardiac function and reduced exercise capacity, the large majority of patients ($>$90%) were clinically stable at rest, and not on any inotropic support.

Firstly, patients were divided into two groups based on whether the level of mGFR was $<$60 mL/min/1.73 m^2, or $\geq$60 mL/min/1.73 m^2. Secondly, patients were divided in three groups according to HF aetiology: dilated cardiomyopathy (DCM), ischaemic heart disease (IHD), and miscellaneous non-ischaemic heart disease (MNIHD). Finally, in order to investigate the impact of advances in HF treatment over time, patients were split into three groups based on whether they underwent HF work-up before 2008, during or following 2008 or time of HF work-up unknown.

The study design complied with the Declaration of Helsinki, and study approval was obtained from the Institutional Review Board at the University of Gothenburg (Registration number 728-12).

Haemodynamic evaluation

The haemodynamic variables recorded during RHC included heart rate (HR), mean right atrial pressure (RAP), commonly used as an indicator of central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary artery wedge pressure (PAWP), and mean arterial pressure (MAP). Arterial and mixed venous oxygen saturations were also obtained. CO was assessed using the thermodilution technique and determined as the average of three to five measurements. Cardiac index (CI) was computed as CO divided by body surface area according to the formula of DuBois and DuBois.[18] Transpulmonal gradient was defined as the difference between PAWP and MPAP, and pulmonary vascular resistance was determined as transpulmonal gradient divided by CO

and expressed in Wood units. Renal perfusion pressure (RPP) was calculated as the difference between MAP and RAP.

Assessment of renal function

Direct measurements of GFR were performed by plasma clearance of ^{51}Cr-ethylenediamine tetraacetic acid or iohexol and expressed as mL/min/1.73 m^2 body surface area. Quantification using either tracer was considered to be acceptable based on a previous study that described an excellent correspondence between GFR values determined by the two methods.[19] Estimated GFR was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[20]

Statistical analysis

All statistical analyses were performed using SAS 9.4 statistical software packages (SAS Institute, Cary, NC). Descriptive statistics are presented as mean ± standard deviation (SD) for continuous variables, and categorical variables as numbers with percentages in parentheses. Missing data were handled using both complete case analysis as well as multiple imputation. For the multiple imputation, a total of 100 replicas of the dataset were generated with imputed values replacing missing data using the fully conditional specification method. For continuous variables, predictive mean matching was employed (SAS Proc MI).

Comparisons between participants with mGFR$<$ and $\geq$60 mL/min/1.73 m^2 at baseline were performed with analysis of variance for continuous variables and Fisher's exact test for categorical data. Penalized spline regression was performed to further evaluate the relationship between haemodynamic variables and mGFR.

After testing for multicollinearity, and adjusting for age, sex, and centre, the effect of haemodynamic variables on mGFR was explored using analysis of covariance (ANCOVA), first, in an analysis for each haemodynamic variable separately and, second, in a multivariable analysis including all relevant haemodynamic variables. Furthermore, based on the same multivariable ANCOVA model, we obtained estimates of absolute standardized (dimensionless) coefficients to enable a comparison of how different haemodynamic variables contributed to mGFR. The multivariable analyses were performed on the imputed data sets and results were combined using Rubin's rules.

In addition, an age-adjusted, sex-adjusted, and centre-adjusted multivariate ANCOVA analysis was performed for each HF aetiology (DCM, IHD, and MNIHD) and each HF work-up period ($<$2008, $\geq$2008, and unknown HF work-up time).

To study the effect of RAP as opposed to MAP on mGFR, we created four subgroups by using median splits for RAP ($\geq$ or $<$10 mmHg) and MAP ($\geq$ or $<$73.5 mmHg). Furthermore, to investigate the impact of RPP against forward blood flow on GFR, we generated four subgroups by using median splits for RPP ($\geq$ or $<$64 mmHg) and CI ($\geq$ or $<$1.9 L/min/m^2). Analysis of variance was used to calculate an estimate for the mean of GFR for each subgroup, to create confidence intervals, and to compare pairwise differences between subgroups.

