SUBCLINICAL CONGESTION

from physical examination to prognosis: translating a mechanical model into an ultrasound approach

Insubria University - Research Doctorate
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Summary

Introduction

Heart failure and congestion

In heart failure (HF) patients, congestion is the main therapeutic target as well as the main cause of hospitalization; moreover, it may be responsible for cardiac adverse remodeling and disease progression.

Congestion can be divided into “hemodynamic congestion”, in which the increase in ventricular filling pressures and volume overload are not necessarily associated with clinical manifestations, and “clinical congestion”, when there are signs and symptoms related to the increase in cardiac filling pressures.

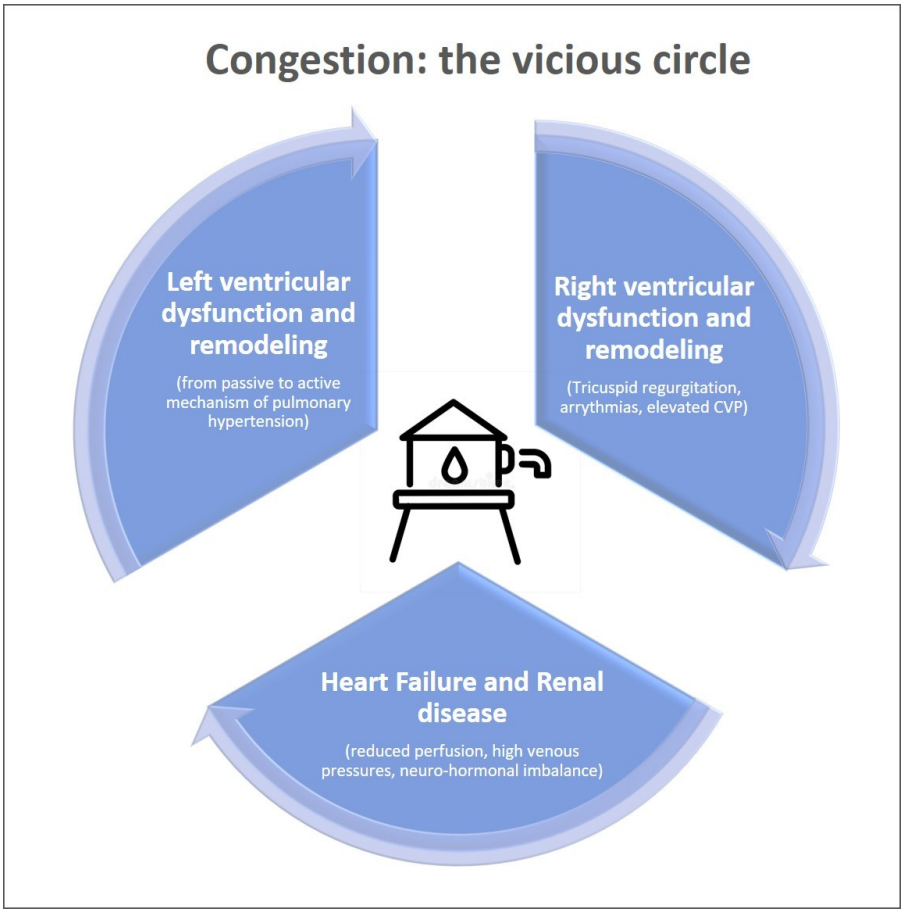


Figure 1: triggers and maintenance factors in the vicious circle of congestion, starting from a left-sided disease to multiorgan failure. CVP: Central Venous Pressure.

The cornerstone of congestion is the increase in left ventricular end-diastolic pressure (LVEDP) due to volume overload or intravascular redistribution. In this vicious circle, the volume overload affects the left ventricular performance, causing a rise in wall stress and further hormonal hyperactivation, leading to an increase in the intravascular pulmonary pressure. The increase in the right heart afterload causes progressive tricuspid insufficiency and right ventricular dysfunction (RVD), finally resulting in the rise of right atrial pressures (RAP). The absence of valve systems or volume reservoirs above the right atrium leads to a direct increase in central venous pressure (CVP), with dramatic consequences on the perfusion pressure of vital organs, progressively leading to systemic congestion and renal damage. The complex hemodynamic and neurohormonal system that connects heart and kidney is summarized in the theory of cardio-renal syndrome, leading cause of HF progression and refractoriness to diuretic therapy. If medical therapy is not administered in the phases immediately preceding the HF event, the hemodynamic congestion evolves into clinical congestion: the characteristic symptoms are asthenia, intolerance to exercise and dyspnea, with a consequent reduction in functional capacity and quality of life.

The impact of congestion on patient's symptoms is usually quantified using the New York Heart Association (NYHA) scale. The prognostic role of congestion appears relevant when considering patient mortality stratified by NYHA class. Considering outpatients with recent hospitalization and advanced heart failure, NYHA class IV patients have a poor prognosis and up to 50% mortality within two years; consistently, cardiovascular adverse events drop to 30% for NYHA III class patients. However, freedom from clinical congestion 4-6 weeks after hospital admission is a positive prognostic marker for these patients: when hospitalized patients with severe symptoms of heart failure are maintained free from congestion 4 weeks after admission, their prognosis significantly improves by increasing their 2-year survival up to 87%[1].

Since the early identification of hemodynamic congestion, clinical evaluation is essential in HF. The clinical examination focuses mainly on the cardiac, thoracic and abdominal physical examination (PE), specifically searching for signs of central and peripheral congestion or reduced tissue perfusion. However, these signs are not always overt or easily detectable: the sensitivity of the PE is extremely variable and ranges from 15% to 86%; besides, its negative predictive value ranges between 38% and 52%[2,3] (Figure 2).

Clinical Finding	Sensitivity	Specificity	PPV	NPV
Rales ≥1/3	15	89	69	38
Edema ≥2+	41	66	67	40
Orthopnea ≥2 pillows	86	25	66	51
JVP ≥12 mm Hg	65	64	75	52
HJR	83	27	65	49

Figure 2: accuracy of clinical findings commonly evaluated in HF patients[3].

The presence of jugular vein distension (JVD) in standing position identifies elevated central venous pressure, conventionally greater than 10 cmH2O. Conversely, when overt signs of JVD are absent, JVD has to be assessed by looking for the internal jugular vein pulse in the supine position at 45°: both sides of the neck must be evaluated and slight pressure may need to be applied to distinguish the jugular vein from the carotid artery. The identification and correct evaluation of the JVD depend both on the clinician's experience and anatomical vascular characteristics[2].

Another useful sign for detecting high venous pressures is hepato-jugular reflux (HJR)[4], which can be evoked by exerting pressure in the right hypochondrium and evaluating the jugular distension; to be positive, the jugular distension must persist for at least 10 seconds. The presence of HJR in left-sided HF patients reliably predicts a capillary wedge pressure greater than 15 mmHg, which indirectly

reflects left atrial end-diastolic pressure at rest[5]. From these assumptions, JVD and HJR have a negative prognostic value as assessed in the ESCAPE study: the persistence of these signs of congestion on discharge is associated with an increased risk of mortality[6]. Moreover, peripheral edema (OED) is the hallmark of congestion and sodium retention. It is typically located at the slope level with different degrees of severity; a slight pressure on edematous tissues typically reveals pitting OED[7].

If the low-flow syndrome prevails over congestion, hypoperfusion inevitably occurs with cold, pale, marbled skin and cyanotic extremities; pulse pressure drops, peripheral resistances increase, the pulse becomes tachycardic in a clinical scenario that could suddenly turn into cardiogenic shock. These manifestations are hemodynamically related to a very low cardiac index (CI), usually less than 2 L/min.

