

# Inferior Vena Cava and Hemodynamic Congestion

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**Background:** Among the indices able to replace invasive central venous pressure (CVP) measurement for patients with acute decompensated heart failure (ADHF) the diameters of the inferior vena cava (IVC) and their respiratory fluctuations, so-called IVC collapsibility index (IVCCI), measured by echocardiography, have recently gained ground as a quite reliable proxy of CVP.

**Objectives:** The aims of our study were to compare three different ways of evaluating cardiac overload by using the IVC diameters and/or respiratory fluctuations and by calculating the inter-method agreement

**Patients and Methods:** Medical records of patients hospitalized for right or bi-ventricular acute decompensated heart failure from January to December 2013 were retrospectively evaluated. The predictive significance of the IVC expiratory diameter and IVC collapsibility index (IVCCI) was analyzed using three different methods, namely a) the criteria for the indirect estimate of right atrial pressure by Rudski et al. (J Am Soc Echocardiogr. 2010); b) the categorization into three IVCCI classes by Stawicki et al. (J Am Coll Surg. 2009); and c) the subdivision based on the value of the maximum IVC diameter by Pellicori et al. (JACC Cardiovasc Imaging. 2013).

**Results:** Among forty-seven enrolled patients, those classified as affected by persistent congestion were 22 (46.8%) using Rudski's criteria, or 16 (34%) using Stawicki's criteria, or 13 (27.6%) using Pellicori's criteria. The inter-rater agreement was rather poor by comparing Rudski's criteria with those of Stawicki (Cohen's kappa = 0.369; 95% CI 0.197 to 0.54), as well as by comparing Rudski's criteria with those of Pellicori (Cohen's kappa = 0.299; 95% CI 0.135 to 0.462). Further, a substantially unsatisfactory concordance was also found for Stawicki's criteria compared to those of Pellicori (Cohen's kappa= 0.468; 95% CI 0.187 to 0.75).

**Conclusions:** The abovementioned IVC ultrasonographic criteria for hemodynamic congestion appear clearly inconsistent. Alternatively, a sequential or simultaneous combination of clinical scores of congestion, IVC ultrasonographic indices, and circulating levels of natriuretic peptides could be warranted.

**Keywords:** Chronic Heart Failure; Ultrasound Monitoring; Inferior Vena Cava

## 1. Background

It is sufficiently proven that an indirect estimate of the values of central venous pressure (CVP) can be drawn from the measurements of the inferior vena cava (IVC) echographic parameters (1-7). When a review of the pertinent literature is performed, various lines of thought can be found. A first current of thought tends to give value to the diameter itself of the IVC at the entrance into the right atrium, and makes a relatively approximate distinction concerning the respiratory kinetics of the IVC wall. This is the case of the "Guidelines for the echocardiographic assessment of the right heart in adults" of the American Society of Echocardiography, elaborated by Rudski et al. (2010) (8). Therein some summary criteria are encoded, including the cut-off value for the maximum (expiratory) venous caval diameter, for which the upper limit of the normality range is established to be 21 mm (Table 1). Moreover, a cut-off is even stated for the collapsibility of the IVC wall, related to the respiratory fluctuations of this vessel, for which a pathological value is assigned to an IVC inspiratory collapse <50%.

Another approach, supported by intensivists, critical

care physicians, and nephrologists, who also

dealt with this topic (10-12), gives value exclusively to the respiratory IVC dynamics, thus disregarding in reality the caval venous diameter in absolute terms as a reliable indicator of congestion or intra-vascular depletion (Table 2).

In contrast, most recently Pellicori et al. (13) attempted to simplify the approach by substantially denying a role for IVC collapsibility index (IVCCI) as a recommended parameter and valuing only the IVC maximum (namely, expiratory) diameter as a marker of congestion and/or heart failure (Table 3).

## 2. Objectives

In the present study centered on patients hospitalized for ADHF, we conducted a cross-sectional search on medical records to evaluate the degree of concordance (inter- method agreement) of the three abovementioned criteria for hemodynamic congestion as well as to evaluate the correspondence of these criteria with the clinical picture of each patient.

