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Central venous pressure at emergency room presentation predicts cardiac rehospitalization in patients with decompensated heart failure

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Aims To investigate the relationship between central venous pressure (CVP) at presentation to the emergency room (ER) and the risk of cardiac rehospitalization and mortality in patients with decompensated heart failure (DHF).

Methods and results Central venous pressure was determined non-invasively using high-resolution compression sonography at presentation in 100 patients with DHF. Cardiac hospitalizations and cardiac and all-cause mortality were assessed as a function of continuous CVP levels and predefined CVP categories (low <6 cm H_2O, intermediate 6–23 cm H_2O, and high >23 cm H_2O). Endpoints were adjudicated blinded to CVP. At presentation, mean age was 78 ± 11 years, 60% of patients were male, mean B-type natriuretic peptide level was 1904 ± 1592 pg/mL, and mean CVP was 13.7 ± 7.0 cm H_2O (range 0–33). During follow-up (median 12 months), 25 cardiac rehospitalizations, 26 cardiac deaths, and 7 non-cardiac deaths occurred. Univariate and stepwise multivariate Cox regression analysis revealed an independent relationship between CVP and cardiac rehospitalization (HR 1.09, 95% CI 1.01–1.18, $P = 0.034$). Kaplan–Meier analyses confirmed a stepwise increase in cardiac rehospitalization for low-to-high CVP (log-rank test $P = 0.015$). No association between CVP and (cardiac) mortality was detectable.

Conclusion Central venous pressure at ER presentation in patients with DHF is an independent predictor of cardiac rehospitalization but not of cardiac and all-cause mortality.

Keywords Decompensated heart failure • Central venous pressure • Compression sonography • Emergency room • Hospitalization • Mortality

Introduction

Decompensated heart failure (DHF) is a major and growing problem in the health care system, with approximately one million hospitalizations occurring annually in the US alone.[1,2] Recent data have shown that a substantial proportion of DHF hospitalizations are caused primarily by volume overload, rather than by low cardiac output.[3,4] High right atrial pressure, as measured using a central venous catheter, indicates coexistent elevated right and frequently left-sided pressure and is associated with signs (weight gain and peripheral oedema) and symptoms (dyspnoea and exercise intolerance) of pulmonary and systemic congestion.[4–6] Venous congestion has been recently demonstrated as a main predictor of organ injury and death.[7,8] Unfortunately, clinical assessment of increased venous congestion, such as jugular vein distension had been shown to be an unreliable tool compared with the invasive measurement of central venous pressure (CVP).[9,10] Although invasive measurement of CVP is the current 'gold-standard' for measuring venous congestion, it remains costly and related to potential major adverse events and

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therefore is not feasible in the vast majority of patients.[11] Controlled compression sonography at the forearm presents an attractive non-invasive alternative for the measurement of CVP.[12,13]

Using this novel technique of CVP measurement, we examined patients with DHF immediately after presentation to the emergency room (ER). Our aim was to establish new insights into the pathophysiology of DHF and to evaluate the relationship between CVP and the two most important clinical outcomes in DHF; cardiac rehospitalization and death.

Methods

Patients

We analysed patients presenting with DHF to the ER of the University Hospital of Basel between April 2006 and September 2008. Patients >18 years of age who presented with shortness of breath as a primary symptom and a reasonable clinical suspicion of DHF were enrolled whenever CVP measurements were promptly available (8:00 a.m.–6:00 p.m.). To avoid time-bias, e.g. CVP interaction with therapy, CVP measurement within 1 h after enrolment was targeted. Patients underwent an initial clinical assessment that included clinical history, physical examination, electrocardiography, pulse oximetry, blood tests including B-type natriuretic peptide (BNP), chest X-ray, non-invasive ultrasound measurement of CVP at presentation to the ER, and echocardiography (when indicated). Before discharge, physical examination, blood tests, and measurement of CVP were repeated. The study was approved by the Ethics Committee of the University of Basel. All patients gave written informed consent to participate in the study. The study conformed to the principles outlined in the Declaration of Helsinki.

