Advances in Medical Sciences 64 (2019) 37–43

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original Research Article

Fluid therapy in non-septic, refractory acute decompensated heart failure patients – The cautious role of central venous pressure

Malgorzata Chlabicz[a,b], Remigiusz Kazimierczyk[a], Paulina Lopatowska[a], Monika Gil-Klimek[a], Bartosz Kudlinski[c], Marcin Ligowski[d], Bozena Sobkowicz[a], Marek Gierlotka[e], Karol Kaminski[a,b], Agnieszka Tycinska[a,*]

[a] Department of Cardiology, Medical University of Bialystok, Bialystok, Poland
[b] Department of Population Medicine and Prevention of Civilization Diseases, Medical University of Bialystok, Bialystok, Poland
[c] Department of Teaching Anaesthesiology and Intensive Therapy, University of Medical Sciences in Poznan, Poznan, Poland
[d] Department of Cardiac Surgery and Transplantology, University Hospital of Lord's Transfiguration, Poznan, Poland
[e] Department of Cardiology, Medical University of Opole, Opole, Poland

ARTICLE INFO

Keywords:
Acute heart failure
Central venous pressure
Fluid therapy

ABSTRACT

Purpose: Fluid therapy in congestive acute decompensated heart failure (ADHF) patients might be inappropriate and worsening the prognosis. The aim of our study was to analyze the effect of fluid administration on mortality in non-septic, ADHF patients with reduced ejection fraction.

Material and methods: We analyzed 41 ADHF consecutive 'cold-wet' patients (mean age 69.3 ± 14.9 years, 27 men, LVEF 22.8 ± 11.1%, lactates 2.2 ± 1.6 mmol/L) without sepsis. At admission central venous pressure (CVP) was measured (17.6 ± 7.2 cm H_2O), and ultrasound examination of inferior vena cava (IVC) was performed (IVC min. 18.6 ± 7.3 mm and IVC max. 24.6 ± 4.3 mm). Moreover, the groups were compared (survivors *vs.* non-survivors as well as 1st and 4th quartile of CVP).

Results: Altogether 17 (41%) patients died: 16 (39%) during a mean of 11.2 ± 7.8 days of hospitalization and 1 during a 30-day follow up. Patients in the lowest CVP quartile (< 13 cm H_2O) had significantly worse in-hospital survival as compared to patients in the highest quartile (> 24 cm H_2O), $P = 0.012$. Higher intravenous fluid volumes within the first 24 h were infused in patients in the lowest CVP quartile as compared to the highest CVP quartile (1791.7 ± 1357.8 mL *vs.* 754.5 ± 631.4 mL, $P = 0.046$). Moreover, more fluids were infused in a group of patients who died during a hospital stay and at 30-day follow up (1362.8 ± 752.7 mL *vs.* 722.7 ± 1046.5 mL, $P = 0.004$; 1348.8 ± 731.0 mL *vs.* 703.6 ± 1068.4 mL, $P = 0.002$, respectively).

Conclusions: CVP-guided intravenous fluid therapy is a common practice which in high risk ADHF 'cold-wet' patients might be harmful and should rather be avoided. Lower CVP seems to be related with worse prognosis.

1. Introduction

Currently, the number of hospitalizations of patients with acute decompensated heart failure (ADHF) is growing rapidly [1]. Among heterogeneous patients' population being admitted to Intensive Cardiac Care Unit (ICCU) the number of ADHF patients exceeds 30% [2]. The bedside classifications based on the signs and symptoms of congestion and the presence or absence of tissue hypoperfusion, according to the current European Society of Cardiology (ESC) guidelines, should be routinely used in the clinical practice [3]. The in-hospital mortality rate in the most severe 'cold-wet' (hemodynamic profile C) ADHF group is the worst and exceeds 40% [4]. The relationship between the fluid balance and adverse outcomes in critically ill - usually septic intensive care patients - is well established and, according to recent data, these patients benefit from strategies to minimize or treat fluid overload [5]. In critically ill adults hospitalized in the Intensive Care Unit (ICU) the use of saline for intravenous fluid administration resulted in a higher rate of death from all causes and a higher rate of renal injury than following the use of balanced crystalloids (lactated Ringer's solution or multiple electrolytes injection) [6]. Several studies suggest that hyperchloraemia associated with saline infusion could cause renal dysfunction and increase mortality [7–9]. However, there are no clear guidelines regarding the definition of the fluid overload, monitoring the volume status and, finally, the preferred method of treatment - diuretic

* Corresponding author at: Department of Cardiology, Medical University of Bialystok, Marii Sklodowskiej-Curie 24a, 15-276, Białystok, Poland.
E-mail address: agnieszka.tycinska@gmail.com (A. Tycinska).

https://doi.org/10.1016/j.advms.2018.11.001
Received 9 October 2018; Accepted 4 November 2018
Available online 14 November 2018
1896-1126/

or fluid therapy in 'cold-wet' ADHF patients. Moreover, the exact importance of central venous pressure (CVP) among severe 'cold-wet' heart failure (HF) cardiac patients, especially without confounding sepsis, is unknown.

The aim of the present study was to assess the effect of fluid administration on mortality in the group of non-septic, refractory, 'cold-wet' ADHF patients with reduced ejection fraction (HFrEF) and with special consideration of CVP.