**Table 1.** Estimation of RA Pressure on the Basis of IVC Diameter and Collapse According to Rudski LG et al. <sup>a,b,c</sup>

Variables	Normal (0 - 5 [3] mm Hg)	Intermediate (5 - 10 [8]mmHg)	High (15 mm Hg)	
IVC diameter	≤ 21 mm	≤ 21 mm	> 21 mm	> 21 mm
Collapse with sniff	> 50%	< 50%	> 50%	< 50%
Secondary indices of elevated RA pressure	- Restrictive filling, - Tricuspid E/e' > 6, - Diastolic flow predominance in hepatic veins (systolic filling fraction < 55%)			

<sup>a</sup> Ranges are provided for low and intermediate categories, but for simplicity, midrange values of 3 mmHg for normal and 8 mm Hg for intermediate are suggested. Intermediate (8 mm Hg) RA pressures may be downgraded to normal (3 mm Hg) if no secondary indices of elevated RA pressure are present, upgraded to high if minimal collapse with sniff (< 35%) and secondary indices of elevated RA pressure are present, or left at 8 mm Hg if uncertain.

<sup>b</sup> Abbreviations: IVC, inferior vena cava; RA, right atrial.

<sup>c</sup> The table synthetically displays the concepts expressed by Rudski LG et al. (8) in the official recommendations of the American Society of Echocardiography. These criteria have been left unchanged in the recent update (9).

**Table 2.** Estimation of Central Venous Pressure on the Basis of IVC Collapsibility Index According to Stawicki et al. (11) <sup>a</sup>

	High Probability of Pathologically Elevated ( ≥ 12mm Hg) CVP	Not Helpful to Discriminate CVP	High Probability of Normal (0 - 7 mm Hg) CVP
IVCCI <sup>b</sup>	≤ 20%	21 - 60%	> 60%

<sup>a</sup> Abbreviations: CVP, central venous pressure; IVCCI, inferior vena cava collapsibility index; IVCD exp, inferior vena cava expiratory diameter; IVCD insp, inferior vena cava inspiratory diameter.

<sup>b</sup> IVCCI = [(IVCD exp - IVCD insp) / IVCD exp] × 100%.

**Table 3.** Estimation of the Risk of Persistent Congestion on the Basis of IVC Diameter in Patients With Previously Ascertained Heart Failure According to Pellicori et al. (13) <sup>a</sup>

	Negligible or low Risk of Congestion	Intermediate Risk of Congestion	High Risk of Congestion
Max IVC <sup>b</sup> diameter	16 (15 - 16) mm	19 (18 - 22) mm	24 (23 - 27) mm

<sup>a</sup> The values are expressed as median and interquartile range.

<sup>b</sup> Abbreviation: IVC, inferior vena cava.

### 3. Patients and Methods

The authors of the present investigation took into account the recommendations contained within the STARD (Standards for Reporting of Diagnostic Accuracy) (14) statement, so as to make the study consistently in keeping with the requirements provided for by the above mentioned guidelines in all of the sections of the study.

The medical records of patients having a clinical picture of ADHF who had been admitted to the hospital between January and December 2013 were carefully evaluated, particularly regarding the ultrasonographic indices of the caval venous system.

#### 3.1. Measurements

According to the customary approach used at our Centre, measurements of IVC diameters were obtained 1 to 2 cm below the level of the suprahepatic veins (Figure 1) using a two-dimensional echographic sector (Vivid 7 ultrasound machine, GE Healthcare Systems, Milwaukee, WI). The IVC diameter recording was made on M-mode

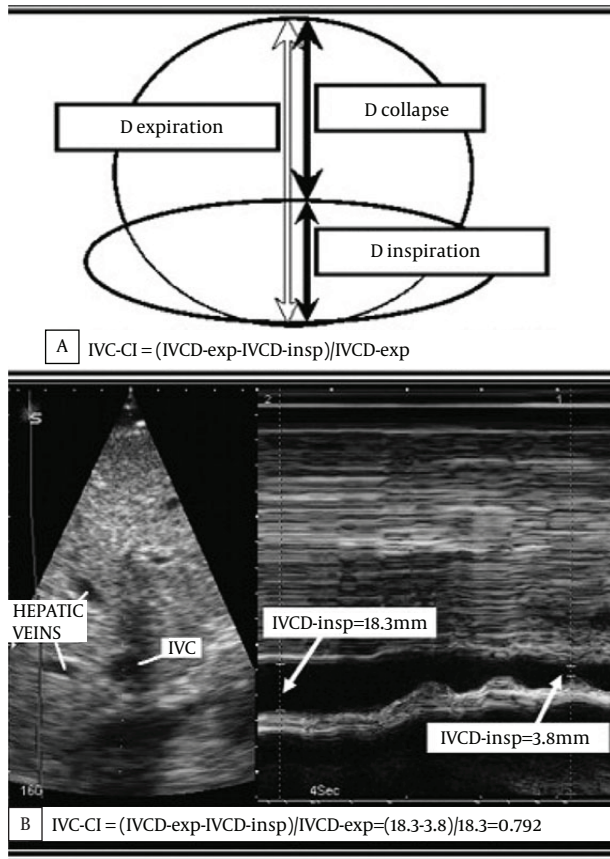
approximately 3 cm from the right atrium with patients in a 45° recumbent position. Subcostal or subxiphoid windows were used based on available views, patient habitus, possible presence of external impediments, and preference of the sonologist. The measurements of the IVC expiratory diameter (IVCD exp) and IVCCI were noted, and their diagnostic significance was respectively analyzed.