All statistical tests were two-tailed (alpha level 0.05), and P values < 0.05 were considered statistically significant. No adjustments for multiplicity were performed.

Results

Patient characteristics

A flow diagram illustrating the inclusion and exclusion of patients is given in *Figure 1*. In total, 1596 patients with advanced HF were screened, 1001 of whom were found to be eligible for inclusion in the study. Patient exclusion was primarily related to missing mGFR measurements. Supporting Information *Figure S1* depicts the aetiology of HF in the study population. DCM was the commonest diagnosis, followed by IHD, and miscellaneous non-ischaemic cardiac conditions.

Table 1 summarizes demographic, clinical, and laboratory characteristics of the whole study cohort as well as for patients with GFR $<$ 60 and GFR $\geq$ 60 mL/min/1.73 m^2 separately. For the whole cohort, mean age was 48.8 ± 12.9 years, 24% of participants were women, and mean body mass index was 25 ± 4.2 kg/m^2. Nearly all patients had symptoms compatible with New York Heart Association class III or IV, with left-ventricular ejection fraction 23.2 ± 11% (mean + SD). Mean mGFR was moderately impaired (60.4 ± 18 mL/min/1.73 m^2) as was eGFR. The relationship between mGFR and eGFR in the entire cohort is presented in *Table S1*.

Table 2 displays invasive haemodynamic measurements. The haemodynamic profile for the whole study group was compatible with advanced HF with elevated left-sided and right-sided filling pressures and low CO, as well as reduced mixed venous oxygen saturation. Patients with mGFR $\geq$ 60 had lower RAP than those with mGFR $<$ 60 ($P < 0.001$), plus slightly higher MAP, HR, CO, and CI ($P < 0.05$ for all).

Impact of haemodynamic variables on renal function

Penalized spline regression for the relationship between each haemodynamic variable and mGFR is displayed in *Figure S2*. *Table 3* displays results from ANCOVA showing the relationship between mGFR and haemodynamic measurements after

Figure 1 Flow diagram depicting the selection of eligible study participants. HF, heart failure; re-HTx, heart re-transplantation; MCS, mechanical circulatory support; mGFR, measured glomerular filtration rate; RHC, right-heart catheterization; RRT, renal replacement therapy.