The pulmonary PE aims to highlight the presence of rales, an expression of pulmonary interstitial edema that results in reduced lung compliance and blood oxygenation. Consequently, dyspnea is the typical symptom of HF and can occur both on exertion and at rest. When exertional dyspnea occurs, it represents the sum of reduced cardiac output and of left ventricular end-diastolic filling pressures rise; on the other hand, when dyspnea is present at rest, it occurs primarily in the supine position (orthopnea), following the gravitational movement of the body fluids. Auscultation, however, is qualitative and subjective, often leading to a negative PE even in the presence of hemodynamic congestion. This result obtained from several studies consists in the low negative predictive value of the pulmonary findings[3].

Finally, the abdominal examination may reveal signs of systemic congestion related to elevated right atrial pressure (RAP): hepatomegaly, splenomegaly and ascites, often related to hepatic functional impairment with a consequent deficiency in protein synthesis.

Additional parameters that could be used in the evaluation of HF patients are functional capacity and changes in body weight. The former is usually assessed by the 6-minute walk test (6MWT), which is simple to perform and reproducible: subjects without severe HF should be able to walk for 6 minutes and complete a distance of at least 200 meters without HF symptoms[3]. Regarding body weight, its rapid fluctuation is the footprint of sodium retention and can be easily monitored by the patient himself. Weight gain can precede the onset of symptoms and re-hospitalization by up to a week, but sometimes it may not be observed or be very modest concerning the complex pathophysiology of congestion, which involves both an absolute increase in circulating volume and intravascular redistribution of fluids[8].

The PE is essential in the follow-up of the chronic patient, playing a pivotal role in the evaluation of the patient with acute HF. Depending on the hemodynamic pattern of congestion, it can be classified in one of the four groups adapted by Stevenson et al: this classification represents the synthesis of the relationship between capillary wedge pressure (PCWP) and the degree of peripheral perfusion. Regarding congestion, subjects with clear signs of pulmonary and/or peripheral congestion are defined as "wet", in which a LVEDP>18 mmHg is estimated, while patients without signs of congestion are considered "dry". Body temperature is used as a marker of peripheral perfusion since, in case of low cardiac output, peripheral vasoconstriction rises to protect the perfusion of vital organs. Cold patients often present with arterial hypotension and are assumed to have a CI <2.2 L/min/m^2; otherwise, patients are classified as “warm”[9].

The best prognosis is intuitively associated with warm and dry patients, who are well perfused and little or non-congested; the clinical picture with the worst prognosis is that of cold and wet patients, who generally could suddenly turn into cardiogenic shock. Surprisingly, according to a recent work by Narang et al, patients with the most severe clinical picture and at greater risk of events are the

worst identified by clinical evaluation, showing an accuracy of the PE of less than 50%, regardless of the physician's experience[10].

From these assumptions, objectifying the findings of the PE with instrumental signs is mandatory. In the last 3 decades, ultrasound has gained a pivotal role, focusing in HF patients on the lung, heart and abdomen. Easily reproducible, widespread in every department and little time-consuming, ultrasound has established itself as the first rapid and reliable tool to screen patients with acute HF within the first minutes of a medical emergency.

In an inpatient setting, ultrasound is widely used as a bedside examination, especially for those patients with a discrepancy between hemodynamic and clinical features. This practice acquired in the emergency context can be easily reproduced in an outpatient setting, allowing a better prognostic risk assessment, perhaps opening to tailored therapeutic options.

Congestion: diagnostic tools

Considering the prognostic relevance of congestion in HF patients, its early identification must be a primary goal for physicians: given that symptoms often arise late, clinical evaluation alone is probably not sufficient to effectively predict HF exacerbation (Figure 3). In addition, HF symptoms and signs, such as dyspnea and peripheral edema, could be related to countless extracardiac comorbidities, often not easily distinguishable. Using additional parameters could increase the ability of a risk model to correctly stratify patients: this additional contribution can be measured by statistical indices, such as the Net Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI). The NRI quantifies the ability of a new model to reclassify subjects compared to a previous model; the IDI expresses how much a risk factor, which is added to a predictive model, could modify the discrimination curve.

Table 1 Diagnostic value of clinical markers of congestion

Sign or symptom	Sensitivity	Specificity	PPV	NPV
Dyspnoea on exertion	66	52	45	27
Orthopnoea	66	47	61	37
Oedema	46	73	79	46
Resting JVD	70	79	85	62
S3	73	42	66	44
Chest X-ray				
Cardiomegaly	97	10	61	—
Redistribution	60	68	75	52
Interstitial oedema	60	73	78	53
Pleural effusion	43	79	76	47

Figure 3: accuracy of clinical markers of congestion in HF patients[3].

The importance of early detection of HF events in a high-risk population has long been the subject of study by several manufacturers of remote monitoring devices. Especially after the outbreak of the Covid-19 pandemic, eHealth has become a valuable aid to the clinicians, further accelerating research in the field of early detection of congestion. Over the years, manufacturers of implantable devices have tried to develop detection algorithms dedicated to identifying congestion, measuring changes in thoracic impedance, daily activity and the patient's vital parameters. In some cases, a reduction in outpatient visits and an earlier clinical intervention were observed, however no significant results were obtained on hard endpoints such as mortality and hospitalization[11,12].

To monitor changes in pulmonary intravascular pressure, dedicated devices have been designed that require invasive implantation in the pulmonary artery. The CHAMPION Trial randomized 550 HF patients to implant pulmonary artery pressure monitoring devices (CardioMEMS, Atlanta, GA, USA) after performing right heart catheterization. 6 months after randomization, a significant reduction of the primary endpoint was observed in patients undergoing device-guided therapy (HF-related hospitalization HR 0.72, 95% CI 0.60-0.85, P = 0.0002). Extending the follow-up to 15 months, resulted in a consistent reduction of the primary endpoint (HR 0.63, 95% CI 0.52-0.77, P<0.0001)[13]. Despite the results, these devices are not currently used in clinical practice.

The easiest and most reliable tool to confirm or exclude the presence of peripheral and pulmonary congestion still remains ultrasound; although it is widely present in every cardiology unit, it is not suitable for home monitoring.

Lung ultrasound (LUS) allows to identify several signs of congestion such as pleural effusion and B lines: these are vertical hyperechoic reverberation artifacts which represent air-water acoustic reflection phenomena beyond the pleural line. To detect thoracic signs of congestion, the examination is performed using a cardiological or convex probe, exploring the chest of a supine

patient from the second to the fifth intercostal space, on the parasternal line and the hemi-clavicular line. Ultrasound is then performed in lateral decubitus to evaluate the intercostal spaces on the anterior and middle axillary lines. The resulting semi-quantitative information is very accurate for excluding a cardiogenic genesis of dyspnea, according to a negative predictive value very close to 100%[14].

In recent years some studies on peripheral instrumental congestion have been published, mostly focused on patients hospitalized for HF[15,16]. A decade has passed since Pellicori et al. demonstrated the negative prognostic role of inferior vena cava (IVC) diameter in an outpatient HF setting[17]. Since then, several research groups have expanded the series by adding new parameters and diagnostic tools[18–21].

From these evidence and meta-analyses[22], the most influential study groups have repeatedly suggested the need to implement the outpatient congestion assessment in order to optimize diuretic therapy[23–25].

Clinical and subclinical congestion: a focus on prognosis

Although HF is a chronic condition that is cyclically associated with hypervolemia, the presence of clinical congestion is associated with an increase in morbidity and mortality[9], as well as re-hospitalization, with a more than doubled hazard ratio in mortality from all causes at multivariate analyses (HR 2.48, p = 0.003). Confirming that congestion itself is associated with disease progression, the hazard ratio of death from HF is significantly increased, without modifying the risk of death from arrhythmic causes[26]. Several studies consistently show that the causes of death are different in subjects in lower functional classes than in higher ones: if the arrhythmic cause prevails in NYHA II

class, death in advanced NYHA class depends on the progressive worsening of the hemodynamic status up to advanced and refractory HF[1,27].