#### 3.2. Criteria

Three different keys of interpretation were used. These were: a) the criteria for the indirect estimate of the right atrial pressure, as described by Rudski et al. (8) (Table 1); b) the categorization into three IVCCI classes, indicating different ranges of CVP as drawn up by Stawicki et al. (11) (Table 2); and c) the subdivision into three classes according to the values of the maximum IVC diameter (IVC-D max), implemented by Pellicori et al. (13) (Table 3), in which the risk of congestion increases with IVC-D max

increasing. Another point to be underscored is the fact that the IVC measurements i.e., the diameters (IVC-D exp and IVC-D insp of the caval ostium) as well as the inspiratory collapse expressed as a percentage (IVC collapsibility index) were taken by the cardiologist who performed the echocardiograms, whereas the subsequent categorizations which led to affirm or to exclude a condition of hemodynamic congestion were inferred by the authors of the present retrospective research on the basis of the three aforementioned criteria.

**Figure 1.** (A) Representation of the IVC Collapsibility Index (IVCCI) and (B) IVCCI Measurement Using M-Mode Ultrasonography



IVCCI consists of the difference between the end-expiratory (IVCd-exp) and end-inspiratory IVC diameter (IVCd-insp) divided by IVCd-exp. (B). Based on the measurements in this example, the IVCCI would be  $(18.3 - 3.80 \text{ mm}) / 18.3 \text{ mm}$ , or 79.2 %.

### 3.3. Diagnosis of ADHF

All of the patients included in the study were characterized by right or bi-ventricular acute decompensated heart failure (ADHF) with NYHA functional class III-IV. ADHF was diagnosed at the admission on the basis of clinical picture and medical history (presence of dyspnea on minimum effort and/or at rest, orthopnea, peripheral edema, jugular venous distention, and gallop rhythm on cardiac auscultation, in addition to pre-existing medical history of known or strongly suspected heart disease)

and also on the basis of the determination of the circulating natriuretic peptides (either BNP or NTproBNP).

### 3.4. Timing of Echocardiography

Echocardiography was performed at the admission, and more in detail after the phase of acute hemodynamic instability had been overcome. The latest echocardiogram, generally performed on occasion of the last day of hospital stay, was taken into account for statistical analyses.

Inclusion criteria were: history of bi-ventricular chronic heart failure; evidence of right or bi-ventricular acute decompensated heart failure (ADHF) with functional class III-IV at hospital admission. Exclusion criteria were: major cardiac surgery; primary pulmonary hypertension; severe or moderate-severe tricuspid regurgitation; right myocardial infarction; cor pulmonale and advanced pulmonary disease; cancer; and other life-threatening disease.

### 3.5. Statistical Analysis

All statistical tests were performed with a commercially available statistical analysis program (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL, USA). The distribution of the data was assessed using the one-sample Kolmogorov-Smirnov test. Continuous variables displaying normal distribution were expressed as mean  $\pm$  SD, while values with asymmetric distribution were expressed as medians with interquartile ranges. Categorical variables were presented as %. The comparisons were made by means of Student's T-test (continuous variables) or by applying the Chi square test (categorical variables). Cox proportional hazards regression analysis was performed to explore the association between independent variables and outcome variables. In particular, the definitions of systemic venous congestion derived from Rudski's criteria or based on Stawicki's or Pellicori's criteria, respectively, were assumed as outcome variables. In addition, the following variables were assumed as exposure variables: BNP at discharge more than 400 pg/ml; NYHA class IV at admission; intravenous dose of furosemide during hospital stay more than 80mg per day; left ventricular ejection fraction  $\leq$  35%; systolic arterial pressure at admission equal or less than 100 mm Hg. Moreover, Cox proportional hazards regression analysis was used to estimate the possible significant association between some exposure variables and mortality from all causes at a follow-up of 90 days, taken as an outcome variable. The level of significance was set at  $P < 0.05$ . In addition, inter-rater agreement (Cohen's kappa) was used for estimating the degree of diagnostic concordance between the three adopted methods. For this purpose, the Cohen's kappa value was interpreted according to the scheme proposed by Altman (15), which is synthetically represented in Table 4.

