

# Inferior Vena Cava Collapsibility and Heart Failure Signs and Symptoms. New Insights about Possible Links

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## Abstract

**Background:** In chronic heart failure patients (CHF), ultrasound measurement of inferior vena cava collapsibility index (IVCCI) has been proposed to yield careful assessment and grading of the hemodynamic congestion.

**Objective:** The purpose of this study was to correlate the findings of physical examination with IVCCI in CHF patients.

**Methods:** According to a retrospective cohort design, we analyzed 54 CHF patients with right or biventricular CHF, belonging to III NYHA class. We planned to determine whether any basal IVCCI range would be able to predict persistent or worsening clinical congestion found at the end of subsequent follow up (i.e. after 1-2 months of oral optimized therapy). For this purpose, the patients were subdivided by three groups according to the basal IVCCI value:  $\leq 15\%$  (13 pts), 16 - 40% (21 pts) and  $> 40\%$  (20 pts). Several clinical criteria of congestion were compared across the three groups and subsequently entered in the Cox multivariate model.

**Results:** Multivariate predictors of high congestion score were jugular venous distension (HR: 13,38 95% C.I.: 2,13 - 84  $p = 0,0059$ ) and rales (HR: 11 95% C.I. : 1,45 - 83,8  $p = 0,0213$ ). IVCCI  $\leq 15\%$  was always associated with high congestion score at the second visit; but IVCCI  $\leq 15\%$  failed to predict high congestion score at the second visit.

**Conclusions:** In CHF setting, low IVCCI did not reliably predict high congestion score. Nevertheless, the cluster with IVCCI  $\leq 15\%$  was always found associated with signs and symptoms from both right and left-sided decompensated CHF. (Arq Bras Cardiol 2012;98(6):544-552)

**Keywords:** Heart failure, symptoms; vena cava, inferior; ultrasonography

## Introduction

Hemodynamic congestion<sup>1</sup> is thought to derive primarily from impaired cardiac index - with or without reduction in left ventricular ejection fraction- . This in turn generates elevation in pulmonary capillary wedge pressure (PCWP), in the case of left chambers isolated decompensation, or combined increase in both PCWP and right atrial pressure, in the case of biventricular heart failure<sup>2-3</sup>. Impaired cardiac index, for left only ventricular heart failure, or the combination of impaired cardiac index plus elevated central venous pressure, in the case of right or biventricular heart failure, with or without patent fall in blood pressure, substantially reduce renal blood flow, the most important variable of kidney filtration gradient in patients presenting with congestive heart failure, thus generating neuro-hormonal stimulation and development of hydrosaline retention<sup>4-8</sup>. Hemodynamic worsening consisting in impaired cardiac index and increased filling pressures will further activate the renin-angiotensin and sympathetic nervous system, reduce nitric oxide in the endothelium, and induce inflammatory mediators, so as to aggravate the hypoperfusion

state of the glomeruli and so as to further worsen the renal function<sup>9</sup>. Reduction in water and salt clearance in turn propitiates persistence of hemodynamic congestion so as to create and maintain over time a condition of cardiac overload. Hemodynamic congestion contributes to the progression of HF by further activating neurohormones and by causing subendocardial ischaemia, resulting in myocardial necrosis/apoptosis and/or secondary mitral insufficiency by its effects on LV geometry (changing it from an ellipsoid to a sphere)<sup>10</sup>. In addition, elevated right atrial pressure may contribute to the cardio-renal syndrome through reduction of the perfusion gradient across the kidneys<sup>11-12</sup>.

Among the proposed methods for estimating and grading hemodynamic congestion in right or biventricular heart failure, a remarkable role is played by ultrasound evaluation of the inferior vena cava diameter (IVCD) and its collapsibility index (IVCCI)<sup>13</sup>. This technique is aimed to identify any changes in respiratory pattern of IVC indicating the presence of abnormalities in volume status (that is hemodynamic congestion or intravascular depletion). Based on well-established knowledge, wide respiratory fluctuations of IVCCI would indicate that intravascular depletion is likely, whereas low values of this parameter would mean high probability of hemodynamic congestion. These inferences have received exhaustive confirmation by many large well-conducted studies<sup>13-20</sup>.

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## Objectives

In a number of patients with right or biventricular CHF, we have tested the possible relationships between IVCCI and some signs and symptoms of CHF. Besides, we have tried to establish whether in these CHF patients a low IVCCI value, as found at the first visit, can be assumed as a reliable predictor of subsequent clinical congestion – after a clinical follow up of one-two months - .