2. Material and methods

Among 84 patients with previously diagnosed chronic heart failure (CHF) due to reduced (< 40%) left ventricle ejection fraction (HFrEF) admitted between May 2016 and October 2017 to ICCU of the Department of Cardiology, Medical University of Bialystok (Poland) a group of 41 patients was retrospectively analyzed. The inclusion criteria for the analysis were: previously known and currently decompensated heart failure patient, belonging to the 'cold-wet' − hemodynamic profile C of the acute heart failure, demanding central venous access. This was diagnosed at admission based on the clinical signs and symptoms of both left- and/or right-side heart congestion accompanied by symptomatic (*i.e.* the presence of peripheral hypoperfusion) hypotension. The exclusion criterion was the clinical and/or microbiological diagnosis of sepsis or septic shock. At admission, basic vital signs, including the presence of atrial fibrillation as well as biochemical analysis and routine echocardiographic examination, including detailed right-side heart assessments (right atrium area - RAA, tricuspid annular plane systolic excursion - TAPSE and tricuspid regurgitation peak gradient - TRPG) were performed. Moreover, ultrasound measurements of inferior vena cava (IVC) during inspiration (IVCi/IVC min.) and expiration (IVCe/IVC max.) as well as left and right internal jugular veins (IJVs) dimensions were performed.

CVP (in cm H_2O) was measured at presentation, as soon as the central venous access was obtained, using the fluid fill tube connected to water column in supine position as described previously [10]. Before pressure measurement, calibration was conducted and zero was put in the mid thorax [10].

Admission illness severity scores, including Sequential Organ Failure Assessment (SOFA) and Acute Physiology And Chronic Health Evaluation II (APACHE II) for each patient were calculated [11,12]. Intravenous fluid infusion, hourly fluid output (diuresis) as well as net fluid balance within the first 24 h were assessed.

Particular patients' groups were compared (survivors *vs.* non-survivors as well as 1st and 4th quartile of CVP).

2.1. Ethical issues

Ethical approval for this study was provided by the Ethics Committee of the Medical University of Bialystok (Poland) on 27th April 2017 (approval number: R-I-002/147/2017). The study was conducted in accordance with the Declaration of Helsinki.

2.2. Statistical analysis

The distribution of all variables was verified with the Kolmogorov-Smirnov test. Data are expressed as mean ± standard deviation (SD) or median [interquartile range], depending on distribution. Statistical analysis was performed using the Student's *t*-test or Mann-Whitney test for continuous data and the Pearson's chi-square test for categorical variables. Spearman's correlation coefficient was used to examine the relationship between two continuous variables. P value < 0.05 was deemed statistically significant. A statistical software package Statistica 10 (USA) was used for the analysis.

Primary end point was death (either in-hospital or assessed at 30-day follow up).

Table 1
The baseline characteristics of the study patients.

Age, years	69.3 (14.9)
Body weight, kg	86.7 (22.9)
APACHE II, points	13.8 (6.3)
SOFA, points	7.9 (3.5)
GCS, points	13.2 (3.8)
HR, beats per minute	94.3 (19.9)
MAP, mmHg	77.7 (10.8)
CVP, cmH_2O	17.6 (7.2)
LVEF, %	22.8 (11.1)
TAPSE, mm	15.0 (3.8)
TRPG, mmHg	36.1 (12.0)
RAA, cm^2	26.1 (6.8)
IVC min., mm	18.6 (7.3)
IVC max., mm	24.6 (4.3)
IJVd right, mm	14.4 (3.6)
IJVd left, mm	12.1 (2.8)
SvO_2, %	67.49 (12.8)
Creatinine, mg/dL	1.8 (1.0)
GFR, mL/min/1.75 m^2	48.7 (25.7)
BNP, pg/mL	1895.2 (1254)
Troponin I hs, ng/L	190.7 [32.4-1218.1]
Lactates, mmol/L	2.2 (1.6)
Platelets, x10^3/μL	193.7 (83.9)
Bilirubin, mg/dL	1.2 (2.2)
Procalcitonin, ng/mL	1.2 (2.6)
Fluids given intravenously in the first 24 h, mL	992.2 (976.6)
Diuresis in the first 24 h, mL	1837.9 (1623.2)
Fluid balance in the first 24 h, mL	2906.8 (1649)
Daily dose of furosemide in the first 24 h, mg	270.5 (313.1)
Dose of dobutamine, μg/kg/min.	2.93 (2.2)
Dose of norepinephrine, μg/kg/min.	0.05 (0.1)

APACHE II - Acute Physiology And Chronic Health Evaluation II, BNP - B-type natriuretic peptide, CVP - central venous pressure, GCS - Glasgow Coma Scale, GFR - glomerular filtration rate, HR – heart rate, IJVd - internal jugular vein dimension, IVC max. - inferior vena cava maximal diameter, IVC min. - inferior vena cava minimal diameter, LVEF - left ventricular ejection fraction, MAP - mean arterial pressure, RAA - right atrium surface area, SvO_2 - mixed venous oxygen saturation, SOFA - Sequential Organ Failure Assessment, TAPSE - tricuspid annular plane systolic excursion, TRPG - tricuspid regurgitation peak gradient.
Data shown as mean (SD) or median [interquartile range].

3. Results

3.1. Baseline characteristics

The study group comprised of 41 patients with previously diagnosed CHF due to reduced HFrEF (< 40%) (mean age 69.3 ± 14.9 years; 27 men; mean LVEF 22.8 ± 11.1%; 24 patients with ischemic and 17 with non-ischemic etiology; atrial fibrillation was present in 43% (n = 18) of the patients). The majority of the patients received either inotropic agent alone (dobutamine, n = 6) or vasopressor alone (dopamine, n = 2) or both – dobutamine and norepinephrine (n = 23) in infusion. Ten patients received none of these agents within the first 24 h. Twenty-four (58%) patients needed either invasive (IV) or non-invasive (NIV) ventilation support and two patients needed renal replacement therapy. Baseline patients' characteristics is shown in Table 1.

