

Increased Central Venous Pressure Is Associated With Impaired Renal Function and Mortality in a Broad Spectrum of Patients With Cardiovascular Disease

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- Objectives** We sought to investigate the relationship between increased central venous pressure (CVP), renal function, and mortality in a broad spectrum of cardiovascular patients.
- Background** The pathophysiology of impaired renal function in cardiovascular disease is multifactorial. The relative importance of increased CVP has not been addressed previously.
- Methods** A total of 2,557 patients who underwent right heart catheterization in the University Medical Center Groningen, the Netherlands, between January 1, 1989, and December 31, 2006, were identified, and their data were extracted from electronic databases. Estimated glomerular filtration rate (eGFR) was assessed with the simplified modification of diet in renal disease formula.
- Results** Mean age was 59 ± 15 years, and 57% were men. Mean eGFR was 65 ± 24 ml/min/1.73 m², with a cardiac index of 2.9 ± 0.8 l/min/m² and CVP of 5.9 ± 4.3 mm Hg. We found that CVP was associated with cardiac index ($r = -0.259$, $p < 0.0001$) and eGFR ($r = -0.147$, $p < 0.0001$). Also, cardiac index was associated with eGFR ($r = 0.123$, $p < 0.0001$). In multivariate analysis CVP remained associated with eGFR ($r = -0.108$, $p < 0.0001$). In a median follow-up time of 10.7 years, 741 (29%) patients died. We found that CVP was an independent predictor of reduced survival (hazard ratio: 1.03 per mm Hg increase, 95% confidence interval: 1.01 to 1.05, $p = 0.0032$).
- Conclusions** Increased CVP is associated with impaired renal function and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease. (J Am Coll Cardiol 2009;53:582–8) © 2009 by the American College of Cardiology Foundation

Renal dysfunction is a strong and independent predictor of prognosis in the general population but also in patients with diabetes, hypertension, coronary artery disease, and heart failure (1–7). The pathophysiology is multifactorial and associated with decreased renal perfusion, atherosclerosis and inflammation, endothelial dysfunction, and neurohormonal activation (8–10). We recently showed that in patients with cardiac dysfunction secondary to pulmonary

hypertension, not only was renal perfusion strongly associated with renal function impairment but also with venous congestion (11). However, it is unclear whether this observation is limited to those patients with reduced cardiac function and pulmonary hypertension or whether it also may be present in patients with a mixture of cardiovascular diseases with varying etiologies and treatments. In addition, there are only limited data on the relationship between

See page 597

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venous congestion, as estimated by central venous pressure (CVP) and the impact on prognosis, even in patients with and without heart failure. The studies that have been conducted are either small or include only noninvasive assessment of increased venous congestion, such as jugular

venous pressure (12–15). In the present study, we therefore aimed to investigate the relationship between CVP, renal function, and mortality in patients with a mixture of cardiovascular diseases with varying etiologies and treatments.

Methods

Case identification. Using the patient registration system of the University Medical Center Groningen, the Netherlands, all patients that underwent right heart catheterization between January 1, 1989, and December 31, 2006, were identified.

Data extraction. Retrospective chart review was performed to analyze characteristics of all patients that were identified during the electronic search. For each patient, date of birth, sex, race, and weight and height were collected. Comorbid conditions, including hypertension, coronary artery disease, cardiac valve disease, congenital heart disease, history of stroke, hypercholesterolemia, and diabetes, in addition to medical treatment at the time of catheterization also were extracted for each patient. Furthermore, the reason for performing right heart catheterization was identified. The study was approved by the institutional review board of the University Medical Center Groningen.

Heart catheterization. Hemodynamic variables obtained during catheterization included systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), cardiac output (thermodilution, l/min), and right atrial pressure as indicator of CVP (CVP, mm Hg). Cardiac index (l/min/m²) was determined as cardiac output divided by the body surface area, which was calculated as: $0.007184 \cdot \text{weight}^{0.425} \cdot \text{length}^{0.725}$. Measurements obtained from cardiac catheterization were obtained from the patient during a resting state.