## Methods

An observational retrospective study was carried out by enrolling patients from two Centers (C.U. E. d'A. and N.R. S.M.d P.). For enrollment in the study, documented evidence of right or bi-ventricular chronic heart failure in II- III NYHA class was required. Exclusion criteria were: patients with pace-maker or treated by cardiac resynchronization therapy; myocardial infarction within 30 days, arrhythmia-related syncope, major cardiac surgery, unstable angina, uncontrollable hypertension, cor pulmonale, advanced pulmonary disease, major neurologic disease or cerebrovascular disease, suspected renal artery stenosis, advanced renal failure (i.e. serum creatinine  $>2,5$  mg/dl at baseline), other life-threatening disease.

Retrospective chart review was performed to analyze characteristics of all eligible patients. For each patient, date of birth, sex, race, and weight and height were noted. Comorbidities, including diabetes, dyslipidemia, nicotine abuse, hypertension, ischemic heart disease, preexisting diabetic nephropathy or other chronic renal disease in addition to medical treatment at the time of hospital stay also were extracted for each patient. IVCCI was defined as the difference between maximum expiratory diameter and minimum inspiratory diameter divided by the maximum expiratory diameter. IVCCI measurements were obtained 1 to 2 cm below the level of the hepatic veins, 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*, presence of external impediments (e.g., drains, surgical dressings), and preference of the sonologist.

The patients were divided into three groups according to IVCCI values: IVCCI  $\leq 15\%$  (13 pts), IVCCI 16-40% (21 pts), IVCCI  $>40\%$  (20 pts). Among these, first and third layers were assumed to indicate the presence of systemic venous congestive status or of likely intravascular depletion, respectively; whereas an IVCCI in the intermediate range (0,16 to 0,40) was considered not helpful in discriminating CVP.

The following clinical criteria of congestion were compared across the three groups: dyspnea/orthopnea, dyspnea on exertion, jugular venous distension, peripheral edema, congestive hepatomegaly, pulmonary rales, mean weight gain  $\geq 1$  kg per week through the follow up.

These signs and symptoms were chosen due to their proven relationship with CHF syndrome. Particularly, dyspnea at

rest with orthopnea was selected as being a symptom usually associated with severe impairment in left ventricle pump function (in our case to be set in the context of biventricular cardiac decompensation, as right heart failure was present in all recruited cases by definite enrollment criterion). Orthopnea was defined as any respiratory distress associated with lying down or the perceived need to use more than one pillow to avoid respiratory distress. Rales were considered owing to their well-known association with pulmonary capillary and venous hematic stagnation usually related to relatively high levels of pulmonary capillary wedge pressure (PCWP). Dyspnea on exertion was included in analysis as being a symptom that usually indicates lesser cardiac impairment compared to orthopnea, generated by right-sided as well as by combined biventricular heart failure. Besides, the other four signs (jugular venous distension, peripheral edema, congestive hepatomegaly and weight gain  $\geq 1$  kg per week) were evaluated in the study as markers of hydrosaline retention as usually found in systemic congestion from right or biventricular advanced CHF. Particularly, jugular venous distension was considered present if visualized at least 10 cm vertically above the right atrium. Weight gain was defined as  $\geq 1$  kg mean increase per week.

In addition, a congestion score was set up and defined retrospectively for this analysis as the sum of the seven criteria for congestion, with a possible range from 0 to 7. A score  $\geq 4$  was termed “high congestion score” and used as outcome variable (“end – point”) in the subsequent statistical analysis. According to the customary approach applied at the two Centers, every patient in each of the day hospitals underwent a careful clinical examination along with a complete echocardiography including a thorough assessment of IVC with IVCCI calculation. Subsequently, a second scheduled visit was usually accomplished within one-two months in order to timely establish any appropriate pharmacologic and dosing change to be done based on the evolving clinical picture. Should any complaint or unexpected complication arise, the patients were recommended to bring forward the date of the visit.

In our retrospective study, we tried to ascertain whether any association could exist between IVCCI values, as detected at the first visit, and one or more of the abovementioned signs and symptoms of congestion, as noticed after 1-2 months of clinical follow up. We investigated this hypothesis by using the preliminary categorization of IVCCI values by three layers (IVCCI  $\leq 15\%$ , IVCCI 16-40%, IVCCI  $>40\%$ ) and by considering the clinical picture after adequate oral therapy kept for one-two months. We also verified the possible existence of any significant association between the cluster characterized by the lowest IVCCI ( $\leq 15\%$ ) at baseline and the finding of “high congestion score”, as found at the second visit after one-two months. The prescribed oral therapy usually included ACE-inhibitors, beta-blockers and diuretics; in addition, according to the physician’s judgment, aldosterone receptor antagonists, oral or transdermal nitrates, antiaggregant drugs, warfarin, amiodarone and digoxin were also administered if necessary. It was also established that every patient requiring intravenous diuretics or inotropes for worsening HF during follow up would have been excluded from the statistical analysis, as being considered to demonstrate treatment failure.