3.2. In-hospital mortality

During a mean of 11.2 ± 7.8 days of hospitalization 16 (39%) patients died (a mean time to death was 6.1 ± 5.1 days). The group of patients who died during the hospitalization received more intravenous fluids within the first 24 h, and were also found to have higher TAPSE, lactates as well as SOFA score (Table 2). Among the patients who died there were 13 (32%) with lactates > 2.0 mmol/L as compared to 3 (7%) patients with lactates < 2.0 mmol/L (chi-square test, $P = 0.01$). Additionally, there were 11 (27%) patients with SvO2 < 65% who died compared to 5 (12%) patients with SvO2 > 65% (chi-square test,

Table 2
The comparison of patients who died and survived during hospitalization.

	Survivors n = 25	Deaths n = 16	p
Age, years	69.0 (14.4)	69.9 (16.3)	0.82
APACHE II, points	12.5 (5.6)	15.7 (7.0)	0.08
SOFA, points	7.2 (3.5)	9.1 (3.2)	0.05
GCS, points	14.1 (2.7)	11.8 (4.9)	0.27
HR, bpm	93.5 (19.2)	95.6 (21.6)	0.76
MAP, mmHg	79.0 (9.9)	75.5 (12.0)	0.42
CVP, cmH_2O	18.7 (7.2)	15.9 (7.0)	0.15
LVEF, %	24.1 (11.4)	20.8 (10.5)	0.37
TAPSE, mm	13.9 (3.6)	17.3 (3.1)	0.004
TRPG, mmHg	37.0 (12.9)	34.7 (10.7)	0.66
RAA, cm^2	26.1 (6.13)	26.2 (7.9)	0.76
IVC min., mm	20.0 (7.0)	16.5 (7.4)	0.21
IVC max., mm	25.8 (4.2)	22.7 (3.8)	0.07
IJVd, right, mm	13.4 (3.0)	15.4 (4.1)	0.15
IJVd, left, mm	11.9 (2.7)	12.4 (2.9)	0.57
SvO_2, %	69.94 (10.21)	63.66 (12.23)	0.15
Creatinine, mg/dL	1.6 (0.8)	2.1 (1.2)	0.25
GFR, mL/min/1.75 m^2	50.9 (25.1)	45.2 (26.9)	0.57
BNP, pg/mL	1982.9 (1354.0)	1748.9 (1095.7)	0.87
Troponin I hs, ng/L	381.5 [48.2-3354.5]	186.0 [31.2-623.5]	0.83
Lactates, mmol/L	1.6 (0.9)	3.0 (2.2)	0.01
Platelets, x103/μL	213.6 (89.1)	162.6 (66.0)	0.05
Fluids given intravenously in the first 24 h, mL	722.7 (546.5)	1362.8 (752.7)	0.004
Diuresis in the first 24 h, mL	3144.3 (1628.8)	2477.8 (1602.3)	0.2
Fluid balance in the first 24 h, mL	−2201.2 (1608.7)	−1383 (1031.4)	0.09
Daily dose of furosemide in the first 24 h, mg	197.6 (267.9)	260.0 (183.6)	0.07
Dose of dobutamine μg/kg/min.	2.8 (2.1)	3.2 (2.3)	0.68
Dose of dopamine μg/kg/min.	0.0 (0.0)	0.3 (0.9)	0.52
Dose of norepinephrine μg/kg/min.	0.03 (0.01)	0.06 (0.02)	0.47

APACHE II - Acute Physiology And Chronic Health Evaluation II, BNP - B-type natriuretic peptide, CVP - central venous pressure, GCS - Glasgow Coma Scale, GFR - glomerular filtration rate, HR – heart rate, IJVd - internal jugular vein dimension, IVC max. - inferior vena cava maximal diameter, IVC min. - inferior vena cava minimal diameter, LVEF - left ventricular ejection fraction, MAP - mean arterial pressure, RAA - right atrium surface area, SvO_2 - mixed venous oxygen saturation, SOFA - Sequential Organ Failure Assessment, TAPSE - tricuspid annular plane systolic excursion, TRPG - tricuspid regurgitation peak gradient.
Data shown as mean ± SD or median [interquartile range].

P = 0.02). Moreover, in the patients with SvO2 < 65% as compared to the patients with SvO2 > 65% mean CVP was higher and mean arterial pressure (MAP) was lower (19.5 ± 6.8 *vs.* 16.0 ± 7.2 cm H_2O, P = 0.04, and 69.2 ± 9.7 *vs.* 74.9 ± 10.3 mmHg, P = 0.04, respectively). Patients with lactates > 2.0 mmol/L revealed a tendency towards higher CVP and lower MAP as compared to those with lower lactates levels (P=ns).

3.3. 30-day mortality

At a 30-day follow up after discharging home, one more patient died, thus, altogether 17 (41%) patients died. Patients who died during the 30-day follow up differed in the same parameters and additionally had smaller IVC max. dimension and lower diuresis within the first 24 h (data not shown).

3.4. Fluid therapy

For further analysis, we divided the study population based on the median amount of intravenous fluids given within the first 24 h (patients who received a higher or lower than median value of 775 mL, which also included the fluids contained in the administered medicines). The condition of patients who received more fluids was more severe at admission as they had lower MAP, higher SOFA score and needed higher doses of norepinephrine. More fluids were also given to patients with lower IVC max. and lower diuresis (Table 3).

Higher CVP negatively correlated with lower diuresis (r = −0.4, P = 0.03) and positively with higher doses of furosemide (r=0.4, P = 0.04). Higher CVP positively correlated with larger IVC dimension during expiration (IVC max.: r=0.5, P = 0.001, Fig. 1) and during inspiration (IVC min.: r = 0.4, P = 0.01).

Table 3
The comparison of patients who received intravenous fluids lower and higher than the median value (775 mL) during the first 24 h.