## 4. Results

In our retrospective study, 47 patients were enrolled,

whose main clinical features, derived from the data of the clinical case records, are shown in Table 5. With regard to the echocardiographic phenotype of heart failure, this was represented in about 64% of cases (30 patients) by heart failure with reduced left ventricular ejection fraction (HFREF) and only in 36% of cases (17 patients) by heart failure with preserved left ventricular ejection fraction (HFpEF). Depending on the method used, patients classified as affected by persistent congestion were 22 (Rudski's criteria), accounting for 46.8% of the total, or 16 using the criteria of Stavicki, accounting for 34 % of the total, or 13 (27.6%) using the criteria of Pellicori.

The comparisons were made by means of Student's T-

test (continuous variables) or by applying Chi - square test (categorical variables)

**Table 4.** Interpretation of the Cohen's kappa value, re-adapted (15)

Value of K	Strength of Agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

**Table 5.** Characteristics of CHF Patients by Clinical and Biochemical Pattern and by IVC Ultrasonographic Criteria for Determining Hemodynamic Congestion <sup>a,b,c</sup>

	A		P Value (A vs. B)	C		P Value (C vs. D)	E		P Value (E vs. F)	G		P Value (G vs. H)
	No.22	No.25		No.13	No.34		No.13	No.34		No.11	No.36	
Age (y)	68 ± 15	71 ± 16	0.51	66 ± 16	64 ± 18	0.73	66 ± 12	67 ± 19	0.86	70 ± 19	65 ± 14	0.34
Males	11 (50)	13 (52)	0.87	6 (46)	18 (53)	0.92	7 (54)	17 (50)	0.92	8 (72.7)	16 (44)	0.19
Previous hyp	13 (59)	16 (64)	0.96	12 (92)	17 (50)	0.019	9 (69)	20 (59)	0.74	7 (63.6)	22 (61)	0.83
CAD	14 (63.6)	15 (60)	0.96	10 (77)	19 (56)	0.32	9 (69)	20 (59)	0.74	7 (63.6)	22 (61)	0.83
Diabetes	9 (41)	7 (28)	0.53	8 (61.5)	8 (23.5)	0.034	6 (46)	10 (29.4)	0.46	4 (36.3)	12 (33)	0.85
LVEF (%)	38 ± 20	43 ± 21	0.409	35 ± 20	44 ± 18	0.17	40 ± 15	44 ± 18	0.5	33 ± 20	41 ± 23	0.30
SBP, mm Hg	135 ± 26	130 ± 22	0.47	125 ± 25	128 ± 16	0.627	126 ± 26	132 ± 18	0.37	105 ± 20	134 ± 24	0.00
Heart rate, bts/ min at discharge	88 ± 19	82 ± 20	0.29	95 ± 10	80 ± 16	0.003	90 ± 26	84 ± 18	0.37	95 ± 10	85 ± 14	0.06
HFREF	12 (54.5)	18 (72)	0.34	7 (53.8)	23 (68)	0.58	7 (53.8)	23 (67.6)	0.58	9 (81.8)	21 (58.3)	0.28
HFPEF	10 (45.5)	7 (28)	0.34	6 (46.2)	11 (32.4)	0.588	6 (46.2)	11 (32.4)	0.58	2 (18.2)	15 (42)	0.28
Rales > 1/2 lung fields	14 (63.6)	10 (40)	0.185	11 (84.6)	13 (38)	0.011	7 (54)	17 (50)	0.92	9 (81.8)	15 (42)	0.04
JVD	12 (54.5)	2 (8)	0.001	10 (76.9)	4 (13.3)	0.0001	6 (46)	8 (23.5)	0.24	5 (45.5)	9 (25)	0.35
Hb (g/dl)	11 ± 1.9	13.8 ± 2.1	< 0.001	10 ± 2	13.9 ± 1.4	< 0.0001	11.9 ± 2	13.8 ± 4	0.11	10.5 ± 2	13.9 ± 2	< 0.001
Serum Na <sup>+</sup> , mEq/l	139 ± 4.5	138 ± 4.0	0.42	139 ± 3	138 ± 4	0.41	140 ± 23	139 ± 22	0.890	137 ± 20	139 ± 15	0.89
serum creatinine, mg/dl	1.9 ± 0.4	1 ± 0.3	< 0.001	2.1 ± 0.9	1.7 ± 0.5	0.048	1.9 ± 0.3	1.7 ± 0.3	0.045	2.3 ± 0.5	1.4 ± 0.6	< 0.001
eGFR, ml/min(discharge)	45 ± 32	80 ± 31	0.0004	45 ± 12	85 ± 22	< 0.0001	68 ± 24	81 ± 21	0.074	46 ± 6	83 ± 16	< 0.001
Moderate renal failure (eGFR = 30 to 60ml/min/1.73m <sup>2</sup> )	11 (50)	8 (32)	0.33	9 (69)	10 (29.4)	0.031	9 (69)	10 (29)	0.031	5 (45)	14 (39)	0.82
BNP, pg/ml (discharge)	705 ± 120	500 ± 350	0.012	850 ± 150	700 ± 200	0.018	670 ± 300	550 ± 180	0.099	905 ± 10	560 ± 80	< 0.001
Fluid removal after 48 h, l	3.95 ± 3.8	4.85 ± 1.9	0.301	3.6 ± 3.8	5.4 ± 1.9	0.035	4.05 ± 2	3.95 ± 4	0.93	3.5 ± 1.6	4.8 ± 1.6	0.023