### Statistical analysis

We used the Statistical Package of Social Sciences (SPSS Version 14, SPSS Inc, Chicago, IL, USA) and Excel® (Microsoft Office Excel® release 2007, Microsoft Inc, Seattle, USA) to perform the analysis. Baseline demographics, physical examination, and laboratory findings were compared between patients across the three IVCCI layers. The  $\chi^2$  (chi square) test and the unpaired t-test were respectively applied for comparison of dichotomous or continuous variables. One-way analysis of variance (ANOVA) and Student-Newman-Keuls test for all peer comparisons ("post hoc" analysis) were used for multiple comparisons. Kruskal Wallis test was also employed for comparison of data with asymmetric distribution.

For identifying the predictors of hemodynamic congestion, univariate and multivariate Cox proportional hazards regression analyses were used. The following variables were entered into the model as exposure variables:

- IVCCI  $\leq$  15%
- mean weight gain  $\geq$  1 Kg per week
- edema
- orthopnea
- rales
- jugular venous distension
- dyspnea on exertion during optimized therapy
- congestive hepatomegaly

### Results

A total of 54 patients were retrospectively enrolled, by drawing them from the charts of all CHF patients admitted for day-hospital stay between June 2009 and June 2010 at the two Centers. This group consisted of 28 women and 26 men, with mean age of  $78 \pm 5,5$  years. Their basal clinical and hematochemical characteristics are described in Table 1. In Table 2, the respective percentages of all of the investigated clinical signs and symptoms are listed.

Table 3 shows the results of the multivariate Cox proportional hazards regression analysis including 8 covariates entered in the model, with high congestion score being used as outcome variable.

Multivariate predictors of high congestion score were jugular venous distension (hazard ratio: 13,38 95% C.I.: 2,13 to 84 p = 0,0059) and rales (hazard ratio: 11 95% C.I.: 1,45 to 83,8 p = 0,0213).

Figure 1 shows the distribution (%) of the cases (17 on the whole) of jugular venous distension (jvd) across the 3 IVCCI groups, as found at the second visit. It documents that in the IVCCI  $\leq$ 15% group, occurrence of jugular venous distension was higher than in IVCCI=16-40% and IVCCI>40% groups: p (Kruskal Wallis) <0.05 for both comparisons.

Furthermore, by considering the relation between every category of IVCCI and the probability of developing orthopnea (Figure 2), a remarkable difference emerges: actually, the patients with IVCCI  $\leq$  15% were burdened with a much higher risk of being involved by orthopnea during the subsequent follow up. In addition, low venous collapsibility

was found to entail high rate of early referral to heart failure unit, due to unscheduled re-admission for worsening symptoms and signs of systemic and pulmonary congestion. By comparing the three classes of caval collapsibility, the most severe impairment of the clinical picture was exhibited by patients belonging to the lowest class of IVCCI values (Figures 3-5). Nevertheless, Cox multivariate proportional hazard model failed to identify IVCCI  $\leq$  15% as a significant multivariate predictor of worsening clinical congestion (Table 3). In addition, it would be noted that this pattern was accompanied in any case by simultaneous involvement of signs and symptoms from both left-sided and right-sided cardiac failure; on the contrary, the patients belonging to the intermediate range of caval collapsibility (IVCCI 16-40%) exhibited the highest rate of isolated systemic - but not pulmonary - congestion at the end of the prescribed follow up (30-60 days after the first visit) (Figure 4).

### Discussion

Based on the pathophysiological concepts represented above, prognostic importance of clinical congestion in HF patients is expected. However, clinical congestion may be the 'tip of the iceberg' of the hemodynamic derangements that precede symptoms<sup>21-22</sup>. For instance, in chronic biventricular HF, even severe hemodynamic congestion rarely causes rales and/or radiographic pulmonary edema. This may be related to several adaptive pathophysiological changes such as increases in alveolar capillary membrane thickness, increased lymphatic drainage, and/or pulmonary hypertension<sup>3,21</sup> (3,21). Thus, in the opinion of several Authors<sup>13,22</sup>, it would be very interesting and useful to explore not only clinical but also hemodynamic congestion in order to achieve a really careful patient assessment. In truth, this would be opportune considering that patients with even only hemodynamic congestion were shown to have poor outcomes<sup>23-25</sup>.