	Fluids < 775 mL[a] n = 19	Fluids > 775 mL n = 19	p
Age, years	67.8 (14.2)	68.2 (15.6)	0.93
APACHE II, points	11.8 (6.3)	15.6 (6.1)	0.06
SOFA, points	6.6 (2.9)	9.7(3.3)	0.004
GCS, points	14.4 (2.3)	11.7 (4.8)	0.08
HR, bpm	88.9 (15.7)	101.4(22.5)	0.13
MAP, mmHg	81 (10.3)	73.6 (10.2)	0.046
CVP, cmH_2O	19.5 (7.8)	15.3 (6.0)	0.05
LVEF, %	21.1(10.4)	22.6 (11.6)	0.79
TAPSE, mm	14.5 (4.4)	15.5 (2.5)	0.19
TRPG, mmHg	36.9 (14.3)	34.3 (10.5)	0.76
RAA, cm^2	27.1 (5.8)	25.9 (7.9)	0.37
IVC min., mm	20.2 (7.7)	17.1 (7.2)	0.3
IVC max., mm	26.1 (4.2)	23.0 (4.1)	0.03
IJVd right, mm	14.3 (3.1)	13.6 (3.9)	0.58
IJVd left, mm	11.9 (3.0)	12.0 (2.6)	0.91
SvO_2, %	64.2 (12.5)	70.2 (12.2)	0.14
Creatinine, mg/dL	1.6 (0.9)	1.8 (1.1)	0.66
GFR, mL/min/1.75 m^2	52.1 (24.4)	50.1 (26.4)	0.91
BNP, pg/mL	1922.4(1248.1)	1757.6 (1148.4)	0.77
Troponin I hs, ng/L	183.8 [31.2-667.7]	190.7 [27.0-1298.5]	0.93
Lactates, mmol/L	2.0 (1.5)	2.4 (1.9)	0.58
Platelets, $x10^3$/μL	210.1 (93.9)	177.0 (74.7)	0.26
Diuresis in the first 24 h, mL	3374.2 (1780.2)	2593.3 (1321.1)	0.03
Fluid balance in the first 24 h, mL	−2692.4 (1706.3)	−1213.1 (1172.1)	0.08
Daily dose of furosemide in the first 24 h, mg	251.3 (276.5)	202.1 (191.3)	0.53
Dose of dobutamine μg/kg/min.	2.4 (2.2)	3.7 (1.9)	0.12
Dose of dopamine μg/kg/min.	0.0 (0.0)	0.3 (0.8)	0.58
Dose of norepinephrine μg/kg/min.	0.01 (0.002)	0.07 (0.01)	0.005

APACHE II - Acute Physiology And Chronic Health Evaluation II, BNP - B-type natriuretic peptide, CVP - central venous pressure, GCS - Glasgow Coma Scale, GFR - glomerular filtration rate, HR – heart rate, IJVd - internal jugular vein dimension, IVC max. - inferior vena cava maximal diameter, IVC min. - inferior vena cava minimal diameter, LVEF - left ventricular ejection fraction, MAP - mean arterial pressure, RAA - right atrium surface area, SvO_2 - mixed venous oxygen saturation, SOFA - Sequential Organ Failure Assessment, TAPSE - tricuspid annular plane systolic excursion, TRPG - tricuspid regurgitation peak gradient.
Data shown as mean (SD) or median [interquartile range].
[a] 3 patients who received equally the amount of 775 mL of fluids were excluded from the analysis.

3.5. Central venous pressure

We further divided the study group based on the CVP quartiles and compared the patients from the first quartile (the lowest CVP < 13 cm H_2O) with the fourth quartile patients (the highest CVP > 24 cm H_2O). The distribution of CVP into quartiles disclosed that in the lowest CVP quartile 8 out of 9 patients died, and in the highest CVP quartile only 4 out of 11 patients died (chi-square test, P = 0.017).

The patients from both - the lowest and the highest - quartiles died

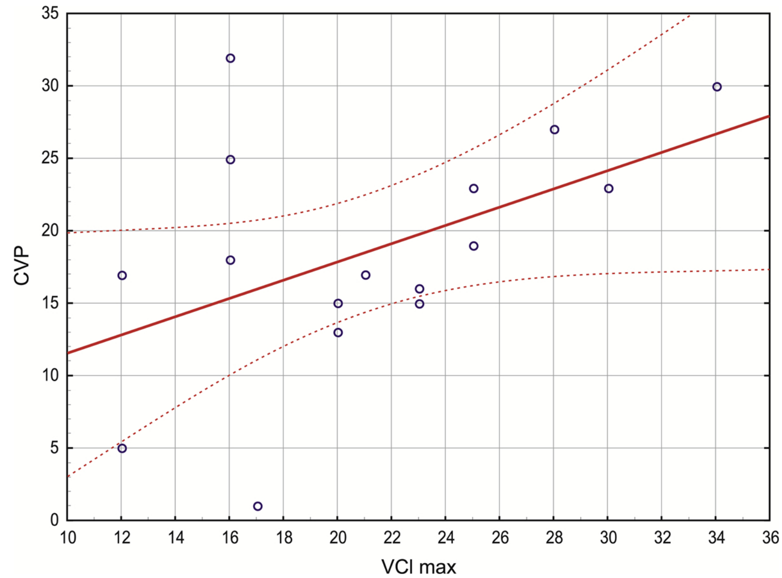

Fig. 1. Spearman correlation between central venous pressure (CVP) and inferior vena cava diameter during expiration (IVC max.).