The increase in left ventricular filling pressures always precedes the onset of overt HF symptoms by days or weeks; however, this pressure rise is very difficult to identify, especially when other pathologies coexist. Numerous studies have shown how monitoring changes in pulmonary pressure by implantable devices algorithm could anticipate and prevent hospitalizations for HF; a further trial evaluating the impact that these data on mortality has been recently published[28].

Therefore, hospitalization takes place due to the presence of signs and symptoms of congestion and the guidelines recommend therapeutic treatment until an optimal volume balance is achieved. However, despite the clinical improvement and an apparent effective decongestion assessed by PE, about 50% of patients hospitalized for acute HF are discharged with varying degrees of residual congestion; even more sensitive instrumental examinations such as chest X-rays show suboptimal accuracy in identifying subclinical congestion compared to ultrasound techniques[29,30]. A paper by Coiro et al. demonstrates that at the time of discharge after hospitalization for HF, 30% of patients show signs of congestion identified by LUS. When using B-lines in addition to NYHA class and natriuretic peptides, the accuracy of risk classification significantly improves (IDI 15%, P = 0.02; continuous net reclassification improvement, cNRI 65%, P = 0.03)[30]. Furthermore, clinical decongestion alone does not seem sufficient to guarantee a good post-discharge outcome; in the EVEREST study, patients who have been discharged without clinical signs and symptoms of congestion invariably had high mortality and re-hospitalization rate[31]. For this reason, the evaluation of congestion during hospitalization and discharge should be performed not only considering symptoms and signs at rest, but through an integrated approach that includes dynamic maneuvers and laboratory data (Figure 4). Based on these assumptions, ultrasound evaluation could provide consistent support in identifying subclinical congestion.

Variable	Score				
	−1	0	1	2	3
Bedside assessment					
Orthopnoea[a]		None	Mild	Moderate	Severe/worst
JVP (cm)	<8 and no hepatojugular reflux		8–10 or hepatojugular reflux	11–15	>16
Hepatomegaly	Absent in the setting of normal JVP	Absent	Liver edge	Moderate pulsatile enlargement	Massive tender enlargement extending to midline
Oedema		None	1+	2+	3+/4+
Laboratory					
Natriuretic peptides (one)					
BNP		<100	100–299	300–500	>500
NT pro-BNP		<400	400–1500	1500–3000	>3000
Dynamic manoeuvres					
Orthostatic testing	Significant decrease in SBP or increase in HR	No change in SBP or HR			
		No difficulty	Mild	Moderate	Severe/worst
6 min walk test	>400 m	300–400 m	200–300 m	100–200 m	<100 m
Valsalva manoeuvre	Normal response		Absent overshoot pattern	Square wave pattern	

Congestion grade: <1, none; 1–7, mild; 8–14, moderate; 15–20, severe. Oedema, in the absence of other cause of oedema.
[a]Orthopnoea: 0, absent; mild (use of one pillow); moderate (use of more than one pillow); severe, sleeps in an armchair on in a seated position.

Figure 4: congestion score proposed by Georghiade et al[3].

Similar to what happens in hospitalized patients, a careful evaluation of hemodynamic congestion is essential in the outpatient setting to correctly stratify the risk and to optimize medical therapy. As well as the procedures performed during hospitalization, the outpatient assessment of subclinical congestion is mainly performed with an ultrasound method which aims to evaluate the pulmonary B lines and the inferior vena cava diameter. Some studies show that the prevalence of residual congestion in this patient population is high: a recent paper by Pellicori et al. has shown various degrees of ultrasound congestion in about half of the patients considered clinically non-congested by PE, negatively correlating with prognosis[21]. Few studies on subclinical congestion in outpatients had already correlated the prognosis to the number of B lines identified with LUS, specifically patients with ≥ 3 B lines in eight areas of the chest, have a more than threefold risk of hospitalization for HF or death from any other cause within 180 days, regardless of age, gender and NYHA class[32]. The

recent paper by Pellicori et al. confirmed the previous data and assessed the clinical relevance of congestion in outpatients: the parameters used for the definition of congestion were the presence of more than 14 B-lines, dilated IVC more than 20 mm and JVD ratio <4. The study showed a correlation between ultrasound and laboratory data: patients with ultrasound signs of congestion had higher values of natriuretic peptides. In addition, congested patients, including subclinical ones, had a greater risk of events: the higher the degree of congestion itself (presence of one or more parameters), the greater was the hazard ratio: the rate of events in the entire population was settled at 18% (death or HF hospitalization) and NTproBNP, IVC diameters and JVD ratio were the independent predictors in the multivariate analysis[21]. Patients with dilated IVC and lung B lines are therefore at increased risk of adverse events regardless of the ejection fraction; moreover, an integrated approach allows to better identify these high-risk patients by improving IDI. It is noteworthy that even in patients with high NTproBNP values, already considered to be at high risk, adding the echographic data allows the researchers to better predict the 1-year outcome (Figure 5).

Table 5 The model's discrimination and reclassification

Model no.	Discrimination				Reclassification[a]			
	Model	C-statistics (95% CI)	Difference		cNRI (95% CI)	*P*-value	IDI (95% CI)	*P*-value
1	Base model[b]	0.74 (0.68–0.80)	Compared to 1 (*P*-value)	Compared to 2a (*P*-value)	–	–	–	–
2a	1 + log NT-proBNP	0.77 (0.71–0.83)	0.26	–	0.76 (0.41–1.11)	<0.001	0.16 (0.10–0.21)	<0.0001
2b	1 + B-lines	0.75 (0.69–0.81)	0.75	–	0.35 (0.00–0.70)	0.047	0.04 (0.01–0.07)	0.027
2c	1 + IVC	0.77 (0.71–0.83)	0.09	–	0.56 (0.21–0.91)	0.002	0.06 (0.02–0.10)	0.006
2d	1 + JVD ratio	0.76 (0.70–0.82)	0.37	–	0.73 (0.38–1.08)	<0.001	0.10 (0.04–0.15)	0.0003
2e	1 + clinical signs of congestion (vs. no signs)	0.76 (0.69–0.82)	0.39	–	0.50 (0.15–0.85)	0.005	0.02 (−0.01, 0.04)	0.13
3	2a + B-lines	0.77 (0.71–0.83)	0.31	0.85	0.03 (−0.32, 0.38)	0.88	0.00 (−0.00, 0.01)	0.92
4	2a + IVC	0.78 (0.73–0.84)	0.09	0.11	0.08 (−0.27, 0.43)	0.65	0.01 (−0.01, 0.02)	0.45
5	2a + JVD ratio	0.79 (0.73–0.85)	0.10	0.09	0.17 (−0.18, 0.52)	0.34	0.03 (0.00–0.06)	0.029
6	2a + B-lines and IVC	0.78 (0.72–0.84)	0.09	0.12	0.07 (−0.28, 0.42)	0.68	0.01 (−0.01, 0.02)	0.46
7	2a + B-lines and JVD ratio	0.79 (0.75–0.88)	0.10	0.08	0.23 (−0.12, 0.58)	0.19	0.03 (0.01–0.06)	0.023

CI, confidence interval; cNRI, continuous net reclassification improvement; IVC, inferior vena cava; IDI, integrated discrimination improvement; JVD, jugular vein diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a]Note that the reclassification is based on the event at 1 year ($n = 125$ patients with 59 events) as the method is based on logistic regression.
[b]Base model: age, sex, New York Heart Association class (III vs. II/I), creatinine, haemoglobin, and left ventricular ejection fraction.

Figure 5: Net Reclassification Improvement and Integrated Discrimination Improvement in the model proposed by Pellicori et al.[21]

Recently these first evidence on a heterogeneous group of HF patients have been confirmed by further studies on preserved ejection fraction HF populations (HFpEF)[33].

The drugs that most affect congestion are diuretics which are the most prescribed therapy in patients with HF: according to the EuroHeart Failure Survey 82% of HF patients take a daily dose of diuretics[34].