Ultrasound assessment of IVC respiratory fluctuations has been proposed from a long while as a possible diagnostic tool for obtaining noninvasive reliable estimation of volume status and/or right atrial pressure in CHF patients. Briefly, in spontaneously breathing subjects, intrathoracic pressure decreases during inspiration, thereby increasing venous return and inducing collapse of the IVC; inversely, during expiration, venous return decreases, so causing an increase in the diameter of the IVC<sup>26</sup>. High right atrial pressures dilate the IVC and worsen this normal IVC collapsibility. According to these observations, congestion would be indicated by relatively small IVCCI values, while intravascular depletion would be revealed by wide fluctuations of IVC diameter, generating relatively high values of IVCCI. Therefore, small, collapsible IVCs as visualized by echocardiography represent low right atrial pressures, whereas large, non-collapsible IVCs reflect high right atrial pressures<sup>13</sup>. In the presence of marked volume overload, the respiratory cycle leads to minimal change in diameter of IVC, regardless of its absolute diameter<sup>27</sup>. This depends on 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 IVC diameter can be observed<sup>28</sup>. This has been confirmed by a

**Table 1 - Baseline hematochemical and clinical characteristics of patients who kept a clinical picture characterized by high congestion score at 4-8 weeks and in controls who did not. The  $\chi^2$  (chi square) and the unpaired t tests were applied for the comparison of dichotomous or continuous variables, respectively.**

	High congestion score at 4-8 wk		p
	Yes (n°20 pts)	No (n°34 pts)	
Age	79 ± 6	77 ± 6	0,2422
Male	8	15	0,9916
Mean duration of symptoms of heart failure(months)	8 ± 3	7 ± 3	0,2422
LVEF(%)	45 ± 6	47 ± 7	0,2909
History of co-morbidities			
Diabetes	4	7	0,7657
Dyslipidemia	3	7	0,8825
Nicotine abuse	7	17	0,4309
Hypertension	12	26	0,3313
Ischemic heart disease	11	24	0,3880
History of preexisting diabetic nephropathy or other chronic renal disease	3	7	0,8825
Estimated GFR(ml/min/ 1,73 m <sup>2</sup> )at first visit	44 ± 12	68 ± 14	< 0,0001
Preexistent pharmacotherapy			
Digitalis	5	9	0,8396
Beta-blockers (carvedilol or bisoprolol)	12	28	0,7174
ACE-inhibitor/angiotensin receptor blocker	13	28	0,2667
Aldosterone receptor antagonist	12	33	0,8562
Nitrate	5	12	0,9531
Mean dose of oral furosemide through the follow up of 4-8 wk	91 ± 24	50 ± 12	< 0,0001
Clinical parameters			
Systolic BP (mmHg)	122 ± 10	132 ± 18	0,0267
Heart rate (b.p.m.)	91 ± 25	85 ± 17	0,2989
Body mass index	28 ± 5,6	26,9 ± 4,8	0,4481
Laboratory and echographic variables			
IVCCI(%)	16,33 ± 6,8	26,27 ± 11	0,0006
Hemoglobin (mg/dl)	13 ± 1	12,7 ± 1,8	0,4969
serum Na <sup>+</sup> (mmol/L)	136.5 ± 4.7	139 ± 4	0,0427
serum K <sup>+</sup> (mmol/L)	4,3 ± 0,7	4,5 ± 0,5	0,2275
BNP (pg/mL)	700 ± 110	421 ± 95	< 0,0001

LVEF - left ventricular ejection fraction; GFR - glomerular filtration rate; IVCCI - Inferior vena cava collapsibility index; BNP - brain natriuretic peptide.

**Table 2 – Different contributors to clinical picture in a group of 54 pts with right or biventricular chronic heart failure belonging to III-IV NYHA class at admission**

	Cases (absolute number)	Percentage
jugular venous distension	17	31,5%
congestive hepatomegaly	25	46,3%
orthopnea	17	31,5%
dyspnea on exertion during optimized therapy	34	63,0%
rales	20	37,0%
peripheral edema	48	88,9%
weight gain $\leq$ 1 Kg since the previous week	18	33,3%

**Table 3 – Multivariate predictors of elevated congestion score found in CHF patients after 4-8 weeks of optimized oral therapy: Cox proportional hazards regression analysis**

Covariate	b	SE	P	Exp(b)	95% CI of Exp(b)
IVCCI $\leq$ 15%	-0,04568	0,6420	0,9433	0,9553	0,2732 to 3,3406
mean weight gain $\geq$ 1 kg per week	1,1133	0,5769	0,0536	3,0444	0,9884 to 9,3771
edema	0,07404	1,1362	0,9480	1,0768	0,1175 to 9,8721
orthopnea	1,5608	0,9462	0,0990	4,7628	0,7526 to 30,1415
rales	2,3981	1,0411	0,0213	11,0025	1,4449 to 83,7825
jugular venous distension	2,5935	0,9421	0,0059	13,3766	2,1306 to 83,9822
dyspnea on exertion during optimized therapy	0,2594	1,1167	0,8163	1,2962	0,1469 to 11,4396
congestive hepatomegaly	1,4932	1,5946	0,3491	4,4512	0,1986 to 99,7537

**Caption:** **b:** regression coefficient; **SE:** standard error of **b;** **Exp(b):** hazard ratio

recent study in which a IVCCI  $\leq$  15% was highly sensitive and specific for the diagnosis of acute decompensated heart failure, whereas the absolute diameter of the IVC in itself was non diagnostic<sup>19</sup>.