Renal function measurement. Serum creatinine at the day of catheterization was extracted. For the patients who did not have laboratory measurements on the day of catheterization, measurements obtained within 3 days before catheterization were taken as the baseline value. Of patients included in the study, 2,282 (89%) had at least 1 serial creatinine measurement within 3 days of catheterization. Renal function was estimated as glomerular filtration rate (GFR) by using the simplified modification of diet in renal disease equation (estimated glomerular filtration rate [eGFR] [ml/min/1.73 m²] = $186.3 \times [\text{serum creatinine}]^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ if female}]$) (16). Estimated GFR values >200 ml/min/1.73 m² were set equal to 200 ml/min/1.73 m², according to Coresh et al. (17).

Mortality data. Survival status was determined using the electronic patient registration database of the University Medical Center Groningen. Follow-up started directly after right heart catheterization. The primary end point consisted of death from any cause.

Statistical analysis. Data are given as mean ± standard deviation when normally distributed, as median and interquartile range when skewed distributed, and as frequencies

and percentages for categorical variables. Associations between baseline variables were evaluated by means of 1-way analysis of variance, the Kruskal-Wallis test, and chi-square or Fisher exact tests, when appropriate. Two-sided p values were used, taking $p < 0.05$ to be statistically significant. CVP was divided into

tertiles to assess relationships between baseline characteristics and CVP. A fractional polynomial parameterization of exposure was used to explore nonlinearity between different predictors and renal function. In this technique, each exposure value is expressed as a polynomial of degree >1 (e.g., quadratic, cubic, and so on), yielding an estimated model with multiple predictors (i.e., separate predictors for the linear, quadratic, terms, respectively). We used a Cox proportional hazards survival model to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). At first, in multivariate analysis, CVP was fitted into a stepwise multivariate Cox regression analysis on a continuous scale. In secondary analysis, CVP was fitted into the model and, in multiple steps, the model was adjusted for other variables and parameters. The internal validity of the regression model was assessed by the bootstrap resampling technique (18). For each of 100 bootstrap samples, the model was refitted and tested on the original sample to obtain a bias-corrected estimate of predictive accuracy. Statistical analyses were performed using SPSS version 12.0 (Chicago, Illinois) and STATA version 9.0 (College Station, Texas).

Abbreviations and Acronyms

CI = confidence interval
CVP = central venous pressure
eGFR = estimated glomerular filtration rate
HR = hazard ratio

Results

Baseline characteristics. A total of 3,757 right heart catheterizations were conducted between 1989 and 2006. Of these, 2,557 (68%) were first or only right heart catheter-

Table 1 Primary Indication for Heart Catheterization

	Percentage of Patients
Aortic valve disorders	29
Aortic valve stenosis	23
Aortic valve insufficiency	6
Mitral valve disorders	15
Mitral valve insufficiency	14
Mitral valve stenosis	1
Pulmonary valve disorders	1
Pulmonary valve insufficiency	0.8
Pulmonary valve stenosis	0.2
Heart failure	16
Coronary artery disease	13
Pre-transplantation (noncardiac)	11
Rhythm disorders	5
Pulmonary hypertension	3
Congenital heart disease	2
Post-heart transplantation	2
Other	6

Table 2 Baseline Characteristics According to Tertiles of CVP

	Total	Tertile 1 (0 to 3 mm Hg)	Tertile 2 (4 to 6 mm Hg)	Tertile 3 (>6 mm Hg)	p Value for Trend
n	2,557	911	855	791	
Age (yrs)	59 ± 15	60 ± 15	59 ± 15	58 ± 15	0.0032
Sex (% male)	57	59	58	54	NS
SBP (mm Hg)	133 ± 29	133 ± 28	134 ± 27	129 ± 31	0.0100
DBP (mm Hg)	68 ± 13	66 ± 12	68 ± 12	69 ± 13	0.0010
CO (l/min)	5.5 ± 1.6	5.7 ± 1.6	5.5 ± 1.5	5.0 ± 1.5	<0.0001
Cardiac index (l/min/m ²)	2.9 ± 0.8	3.1 ± 0.7	3.0 ± 0.7	2.7 ± 0.8	<0.0001
CVP (mm Hg)	5.9 ± 4.3	2 ± 1	5 ± 1	11 ± 4	<0.0001
eGFR (ml/min/1.73 m ²)	65 ± 24	65 ± 23	67 ± 24	62 ± 24	0.0001
Medical history (%)					
Heart failure	16	15	15	19	NS
Coronary artery disease	24	24	25	24	NS
Congenital heart disease	5	4	5	7	0.0189
Valve disease	51	50	55	49	NS
Hypercholesterolemia	6	7	5	6	NS
Diabetes mellitus	9	8	8	10	NS
Hypertension	20	21	20	18	NS
Stroke	5	4	5	6	NS
Medication (%)					
Diuretics	42	37	38	53	0.0001
Beta-blocker	28	25	29	31	0.0388
ACEI or ARB	38	36	32	45	0.0001
Aldosterone antagonist	9	5	6	15	0.0001