About tackling congestion, the most common type of diuretic is represented by loop diuretics which are the most effective in reducing volume overload. The most used and manageable molecule is furosemide, which has a powerful dose-dependent natriuretic effect; it significantly reduces the absorption of sodium and water on the ascending tract of the loop of Henle and on the distal tubule; its effect occurs within 30-60 minutes after oral intake and may be reduced over time due to the development of diuretic resistance. Unlike other drugs used in the management of HF, the favorable effect on mortality of loop diuretics has never been demonstrated in a randomized clinical trial. Therefore, diuretic therapy has the sole purpose of maintaining euvolemia and relieving symptoms related to congestion; it should be administered at the minimum effective dose[35].

In contrast to loop diuretics, minaralocorticoid antagonists (spironolactone and eplerenone, MRAs) are molecules with a modest diuretic effect, which are strongly recommended in HF therapy. MRAs have been shown to impact the disease evolution in several randomized trials, significantly reducing mortality and hospitalizations in almost all stages of disease severity[36,37]. Their action is exerted on the reduction of sodium reabsorption in the collecting duct of the nephron and the interference with the Na-K exchange: their diuretic effect is modest, but used in combination with other diuretics counteracts hypokalaemia, ensuring anti-remodeling effects.

A new class of diuretics currently under investigation, mostly used in chronic kidney disease patients, is represented by vasopressin V2 receptor antagonists, which induce the excretion of free water without affecting the ion's loss. Initially promising in HF patients, they did not confirm expectations in terms of prognosis and handling. The EVEREST study tested the effect of Tolvaptan in a large group

of patients hospitalized for HF symptoms, resulting in a prompt resolution of symptoms in the group treated with Tolvaptan, without significant differences in terms of mortality[38].

To conclude, since congestion is an important prognostic marker, it must be one of the main therapeutic targets, both in the acute and outpatient setting. However, congestion can only be treated if adequately recognized and, for this purpose, the patient evaluation must be integrated as much as possible with instrumental and laboratory tests, to adequately optimize medical therapy and impact on hospitalization and mortality that congestion negatively affects, even if subclinical.

Right ventricular-arterial coupling and congestion: translating a mechanical model into clinical perspectives

Ventricular-arterial coupling refers to the complex set of mechanisms by which the ventricle adapts its performance in response to increases in pressure and compliance of the downstream circulation. The increase in arterial pressures leads to an increase in cardiac inotropism which aims to keep the stroke volume (SV) and the cardiac output unchanged. Contrary to the left ventricle, the right ventricle is extremely sensitive to afterload variations in proportion to the extent of the variation and the time in which it occurs. Invasive measurement of pressure/volume curves (PV loop) during cardiac catheterization is considered the gold standard method for evaluating ventricular-arterial coupling (V-A coupling); in normal conditions, unlike the well-known rectangular PV loop of the left ventricle, the PV loop of the right ventricle has a triangular shape. This phenomenon is due to the low physiological pulmonary resistance, resulting in a circulatory system with high vascular compliance. In response to an increase in preload, the right ventricle can increase its contractility up to 4-5 times; the PV loop then becomes less triangular and takes on the appearance of a rectangle (not surprisingly it is called "left ventricle shaped PV loop") with a right shift in the pressure/volume curve (Fig. 6)[39].

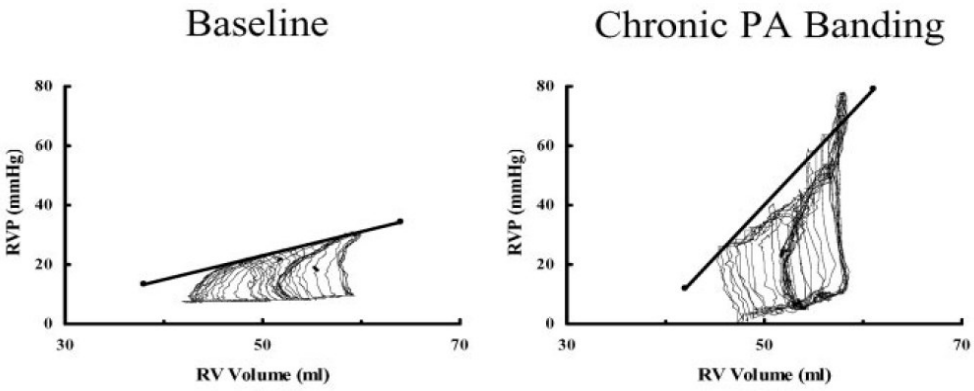


Figure 6: variations in the right PV loop at increasing volumes in an animal model before and after 100 days from pulmonary artery ligation[39].

In advanced stages of the disease, the right ventricle dilates and the PV loop moves towards unfavorable hemodynamic conditions, while the increase in preload is no longer followed by an increase in inotropism. In this advanced stage, the heart rate rises to maintain an adequate cardiac index. However, this compensatory mechanism increases wall stress and myocardial oxygen demand. The dilation of the tricuspid annulus progressively reduces the valvular coaptation area due to the geometric deformations induced by the remodeling of the right cavities, inevitably leading to increasing degrees of valve insufficiency, a defect that further aggravates right ventricular failure. Finally, these phenomena lead to a further volume overload, significantly reducing the antegrade SV. The worsening of the pathophysiological mechanisms underlying the RVD leads to the exhaustion of the right ventricular adaptation resources; pulmonary pressures become higher, inotropism and SV drop, ultimately resulting in an overt ventricular-arterial decoupling[39].

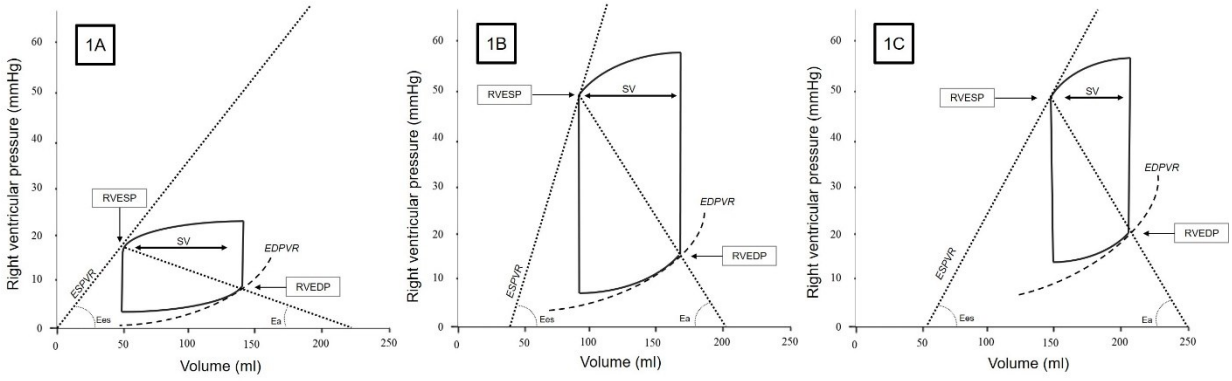


Figure 7: A - right ventricle PV loop: 1 A - physiological conditions of V-A coupling, normal compliance and systolic output of the right ventricle, pulmonary pressures within normal limits. 1 B – right ventricular adaptation in conditions of pulmonary hypertension: to ensure adequate cardiac output, the cavity dilates and inotropism increases (Ees angle increases; the slope of the ESPVR curve increases); in these conditions of compensated V-A decoupling, the SV is unchanged at the expense of high filling pressures (high RVEDP). 1 C - conditions of overt right V-A decoupling: the right ventricle dilates further, inotropism is reduced with a significant drop in systolic output despite the high right ventricular filling pressures. SV: stroke volume; RVESP: right ventricle end-systolic pressure; RVEDP: right ventricle end- diastolic pressure; Ees: systolic elastance; Ea: arterial elastance; ESPVR: end systolic pressure/volume relationship, the slope of this curve is an index of contractility; EDPVR: end diastolic pressure/volume relationship, it is an index of ventricular compliance and filling pressures[40].