Non-invasive measurement of central venous pressure

Ultrasound imaging was performed by two experienced investigators (C.T. and M.A.) using a HDI 5000 duplex device (Philips, Best, the Netherlands) with a 12–5 MHz linear array transducer (SonoCT, XRes) and an attached pressure manometer (PPM0310, Baumann, Muensingen, Switzerland). The manometer consists of a translucent silicon membrane (MVQ, Angst and Pfister AG, Zurich, Switzerland) connected to a commercially available pressure metre (Bourdon Haenni AG, Jegenstorf, Switzerland) with a flexible pressure tubing. Patients were placed in a comfortable supine position in a temperature-controlled room and measurements were done at the forearm placed on the bed. After zero adjustment, slowly increasing pressure was applied by the transducer until complete compression of the selected superficial forearm vein (preferentially the distal cephalic vein) was achieved. The pressure when the vein completely collapsed corresponds to the intravasal venous pressure and was measured continuously. The difference between the level of the sonographic measurement point and the right atrial level (median 8 cm, interquartile range 5–10 cm) was subtracted from the crude values for correction of the blood column height. Non-invasive CVP can be adequately obtained within less than 4 min.[12] In healthy subjects as well as in intensive care unit patients, a high correlation and negligible difference between the non-invasive and the invasive measurement of CVP has been demonstrated.[12,13]

Endpoint assessment

The primary endpoints in the present study consisted of time to cardiac rehospitalization and cardiac or all-cause mortality as a function of CVP measured at presentation to the ER. Mortality and morbidity data were attained by telephone interview in a blinded fashion by physicians who were not involved in patient care and by collection of all available medical records pertaining to each patient. All rehospitalizations and deaths were classified as being due to cardiac or non-cardiac causes according to the most proximate cause by a clinical events committee whose members were blinded to CVP results.

Statistical analysis

Data analysis was performed using SPSS 16.0 (Apache Software Foundation, Forest Hill, Maryland). Baseline demographics, physical examination, and laboratory findings were compared between patients with and without cardiac rehospitalization and patients who survived or died using the unpaired *t*-test or Mann–Whitney *U* test for continuous variables as appropriate or the Pearson chi-square test for categorical variables. Univariate and stepwise multivariate Cox regression analyses were used to determine the independent relationship between CVP and baseline characteristics with the outcome. A forward selection method with an entry *P*-value of <0.10 was used to select covariates. With regard to cardiac rehospitalization age, CVP, estimated glomerular filtration rate (eGFR) as calculated using the Cockcroft–Gault formula, potassium, creatinine kinase (CK), in-hospital change in sodium levels, and body-mass index (BMI) were included in the analyses. Central venous pressure, eGFR, blood urea nitrogen (BUN), potassium, CK, BMI, systolic blood pressure (BP), diastolic BP, New York Heart Association (NYHA) functional class, and BNP were included in the analyses concerning all-cause mortality.

Central venous pressure categories were defined according to previous publications (low CVP <6 cm H_2O, intermediate CVP 6–23 cm H_2O, and high CVP >23 cm H_2O).[7,8] Kaplan–Meier curves for both endpoints were calculated according to the predefined CVP categories and compared with the log-rank statistic. Statistical significance was set at a two-tailed probability level of <0.05.

Results

Non-invasive measurement of CVP was performed in 100 patients within 35 min (range 6–35) after enrolment. During a median follow-up of 12 months (range 0–20 months), 25 (25%) patients were rehospitalized for cardiac reasons (DHF of any cardiac aetiology) and 33 patients (33%) died (26 cardiac and 7 non-cardiac deaths). Patient characteristics at presentation according to subsequent cardiac rehospitalization and all-cause mortality are shown in *Table 1*.

Central venous pressure at presentation was 16.3 ± 6.9 cm H_2O in patients with cardiac rehospitalization and 12.8 ± 6.9 cm H_2O in patients without cardiac rehospitalization during follow-up ($P = 0.029$). Rehospitalized patients were younger and presented with a higher glomerular filtration rate but had higher potassium levels at initial presentation than non-rehospitalized patients.

Multivariate analysis showed that CVP at presentation independently predicted cardiac rehospitalization rates (*Table 2*). Kaplan–Meier curves confirmed a stepwise increase in cardiac rehospitalization with higher CVP levels (log-rank $P = 0.015$) (*Figure 1A*). Calculated mean time to cardiac rehospitalization was 19.2 (95% CI 16.5–22), 13.7 (95% CI 11.9–15.4), and 6.3 (95% CI 2.7–9.8) months for initial low, intermediate, and high CVP levels, respectively.