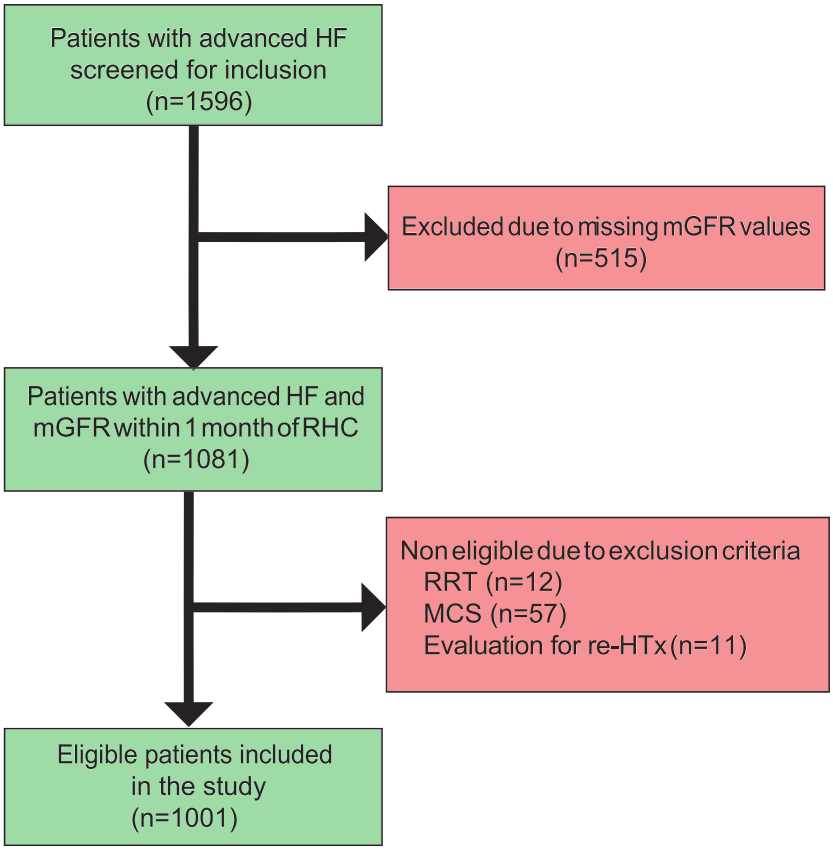


Table 1 Baseline characteristics of the whole study cohort and participants displaying mGFR < 60 mL/min/1.73 m^2 vs. ≥60 mL/min/1.73 m^2[a]

Variable	Whole study cohort (n = 1001)	mGFR < 60 mL/min/1.73 m^2 (n = 505)	mGFR ≥ 60 mL/min/1.73 m^2 (n = 496)	P value
Age (years)	48.8 ± 12.9	51.6 ± 11.7	45.9 ± 13.4	<0.001
Female sex	242 (24.2)	127 (25.1)	115 (23.2)	0.515
DCM	542	278	264	0.569
IHD	229	113	116	0.881
Other non-ischaemic HF	230	114	116	0.764
BMI (kg/m^2)	25.2 ± 4.2	25.4 ± 4.1	25 ± 4.2	0.175
NYHA class III/IV	599/209 (96.4)	320/127 (96.4)	148/48 (96.5)	0.154
LVEF (%)	23.2 ± 11	24.1 ± 10.8	22.3 ± 11.1	0.021
Haemoglobin (g/L)	131 ± 19	128.9 ± 19	133.4 ± 18.7	0.009
Creatinine (μmol/L)	109.5 ± 48.7	125.5 ± 51.4	93 ± 39.4	<0.001
mGFR (mL/min/1.73 m^2)	60.4 ± 18	45.9 ± 9.6	75.2 ± 11.1	<0.001
eGFR (mL/min/1.73 m^2)[b]	71.8 ± 25.8	58.5 ± 22.1	84.5 ± 23	<0.001

BMI, body mass index; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HF, heart failure; IHD, ischaemic heart disease; mGFR, measured glomerular filtration rate; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association.
[a]Data are presented as mean ± standard deviation or as numbers with percentages in parentheses.
[b]Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[21]

Table 2 Invasive haemodynamic measurements for the whole study cohort and for patients displaying mGFR < 60 mL/min/1.73 m^2 vs. ≥60 mL/min/1.73 m^2[a]

Variable	Whole study cohort (n = 1001)	mGFR < 60 mL/min/1.73 m^2 (n = 505)	mGFR ≥ 60 mL/min/1.73 m^2 (n = 496)	P value
HR (beats/min)	78 ± 18	75 ± 17	80 ± 19	0.001
RAP (mmHg)	11 ± 7	11 ± 6	9 ± 6	<0.001
MPAP (mmHg)	31 ± 10	30 ± 10	31 ± 10	0.166
PAWP (mmHg)	21 ± 8	21 ± 8	21 ± 8	0.207
MAP (mmHg)	75 ± 11	73 ± 11	76 ± 10	0.002
CO (L/min)	3.7 ± 1	3.6 ± 1	3.8 ± 1.1	0.016
CI (L/min/m^2)	1.9 ± 0.5	1.9 ± 0.5	2 ± 0.5	0.002
TPG (mmHg)	9.7 ± 5.5	9.6 ± 5.1	9.9 ± 5.9	0.516
PVR (Wood units)	2.8 ± 1.9	2.9 ± 2	2.7 ± 1.7	0.332
SaO_2 (%)	95 ± 6	94.8 ± 6	95 ± 5.1	0.595
SvO_2 (%)	57 ± 10	56.5 ± 9	57.6 ± 10.6	0.225

CI, cardiac index; CO, cardiac output; HR, heart rate; IHD, ischaemic heart disease; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; TPG, transpulmonary pressure gradient.
[a]Data are presented as mean ± standard deviation unless otherwise specified.