In HF patients the most important mechanism leading to right ventricular failure is due to the imbalance between pump function and excessive afterload, a phenomenon known as afterload mismatch[41]. Mean pulmonary pressure increases beyond the right ventricular adaptation threshold, leading to increasingly severe degrees of V-A decoupling. The diastolic dysfunction of the left ventricle and the loss of left atrial compliance change the physiological morphology of the pulmonary pressure wave by imposing a markedly pulsatile flow to the pulmonary artery: this phenomenon leads to a passive increase in pulmonary pressure. In many cases, a component of pulmonary vasoconstriction is added to a passive increase in pulmonary pressure, the extent of which is not proportional to the left ventricular filling pressure[42]. The presence of both pre-capillary and post-capillary pulmonary hypertension is defined as combined pulmonary hypertension.

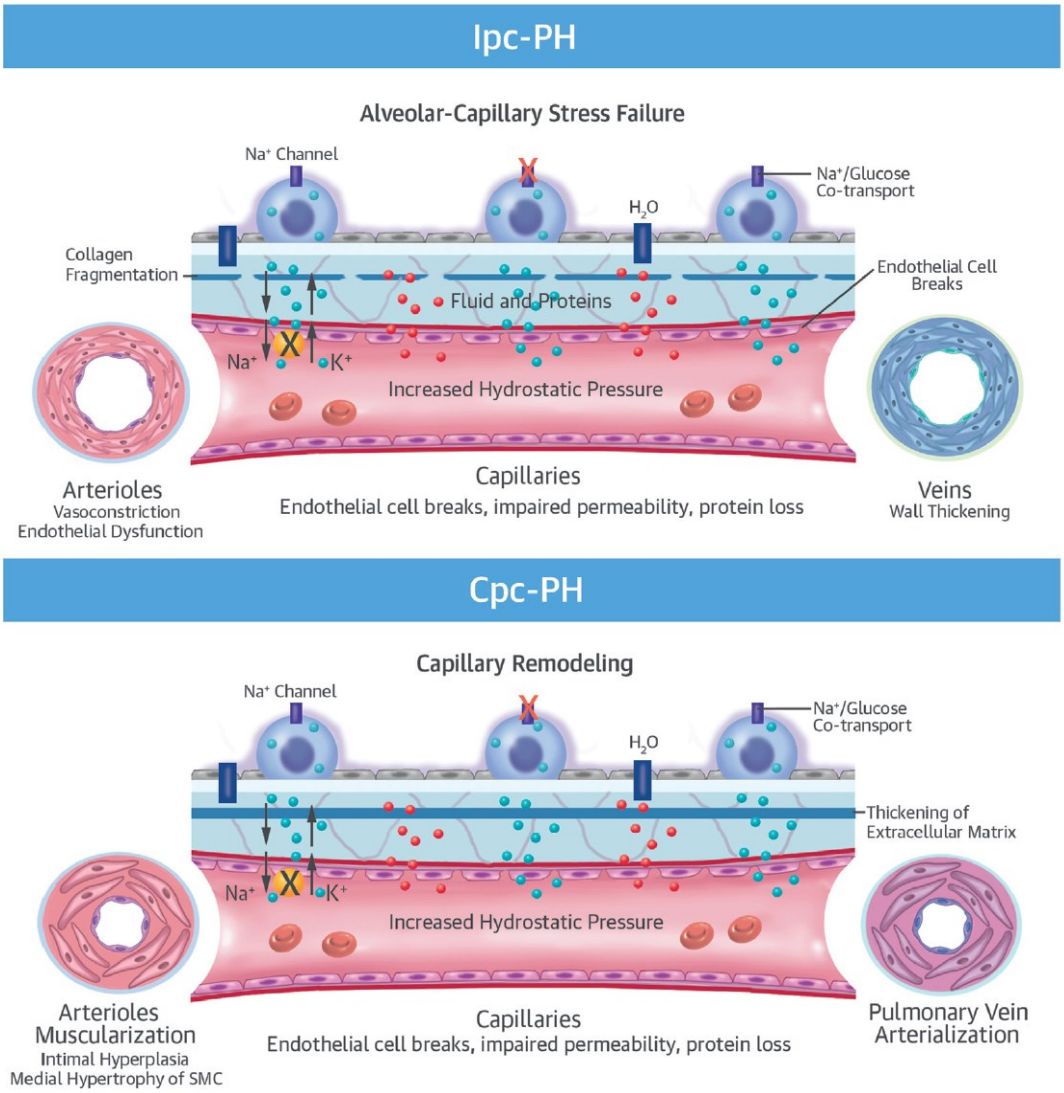


Figure 8: complex adaptive mechanism of the pulmonary circulatory system to post-capillary hypertension conditions. From damage of the alveolar-capillary barrier to vascular and interstitial remodeling. These mechanisms predispose to a reduction of right SV and RV/LV cardiac output mismatch, even if the the left cardiac output reduction is the *primum movens* [43].

Recent studies have analyzed non-invasive methods to quantify the degree of right V-A decoupling using easily and reproducible ultrasound parameters[44]: the TAPSE/ PAPS ratio is obtained from the relationship between the longitudinal function of the right ventricle and the pulmonary systolic pressure. The TAPSE/PAPS ratio was found to be an independent predictor of mortality in HF patients regardless of left ventricular ejection fraction (LVEF)[45]; the cut-off identified by these studies is 0.36,

354 a value below which mortality increases by 2.5 in patients under the age of 65 and by more than 4
355 times in patients over 65. Deterioration of the right ventricular function also appears progressive in
356 patients with HF, regardless of LVEF[46]. Although it explores right ventricular function and pulmonary
357 pressure with a single-parameter method, the prognostic power and ease of acquisition of the
358 TAPSE/PASP value have made this ratio widely used in daily clinical practice.

359 The relationship between right ventricular dysfunction (RVD) and congestion is still a subject of
360 scientific debate. As already explained in previous studies, right ventricular function, pulmonary
361 pressure and V-A coupling are closely related to relapses of overt congestion in the population
362 affected by HF. However, no correlation data with subclinical congestion are currently available.

363 Considering the thesis proposed by MacIver on the genesis of acute pulmonary edema, in this
364 simplified mechanistic model the author suggests that pulmonary edema is triggered by an initial SV
365 mismatch between the two vascular circuits. This mechanism initially involves the relationship
366 between right and left cardiac output, which is strictly dependent on SV and heart rate. Once the
367 mechanism is triggered, precipitating factors overwhelm the pulmonary compensation mechanisms,
368 leading to a rapid deterioration of the alveolar membrane and its compensatory capacities. Finally,
369 among the key factors which could promote pulmonary edema, the over-fluid created by adrenergic
370 stress could play a crucial role, inducing a recirculation of a pool of liquids from the venous
371 capacitance system, compromising the weaker circulation, the systemic one in the case of pulmonary
372 edema.