In our study, we decided to categorize IVCCI values by grouping them in three classes:  $\leq$  15%, 16-40 % and  $>$  40 %. These IVCCI cut-off values were determined arbitrarily, with the intention of selecting groups with low, intermediate and high collapsibility indices.

Based on our analysis, rales and jugular venous distension were predictors of elevated score of congestion as measured after a follow up period of 60 days.

Moreover, a low ( $\leq$  15%) IVCCI value indicated higher probability of presenting with elevated congestion score - that is  $\geq$  4 symptoms and/or signs of congestion within a range extending from 0 to 7 - compared to the other two IVCCI clusters; but, when evaluated by Cox proportional hazards regression analysis including 8 covariates, the lowest IVCCI category was not demonstrated to be a significant multivariate predictor of clinical congestion kept over a 60 day follow-up on optimized oral therapy.

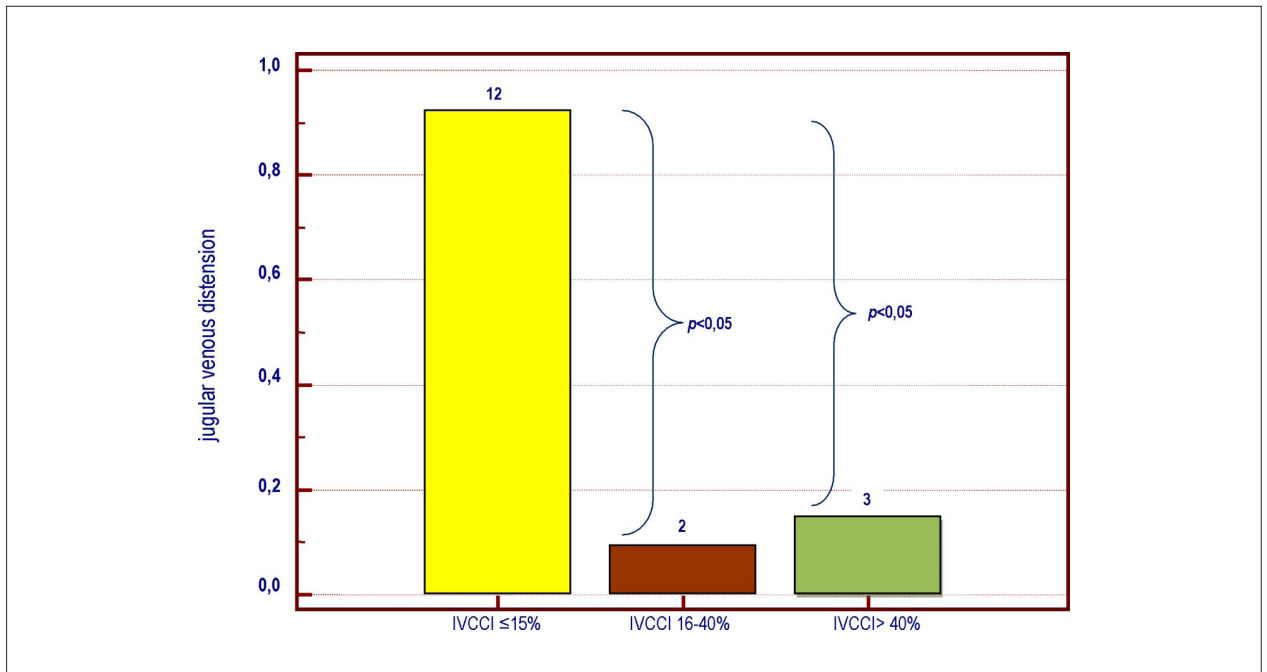
Furthermore, all of the patients presenting with IVCCI  $\leq$  15% were found to have a clinical picture of combined right and left heart failure, this finding being presumably associated with both high PCWP and right atrial pressure.