Table 3 ANCOVA adjusted for age, sex, and centre showing (A) the effect of each haemodynamic variable on mGFR separately and (B) the multivariable effect of all relevant haemodynamic variables on mGFR

	(A) Effect of each variable on mGFR			(B) Multivariable effect of all variables on mGFR		
Variable	β coefficient	95% *CI*	*P*	β coefficient	95% *CI*	*P*
Heart rate (beats/min)	0.07	−0.01 to 0.16	0.106	0.05	−0.04 to 0.11	0.323
RAP (mmHg)	−0.51	−0.69 to −0.33	<0.001	−0.59	−0.69 to −0.48	<0.001
PAWP (mmHg)	−0.01	−0.16 to 0.14	0.881	0.19	0.09 to 0.28	0.044
MAP (mmHg)	0.26	0.13 to 0.38	<0.001	0.26	0.14 to 0.37	<0.001
CI (L/min/m^2)	4.32	2.07 to 6.57	<0.001	3.51	2.14 to 4.84	0.003

ANCOVA, analysis of covariance; *CI*, confidence interval; CI, cardiac index; mGFR, measured glomerular filtration rate; MAP, mean arterial pressure; PAWP, pulmonary artery wedge pressure; RAP, mean right atrial pressure.

adjustment for age, sex, and centre. In the analysis studying each haemodynamic variable separately, mGFR displayed a negative relationship with RAP and a positive association with MAP and CI. There was no significant relationship between mGFR with either HR or PAWP. The haemodynamic variables RAP, MAP, and CI remained independently and significantly related to mGFR in the multivariable analysis. PAWP, which was not significantly associated with mGFR in univariable analysis, displayed an independent and positive association with mGFR in the multivariable analysis (P = 0.044; *Table 3*). In all patients, the proportion of explained variance, R-squared, was 0.05 when using age, centre, and sex as explanatory variables. Adding haemodynamic variables to the model yielded R-squared of 0.16. The latter analysis was however based on patients with complete data. The relationship between haemodynamic measures and mGFR was consistent across different HF aetiologies (DCM, IHD, and MNIHD, *Table S2*) and over time (<2008, ≥2008, and unknown HF work-up time, *Table S3*).

Figure 2 displays absolute standardized (dimensionless) coefficients, enabling comparison of the impact of different haemodynamic variables on mGFR. *Figure 2A* shows that RAP had the greatest effect on mGFR (negative impact), followed by MAP and CI (positive impact). Among the haemodynamic variables with a statistically significant effect on mGFR, PAWP had the least impact on mGFR. *Figure 2B* shows that RPP (MAP-RAP) had the greatest effect on mGFR (positive impact), followed by CI (positive impact). HR did not display a significant relationship to mGFR in either of the two models.

Figure 3A shows that a combination of high RAP and low MAP was associated with markedly worse mGFR than any other RAP/MAP profile. Similarly, *Figure 3B* shows that patients with high RPP had greater mGFR compared with those with low RPP, irrespective of whether CI was high or low.

Discussion

In this Swedish, nationwide, retrospective cohort study in patients with advanced HF, a higher RAP, as of a proxy for renal venous pressure, was the haemodynamic variable that displayed the strongest relationship with impaired kidney function. Lower MAP was the second most important variable associated with reduced mGFR, followed by impaired CI. Notably, a high RPP (MAP minus RAP) was more closely linked to enhanced kidney function than increased forward flow represented by CI. Our findings were consistent with respect to HF aetiology and constant over time. The results, which are based on a large nationwide population, provide

Figure 2 Analysis of covariance with absolute standardized (dimensionless) coefficients enabling comparison of the impact of different haemodynamic variables on measured glomerular filtration rate. CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.