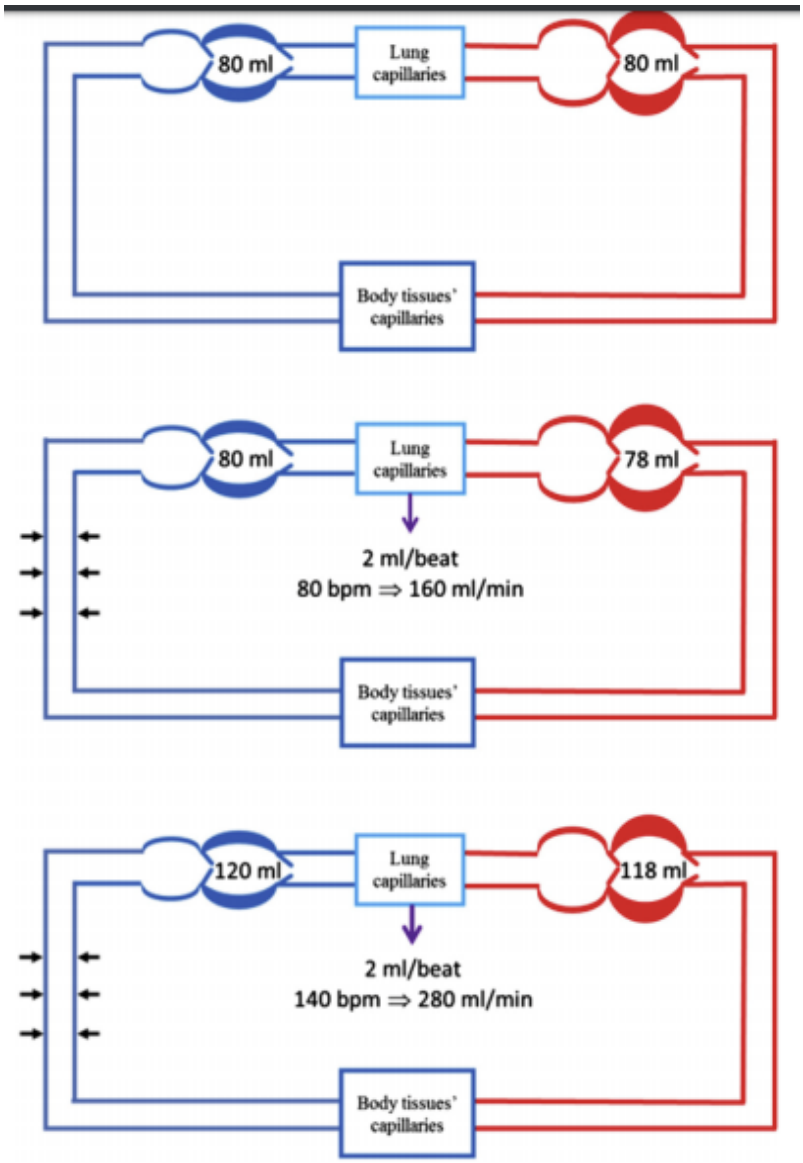


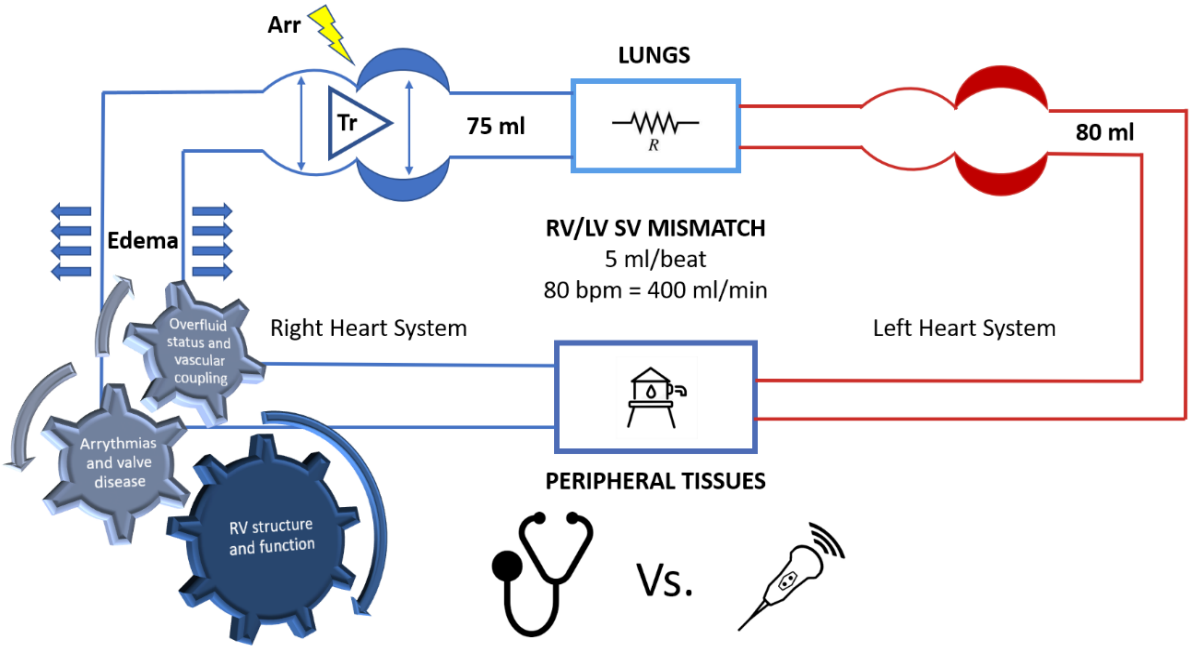
Figure 9: Hemodynamic model of pulmonary edema. The circuit consists of two hydraulic pumps representing the pulmonary and systemic circles. In order to maintain a compensated hemodynamic condition, the right and left heart must maintain the same SV; any condition causing an imbalance will cause system anomalies. Above: represents balanced flows and assumes a normal SV at rest of 80 ml and 120 ml during exercise. Center: pulmonary edema situation at rest; a reduction in left ventricular SV of 2 ml/beat triggers the mismatch. Assuming a basal heart rate of 80 bpm, there will be a total of 160 ml/min of excess fluid in the pulmonary circulation. Bottom: similar SV discrepancy can occur during exercise or arrhythmia: the higher the heart rate, the higher the congestion rate (in the example at 140 bpm -> 280 ml/min). This simplified scheme ignores the lymphatic system and the venous flow in the bronchial and Tebesium veins, considering an exquisitely hemodynamic model that excludes cell damage and intravascular oncotic component from the analysis. Alveolar edema results from a disproportion between the left and right flow, with progressive accumulation of fluids in the interstitium and therefore in the alveoli[47].

What would happen if the weak circuit between the two were the pulmonary one instead of the systemic one? Is it possible that in advanced phases of HF the SV mismatch is at the expense of the right ventricle? Can the adaptation of the pulmonary circulation and the consequences on the right V-A coupling drive congestion towards the periphery rather than towards the lung?

To support the hypothesis that an over-fluid condition may worsen RVD and pulmonary hypertension, the guidelines for the diagnosis and evaluation of pulmonary hypertension secondary to left HF recommend fluid challenge as a validated method for determining borderline cases of pulmonary hypertension[48]. The fluid challenge also causes an increase in LVEDP in healthy volunteers with varying degrees depending on sex, age, amount of infused liquid and infusion rate[49]; however, up to 20% of patients with pre-capillary pulmonary hypertension show an increase in LVEDP after infusion, suggesting that fluid overload could modify right V-A coupling[50,51].

Deterioration of the right ventricle is a progressive phenomenon in HF that probably involves more advanced stages of disease regardless of LVEF[52]. This suggests that there may be distinct phases of HF that start with left ventricular dysfunction and result in RVD over time, with significant geometric and structural changes in the right heart chambers, worsening of right V-A coupling and dramatic clinical correlations[46].

Starting from the mechanistic hypothesis proposed by MacIver applied to the right ventricle, this study aims to analyze the relationship between right V-A coupling and congestion, confirming the prognostic data, exploring subclinical congestion in the real-life population.



405

406 **Figure 10: the hemodynamic model of peripheral congestion. The high resistance of the pulmonary circulation reduces**
407 **the SV of the right ventricle triggering the mismatch, the right cavities dilate and become dysfunctional. As the annulus**
408 **dilates, the degree of tricuspid insufficiency increases, further reducing the right SV. Volume overload further worsens**
409 **pulmonary hypertension, myocardial dysfunction and the degree of valvular insufficiency, triggering arrhythmias and**
410 **inevitably relapses of acute HF.**

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Study

414

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Materials and methods

Study population

In this study, 110 chronic HF outpatients were enrolled (Di Circolo Hospital – Macchi Foundation, Varese; Galmarini Hospital, Tradate) from December 2018 to June 2019. For all enrolled patients, the ultrasound study was always performed immediately after the PE.