<sup>a</sup> Data are presented as No. (%) and Mean ± SD.

<sup>b</sup> A = patients discharged with congestion (exp IVC diameter ≥ 21 mm plus IVCCI < 50%) (Rudski's criteria); B = patients discharged without congestion (Rudski's criteria); C = patients discharged with congestion (IVCCI < 20%) (Stawicki's criteria); D = patients discharged without congestion (Stawicki's criteria); E = patients discharged with congestion (max IVC-D > 23mm (Pellicori)); F = patients discharged without congestion (Pellicori); G = patients dead within 90 days after discharge; H = patients alive at 90th day after discharge.

<sup>c</sup> Abbreviations: ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; exp, expiratory; HFPEF, heart failure with preserved left ventricular ejection fraction; HFREF, heart failure with reduced left ventricular ejection fraction; IVC, inferior vena cava; IVCCI, inferior vena cava collapsibility index; IVC-D, maximum IVC diameter; JVD = jugular venous distention.



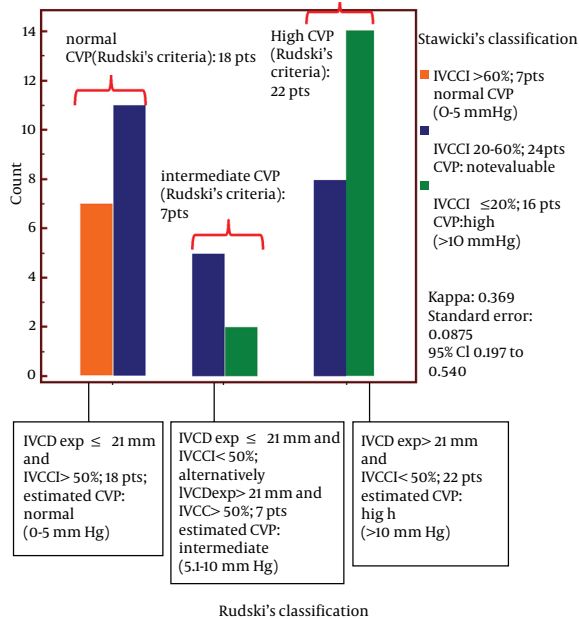
### 4.1. Estimates of Inter-Rater Agreement

As regards the estimation of positive cases when detected with the criteria of Stavicki or Pellicori, this was characterized by an unsatisfactory (“moderate”, according to the terminology used by Altman, Table 4) value of concordance (Cohen’s K: 0.468; CI 95%, 0.187 to 0.750). Likewise, the inter-rater agreement turned out rather poor (“fair”, Table 4) by comparing Rudski’s criteria with those of Stavicki (Cohen’s K: 0.369; 95% CI 0.197 to 0.540; Figure 2), as well as by comparing Rudski’s criteria with those of Pellicori (Cohen’s K: 0.299; CI 95%, 0.135 to 0.462; Figure 3). This argues for the fact that these criteria cannot be overlapped and that they are potentially contradictory and unfitted for mutual integration targeted to clinical purposes.