Table 1 Patient characteristics at presentation according to outcome

	All patients ($n = 100$)	Cardiac rehospitalization			All-cause mortality		
		No ($n = 75$)	Yes ($n = 25$)	*P*-value	Survived ($n = 67$)	Died ($n = 33$)	*P*-value
Age (years)	78 ± 11	80 ± 11	74 ± 9	*0.020*	76 ± 11	84 ± 7	*<0.001*
Male sex (%)	60	44 (59)	16 (64)	0.814	40 (60)	20 (61)	0.998
History of comorbidities							
Diabetes	42	30 (40)	12 (48)	0.483	27 (40)	15 (46)	0.623
Dyslipidaemia	38	27 (36)	11 (44)	0.585	31 (46)	7 (21)	0.051
Nicotine abuse	51	36 (48)	15 (60)	0.604	38 (57)	13 (39)	0.115
Hypertension	78	59 (79)	19 (76)	0.780	54 (81)	24 (73)	
Ischaemic heart disease	48	34 (45)	14 (56)	0.355	31 (46)	17 (52)	0.621
Non-ischaemic heart disease	34	25 (33)	9 (36)	0.828	22 (33)	12 (36)	0.745
Medication							
Diuretic	85	29 (39)	22 (88)	0.793	56 (84)	29 (88)	0.232
β-Blocker	60	42 (56)	18 (72)	0.338	43 (64)	17 (52)	0.207
ACE-inhibitor	57	40 (53)	17 (68)	0.400	42 (61)	16 (49)	0.207
Angiotensin receptor blocker	20	18 (24)	2 (8)	0.142	15 (22)	5 (15)	0.627
Calcium antagonist	18	14 (19)	4 (16)	0.801	11 (16)	7 (21)	0.289
Spironolactone	14	10 (13)	4 (16)	0.806	10 (15)	4 (12)	0.341
Digoxin	5	5 (7)	0	0.345	2 (3)	3 (9)	0.144
Nitrate	30	23 (31)	7 (28)	0.810	19 (28)	11 (33)	0.298
Antiplatelet	47	34 (45)	13 (52)	0.834	30 (45)	17 (52)	0.239
Anticoagulant	44	32 (43)	12 (48)	0.775	30 (45)	14 (42)	0.357
Statin	40	29 (39)	11 (44)	0.772	30 (45)	10 (30)	0.159
Clinical parameters							
CVP (cm H_2O)	13.7 ± 7.0	12.8 ± 6.9	16.3 ± 6.9	*0.029*	13.7 ± 7.0	13.5 ± 7.3	0.863
Systolic BP (mmHg)	139 ± 27	138 ± 29	143 ± 22	0.366	143 ± 28	132 ± 26	0.066
Diastolic BP (mmHg)	86 ± 19	86 ± 20	86 ± 17	0.911	89 ± 19	81 ± 19	0.071
Heart rate (b.p.m.)	90 ± 25	90 ± 26	92 ± 21	0.761	91 ± 27	90 ± 21	0.861
NYHA functional class III or IV (%)	98	73 (97)	25 (100)	0. 633	65 (97)	33 (100)	0.092
LVEF (%)	41 ± 15	41 ± 15	41 ± 16	0.868	42 ± 15	38 ± 13	0.201
BMI (kg/m^2)	26.9 ± 5.3	26.4 ± 4.8	28.6 ± 6.3	0.069	28.1 ± 5.3	24.4 ± 4.3	*0.001*
Laboratory tests							
Haemoglobin (g/L)	126 ± 22	126 ± 22	128 ± 21	0.640	127 ± 21	124.6 ± 22	0.598
Creatinine (umol/L)	138 ± 107	141 ± 113	128 ± 88	0.598	118 ± 73	179 ± 149	*0.007*
eGFR (mL/min/1.73 m^2)	53.8 ± 34.7	48.4 ± 27.5	70.2 ± 47.4	*0.006*	63.4 ± 36.6	34.4 ± 19.3	*<0.001*
BUN (mmol/L)	12.7 ± 7.7	13.2 ± 7.8	11.2 7.3	0.264	10.9 ± 6.6	16.4 ± 8.4	*0.001*
Sodium (mmol/L)	138 ± 5.1	138 ± 5.3	136 ± 4.4	0.123	137 ± 4.4	138 ± 6.4	0.355
Potassium (mmol/L)	4.2 ± 0.6	4.1 ± 0.6	4.5 ± 0.5	*0.013*	4.2 ± 0.6	4.2 ± 0.7	0.756
BNP (pg/mL)	1904 ± 1592	1950 ± 1606	1764 ± 1572	0.616	1512 ± 1213	2699 ± 1958	*<0.001*
CK (U/L)	134 ± 151	150 ± 168	84 ± 49	0.071	109 ± 89	184 ± 223	*0.022*

Values are mean ± SD or *n* (%). Significant *P*-values are given in italics.
ACE, angiotensin converting enzyme; CVP, central venous pressure; BP, blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BMI, body-mass index; eGFR, estimated glomerular filtration rate (Cockroft–Gault formula); BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; CK, creatinine kinase.