### Study limitations

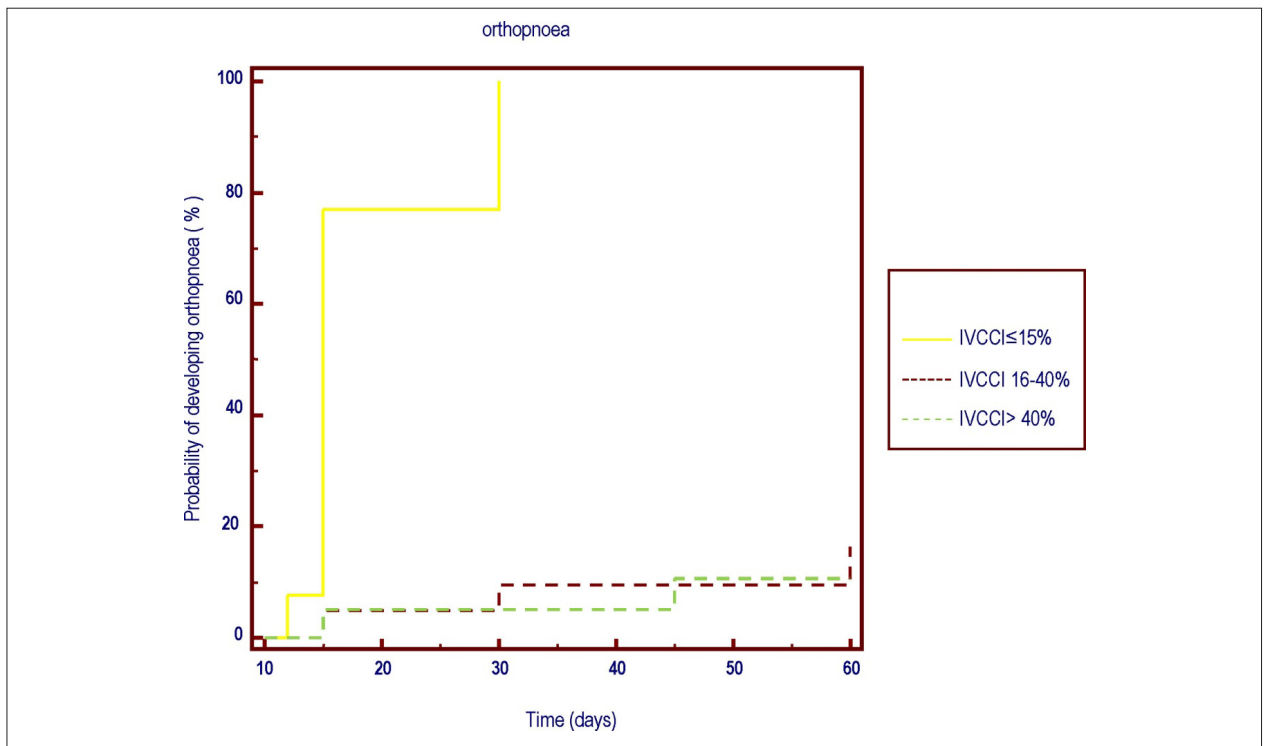
This study is limited by its retrospective nature as well as by relatively small sample size. IVC measurements were not done by a single operator, so inter-observer bias cannot be excluded. Moreover, we cannot exclude that tricuspid regurgitation affected inferior vena cava diameter, although this influence is less pronounced on IVCCI. Besides, measurement of the jugular venous pressure remains hard to be exactly performed and it also exposes to considerable risk of bias, related to high inter-observer variability expected.

In conclusion, in CHF setting both jugular venous distension and rales were useful predictors of outcome when assessed after 4 to 8 weeks of therapy to eliminate them. Low ( $\leq$  15%) IVCCI did not reliably predict high congestion score as well as IVCCI classes did not reliably separate CHF patients with different congestion scores. Nevertheless, the cluster with IVCCI  $\leq$  15% was always found associated with