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II receptor blocker; CO = cardiac output; CVP = central venous pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; NS = not significant; SBP = systolic blood pressure.

ization of unique patients and formed the study population. Main reasons for right heart catheterization are shown in Table 1. Aortic and mitral valve disorders accounted for 44% of indications, whereas in 16%, acute or chronic heart failure was the predominant reason. Mean age was 59 ± 15

years, and 57% were men (Table 2). In the total study population, both mean cardiac index (2.9 ± 0.8 l/min/m²) and mean CVP (5.9 ± 4.3 mm Hg) were within the normal range. The distribution of CVP among the study population is shown in Figure 1. Mean eGFR was moderately impaired: 65 ± 24 ml/min/1.73 m².

The distribution of different factors over tertiles of CVP is shown in Table 2. Most of the characteristics were equally distributed across tertiles of CVP, except for the highest tertile (CVP >6 mm Hg). Both cardiac output and cardiac index were significantly lower in the highest tertile compared with lower tertiles (p < 0.0001), corresponding to r = -0.259 (p < 0.0001) for the association between CVP and cardiac index. Furthermore, patients in the highest tertile were treated more frequently with angiotensin-converting enzyme inhibitor/angiotensin-II receptor blockers, beta-blockers, diuretics, and aldosterone antagonists. Prevalence of heart failure showed a trend toward increasing with higher tertiles of CVP (p = 0.0781), whereas congenital heart disease was also more prevalent in the highest tertile. Finally, eGFR was significantly lower in the highest tertile of CVP, compared with both lower tertiles (p < 0.001).

Curvilinear fitting and the relationship between CVP and eGFR. Figure 1 shows the curvilinear relationship between CVP and eGFR in the total study population as obtained by fractional polynomial modeling. Estimated GFR showed a small increase when CVP increased from 1 to 6 mm Hg. However, in CVP values >6 mm Hg, a steep

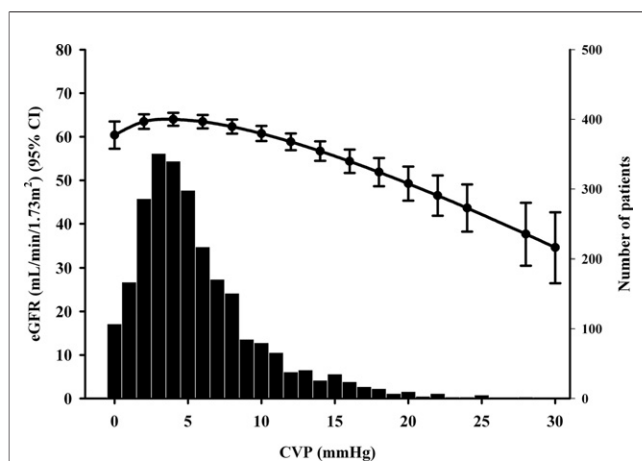


Figure 1 Distribution of CVP and Curvilinear Relationship Between CVP and eGFR in the Study Population

Adjusted for age, sex, and cardiac index. The curvilinear model had the following individual polynomial components for the relationship between CVP and eGFR: First order: $Y = -25.8 \cdot (CVP + 1)/10$ (Wald 28.2, p < 0.0001) and second order: $Y = 35.7 \cdot [(CVP + 1)/10]^{0.5}$ (Wald 17.4, p < 0.0001). CVP = central venous pressure, eGFR = estimated glomerular filtration rate.

decrease is observed with increasing CVP values. This finding resulted in a partial correlation of $r = 0.064$, $p = 0.0218$ in patients with $CVP \leq 6$ mm Hg, and $r = -0.212$, $p < 0.0001$ in patients with $CVP > 6$ mm Hg (adjusted for age, sex, and cardiac index). On a continuous scale, CVP was also significantly associated with eGFR ($r = -0.110$, $p < 0.0001$) after transformation.