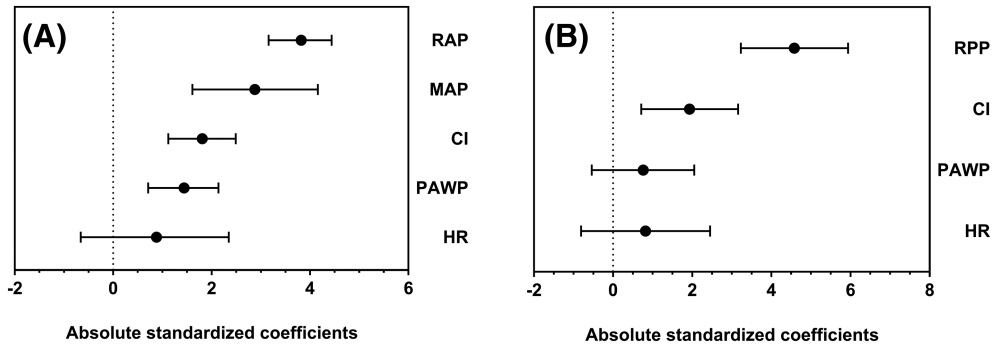
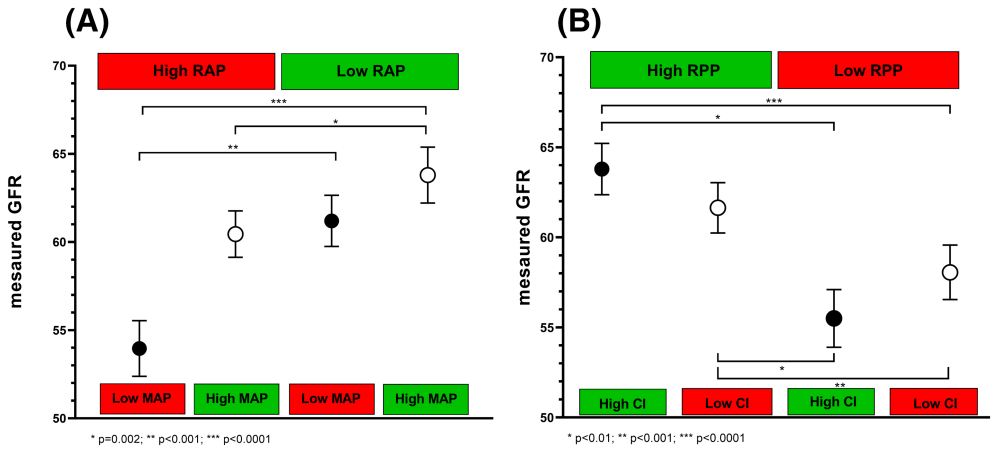


Figure 3 Effects of (A) high or low RAP (≥ or <10 mmHg) on mGFR in participants with high or low MAP (≥ or <73.5 mmHg) and (B) high or low RPP (≥ or <64 mmHg) on mGFR in participants with high or low CI (≥ or <1.9 L/min/m^2). CI, cardiac index; MAP, mean arterial pressure; mGFR, measured glomerular filtration rate; RAP, right atrial pressure; RPP, renal perfusion pressure.



new insights into the relationship between central haemodynamics and measured GFR, whereas most previous studies have reported single-centre findings based on estimated GFR.