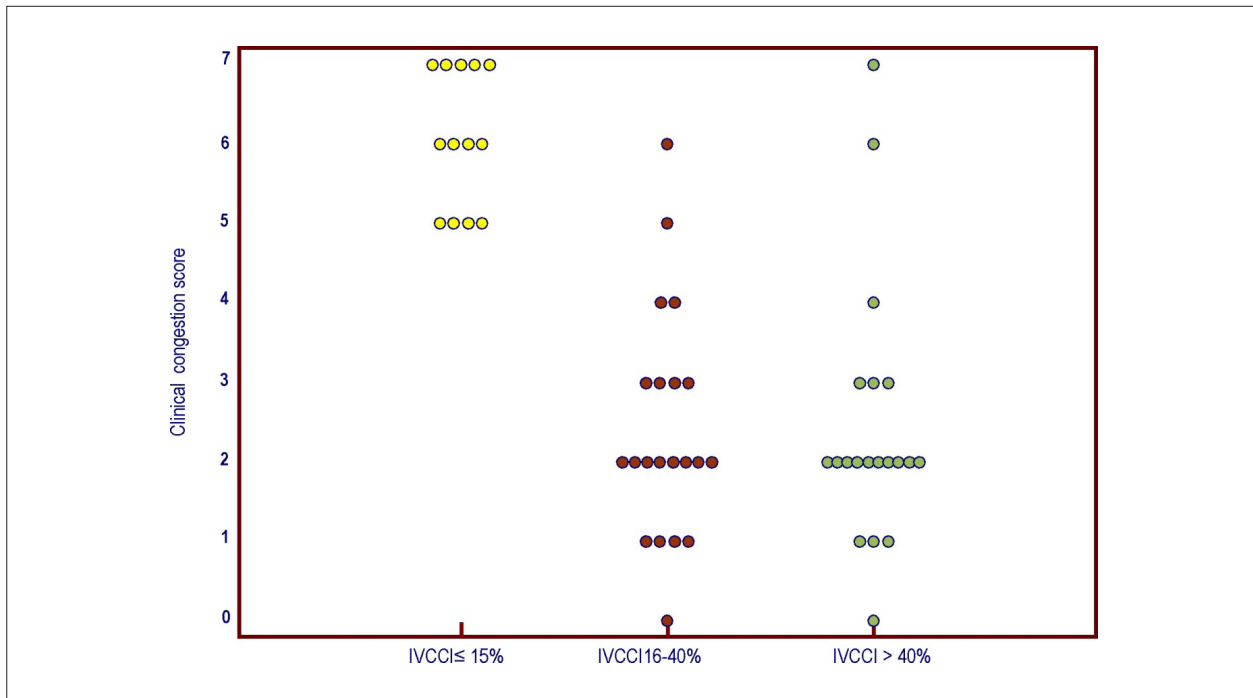




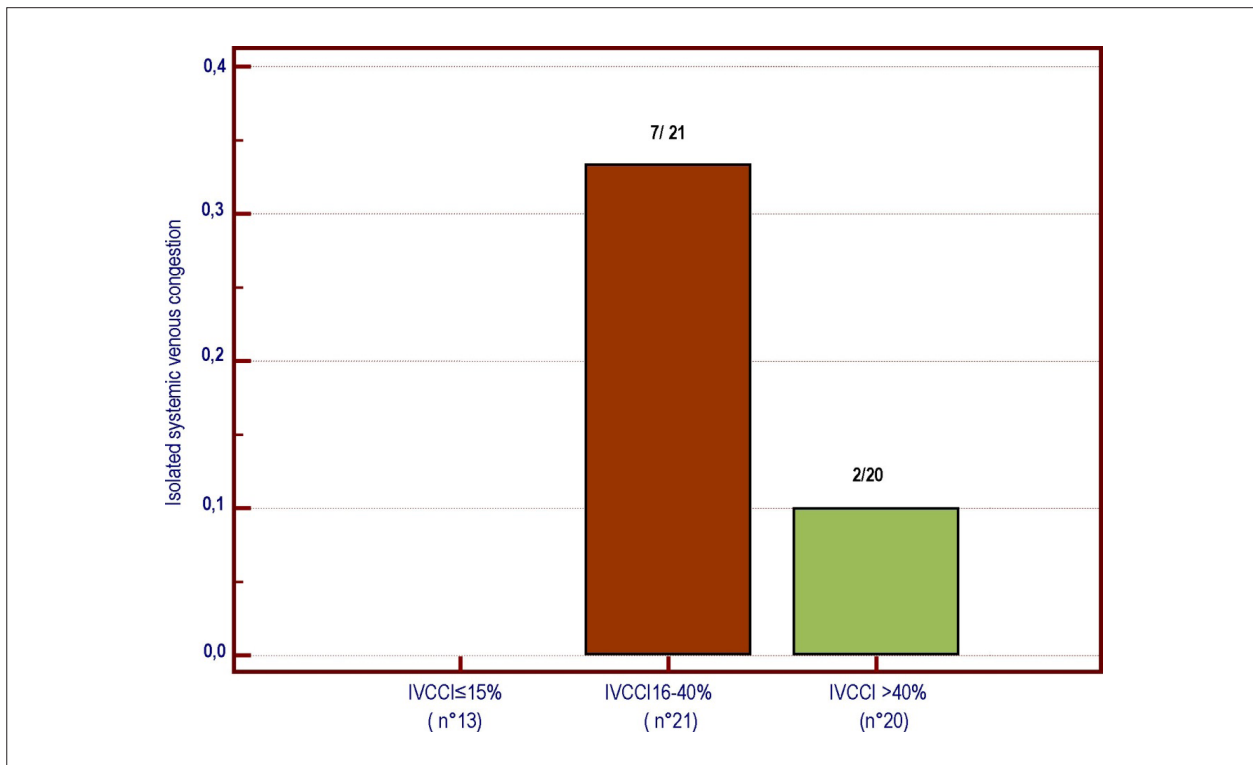
**Figure 1** – Distribution of the symptom “jugular venous distension” through the three layers of IVCCI. In the IVCCI ≤ 15% range, jugular venous distension was more frequent: 12 cases (92,3%) compared to 2 (9,5%) and 3 (15%) cases found in the other 2 layers, respectively.  $p(\text{Kruskal-Wallis}) < 0,05$  for both comparisons  
 IVCCI: inferior vena cava collapsibility index