Relationships between all-cause mortality and CVP are displayed in *Tables 1* and *2*. Univariate analysis displayed no difference in CVP between patients who died or survived (13.7 ± 7.0 vs. 13.5 ± 7.3 cm H_2O, $P = 0.863$). In contrast, higher age, creatinine, BUN, CK, BNP levels, lower eGFR, and BMI were associated with a grave outcome (*Table 1*). In multivariate analysis, only BNP at presentation remained an independent predictor of all-cause mortality ($P = 0.036$), whereas CVP at presentation did not independently predict all-cause mortality ($P = 0.979$) (*Table 2*). Corresponding hazard ratios of the multivariate analyses are displayed in *Table 2*. Kaplan–Meier curves are plotted in *Figure 1B* and once again displayed no association between CVP levels and

Table 2 Cox regression multivariate analysis

	Cardiac rehospitalization			All-cause mortality		
	HR (95% CI)	**Wald statistic**	***P*-value**	**HR (95% CI)**	**Wald statistic**	***P*-value**
CVP (cm H_2O)	1.09 (1.01–1.18)	5.64	*0.034*	1.00 (0.94–1.06)	0.01	0.979
CK (U/L)	1.00 (0.99–1.00)	0.81	0.341	1.00 (1.00–1.00)	1.28	0.259
Age (years)	0.99 (0.94–1.04)	0.68	0.652	1.06 (1.00–1.13)	3.45	0.063
Potassium (mmol/L)	1.24 (0.37–4.18)	0.56	0.728	1.25 (0.65–2.40)	0.43	0.510
eGFR (mL/min/1.73 m^2)	1.00 (0.98–1.02)	0.44	0.956	1.01 (0.97–1.04)	0.83	0.773
BMI (kg/m^2)	1.00 (0.89–1.13)	0.33	0.994	0.89 (0.79–1.00)	3.63	0.057
BNP (μg/mL)	NA	NA	NA	1.27 (1.02–1.59)	4.42	*0.036*
BUN (mmol/L)	NA	NA	NA	1.05 (0.97–1.13)	1.48	0.224
systolic BP (mmHg)	NA	NA	NA	1.01 (0.99–1.02)	0.27	0.600
diastolic BP (mmHg)	NA	NA	NA	0.99 (0.96–1.01)	1.75	0.186
NYHA functional class	NA	NA	NA	1.53 (0.67–3.5)	1.02	0.312

Significant *P*-value is given in italics.
Hazard ratios (HR) and 95% confidence intervals (CI) for post-discharge cardiac rehospitalization and all-cause mortality.
CVP, central venous pressure; eGFR, estimated glomerular filtration rate (Cockroft–Gault formula); CK, creatinine kinase; BMI, body-mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; BP, blood pressure; NYHA, New York Heart Association; NA, not assessed because $P > 0.1$ in univariate analysis.