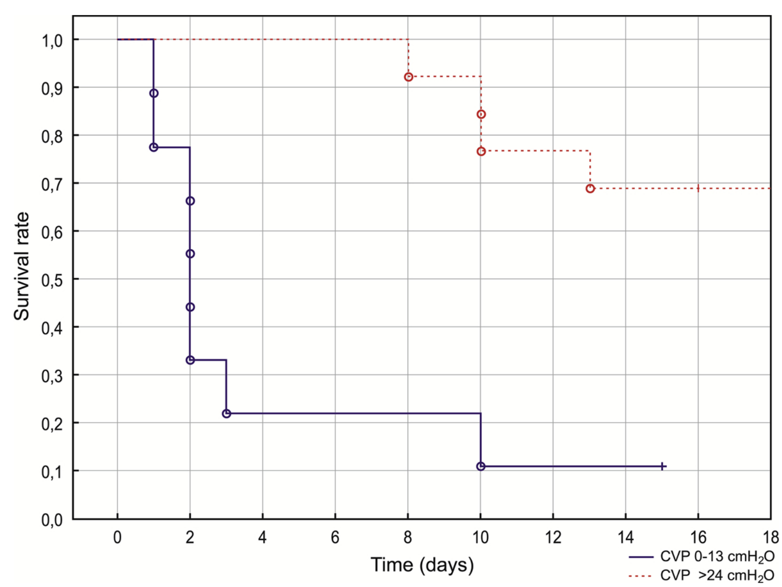

Fig. 2. Kaplan-Meyer curves presenting deterioration free survival in patients depending on the lowest central venous pressure values (CVP 0–13 cm H_2O) and the highest values (CVP > 24 cm H_2O), log-rank test, $P = 0.012$.

during hospitalization (up to 10 and 13 days, respectively). Furthermore, survival analysis revealed that patients with the lowest CVP values had statistically significantly worse in-hospital survival as compared to the patients with the highest values (log-rank test, $P = 0.012$, Kaplan-Meier curves, Fig. 2). Patients with the lowest CVP values had lower mean values of echocardiographic parameters of right ventricle (RV) overload (RAA and TRPG) as well as lower IVC diameters assessed in ultrasound as compared to the patients with the highest CVP levels (Table 4). Higher intravenous fluid volumes were infused within the first 24 h in the patients from the lowest CVP quartile as compared to the highest CVP quartile. Moreover, we observed a less negative fluid balance in the lowest CVP quartile (Table 4). Among the patients within the lowest CVP quartile 8 patients received intravenous fluid above the median value (775 mL), and in this group 7 patients died. We found a significant negative correlation between the baseline CVP and intravenous fluid infusion during the first 24 h ($r = -0.4$, $P = 0.04$) (Fig. 3).

4. Discussion

The aim of our study was to investigate the fluid therapy and its consequences in the group of severe ‘cold-wet’, non-septic HFrEF patients. It is obvious that congestion should be treated with diuretic therapy. However, symptomatic (*i.e.* with peripheral tissue hypoperfusion) hypotension is an indication for the use of inotropic agents usually together with vasopressors. Nevertheless, hypotension might lead physicians to unnecessary fluid therapy. The assessment of fluid balance in the ‘cold-wet’ ADHF patients is difficult and various methods, which complement each other, should be used in order to properly interpret and guide the therapy. Hence, the association of lower CVP values with more liberal fluid therapy and higher mortality in ‘cold-wet’ group of patients found in our study, is worth of value. Thus, we can assume that CVP is not a parameter for assessing vascular filling and lower CVP values do not indicate fluid responsiveness. What is more, this approach to CVP turns out to be ‘deadly’ for the heart

Table 4
Distribution of CVP into quartiles. The comparison of patients divided on the basis of CVP quartiles – the lowest (< 13 cm H_2O) and the highest (> 24 cm H_2O).

	Quartiles of mean CVP level		p
	1 n = 9	4 n = 11	
Age, years	65.1 (14.6)	70.0 (17.6)	0.41
APACHE II, points	14.56 (7.7)	19.0 (7.7)	0.86
SOFA, points	10.53 (3.4)	7.0 (3.4)	0.05
GCS, points	12.56 (3.7)	15.0 (3.7)	0.97
MAP, mmHg	77.0 (10.0)	89.0 (12.0)	0.09
LVEF, %	24.89 (11.6)	22.6 (11.1)	1.00
TAPSE, mm	16.10 (4.5)	19.0 (4.5)	0.51
TRPG, mmHg	23.0 (14.0)	42.1 (14.0)	0.04
RAA, cm^2	22.5 (2.6)	35.0 (7.6)	0.03
IVC min., mm	15.22 (2.4)	25.0 (6.4)	0.01
IVC max., mm	20.6 (3.9)	29.5 (7.9)	0.001
IVJd right, mm	13.0 (2.3)	15.0 (2.9)	0.8
IVJd left, mm	12.0 (2.2)	16.0 (2.8)	0.12
SvO_2, %	72.4 (16.2)	65.3 (13.2)	0.18
Creatinine, mg/dL	1.8 (0.75)	2.0 (1.2)	1.00
GFR, mL/min/1.75 m^2	44.8 (18.5)	48.2 (28.5)	0.72
BNP, pg/mL	1944.6 (712.1)	2717.8 (1378.1)	0.75
Troponin I hs, ng/L	378.9 [80.2-2384.4]	186.0 [27.0-667.7]	0.24
Lactates, mmol/L	2.8 (2.5)	1.7 (1.0)	0.86
Platelets, $x10^3/\mu L$	196.0 (62.5)	226.0 (62.5)	0.64
Fluids given intravenously in the first 24 h, mL	1791 (1031.4)	733.3 (583.2)	0.03
Diuresis in the first 24 h, mL	3170.1 (1595.2)	2493.0 (1344.6)	0.03
Fluid balance in the first 24 h, mL	−1047.2 (568.7)	−2256.4 (928.7)	0.02
Daily dose of furosemide in the first 24 h, mg	150.0 (133.3)	384.0 (173.3)	0.08
Dose of dobutamine, µg/kg/min.	3.35 (2.2)	2.15 (1.6)	0.27
Dose of dopamine µg/kg/min.	0.33 (0.1)	0.0 (0.0)	0.64
Dose of norepinephrine µg/kg/min.	0.07 (0.02)	0.02 (0.01)	0.21