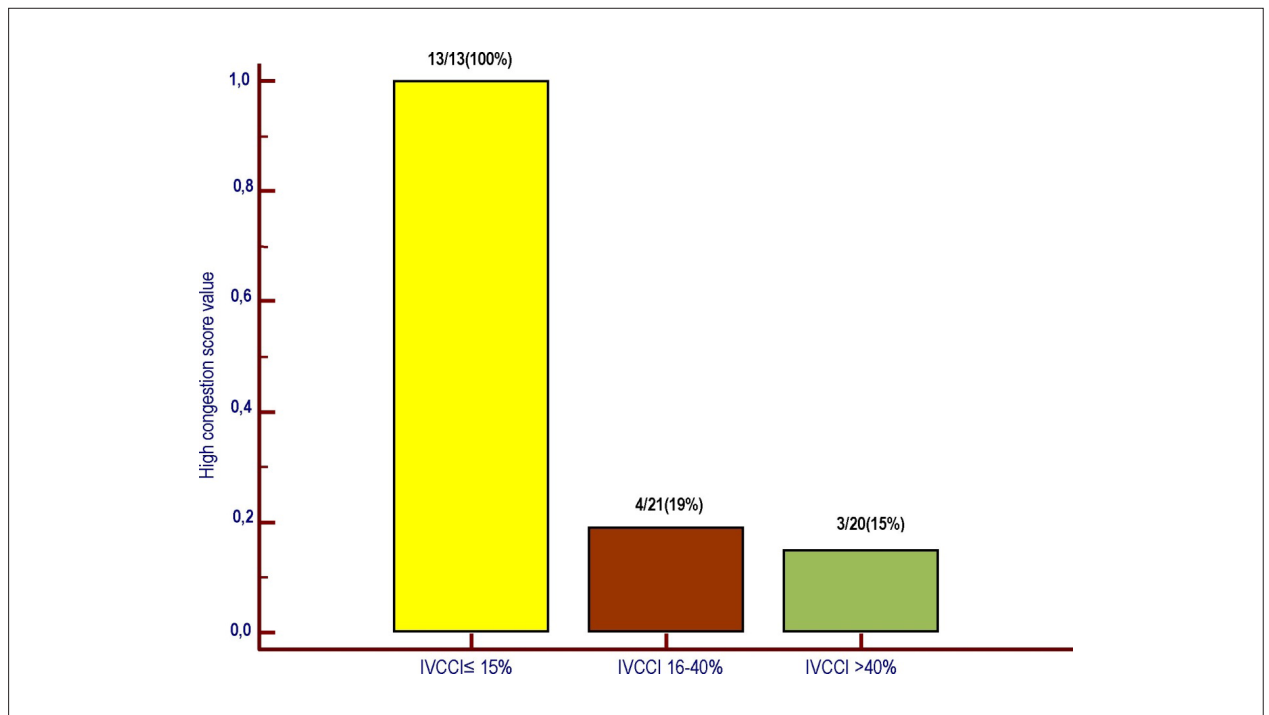
**Figure 2** – Kaplan Meier curve is used to compare the respective risks of orthopnea through a 60-day follow-up according to IVCCI category as detected during the first visit. The category with IVCCI ≤ 15% is shown to have a remarkably higher risk of orthopnea compared to the other two classes.  $p(\text{log rank test}) < 0,0001$   
 IVCCI - inferior vena cava collapsibility index



**Figure 3** – Individual values of clinical congestion score within each IVCCI range. In the IVCCI ≤ 15% range, the clinical congestion score was significantly higher than in the other two intervals.  $p$  (ANOVA) < 0,001;  $p$  (Student-Newman-Keuls test) < 0,05 for both comparisons (IVCCI ≤ 15% versus both IVCCI 16-40% and IVCCI > 40%.) IVCCI: inferior vena cava collapsibility index



**Figure 4** – Systemic but not pulmonary congestion (isolated right heart failure) was found in 9/ 54 CHF patients. As a rule, combined right and left ventricular decompensation was found in IVCCI ≤ 15% range.



**Figure 5** – High congestion score was found in all of the patients with IVCCI ≤ 15%, while its prevalence was relatively low in the other two classes of inferior vena cava collapsibility.  $p$  (Kruskal-Wallis) < 0,0001;  $p$  (post-hoc analysis) < 0,05 for both comparisons (IVCCI ≤ 15% versus both IVCCI 16-40% and IVCCI > 40%)

simultaneous presence of signs and symptoms from both right and left-sided

#### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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#### Study Association

This study is not associated with any post-graduation program.

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