Besides CVP, age ($r = -0.438$, $p < 0.0001$), sex ($r = 0.137$, $p < 0.0001$), and cardiac index ($r = 0.249$, $p < 0.0001$) were associated with eGFR. In addition, lower eGFR values also were found to be related with the use of any type of cardiovascular medication and a history of diabetes and hypertension. There was a significant interaction between CVP and cardiac index on the relationship with eGFR. The observed biphasic relationship between CVP and eGFR was most pronounced in patients with relatively normal cardiac index (Fig. 2).

In multivariate analysis, CVP remained associated with eGFR ($r = -0.108$, $p < 0.0001$, adjusted for covariates), which was confirmed by bootstrap analysis (Online Table 1). After adjustment for the year of catheterization, the association between CVP and eGFR was numerically unchanged: $r = -0.105$, $p < 0.0001$. Excluding patients with a history of heart transplantation, who were likely to receive renal function compromising immunotherapy, CVP remained associated with eGFR ($r = -0.108$, $p < 0.0001$) in multivariate analysis. Including only patients without heart failure, similar associations were present ($r = -0.080$, $p = 0.0034$). Excluding both heart transplant recipients and heart failure patients, the association between CVP and eGFR remained ($r = -0.079$, $p = 0.0042$).

CVP and mortality. Mortality data were available in all patients, whereas time of death was available in 2,424 (95%) of patients. Median follow-up among survivors was 10.7

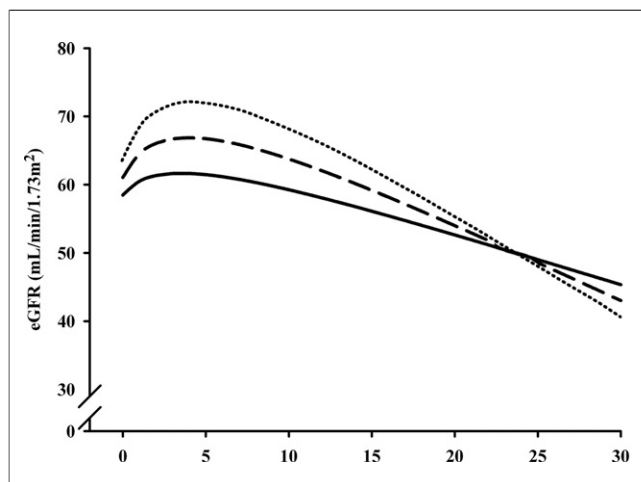


Figure 2 Curvilinear Relationship Between CVP and eGFR According to Different Cardiac Index Values

$p = 0.0217$ for interaction between cardiac index and CVP on the relationship with eGFR. **Solid line** = cardiac index < 2.5 l/min/m²; **dashed line** = cardiac index 2.5 to 3.2 l/min/m²; **dotted line** = cardiac index > 3.2 l/min/m². Abbreviations as in Figure 1.

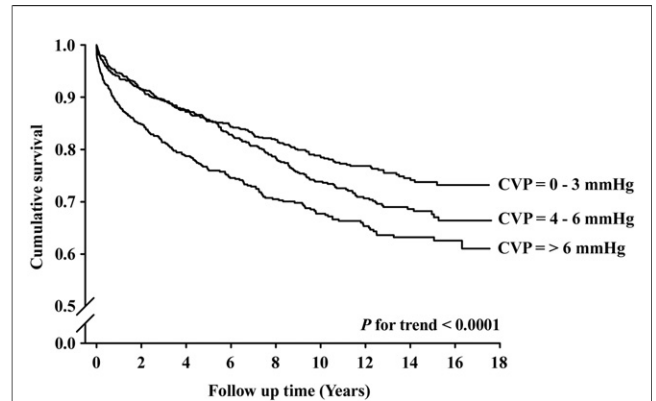


Figure 3 Kaplan-Meier Analysis of Event-Free Survival According to Tertiles of CVP