### 4.2. Clinical Correlates

As regards the possible associations of each of the three criteria with the exposure variables which had been tested, the positivity of Stavicki’s criteria, which value an IVCCI < 20% as an index of central venous hypertension, turned out to be associated with a higher risk (Table 5) of diabetes as well as with a history of hypertension, while

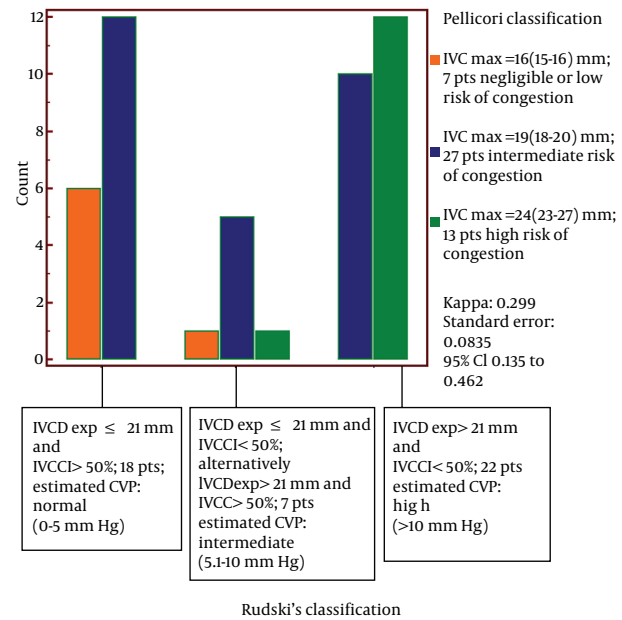
**Figure 2.** Inter-rater agreement between Rudski’s and Stavicki’s classifications in our case-record



A rather poor agreement (Cohen’s Kappa = 0.369) is noticeable by comparing the criteria used for identifying hemodynamic congestion on the basis of exploration by ultrasounds of the inferior vena cava (according to the classifications by Rudski or Stavicki, respectively). For instance, among the 18 patients having normal CVP (0 - 5 mm Hg) according to Rudski (first two columns on the left), only 7 (38.8%) were complying with the criteria for normal CVP provided for by the classification made by Stavicki; Abbreviations: pts, patients; CVP, central venous pressure; IVCDexp, inferior vena cava expiratory diameter; IVCCI, inferior vena cava collapsibility index; CI, confidence interval.

the positivity for congestion detected according to Rudski’s criteria did not show these associations. Both the criteria of Rudski and that of Stavicki showed higher frequency of anemia (defined by serum hemoglobin levels < 11.5 g/dl) in the respective subsets characterized by hemodynamic congestion at discharge (Table 5). Moreover, with the use of the criteria of Rudski as well as with those of Stavicki, relatively high levels of creatinine or relatively low eGFR values or increased BNP values (Table 5) all were proven to be more represented in patients with CHF who had been found positive for the congestion criteria at discharge. As regards the criteria of Pellicori (= central venous hypertension simply defined by a maximum caval diameter > 23 mm), the mean serum creatinine was found to be significantly higher at discharge in patients positive for this criteria; instead, the values of serum hemoglobin, as well as those of eGFR or BNP, were not dissimilar when comparing positive and negative patients defined according to Pellicori’s criteria (Table 5).

**Figure 3.** Inter-rater agreement between Rudski’s and Pellicori classifications in our case-record



A rather poor agreement (Cohen’s Kappa = 0.299) is noticeable by comparing the criteria used for identifying hemodynamic congestion by means of the echographic exploration of the inferior vena cava (according to the classifications by Rudski or Pellicori, of whom the former uses the combined evaluation of IVC expiratory diameter and IVCCI, whereas the latter is based only on the assessment of IVC max). For instance, among the 18 patients having normal estimated CVP (0 - 5 mm Hg) according to Rudski (first two columns on the left), only 6 (33.3%) were complying with the criterion (namely, IVC max = 16 [15 - 16] mm) for determining the presence of negligible or low risk of congestion, provided for by the classification made by Pellicori. Within the classification by Pellicori, note also that the reference values for each class of risk are expressed as median and inter-quartile range; Abbreviations: pts, patients; CVP, central venous pressure; IVCD exp, inferior vena cava expiratory diameter; IVCCI, inferior vena cava collapsibility index; IVC max, maximum inferior vena cava diameter; CI, confidence interval.