Right atrial pressure

The perception that decreased renal function in HF is mainly driven by impaired CO and intravascular volume depletion following treatment with diuretics is still prevalent.[22] However, in the present study, high RAP was the haemodynamic variable most strongly related to impaired GFR. Furthermore, when RAP and MAP were well balanced, mGFR was adequate regardless of whether the two pressures were high or low. Although the cross-sectional nature of our study prohibits causal inference, it is tempting to suggest that congestion of the kidney, rather than poor forward flow or hypovolemia, is a major determinant of renal insufficiency. This is mechanistically plausible because a rise in RAP, which is transferred backwards into the venous system, may be expected to generate an increase in renal interstitial pressure due to the encapsulated nature of the organ. A high renal interstitial pressure will in turn lead to reduced renal blood flow, the collapse of kidney nephrons, and a progressive decline in GFR.[23]

Other lines of evidence support our hypothesis. Early experimental studies observed that elevated CVP caused renal congestion and worsening renal function.[23,24] In clinical studies, a reverse relationship between renal plasma flow and venous pressure in patients with chronic HF was demonstrated by Kos *et al.*[25] This concept was broadened by Damman *et al.*,[10] who demonstrated that increased CVP was strongly associated with renal impairment in patients with right-sided HF due to pulmonary hypertension. Furthermore, in a retrospective study of 178 HF patients, Guglin *et al.*[7] observed that the development of impaired kidney function was more dependent on venous congestion than

on impairment of CI. Also, increased CVP, in combination with low systolic blood pressure, has been shown to induce a substantial reduction in eGFR in acute HF.[11]

Mean arterial pressure

A MAP of 65–70 mmHg is empirically thought to be the minimal adequate MAP for organ perfusion, which is also relevant to the normal function of the kidney.[26] In the present study, we showed that lower MAP was independently associated with impaired renal function at any level of RAP (*Figure 3A*). Nevertheless, an increase in RAP exerted a larger adverse influence on mGFR than a corresponding decrease in MAP. This is in line with experiments on isolated kidney models, which showed that an increase in CVP reduces renal blood flow and decreases urine formation to a greater degree than an equivalent decrease in systemic blood pressure.[23,24]

The filtration function of the kidneys depends on several factors besides renal blood flow, including the number of functional nephrons, the balance of vascular tone between the afferent and efferent arterioles, the Starling forces within the glomerulus and the surface, as well as the permeability characteristics of the glomerular basement membrane.[24,27] As a result, renal blood flow can be preserved by local autoregulation systems[8,24] in the event of decreasing forward flow and declining arterial blood pressure. When CVP increases, however, there are no similar compensatory mechanisms capable of upholding adequate renal blood flow.[27] The combination of high venous pressure and low arterial blood pressure will therefore inevitably impair kidney perfusion[10] (*Figure 3A*). Over time, this will lead to renal hypoxia, loss of nephrons, and irreversible kidney damage.[24] Furthermore, neurohormonal activation associated with HF results in vasoconstriction of pre-glomerular arterioles,[24] which reduces GFR, leading to enhancement of proximal tubular sodium absorption and creating a vicious cycle precipitating the deterioration of kidney function.[24]

Renal perfusion pressure

We found that higher RPP was associated with superior renal function irrespective of the level CI. When MAP is severely reduced, elevation of CVP may neutralize the local autoregulation of renal blood flow, rendering it directly dependent on RPP.[28] Thus, augmented forward flow does not necessarily reverse renal insufficiency, because an increase in CO may be distributed through organ systems other than the kidneys. Experience in the multicentre ESCAPE trial is supportive of this suggestion.[29] Likewise, studies showing improvement in CI did not result in improved renal function, prevent re-hospitalization, or increase survival.[30,31] These other data are consistent with our own in suggesting that a positive effect of forward flow on renal function is highly likely to be dependent on adequate RPP.

Pulmonary artery wedge pressure

The independent relationship between increasing levels of PAWP and higher GFR after adjustment for RAP and other haemodynamic measurements is noteworthy. PAWP was the least influential of the four significant haemodynamic variables identified in our research and it is possible that its identification is a spurious finding due to overfitting of the statistical model.[32] However, a higher PAWP would be expected to result in higher circulating levels of natriuretic peptides,[33] thus increasing GFR through vasodilatory effects on glomerular afferent arterioles.[34] There are thus plausible pathophysiological explanations for the positive relationship between PAWP and GFR observed in our multivariable analysis.