APACHE II - Acute Physiology And Chronic Health Evaluation II, BNP - B-type natriuretic peptide, CVP - central venous pressure, GCS - Glasgow Coma Scale, GFR - glomerular filtration rate, HR – heart rate, IJVd - internal jugular vein dimension, IVC max. - inferior vena cava maximal diameter, IVC min. - inferior vena cava minimal diameter, LVEF - left ventricular ejection fraction, MAP - mean arterial pressure, RAA - right atrium surface area, SvO_2 - mixed venous oxygen saturation, SOFA - Sequential Organ Failure Assessment, TAPSE - tricuspid annular plane systolic excursion, TRPG - tricuspid regurgitation peak gradient.
Data shown as mean (SD) or median [interquartile range].

failure (HF) patients, because it allows more liberal fluid approach and, as a consequence less negative fluid balance.

In order to avoid a confounding effect and to get a more homogenous group we excluded all patients with clinical or microbiological suspicion of sepsis or septic shock. Baseline procalcitonin (PCT) concentrations were elevated, however, PCT is also known as a sensitive marker of non-infectious inflammation [13]. In a group of acute HF patients without an infection, elevated PCT is a marker of poor outcome [14].

The mortality rate among 'cold-wet' HF patients is high. In the variety of studies it balances between 22% to over 60% [15,16]. In our study, the patients who died had more severe condition at admission as well as higher SOFA score and higher levels of lactates. Higher lactates are found to be a marker of poor prognosis also among HF patients without the clinical signs and symptoms of tissue hypoperfusion ('warm hemodynamic profile') [17]. Thus, it is not surprising that the majority of our patients with elevated lactates and lower values of SvO2 died. Moreover, the majority of our patients needed inotropic agent infusion support, which was usually given together with the vasopressor. Despite the data suggesting increased mortality, dobutamine is the most widely used inotropic agent and recommended by ESC guidelines as a first-line therapy in the presence of tissue hypoperfusion [3,18]. This explains high mortality rate in our patients, but, compared to similar studies, vasopressor use might increase the mortality even up to 88%, and in patients at the age > 70 years reaches 100% [16]. Surprisingly, the CVP values did not differ significantly between the patients who died and survivors and there was a trend towards lower, not higher, values in the first group.

We showed that both echocardiographic and ultrasound examination results are marked in the assessment of fluid balance. Especially the echocardiographic parameters of RV function in this aspect are of value. In our study, the RAA as well as the TRPG values correlated with CVP, but regarding the mortality, only TAPSE remained significant. Higher TAPSE might be a sign of preserved RV function, which is known to be related with better outcome as compared to the left ventricle dysfunction [16]. Surprisingly, in our study, TAPSE values were higher in the patients who died. The only explanation could be that higher TAPSE values prompted physicians to start more intensive fluid therapy. When choosing therapy, physicians are also suggested to consider the IVC dimension and observe the amount of diuresis. But in our study while choosing the type of therapy, CVP was the most important parameter that was taken into account by the physicians. Elevated RA pressure and CVP quite often occur in critical care patients [19,20]. It may be caused by several conditions, such as congestive HF, pericardial effusion, pneumothorax and others [19]. In congestive HF, reduced cardiac output is the reason for the increased resistance to venous return, which leads to tissue hypoperfusion and subsequent splanchnic organ damage [20,21]. Based on the Starling curves and Guyton model on cardiac function, CVP should be determined as an interaction between the blood return to the heart and cardiac function. Elevated CVP can indicate an obstruction to the venous return and an increase of microcirculatory blood flow (mean circulatory filling pressure - MCFP), which in critically ill patients may further aggravate organ failure [21,22]. Fluid therapy almost always increases the MCFP, but venous return will increase only if the CVP is low (greater pressure difference between MCFP and CVP). If CVP increases, venous return will not increase, thus cardiac output will not rise, and the transfused fluids will be placed in the splanchnic organs and tissues, which is commonly seen in HF patients. Therefore, there is no single fixed CVP value for HFrEF patients, but elevated CVP in patients with cardiovascular diseases is associated with impaired hepatic and renal function and may be independently related to all-cause mortality [23,24]. In septic patients, increased CVP is associated with worse outcome [25,26]. But, especially among the patients hospitalized in the ICU, an elevated CVP value should not be a benchmark in diagnosing fluid overload and targeting fluid balance determined by a physician [26]. In our study, although the mean CVP was high in the whole group of patients, indicating poor cardiomyocytes response to the increased preload, lower values were related to worse survival. Higher CVP levels escalated the diuretic therapy, yet, without evident effect, which might be related to more prominent presence of cardio-renal syndrome. On the other hand, fluid therapy in high CVP patients was more restrictive, which could affect the better outcome observed in this group. Less negative fluid balance in the patients with the lowest CVP might suggest that physicians manage the diuretic therapy under CVP control which might be the reason of increased mortality. At the same time, lower CVP and IVC values together with lower diuresis led to more liberal fluid therapy, which might not be a correct procedure in ADHF patients, since we found more intensive fluid therapy used in patients who died. It is good to be aware that 'more liberal' fluid therapy was largely based on the volume administered in medicines within the first 24 h. Still, almost all the patients with lower CVP values who received fluid therapy died. Thus, patients with the lowest CVP values had the worst prognosis. It