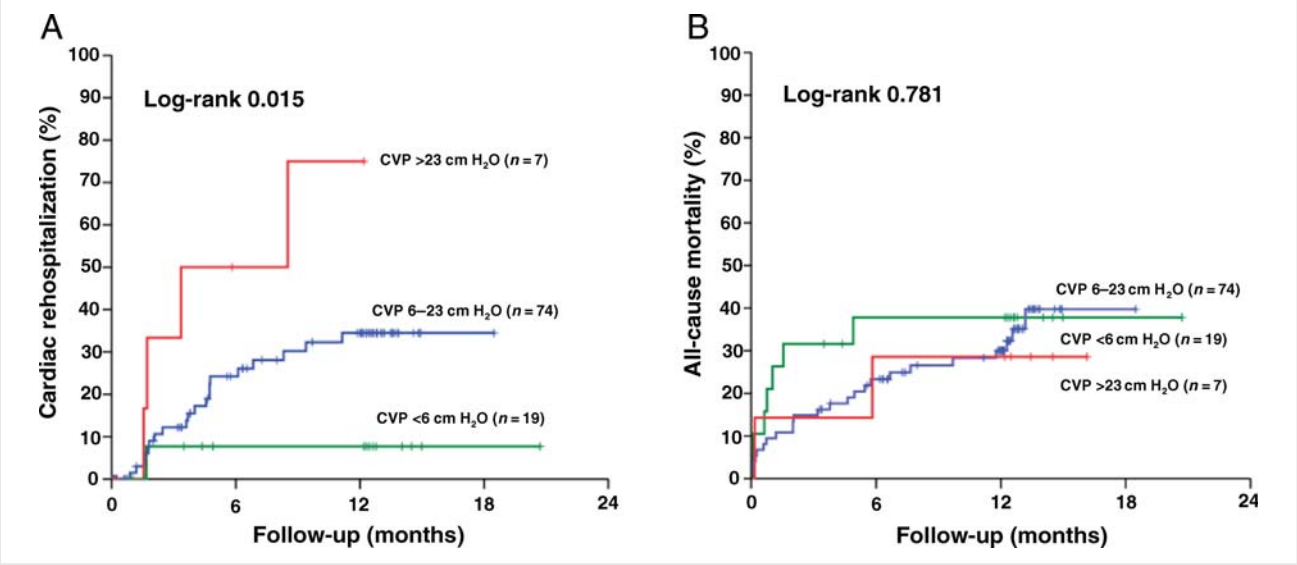

Figure 1 Kaplan–Meier analysis for cardiac rehospitalization (*A*) and all-cause mortality (*B*) according to central venous pressure at presentation.

all-cause mortality. Sub-analyses of cardiac mortality revealed comparable results with no significant associations: CVP in patients with subsequent cardiac death was 13.8 ± 7.0 vs. 13.3 ± 7.2 cm H_2O; $P = 0.769$ and the multivariate analysis accordingly was non-significant [$P = 0.292$; hazard ratio 1.03 (95% CI 0.97–1.10)].

Length of hospital stay did not differ significantly between patients with or without post-discharge cardiac rehospitalization and between patients who survived or died (14 ± 8 vs. 16 ± 12 days, $P = 0.412$ and 16 ± 12 vs. 13 ± 8 days, $P = 0.155$; respectively) (*Table 3*). During hospitalization, all patients experienced a significant reduction in CVP and body weight (BW) (−6.6 ± 7.2 cm H_2O, −4.2 ± 5.8 kg; both $P < 0.001$), but inpatient CVP and BW reduction were not associated with subsequent cardiac rehospitalization or all-cause mortality ($P = 0.237$ and $P = 0.962$ for CVP, $P = 0.278$ and P=0.548 for BW reduction, respectively). Similarly, no differences for inpatient days, CVP, or BW reduction were detectable between patients without or with cardiac death (16 ± 12 vs. 13 ± 9 days, $P = 0.193$; −6.7 ± 6.9 vs. −6.1 ± 9.1 cm H_2O, $P = 0.830$, and −4.2 ± 5.9 vs. −4.0 ± 5.8 kg, $P = 0.906$).

Table 3 Patient characteristics at discharge according to outcome

	All patients ($n = 100$)	Cardiac rehospitalization			All-cause mortality		
		No ($n = 75$)	Yes ($n = 25$)	*P*-value	Survived ($n = 67$)	Died ($n = 33$)	*P*-value
Inpatient days	15 ± 11	16 ± 12	14 ± 8	0.412	16 ± 12	13 ± 8	*0.155*
CVP (cm H_2O)	7.6 ± 5.6	7.1 ± 5.6	8.8 ± 5.4	0.257	7.8 ± 5.6	7.1 ± 5.4	*0.702*
Inpatient CVP reduction (cm H_2O)	−6.6 ± 7.2	−5.8 ± 6.5	−8.1 ± 8.2	0.237	−6.6 ± 6.9	−6.5 ± 8.3	*0.962*
Inpatient BW reduction (kg)	−4.2 ± 5.8	−4.7 ± 6.2	−3.0 ± 4.8	0.278	−4.0 ± 5.4	−4.9 ± 7.0	*0.548*
Medication							
Diuretic	87	63 (84)	24 (96)	0.122	63 (94)	24 (73)	*0.003*
β-Blocker	64	44 (59)	20 (80)	0.054	53 (79)	11 (33)	*<0.001*
ACE-inhibitor	65	46 (61)	19 (76)	0.183	49 (73)	16 (49)	*0.015*
Angiotensin receptor blocker	24	19 (25)	5 (20)	0.589	20 (30)	4 (12)	0.051
Calcium antagonist	15	10 (13)	5 (20)	0.419	10 (15)	5 (15)	0.976
Spironolactone	31	15 (20)	6 (24)	0.671	17 (25)	4 (12)	0.126
Digoxin	12	10 (13)	2 (8)	0.477	9 (13)	3 (9)	0.53
Nitrate	36	23 (31)	13 (52)	0.054	22 (33)	14 (42)	0.348
Antiplatelet	44	32 (43)	12 (48)	0.807	31 (46)	13 (39)	0.376
Anticoagulant	45	28 (37)	17(68)	*0.008*	36 (54)	9 (27)	*0.012*
Statin	34	25 (33)	9 (36)	0.807	27 (40)	7 (21)	0.058