Clinical perspectives

The reciprocal pathways leading to deterioration of both cardiac and renal function, termed the cardiorenal syndrome, remain ill-defined, as are the therapeutic options for this condition.[24] The present study brings some clarity to this topic by highlighting the importance of identifying the central haemodynamic aberrations related to decreased renal function and fluid retention. Our study showed that increased RAP was more closely related to impaired kidney function than decreased MAP and that a lower RPP was more strongly associated with renal insufficiency than a high CI. Therefore, when treating with diuresis fluid overload due to worsening renal function in HF, it is not unlikely that reducing CVP and/or increasing MAP, to maintain sufficient RPP, could be a successful treatment strategy if intravascular hypovolemia is avoided. If systolic blood pressure is adequate ($>$110 mmHg), it is reasonable to lower CVP with a pharmacological treatment such as low-dose nitroglycerin to increase renal blood flow, enhance GFR, and reduce oedema.[35,36] If systolic blood pressure is moderately lowered (90–110 mmHg), augmentation of diuresis can be stimulated by use of an inodilator such as dobutamine or levosimendan (not approved in the United States), which reduce CVP and increase CO, but require haemodynamic monitoring.[35,36] Finally, when systolic blood pressure is low ($<$90 mmHg), it may be necessary to add a vasopressor such as norepinephrine to increase MAP[35,36] to support RPP and thereby maintain renal blood flow and GFR.[35–37]

Prospective studies are needed to assess whether lowering RAP and/or increasing MAP to optimize RPP is clinically useful when treating fluid overload due to worsening renal function in advanced HF.

Strengths and limitations

The main strengths of our study are that it is based on a nationwide sample of real-world patients with advanced HF in whom RHC was used to obtain estimates of haemodynamic indices and GFR was measured directly. The limitations include the retrospective study design, in which we were unable to retrieve data on, and control for, confounders such as comorbidities and medications. Although most patients had stable chronic HF, the fact that GFR measurements were not performed on the same day as RHC may have introduced a bias. Furthermore, a substantial proportion of patients initially considered for inclusion in our research were excluded from the study due to missing mGFR values. Nevertheless, we feel that our study provides robust and valuable findings that aid to the understanding of the relationship between central haemodynamics and renal insufficiency and provides support for goal-directed haemodynamic treatment strategies to manage worsening renal function in different HF conditions.

Conclusions

In a large cohort of patients with chronic advanced HF, a higher RAP, reflecting greater CVP, was the haemodynamic factor most strongly related to impaired renal function, followed by lower MAP and reduced CI. Higher RPP was associated with superior renal function, irrespective of the degree of CI.

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Conflict of interest

None of the authors have any conflicts of interest to declare for the present study.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Underlying heart failure etiology. ACHD = Adult congenital heart disease; ARVD = arrhythmogenic right ventricular dysplasia; CA = cardiac amyloidosis; CS = cardiac sarcoidosis; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; IHD = ischemic heart disease; RCM = restrictive cardiomyopathy; VD = valvular disease.

Figure S2. Penalized spline regression for the relationship between each hemodynamic variable and mGFR. CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery wedge pressure; RAP = right atrial pressure; RPP = renal perfusion pressure.

Table S1. Correlation between eGFR and mGFR.

Table S2. ANCOVA with absolute standardized (dimensionless) coefficients adjusted for age, sex, and center showing the multivariable effect of all relevant hemodynamic variables on mGFR for patients with DCM, IHD, and miscellaneous non-ischemic heart disease.

Table S3. Analysis of covariance with absolute standardized (dimensionless) coefficients adjusted for age, sex, and center enabling comparison of the impact of different HTx work-up eras on measured glomerular filtration rate.

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