The following inclusion criteria were considered: age >18 years, previous diagnosis of HF regardless of left ventricular ejection fraction (LVEF) and etiology of heart disease; recent blood tests (blood sample acquired in the last 3 months or the month following the visit) including creatinine, urea, hemoglobin, hematocrit, NTproBNP, sodium, potassium.

The following exclusion criteria were considered: estimated glomerular filtration rate <15 ml/min/1.73m2 (calculated using the Modification of Diet in Renal Disease equation); poor acoustic window; patients followed by heart failure surveillance telemedicine or treated with periodic inotropic infusions; recent hospitalization for HF (in the previous 30 days); acute coronary syndromes or myocardial revascularization in the previous 3 months; cardiac surgery in the previous 6 months; isolated right ventricular dysfunction and isolated tricuspid insufficiency; idiopathic pulmonary hypertension; severe pulmonary disease; BMI> 40; pregnancy.

Prior medical history of hypertension was defined as arterial hypertension. Atrial fibrillation was defined as a clinical history of sustained atrial fibrillation and atrial flutter. Previous history of myocardial infarction or angiographic evidence of significant coronary artery disease defined ischemic heart disease. Diabetes was considered comorbidity in presence of a previous diagnosis of type 1 or type 2 diabetes mellitus. Chronic kidney disease was defined as an estimated glomerular

filtration rate < 60 mL/min/1.73 m2 using MDRD formula. Anemia was defined by hemoglobin level < 12 g/dl in females and < 13 g/dl in males.

Physical examination and echocardiographic analysis

PE was performed by 2 cardiologists experienced in the field of HF. PE was systematically performed in each patient to identify clinical signs of congestion and elevated central venous pressure; the presence of these clinical signs was not graduated and was analyzed as dichotomic classification. The parameters which were systematically acquired are the following: jugular vein distention (JVD), hepato-jugular reflex (HJR), peripheral edema (OED) and rales. JVD was systematically inspected in the supine position, at 30° - 45°, on both sides of the neck, with a careful evaluation of the internal jugular venous waveform. HJR was considered as positive when a sustained increase in JVD, during 10 s of continuous pressure on the abdomen was identified, with an immediate drop after the pressure was released. A detailed clinical history, electrocardiogram and vital signs were always collected before transthoracic echography (TTE).

TTE was performed in a blinded fashion by an experienced cardiologist, using a Vivid E9 (GE Healthcare, Boston, MA, US) and a Philips IE33 (Philips Healthcare, Eindhoven, NL), equipped with a cardiac probe (2.5–3.5 MHz); all measures were collected according to current guidelines. A systematic evaluation of the inferior vena cava (IVC) diameter and its collapsibility degree was performed whereby the IVC diameter was measured at end-expiration by a subxiphoid view, approximately 2 cm from venous ostium, and its collapse was estimated following deep inspiration. The RAP was estimated as 3 mmHg when an IVC diameter < 21 mm and collapsibility > 50% were both detected; IVC diameter ≥ 21 mm with a collapse < 50% arbitrary esteemed a right atrial pressure of 13 mmHg; 8 mmHg was esteemed for intermediate values of IVC diameter and collapsibility

degree. Right ventricular systolic function was assessed from right focused views, by a multiparametric evaluation composed of fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and systolic S' wave using tissue Doppler technique. TAPSE < 17 mm, FAC < 35% and S'<9.5 cm/s were considered pathologic values. Tricuspid regurgitation degree was assessed by qualitative estimation as trivial, mild, moderate or severe, respectively. Pulmonary Artery Systolic Pressure (PAPS) was derived by peak tricuspid jet velocity plus the estimated RA pressure, 36 mmHg was considered the upper normal range. The TAPSE/PAPS ratio was assumed as a surrogate of right ventricular–arterial coupling: values > 0.57 were considered normal. The presence of at least 2 pathologic criteria among TAPSE, FAC and S' was considered as RVD.

Outcome data

The composite outcome was represented by HF rehospitalization, Emergency Department (ED) admission due to HF symptoms requiring diuretics and cardiovascular mortality.

Outcome data were obtained by scheduled visits and Emergency Department admissions using the local electronic database (Portale application). All outcome missing data were obtained directly by the patients by phone calls and scheduled visits.

Statistical analysis

Normally distributed continuous variables are presented as means ± standard deviation, or median and confidence intervals in case of non-Gaussian distribution. Between-group differences were compared by Chi square test, Analysis of Variance test (ANOVA) and Student–Newman–Keuls (SNK) as appropriate. Kaplan-Meier curve analysis was used to assess event rate and for graphic representations of outcomes. The accuracy data were expressed by area under curve (Receiver Operating Characteristic, ROC curve) and by inter-rater agreement (kappa) analysis. The associations

between echographic and clinical variables were tested using multivariable logistic regression models. The correlation between variables is expressed by Pearson correlation coefficient. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Medcalc software.

Results

Population

110 consecutive patients were screened from December 2018 to June 2019; 6 patients met the exclusion criteria and were removed from the final analysis (3 patients due to low eGFR; 3 patients due to poor acoustic window). Among 104 patients, 72 were men (69%) and 32 women (29%); the average age was 73 ± 11 years. The prevalent etiology of HF was found in idiopathic cardiomyopathy (37%), followed by ischemic disease (34%), valvular disease (12%) and other causes (e.g. infiltrative diseases, alcoholic/drugs). 32% of patients had an implantable cardiac defibrillator (ICD) and 8% had cardiac resynchronization therapy (CRT). The mean time from onset of HF symptoms was 45 (16 – 106) months. Regarding left ventricular function, 42% of the whole population had heart failure reduced ejection fraction (HFrEF), the average LVEF was 45% ± 11%. The baseline characteristics of 104 examined patients are summarized in Table 1. Data from the general population were compared with three main groups according to PE and ultrasound data:

"Non-Cong" (Non-Congested) group: patients without clinical signs of peripheral congestion or ultrasound signs of congestion.

"SubC" (Sub Clinical Congestion) Group: Patients with ultrasound signs of congestion without peripheral clinical congestion.

"Edema" group: patients with peripheral congestion regardless of ultrasound findings.