HR: 1.22 (95% CI: 1.00 to 1.49), $p = 0.0466$ for CVP 4 to 6 mm Hg; HR: 1.65 (95% CI: 1.35 to 2.01), $p < 0.0001$ for CVP > 6 mm Hg, both compared with CVP 0 to 3. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

years and, during follow-up, 741 (29%) of the patients died. Crude mortality ranged from 24% in the lowest tertile to 29% and 35% in the 2 highest tertiles of CVP ($p = 0.0001$ for trend). On a continuous scale, greater CVP levels were associated with impaired survival (HR: 1.05 per mm Hg increase, 95% CI: 1.04 to 1.07, $p < 0.0001$). Kaplan-Meier survival curves for tertiles of CVP are shown in Figure 3, showing that patients with the greatest CVP in particular were at risk for increased mortality (HR for CVP > 6 mm Hg vs. ≤ 6 mm Hg: 1.49, 95% CI: 1.26 to 1.76, $p < 0.0001$). Baseline eGFR (HR: 1.09 per 10 ml/min/1.73 m² decrease, 95% CI: 1.05 to 1.13, $p < 0.0001$) and cardiac index (HR: 0.74 per l/min/m² increase, 95% CI: 0.66 to 0.84, $p < 0.0001$) also were strong predictors of mortality. Other factors associated with reduced survival are shown in Table 3. In stepwise multivariate Cox regression analysis, CVP remained significantly associated with reduced survival (HR: 1.03 per mm Hg increase, 95% CI: 1.01 to 1.05, $p = 0.0032$) (Table 3). Finally, we fitted a second model, adjusting CVP for other covariates (Online Table 2). CVP remained an independent predictor of impaired survival (HR: 1.03 per mm Hg increase, 95% CI: 1.01 to 1.05, $p = 0.0144$). To account for the effects of changing therapy during the study inclusion time, we adjusted for the year of catheterization. This secondary analysis yielded similar results (HR: 1.03 per mm Hg increase, 95% CI: 1.00 to 1.05, $p = 0.0207$). Excluding patients with known heart failure and heart transplant recipients, CVP was still associated with mortality (HR: 1.03 per 5 mm Hg increase, 95% CI: 1.00 to 1.06, $p = 0.0369$).

Discussion

The present study shows that increased CVP is associated with impaired renal function in a broad spectrum of cardiovascular patients who underwent right heart catheter-

Table 3 Multivariate Stepwise Cox Regression Model

Variables	Univariate		Multivariate		
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	Wald Statistic	p Value
Age (per 10 yr increase)	1.05 (1.00–1.10)	0.0880	1.21 (1.12–1.31)	25.4	<0.0001
Sex	1.03 (0.88–1.20)	0.713			
Cardiac index (per l/min/m ² increase)	0.74 (0.66–0.84)	<0.0001	0.81 (0.71–0.93)	9.1	0.0026
CVP (per mm Hg increase)	1.05 (1.04–1.07)	<0.0001	1.03 (1.01–1.05)	8.7	0.0032
eGFR (per 10 ml/min/1.73 m ² decrease)	1.09 (1.05–1.13)	<0.0001			
Medication					
Diuretic use	1.43 (1.22–1.67)	<0.0001			
ACEI or ARB use	1.29 (1.10–1.52)	0.0017			
Aldosterone antagonist use	1.92 (1.50–2.45)	<0.0001	1.50 (1.10–2.02)	6.9	0.0087
Medical history (%)					
Coronary artery disease	1.26 (1.05–1.50)	0.0112			
Diabetes mellitus	1.83 (1.44–2.31)	<0.0001	1.76 (1.34–2.31)	16.6	<0.0001
Indication for catheterization					
Aorta insufficiency	0.63 (0.43–0.93)	0.0203			
Congenital heart disease	0.36 (0.17–0.77)	0.0078			
Pre-transplantation (noncardiac)	1.50 (1.21–1.85)	<0.0001	2.54 (1.90–3.40)	39.2	<0.0001
Heart failure	1.48 (1.21–1.85)	0.0001	1.71 (1.34–2.20)	18.1	<0.0001
Rhythm disorders	0.49 (0.29–0.82)	0.0062			

CI = confidence interval; other abbreviations as in Table 2.

ization. In addition, the slope between CVP and impaired eGFR was steeper with relatively preserved cardiac function. Finally, an increased CVP was a strong and independent determinant of all-cause mortality, which was especially observed in patients with a CVP >6 mm Hg.