### 4.3. Predicting the Positivity for Congestion by Some Signs or Symptoms

Using the cox proportional hazards regression analysis, none of the explanatory variables that were tested was proven to predict a picture of systemic venous congestion that conformed to Rudski's criteria. Instead, the same method (Cox proportional hazards regression) documented that the presence of a value of BNP > 400 pg/ml was associated with a significantly increased risk of systemic venous congestion defined by the criteria of Stawicki (hazard ratio = 31.5394, 95% CI = 1.8783 to 529.5862, P = 0.0170). Finally, when the Cox proportional hazards model was used to investigate the possible association of the exposure factors with Pellicori's criteria for systemic venous congestion, the variables associated with an increased risk of hemodynamic congestion were the following: presence at admission of NYHA class IV (hazard ratio = 6.4168, 95% CI 1.2266 to 33.5672, P = 0.0285) or presence at admission of a SAP  $\leq$  100 mmHg (hazard ratio 5.4362, 95% CI = 1.0160 to 29.0883, P = 0.0490).

Prediction of death from all causes at the time point of 90 days after discharge. After 90 days since discharge, the deaths from all causes were 11 (23.4%) out of a total of 47 patients retrospectively enrolled. The causes were as follows: six deaths for irreversible progression of the heart failure, three deaths for arrhythmic sudden death outside the hospital, one death for cardio-embolic stroke, and one for hemorrhagic stroke. None of the explanatory variables included in the Cox proportional hazards model was shown to be associated with a significantly increased risk of death from all causes at the time point of 90 days.

## 5. Discussion

Only the classification of Rudski (Table 1) uses the information resulting from the combined determination of expiratory IVC diameter and IVCCI. Instead, the classification made by Stawicki (Table 2) exclusively gives value to the IVCCI determination to identify or exclude a state of systemic venous congestion in the course of heart failure. In contrast, the classification adopted by Pellicori (Table 3) only considers the maximum IVC diameter for subdividing the already diagnosed patients with chronic heart failure as patients at low, intermediate, or high risk of hemodynamic congestion.

### 5.1. Pathophysiology

In spontaneously breathing subjects, the inspiration decreases intrathoracic pressure, thereby acting as a factor that increases venous return and induces a cyclic collapse of the IVC. Inversely, during expiration, venous return decreases, thus causing an increase in the diameter of the IVC. High right atrial pressures dilate the IVC and impair this normal IVC collapsibility. Therefore, small, collapsible IVCs as visualized by echocardiography rep-

resent low right atrial pressures, whereas large, non-collapsible IVCs reflect high right atrial pressures. Moreover, in the presence of marked volume overload, the respiratory cycle leads to minimal change in the diameter of the IVC, regardless of its absolute diameter (16). This would be a consequence of the peculiar non-linear pressure-diameter relationship of the IVC, so that, above a threshold pressure (i.e. CVP > 20 mmHg), no further increase in expiratory IVC diameter can be observed (10-12).

### 5.2. Criteria

In the guidelines proposed for evaluating the volume status and the right atrial pressure through the study of the IVC, the way of encoding the suggested operational rules is not free from criticisms. In particular, the criteria by Rudski et al. (8) (Table 1), endorsed by the American Society of Echocardiography and left unaltered even in its recent updates (9, 17) provide for a couple of paradigmatic conditions: the one corresponding to a condition of normal right atrial pressure and the one which considers a pathologically increased right atrial pressure (8 - 15 mm Hg or more). However, it is not clear through what paths the authors have derived their reference values, in particular those adopted for IVCCI (i.e. 50%). In their recommendations it is not specified whether the codification of these reference values has been derived from the preliminary construction of ROC curves, with subsequent identification of the two proposed cut-off values for hemodynamic stability ( $\leq$  21 mm for IVC expiratory diameter and  $>$  50% for the IVCCI). Moreover, additional evaluation criteria for the indirect estimate of right atrial pressure are provided that create a certain degree of confusion (Table 1).

The approach by Stawicki et al. (Table 2) (11) gives value exclusively to the IVCCI, avoiding reporting the measurement of the maximum caval diameter. In fact, in the opinion of these authors, the absolute value of the maximum (expiratory) IVC diameter would have some meaning as a credible indicator of the load conditions of the vascular compartment (insufficient filling or overload) exclusively for patients not affected by chronic heart failure. In the latter, instead, the high usually recorded right atrial pressure (RAP) would enlarge the expiratory caval diameter over time, up to attaining a given limit not further expandable, consistent with the inherent venous parietal resilience. Accordingly, in patients with right chronic heart failure, the respiratory cycle would lead to negligible change in expiratory diameter of the IVC, regardless of its absolute diameter (16), so that the entire change expressed by the respiratory fluctuation of the IVC would be exclusively based on the variation of the inspiratory diameter. Therefore, these authors take into account only the IVCCI, that is  $(IVCD_{exp} - IVCD_{insp}) / IVCD_{exp} \times 100\%$  as a measure of the degree of hemodynamic congestion.