Values are mean ± SD or *n* (%). Significant *P*-values are given in italics.
CVP, central venous pressure; BW, body weight; ACE, angiotensin-converting enzyme.

To address whether therapy differed between patients with different CVP levels, we compared clinical data at presentation and discharge according to initial CVP levels (*Tables 4* and *5*). Though a significantly greater CVP reduction occurred in patients with initially high CVP levels, no significant difference in initial or discharge medication, inpatient BW reduction, or inpatient days was detectable.

Discussion

Using a novel technique of non-invasive CVP measurement, we investigated the relationship between initial CVP levels and the risk of cardiac rehospitalization and mortality in patients with DHF.

We report four major findings. First, CVP at presentation is an independent determinant for cardiac rehospitalization. Second, CVP at presentation is not related to subsequent cardiac or all-cause mortality. Third, CVP and BW reduction during hospitalization did not predict cardiac rehospitalization. Fourth, CVP and BW reduction during hospitalization did not predict cardiac or all-cause death. Therefore, this study adds important new insights into the concept that different pathophysiological aspects might be major players for cardiac rehospitalization and death in patients with DHF.

Many (non-cardiac) factors may contribute to the relation between CVP in DHF and morbidity. Left and right ventricular dysfunction resulting in high ventricular filling pressures, excessive neurohumoral activation with elevated circulating or tissue levels of norepinephrine, angiotensin II, and aldosterone, patient's non-compliance to medication, and sodium and/or fluid restriction might increase (alone or in concert) CVP which reflects the impaired performance of the failing heart. In fact, continuous monitoring of right ventricular haemodynamics in chronic heart failure patients demonstrated that in 9 out of 12 patients, a >20% increase in right ventricular pressure occurred before volume-overload exacerbations caused subsequent hospitalization.[14] Likewise, an increase in BW in the immediate pre-hospitalization period was observed.[15–17] Thus, our observation that CVP predicts subsequent cardiac rehospitalization suggests that CVP at presentation might reflect the patient's 'tolerable reserve' with respect to e.g. fluid-overload ultimately leading to rehospitalization. It is important to note that increases in BW in the post-discharge period are a major predictor for cardiac hospitalization but not for mortality.[17] This is in line with our finding that CVP predicts cardiac rehospitalization but not mortality. Analysing 2557 patients with a mixture of cardiovascular diseases who underwent right heart catheterization, Damman *et al.*[8] showed that increased CVP is associated with mortality. Several population characteristics may account to these contrasting results. First, the patients analysed by Damman *et al.* were substantially younger (59 ± 15 vs. 78 ± 11 years) and in only 16%, acute or chronic heart failure was the predominant reason for right heart catheterization. In addition, our patients had a considerably higher number of comorbidities (e.g. 42 vs. 9% diabetes mellitus, 78 vs. 20% hypertension, and 38 vs. 6% dyslipidaemia) and an extended medical therapy (e.g. 85 vs. 42% diuretics and 60 vs. 28% beta-blockers). Competing, non-cardiac deaths might have masked an association between CVP and mortality in our study, a larger study with a longer follow-up period might reveal an association between CVP level and all-cause mortality. However, from a clinical point of view, it is reasonable that elevated CVP levels might be a

Table 4 Patient characteristics at presentation according to central venous pressure at presentation