There are only limited data on the relationship between increased CVP and renal impairment. Studies in animals have shown that increasing renal venous pressure leads to a reduction in glomerular filtration, which was probably mediated by a decreased renal perfusion (19). Renal vein constriction led to a decrease in GFR in rats (20), whereas renal function decreased when renal vein pressure was increased in dogs, but only when cardiac output was reduced (21). We recently showed that in patients with reduced cardiac function, secondary to pulmonary hypertension, increased CVP was strongly associated with renal impairment, especially when renal perfusion was already impaired (11). Early studies on increased renal vein pressure in heart failure patients and animals showed a marked reduction in renal blood flow as well as water and salt excretion (22,23), but the effect on GFR was not uniform. One small report showed a strong relationship between CVP and renal blood flow in advanced heart failure (24).

Drazner *et al.* (13) reported that in patients with increased jugular venous pressure on examination, serum creatinine was significantly greater. In patients who underwent elective cardiac surgery, pre-operative presence of high CVP was a strong predictor of the occurrence of acute renal injury, independent of the presence of low CO (25).

However, especially in patients with preserved cardiac function, data regarding the relationship between CVP and renal function are scarce. Diastolic dysfunction, a disease characterized by increased filling pressures, often coexists

with renal failure and vice versa (26–28). Interestingly, a recent study showed that renal dysfunction is even more important in defining mortality risk in patients with preserved cardiac function compared with those with systolic dysfunction (29,30). Our present study confirmed that increased CVP is an important risk factor for decreased renal function in patients with preserved and decreased cardiac function.

Curvilinear effect of CVP with eGFR. We observed a biphasic relationship between eGFR and increasing CVP. In the physiologic ranges of CVP, up to 6 mm Hg, eGFR increases gradually. This subtle increase in eGFR may be a reflection of increased cardiac filling to preserve cardiac function by Frank-Starling mechanism (pre-load), and subsequent renal perfusion (31). This gradual increase in eGFR was observed across the full spectrum of low to high cardiac index. We observed a decrease in eGFR when CVP increases above 6 mm Hg. In these patients, the equilibrium among venous return, CO, and CVP may have shifted toward a plateau phase or optimum, where CO is not further increased in response to greater CVP (32). Greater CVP levels will then decrease renal perfusion pressure, which will further impair eGFR. However, if greater CVP levels preserve CO, and despite this mechanism, eGFR decreases with greater CVP, this action suggests that increased CVP also may exert an effect on GFR in this group of patients, independent of renal perfusion.

Importantly, the relationship between CVP and GFR is bound to be bidirectional. Not only may CVP influence GFR, but even mildly impaired renal function may initiate salt and water retention, resulting in increased cardiac filling pressures (33). Because of the cross-sectional nature of our

analysis, we were unable to investigate the cause-effect associations, and our present analysis must be regarded as hypothesis generating.

CVP and eGFR in patients with and without cardiac dysfunction. Of particular interest is the interaction between cardiac index and CVP on eGFR. Patients who have a combination of reduced perfusion (cardiac index) and increased venous congestion (CVP) suffer from fluid overload and decreased organ perfusion, leading, among other things, to renal dysfunction. We showed that patients with high CVP levels often also have decreased cardiac index and reduced eGFR. Remarkably, CVP and cardiac index showed an interaction on the relationship with eGFR, with an even more pronounced relationship in patients with relatively normal cardiac index. This further strengthens the observation of a relationship between CVP and eGFR, which is not exclusively due to reduced cardiac systolic function. It also challenges the intuitive notion that fluid overload, although deleterious from a cardiovascular perspective, will invariably be beneficial from the point of view of preservation of renal function. Because our analysis does not allow to dissect cause and effect relationships, however, it might also well be that the relatively normal cardiac index is maintained at the expense of the increased CVP. In that case, apparently, such a renal hemodynamic profile does not translate into better renal function. Our present findings seem inconsistent with our earlier findings, showing that patients with reduced renal perfusion in particular are prone to a detrimental effect of CVP on GFR (11). However, we did not measure renal hemodynamics or renal function by clearance techniques in the present study, and the population was also different. Furthermore, our previous study consisted of patients with much lower cardiac indexes, all of which makes a comparison difficult. Nevertheless, this inconsistency needs to be further addressed in future studies.

New therapeutic agents in the treatment of acute heart failure that are specifically targeted at improvement of cardiac function and reducing venous congestion recently have shown promising results regarding renal function. A substudy of the SURVIVE (Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support) study, in which levosimendan was compared with dobutamine, showed that improvement of renal function was more pronounced in the group receiving levosimendan, despite the obvious positive inotropic effect of dobutamine (34). The specific venodilatory effect observed with levosimendan, with subsequent reduced CVP, may be the pathophysiologic mechanism, supporting a direct pathophysiologic link between CVP and renal impairment (35).