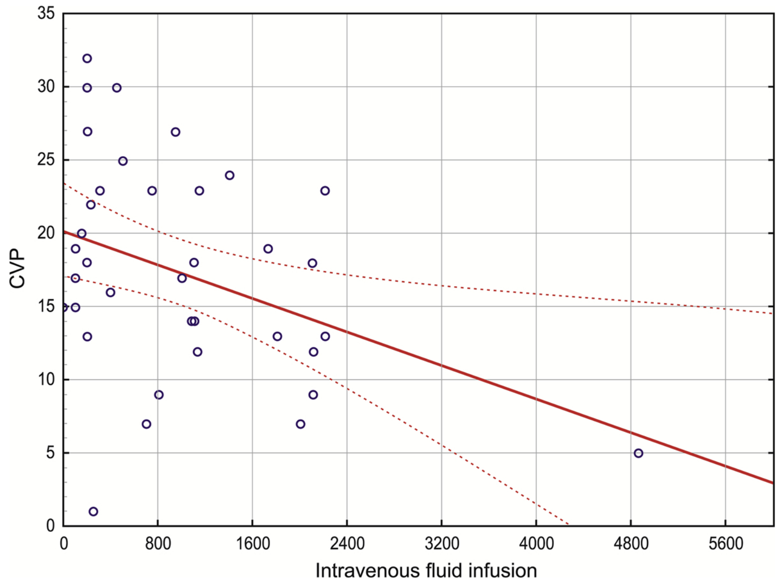

Fig. 3. Spearman correlation between central venous pressure (CVP) and intravenous fluid infusion.

still remains the question of debate, if that was due to more intensive fluid therapy for HFrEF patients with cardiomyocytes of weak reserve and the lack of increased cardiac output (simply called 'cardiomyocyte exhaustion'). In this aspect the fluid responsiveness (FR) assessment and the location of the patients on the Frank-Starling curve could make the study more valuable [27]. FR is defined as the ability of the left ventricle to increase its stroke volume (SV) in response to fluid administration. FR assessed by SV measured after fluid supply or passive leg raising (PLR) can provide relevant information whether fluid administration leads to the harmful overload, and therefore might be deleterious [28,29].

The newest data shows that 0.9% saline infusion is related with increased mortality in critically ill adults hospitalized in the ICU [6]. Nowadays, 0.9% saline solution has been the most widely used resuscitation fluid, which was also shown in our study–the majority of the patients (95%, n = 39) received 0.9% saline at least in combination with other crystalloids. Thus, at least in our study, the assessment of the mortality in this aspect is of limited value. For further analysis we divided the study population - based on the median amount of intravenous 0.9% saline infusion given within the first 24 h – into patients who received higher or lower than 400 mL (the remaining volume up to 775 mL consisted of non-0.9% saline infusion). This analysis revealed that patients who received more than a median value of 0.9% saline had higher in-hospital mortality as compared to those who received less (chi-square test, $P = 0.02$, data not shown). Saline is a hypertonic fluid, which has a higher chloride concentration than the plasma (approximately 40%), and causes hyperchloremic metabolic acidosis with this acidosis derived from the hyperchloraemia [30]. This high concentration of chloride is associated with proinflammatory state, renal vasoconstriction, decreased glomerular filtration rate [31–34] and increased mortality [9]. Moreover, hyperchloraemia can adversely affect the pulmonary, splanchnic, circulatory, and coagulation systems [8,35]. More liberal fluid resuscitation strategy together with the use of 0.9% saline and CVP > 8 mmHg was related to organ damage and death in a variety of diseases and, according to some authors, should be called a 'deadly trio' [19]. This, at least partially, could explain our results.

In summary, a low CVP value may provoke an increase in the amount of fluids transfused in HF patients, including those administered with medications, which may be translated into mortality. CVP measurement alone, especially in HFrEF patients, is not suitable for the estimation of the target volume (goal-directed fluid therapy - GDT) of fluid infusion.

4.1. Study limitations

The study has several limitations, first of all, the lack of CVP changes in response to fluid or diuretic treatment. Moreover, fluid responsiveness (including VTI LVOT assessed in echo) was not examined. Inclusion as well as exclusion criteria were based only on clinical manifestation of congestion and the presence of peripheral tissue hypoperfusion. However, based on the biochemical results as well as CVP levels, the patients were truly belonging to the 'cold-wet' hemodynamic profile. Moreover, in similar studies, in the absence of specificity of PCT a clear cut-off value should exist to confirm sepsis or septic shock, which, especially in severe ADHF patients, might be difficult. Finally, the results would be more obvious, if the study group was larger.

5. Conclusions

The assessment of fluid balance in ADHF patients is difficult to interpret, however, imaging examination results analyzed together with CVP could be complementary in this aspect. CVP values in non-septic ADHF patients are difficult to analyze, but lower values seem to be related with worse prognosis. CVP-guided intravenous fluid therapy is a common practice, which in high risk ADHF 'cold-wet' patients with reduced ejection fraction, might be harmful and should rather be avoided.

Financial disclosure

The authors have no funding to disclose

Conflict of interests

The authors declare no conflicts of interest.

The author contribution

Study Design: Malgorzata Chlabicz, Paulina Lopatowska, Monika Gil-Klimek, Bozena Sobkowicz, Karol Kaminski, Agnieszka Tycinska.

Data Collection: Malgorzata Chlabicz, Paulina Lopatowska, Monika Gil-Klimek, Agnieszka Tycinska.

Statistical Analysis: Remigiusz Kazimierczyk.

Data Interpretation: Malgorzata Chlabicz, Remigiusz Kazimierczyk, Bartosz Kudlinski, Marcin Ligowski, Bozena Sobkowicz, Marek

Gierlotka, Karol Kaminski, Agnieszka Tycinska.