	CVP at presentation			
	<6 cm H_2O (*n* = 19)	**6–23 cm H_2O (*n* = 74)**	**>23 cm H_2O (*n* = 7)**	***P*-value**
Age (years)	83 ± 8	78 ± 11	73 ± 6	0.057
Male sex (%)	10 (53)	46 (62)	4 (57)	0.742
History of comorbidities, *n* (%)				
Diabetes	8 (42)	29 (62)	5 (71)	0.256
Dyslipidaemia	6 (31)	27 (36)	5 (71)	0.302
Nicotine abuse	12 (63)	35 (47)	4 (57)	0.614
Hypertension	15 (79)	57 (77)	6 (67)	0.864
Ischaemic heart disease	11 (58)	32 (43)	5 (71)	0.228
Non-ischaemic heart disease	10 (53)	22 (30)	2 (22)	0.073
Medication, *n* (%)				
Diuretic	17 (89)	61 (82)	7 (78)	0.728
β-Blocker	11 (58)	45 (61)	4 (57)	0.975
ACE-inhibitor	9 (47)	46 (62)	2 (22)	0.344
Angiotensin receptor blocker	4 (21)	16 (22)	0	0.610
Calcium antagonist	2 (11)	13 (18)	3 (33)	0.404
Spironolactone	1 (5)	12 (16)	1 (11)	0.751
Digoxin	2 (11)	3 (4)	0	0.724
Nitrate	8 (42)	18 (24)	4 (57)	0.274
Antiplatelet	7 (37)	36 (49)	4 (57)	0.805
Anticoagulant	11 (58)	30 (41)	3 (33)	0.718
Statin	6 (31)	31 (42)	3 (33)	0.891
Clinical parameters				
Systolic BP (mmHg)	140 ± 33	138 ± 26	152 ± 27	0.386
Diastolic BP (mmHg)	84 ± 15	86 ± 20	95 ± 21	0.441
Heart rate (b.p.m.)	93 ± 24	90 ± 26	87 ± 20	0.790
NYHA functional class III or IV (%)	19 (100)	72 (98)	7 (100)	0.544
LVEF (%)	43 ± 16	39 ± 15	55 ± 10	0.058
BMI (kg/m^2)	24.4 ± 4.0	26.9 ± 4.8	34.2 ± 6.4	*<0.001*
Laboratory tests				
Haemoglobin (g/L)	125 ± 26	127 ± 20	118 ± 24	0.544
Creatinine (umol/L)	137 ± 85	130 ± 87	229 ± 256	0.061
eGFR (mL/min/1.73 m^2)	39.5 ± 19.3	54.7 ± 30.9	83.9 ± 73.3	*0.013*
BUN (mmol/L)	12.8 ± 5.6	12.3 ± 7.5	16.1 ± 13.3	0.466
Sodium (mmol/L)	139 ± 3.5	137.3 ± 5.5	137.9 ± 4.3	0.327
Potassium (mmol/L)	3.9 ± 0.6	4.3 ± 0.6	4.1 ± 0.5	0.063
BNP (pg/mL)	1784 ± 1560	1965 ± 1634	1578 ± 1339	0.778
CK (U/L)	111 ± 104	146 ± 165	70 ± 54	0.387

Values are mean ± SD or *n* (%). Significant *P*-value is given in italics.
ACE, angiotensin converting enzyme; BP, blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BMI, body-mass index, eGFR, estimated glomerular filtration rate (Cockroft–Gault formula); BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; CK, creatinine kinase.

surrogate of predisposition to further congestion and therefore affect short-term hospitalization rates more than long-term mortality.

The observation that CVP predicts cardiac rehospitalization but not mortality in patients with DHF might have important clinical implications. The cardinal manifestations of DHF are pulmonary congestion and fluid overload, which may lead to dyspnoea, peripheral oedema, and limited exercise tolerance.[15,18,19] Thus, therapy to reduce volume overload is the cornerstone of any successful treatment and leads to marked improvement in signs and symptoms of congestion.[6,20] Our patients experienced significant reductions in both BW and CVP, but this reduction in (intravascular) volume was not associated with reductions in cardiac rehospitalization or mortality. Accordingly, growing evidence indicates that fluid removal itself may not necessarily prevent rehospitalizations or reduce mortality.[17,21] For example, in the EVEREST study

Table 5 Patient characteristics at discharge according to central venous pressure at presentation