A completely conflicting view is expressed instead by the recent article by Pellicori et al. (13) (Table 3). Indeed,

they show a significant and independent association of IVC maximum diameter with an increased risk of cardiovascular death and hospitalization for heart failure (combined endpoint) at multivariate analysis without considering the inspiratory venous collapse as a significant parameter to be used. However, the study by Pellicori does not indicate, even with the caution of one who handles preliminary results, what is the cut-off point for the IVC diameter beyond which the risk of heart failure is significantly increased. In fact, it is only affirmed that in the highest tertile of values of IVC diameter there is an increased risk of heart failure compared to that found in patients belonging to the lowest tertile of IVC diameter. Moreover, the choice to ignore the effects, exerted by respiratory dynamics on the size of the IVC lumen, sharply conflicts with the conclusions of several previous studies (10-12) that had instead assigned a crucial role to caval collapsibility and had excluded the simple measurement of the IVC diameter as a sufficient diagnostic tool.

### 5.3. Conflicting Findings

In our study the abovementioned criteria were compared by means of the index known as inter-rater agreement (Table 4) (15). In our opinion, the practical recommendations of Stawicki are more suitable to interpret the changes in the right ventricular preload compared to the criteria encoded by Rudski, and endorsed by the American Society of Echocardiography. This ensues from the fact that the criterion of considering as congested those patients having IVCCI even barely below 50% poses the risk of a very large number of false positives. Furthermore, the echographic definition of IVC congestion, deduced by the values of inspiratory collapse according to Rudski's criteria (IVCC < 50%), may have been encoded in an inappropriate and fallacious manner. In fact, according to some (11), sufficiently accurate prognostic information could only be inferred from the extreme ranges (0 - 20 % and 60 - 100 %) of the entire interval of the possible values of IVCCI, because the intermediate values would not be adequate to discriminate between high, intermediate, or normal values of right atrial pressure.

In addition, in our experience, the criteria of Pellicori et al. seemed to have the lowest diagnostic accuracy, due to the fact of not discriminating the patients with objective clinical signs of congestion from those who are clinical congestion-free (Table 5).

Thus, a marked disagreement exists between the methods for the study of the venous caval district. Therefore, targeted efforts for revising and refining a possible, combined multiparametric approach (18) would be worthwhile. So, in patients with a history of ADHF and suspected latent congestion (defined by a RAP > 8 mmHg), a well-calibrated combination of multiple indicators of hemodynamic overload would be warranted, by means of the sequential or simultaneous use of clinical scores of congestion, IVC-derived ultrasonographic indices, and circulating levels of natriuretic peptides.

### 5.4. Study Limitations

Our study suffers from some limitations, such as small sample size and lack of a gold standard. Indeed, from a quantitative point of view, according to Cantor (19), we calculated that the interval of the estimated k-coefficient at the significance level of 0.95 is  $0.369 \pm 0.25$  (standard error) for the comparison Rudski-Stawicki,  $0.299 \pm 0.25$  for the Rudski-Pellicori comparison and  $0.468 \pm 0.28$  for the Stawicki-Pellicori comparison. Reversely, in order to obtain a width of the estimated k-Cohen coefficient equal to  $\pm 0.2$  around its estimated value at the significance level of 0.05, we would need a sample size ranging from 70 to 85 for the three comparisons. Moreover, with regard to the second point (lack of a gold standard), we have to emphasize that the invasive determination of right atrial pressure (RAP) by right heart catheterization (a recognized gold standard for RAP) was not systematically implemented among the 47 patients retrospectively enrolled in the study. Therefore, the comparison between the three different ways to interpret the respiro-phasic fluctuations of the inferior vena cava on the echocardiogram, even though showing significant divergence of results depending on the adopted criterion, does not allow us to categorically state what is the best non-invasive criterion for achieving the diagnosis of systemic venous congestion. The three ultrasonographic methods for assessing hemodynamic congestion from IVC size and/or respirophasic variation (according to Rudski et al., Stawicki et al. or Pellicori et al. respectively) appear to be clearly inconsistent. Thus, it is reasonable to affirm that non-invasive determination of systemic venous congestion through IVC measurements still suffers from considerable methodological uncertainties and inaccuracies in the interpretation of the interaction between venous pressure and size and respirophasic variations of the cavoatrial junction.

### Authors' Contributions

All of the above mentioned authors declare that they participated in the conception and design of the protocol as well as in the analysis and interpretation of the data. Moreover all authors participated in the drafting of the article or in its critical revision for important intellectual content.

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