Manuscript Preparation: Malgorzata Chlabicz, Paulina Lopatowska, Monika Gil-Klimek, Bartosz Kudlinski, Marcin Ligowski, Bozena Sobkowicz, Marek Gierlotka, Karol Kaminski, Agnieszka Tycinska.

Literature Search: Malgorzata Chlabicz, Paulina Lopatowska, Monika Gil-Klimek, Bartosz Kudlinski, Marcin Ligowski, Karol Kaminski, Agnieszka Tycinska.

Funds Collection: Agnieszka Tycinska.

References

[1] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127(1):e6–245.

[2] Uscinska E, Sobkowicz B, Sawicki R, Kiluk I, Baranicz M, Stepek T, et al. Parameters influencing in-hospital mortality in patients hospitalized in intensive cardiac care unit: is there an influence of anemia and iron deficiency? Intern Emerg Med 2005;10(3):337–44.

[3] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129–200.

[4] Joseph SM, Cedars AM, Ewald GA, Geltman EM, Mann DL. Acute decompensated heart failure: contemporary medical management. Tex Heart Inst J 2009;36(6):510–20.

[5] Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettilä V, et al. CLASSIC Trial Group; Scandinavian Critical Care Trials Group. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 2016;42(11):1695–705.

[6] Handy JM, Soni N. Physiological effects of hyperchloraemia and acidosis. Br J Anaesth 2008;101(2):141–50.

[7] O'Malley CM, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. Anesth Analg 2005;100(5):1518–24.

[8] Zhou F, Peng ZY, Bishop JV, Cove ME, Singbartl K, Kellum JA. Effects of fluid resuscitation with 0.9% saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis. Crit Care Med 2014;42(4):e270–8.

[9] Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: Improved short-term survival and acid-base balance with Hextend compared with saline. Crit Care Med 2002;30(2):300–5.

[10] Abbasian A, Feiz Disfani H, Afzalimoghaddam M, Talebian MT, Masoumi B, Nasr-Esfahani M. Measurement of central venous pressure using ultrasound in emergency department. Iran Red Crescent Med J 2015;17(12):e19403. (Retraction published March 3, 2016, Iran Red Crescent Med J 2016;18(3):e43586.).

[11] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707–10.

[12] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818–29. https://www.ncbi.nlm.nih.gov/pubmed/3928249.

[13] Mallick A, Januzzi JLJr. Biomarkers in acute heart failure. Rev Esp Cardiol (Engl Ed) 2015;68(6):514–25. https://doi.org/10.1016/j.rec.2015.02.009.

[14] Demissei BG, Cleland JG, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, et al. Procalcitonin-based indication of bacterial infection identifies high risk acute heart failure patients. Int J Cardiol 2016;204:164–71. https://doi.org/10.1016/j.ijcard.2015.11.141.

[15] Biegus J, Zymlinski R, Szachniewicz J, Siwolowski P, Pawlus A, Banasiak W, et al. Clinical characteristics and predictors of in-hospital mortality in 270 consecutive patients hospitalised due to acute heart failure in a single cardiology centre during one year. Kardiol Pol 2011;69(10):997–1005.

[16] Prins KW, Wille KM, Tallaj JA, Tolwani AJ. Assessing continuous renal replacement therapy as a rescue strategy in cardiorenal syndrome 1. Clin Kidney J 2015;8(1):87–92.

[17] Zymlinski R, Biegus J, Sokolski M, Siwołowski P, Nawrocka-Millward S, Todd J, et al. Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion. Eur J Heart Fail 2018;20(6):1011–8.

[18] O'Connor CM, Gattis WA, Uretsky BF, Adams Jr KF, McNulty SE, Grossman SH, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999;138(1 Pt 1):78–86.

[19] Li D, Wang X, Liu D. Association between elevated central venous pressure and outcomes in critically ill patients. Ann Intensive Care 2017;7(1):83. https://doi.org/10.1186/s13613-017-0306-1.

[20] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580–637. https://doi.org/10.1097/CCM.0b013e31827e83af.

[21] Vellinga NAR, Ince C, Boerma EC. Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis. BMC Anesthesiol 2013;13:17.

[22] Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009;53(7):582–8.

[23] Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53(7):589–96.

[24] Wang XT, Yao B, Liu DW, Zhang HM. Central venous pressure dropped early is associated with organ function and prognosis in septic shock patients: a retrospective observational study. Shock 2015;44(5):426–30.

[25] Legrand M, Dupuis C, Simon C, Gayat E, Mateo J, Lukaszewicz AC, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care 2013;17(6):R278.

[26] O'Connor ME, Jones SL, Glassford NJ, Bellomo R, Prowle JR. Defining fluid removal in the intensive care unit: a national and international survey of critical care practice. J Intensive Care Soc 2017;18(4):282–8.

[27] Hasanin A. Fluid responsiveness in acute circulatory failure. J Intensive Care 2015;19(3):50. https://doi.org/10.1186/s40560-015-0117-0.

[28] Pickett JD, Bridges E, Kritek PA, Whitney JD. Noninvasive blood pressure monitoring and prediction of fluid responsiveness to passive leg raising. Am J Crit Care 2018;27(3):228–37.

[29] Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. SMART Investigators and the Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in critically Ill adults. N Engl J Med 2018;378(9):829–39.

[30] Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. Chest 2006;130(4):962–7.

[31] Kotchen TA, Welch WJ, Lorenz JN, Ott CE. Renal tubular chloride and renin release. J Lab Clin Med 1987;110(5):533–40.

[32] Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest 1983;71(3):726–35.

[33] Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012;256(1):18–24.

[34] Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 2001;93(4):811–6.

[35] Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 2001;93(4):817–22.