CVP and mortality. Increased CVP and jugular venous pressure predispose to the development of heart failure in patients with cardiac dysfunction and have been associated with reduced survival in patients with heart failure (12,13,36). Small studies have shown that invasive assessment of CVP is a predictor of cardiovascular outcome in patients with advanced heart failure (14,15). In other

selected patient populations, such as patients who underwent Fontan surgery or lung transplantation, greater CVPs were strong predictors of outcome (37,38). The prognostic importance of increased CVP in patients with normal cardiac function has not been reported previously. We show that in a selected patient population, increased CVP remained a determinant of all-cause mortality, independent of cardiac function. This association with mortality was most prominent in patients with severely increased CVP, even after adjustment for other baseline characteristics. This finding was additive to the observation that greater CVP levels predispose to lower eGFR, which may influence survival by different mechanisms.

Clinical implications. Increased CVP frequently is observed in patients with and without reduced cardiac function, comprising almost 20% of patients in the present patient population. Recognition of these patients is essential because not only is renal dysfunction much more frequently observed, but the risk of mortality also increases with increasing CVP levels. Treatment to selectively lower CVP may be favorable to reduce symptoms and signs of congestion, improve GFR, and improve prognosis.

Study limitations. The present study comprises a selected patient population that had a specific indication for right heart catheterization. Patients undergoing right heart catheterization are prone to have greater right-sided filling pressures, and the present observations may therefore not represent the general cardiovascular population. However, this is a large cohort study, with invasive cardiac function and CVP measurements across the full range. Second, this is a retrospective analysis, and no invasive data are available on renal blood flow and true GFR in these patients. Furthermore, it should be addressed that our study population had very different catheterization indications, medical history, and medication regime, all of which could have influenced our results. In our study, the presence of heart failure was a clinical diagnosis, rather than related to reduced cardiac index on catheterization. Therefore, the prevalence of heart failure in our study is most likely underestimated. The relationship between increased CVP and renal perfusion has been observed in heart failure. However our present study is the first to show an independent effect of CVP on renal function. Finally, the retrospective nature of this study and the cross-sectional design limited our ability to investigate the cause-effect relationship between renal impairment and increased CVP, which may actually mutually influence each other.

Conclusion

Increased CVP is associated with impaired renal function and is independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease.