	CVP at presentation			
	<6 cm H_2O (n = 19)	**6–23 cm H_2O (n = 74)**	**>23 cm H_2O (n = 7)**	***P*-value**
Inpatient days (days)	13 ± 6	16 ± 13	16 ± 5	0.647
Inpatient CVP reduction (cm H_2O)	−0.2 ± 1.9	−6.6 ± 5.9	−16.2 ± 10.4	*<0.001*
Inpatient BW reduction (kg)	−3.2 ± 3.8	−4.2 ± 6.3	−6.5 ± 5.3	0.516
Medication				
Diuretic	15 (79)	65 (88)	7 (100)	0.336
β-Blocker	13 (68)	45 (61)	6 (86)	0.383
ACE-inhibitor	9 (47)	51 (69)	5 (71)	0.200
Angiotensin receptor blocker	6 (32)	18 (24)	0	0.245
Calcium antagonist	2 (11)	10 (14)	3 (43)	0.96
Spironolactone	2 (11)	16 (22)	3 (43)	0.193
Digoxin	5 (26)	7 (9)	0	0.078
Nitrate	9 (47)	23 (31)	4 (57)	0.202
Antiplatelet	8 (42)	30 (41)	6 (86)	0.095
Anticoagulant	5 (26)	37 (50)	3 (43)	0.179
Statin	5 (26)	26 (35)	3 (43)	0.675

Values are mean ± SD or n (%). Significant P-values are given in italics.
CVP, central venous pressure; BW, body weight; ACE, angiotensin converting enzyme.

(Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan), rapid and sustained decreases in BW throughout hospitalization and after discharge did not result in mortality benefits.[17] Diuretics are known to effectively remove fluid but may worsen renal function and further activate neurohormones, thus offsetting the positive effect of therapeutic intervention on outcomes.[22,23] In particular, older patients, as seen in our study, demonstrate that survival quality, not survival time, is the most important measure of benefit and represents a major therapy target in patients with advanced heart failure. Our data show that CVP measurement, immediately upon presentation to the ER may help identify patients at higher risk for cardiac rehospitalization and may be used to better tailor therapy and patient surveillance in order to avoid early cardiac rehospitalizations. However, the optimal therapy and surveillance strategy are yet to be established. For example, titration of specific heart failure therapies guided by BNP levels (an indicator of elevated ventricular filling pressures) has resulted in improved outcomes in selected groups.[24,25] Further randomized controlled trials are needed to confirm (or reject) our hypothesis that CVP measurements performed promptly after presentation provide relevant clinical information for potential therapeutic intervention and subsequent outcome. Nevertheless, this study reveals important new insights into the pathophysiology behind the two most important clinical outcomes in DHF: cardiac rehospitalization and death. This observation also raises concern regarding the increasing use of death and cardiac rehospitalization as a combined endpoint in clinical trials enrolling DHF patients. Namely, the inclusion of factors in the composite endpoint that are not similarly affected by the intervention may actually 'dilute' the observed treatment effect and decrease the overall statistical power.

Limitations

There are several limitations to our study. First, we used a novel technique to measure CVP. Accordingly, only limited clinical experience exists with this technique. However, non-invasive controlled compression sonography of the forearm has been demonstrated to be accurate in measuring CVP with a high correlation between invasive and non-invasive ultrasound CVP measurement over a wide range of pressures, not only in a highly selected but also in a more generalized setting.[12,13] Second, we did not enrol consecutive patients with DHF and a selection bias may have occurred. The decision for enrolment was made blinded to patients' clinical characteristics and was only limited by the prompt availability of the CVP measurement (ultrasound machine and examiner). In fact, the baseline characteristics of our study population were similar to the baseline characteristics of a previously published study of 217 patients with DHF presenting at the emergency department of the University Hospital of Basel over 1 year.[26]

Third, our sample size is relatively small. Nevertheless, the study was sufficiently powered to demonstrate a clinically meaningful difference in cardiac rehospitalization rates according to CVP levels and all-cause mortality according to BNP levels, representing a well-known prognostic parameter for mortality in this setting.[27–30]

Fourth, several different CVP level categories could have been used. However, no consensus for CVP graduation exists and therefore we used predefined CVP levels according to the literature and the expected range of CVP values.

Conclusions

Central venous pressure measured at presentation to the ER in patients with DHF is an independent determinant of cardiac

rehospitalization but not of cardiac or all-cause mortality. This study adds important new insights to the concept that different pathophysiological aspects seem to underlie the two most important clinical outcomes in DHF: cardiac rehospitalization and death. Compression sonography at the forearm represents an attractive non-invasive alternative for measuring CVP, which might be used to guide subsequent therapy and follow-up.

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