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REFERENCES

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
2. Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher TF. Renal function: the Cinderella of cardiovascular risk profile. *J Am Coll Cardiol* 2001;38:1782-7.
3. Hillege HL, van Gilst WH, van Veldhuisen DJ, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomized trial. *Eur Heart J* 2003;24:412-20.
4. Nag S, Bilous R, Kelly W, Jones S, Roper N, Connolly V. All-cause and cardiovascular mortality in diabetic subjects increases significantly with reduced estimated glomerular filtration rate (eGFR): 10 years' data from the South Tees Diabetes Mortality study. *Diabetes Med* 2007;24:10-7.
5. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005;165:936-46.
6. Reddan DN, Szczech LA, Tuttle RH, et al. Chronic kidney disease, mortality, and treatment strategies among patients with clinically significant coronary artery disease. *J Am Soc Nephrol* 2003;14:2373-80.
7. Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;113:671-8.
8. Ljungman S, Laragh JH, Cody RJ. Role of the Kidney in Congestive Heart-Failure - Relationship of Cardiac Index to Kidney-Function. *Drugs* 1990;39:10-21.
9. Stam F, van Guldener C, Schalkwijk CG, ter Wee PM, Donker AJM, Stehouwer CDA. Impaired renal function is associated with markers of endothelial dysfunction and increased inflammatory activity. *Nephrol Dial Transplant* 2003;18:892-8.
10. Zoccali C, Mallamaci F, Tripepi G. Inflammation and atherosclerosis in end-stage renal disease. *Blood Purif* 2003;21:29-36.
11. Damman K, Navis G, Smilde TD, et al. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur J Heart Fail* 2007;9:872-8.
12. Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. *Am J Cardiol* 1984;54:147-52.
13. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med* 2001;345:574-81.
14. Gardner RS, Henderson G, McDonagh TA. The prognostic use of right heart catheterization data in patients with advanced heart failure: how relevant are invasive procedures in the risk stratification of advanced heart failure in the era of neurohormones? *J Heart Lung Transplant* 2005;24:303-9.
15. Morley D, Brozena SC. Assessing risk by hemodynamic profile in patients awaiting cardiac transplantation. *Am J Cardiol* 1994;73:379-83.
16. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation* 2006;114:1572-80.
17. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038-47.
18. Harrell FE Jr., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Stat Med* 1984;3:143-52.
19. Doty JM, Saggi BH, Sugerma HJ, et al. Effect of increased renal venous pressure on renal function. *J Trauma* 1999;47:1000-3.
20. Stolarczyk J, Carone FA. Effects of renal lymphatic occlusion and venous constriction on renal function. *Am J Pathol* 1975;78:285-96.
21. Priebe HJ, Heimann JC, Hedley-Whyte J. Effects of renal and hepatic venous congestion on renal function in the presence of low and normal cardiac output in dogs. *Circ Res* 1980;47:883-90.
22. Maxwell MH, Breed ES, Schwartz IL. Renal venous pressure in chronic congestive heart failure. *J Clin Invest* 1950;29:342-8.
23. Blake WD, Wegria R, Keating RP, Ward HP. Effect of increased renal venous pressure on renal function. *Am J Physiol* 1949;157:1-13.
24. Kos T, Pacher R, Wimmer A, et al. Relationship between kidney function, hemodynamic variables and circulating big endothelin levels in patients with severe refractory heart failure. *Wien Klin Wochenschr* 1998;110:89-95.
25. Palomba H, de Castro I, Neto AL, Lage S, Yu L. Acute kidney injury prediction following elective cardiac surgery: AKICS score. *Kidney Int* 2007;72:624-31.
26. Bruch C, Rothenburger M, Gotzmann M, et al. Chronic kidney disease in patients with chronic heart failure—impact on intracardiac conduction, diastolic function and prognosis. *Int J Cardiol* 2007;118:375-80.
27. Miyazato J, Horio T, Takiuchi S, et al. Left ventricular diastolic dysfunction in patients with chronic renal failure: impact of diabetes mellitus. *Diabetes Med* 2005;22:730-6.
28. Ogata C, Horio T, Kamide K, Takiuchi S, Kawano Y. Association between left ventricular diastolic dysfunction and renal hemodynamic change in patients with treated essential hypertension. *Hypertens Res* 2003;26:971-8.
29. Ahmed A, Rich MW, Sanders PW, et al. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 2007;99:393-8.
30. Bruch C, Reinecke H, Rothenburger M, et al. Transmitral flow patterns and the presence of chronic kidney disease provide independent and incremental prognostic information in patients with heart failure and systolic dysfunction. *J Am Soc Echocardiogr* 2007;20:989-97.
31. Guyton AC, Jones CE. Central venous pressure: physiological significance and clinical implications. *Am Heart J* 1973;86:431-7.
32. Magder S, Bafaqeh F. The clinical role of central venous pressure measurements. *J Intensive Care Med* 2007;22:44-51.
33. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol* 2006;47:1-8.
34. Yilmaz MB, Yalta K, Yontar C, et al. Levosimendan improves renal function in patients with acute decompensated heart failure: comparison with dobutamine. *Cardiovasc Drugs Ther* 2007;21:431-5.
35. Damman K, Voors AA. Levosimendan improves renal function in acute decompensated heart failure: cause and clinical application. *Cardiovasc Drugs Ther* 2007;21:403-4.
36. Drazner MH, Rame JE, Dries DL. Third heart sound and elevated jugular venous pressure as markers of the subsequent development of heart failure in patients with asymptomatic left ventricular dysfunction. *Am J Med* 2003;114:431-7.
37. Khairy P, Fernandes SM, Mayer JE Jr., et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation* 2008;117:13-5.
38. Pilcher DV, Scheinkestel CD, Snell GI, Davye-Quinn A, Bailey MJ, Williams TJ. High central venous pressure is associated with prolonged mechanical ventilation and increased mortality after lung transplantation. *J Thorac Cardiovasc Surg* 2005;129:912-8.

Key Words: renal function ■ central venous pressure ■ mortality ■ prognosis ■ heart catheterization.

▶ APPENDIX

For supplementary tables on regression analysis for eGFR and multivariate Cox regression analysis for all-cause mortality, please see the online version of this article.

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