Population characteristics	Total Pop (n 104)	Non-Cong (n 77)	SubC (n 12)	Edema (n 15)	Missing	p value
Sex (male)	72 (69%)	54 (70%)	9 (75%)	9 (60%)	-	ns
Age (years)	73 ± 11	70 ± 11	75 ± 11	81 ± 4	-	<0.01 #
Weight (Kg)	76 ± 15	76 ± 15	77 ± 21	74 ± 14	-	ns
Height (cm)	170 ± 9	170 ± 9	171 ± 6	170 ± 11	-	ns
BMI (Kg/m^2)	26 ± 4	26 ± 4	26.4 ±7.0	25.5 ±3.3	-	ns
BSA (m^2)	1.86 ± 0.20	1.86 ± 0.21	1.89 ±0.21	1.85 ±0.22	-	ns
NYHA class						<0.001
I	29 (28%)	25 (32%)	3 (25%)	1 (7%)	-	
II	54 (52%)	44 (57%)	5 (42%)	5 (33%)	-	
III	20 (19%)	8 (10%)	4 (33%)	8 (53%)	-	
IV	1 (1%)	0 (0%)	0 (0%)	1 (7%)	-	
LVEF < 40%	44 (42%)	34 (44%)	5 (42%)	5 (33%)	-	ns
Etiology						<0.01
Ischemic	35 (34%)	24 (31%)	5 (42%)	6 (40%)	-	
Valvular	13 (12%)	6 (8%)	2 (17%)	5 (33%)	-	
Idiopatic	38 (37%)	36 (47%)	2 (17%)	0 (0%)	-	
Miscellaneous	18 (17%)	11 (14%)	3 (25%)	4 (27%)	-	
Months since HF diagnosis	45 (16 – 106)	49 (19 – 107)	16 (7 – 81)	19 (15 – 61)	-	ns
Comorbidities						
Stroke in past	5 (5%)	4 (5%)	1 (8%)	0 (0%)	-	ns
Previous cardiac surgery	15 (14%)	13 (17%)	0 (0%)	2 (13%)	-	ns
Previous mitral valve repair or clip	9 (8%)	6 (8%)	2 (17%)	1 (7%)	-	ns
Diabetes	26 (25%)	19 (25%)	3 (25%)	4 (27%)	-	ns
History of cancer	16 (15%)	10 (13%)	3 (25%)	3 (20%)	-	ns
Hypertension	71 (68%)	49 (64%)	10 (83%)	12 (80%)	-	ns
Peripheral artery disease	5 (5%)	4 (5%)	0 (0%)	1 (7%)	-	ns
History of atrial fibrillation	43 (42%)	24 (31%)	7 (58%)	12 (80%)	-	<0.001
Permanent atrial fibrillation	25 (24%)	12 (16%)	5 (42%)	8 (53%)	-	<0.001
Therapy						
ACEi	68 (65%)	50 (65%)	7 (58%)	11 (73%)	-	ns
ARB	14 (13%)	10 (13%)	3 (25%)	1 (7%)	-	ns
BetaB	96 (91%)	72 (94%)	12 (100%)	12 (80%)	-	ns
Ivabradine	12 (11%)	11 (14%)	1 (8%)	0 (0%)	-	ns
Digoxin	5 (5%)	3 (4%)	1 (8%)	1 (7%)	-	ns
MRA	48 (46%)	34 (44%)	7 (58%)	7 (47%)	-	ns
NTG	7 (7%)	5 (6%)	2 (17%)	0 (0%)	-	ns
Warfarin	34 (33%)	18 (23%)	6 (50%)	10 (67%)	-	<0.001
NOACs	9 (8%)	4 (5%)	2 (17%)	3 (20%)	-	<0.05
Statins	53 (50%)	42 (55%)	7 (58%)	4 (27%)	-	ns
Furosemide	83 (80%)	59 (77%)	10 (83%)	14 (93%)	-	ns
Amiodarone	24 (23%)	17 (22%)	2 (17%)	5 (33%)	-	ns
ARNI	9 (8%)	7 (9%)	1 (8%)	1 (7%)	-	ns
ICD	34 (32%)	30 39%)	2 (17%)	2 (13%)	-	ns
CRT	9 (8%)	8 (10%)	1 (8%)	0 (0%)	-	ns

(#) = (1) Vs (3) Student-Newman-Keuls test for all pairwise comparisons p < 0.05

Table 1: main clinical and therapeutic characteristics of the enrolled patients divided into subgroups under comparison. Group "Non-Cong": patients without clinical signs of peripheral congestion nor echographic signs of congestion. Group "SubC" (Sub Clinical congestion): patients with echographic signs of congestion without peripheral clinical congestion. Group "Edema": patients with peripheral congestion irrespective of echographic findings.

From the analysis of the population characteristics, it emerged that patients in the "Edema" group had a significantly higher mean age than the "Non-Cong" group ($p < 0.01$); however, there was no significant difference compared to the "SubC" group. Although there were no significant differences regarding the prevalence of patients with left ventricular dysfunction, significant differences were observed regarding the etiology of heart disease. In the "Non-Cong" group there was a higher prevalence of idiopathic cardiomyopathy (47%); in the "SubC" and "Edema" groups there was a higher prevalence of ischemic and valvular heart disease ($p < 0.01$). Not surprisingly, a gradual increase in the prevalence of both history of atrial fibrillation and permanent atrial fibrillation is observed in the "SubC" and "Edema" groups compared to the Non-Cong group ($p < 0.001$).

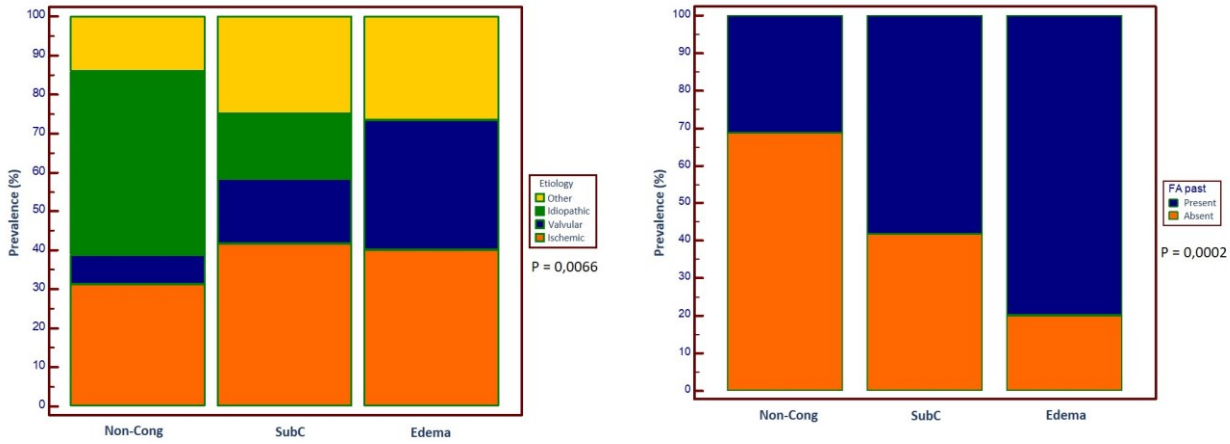


Figure 1: HF etiology and atrial fibrillation prevalence comparison between groups.

Consistently, patients showing ultrasound or clinical signs of congestion had a higher NYHA functional class ($p < 0.001$).

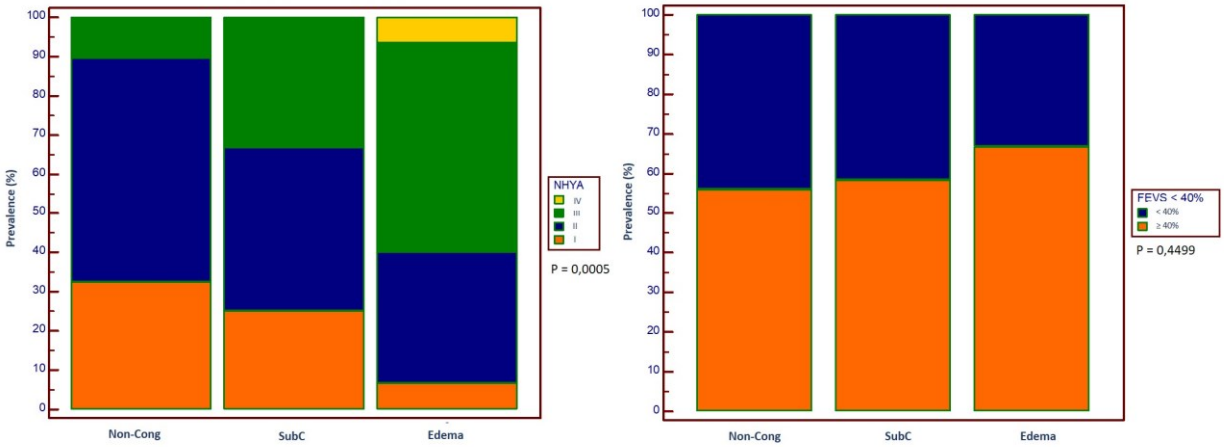


Figure 2: NYHA functional class and HFrEF prevalence, comparison between groups.

Baseline blood sample results are summarized in Table 2.

Population characteristics	Total Pop (n 104)	Non-Cong (n 77)	SubC (n 12)	Edema (n 15)	Missing	p value
Blood tests						
Hematocrit (%)	41.3 (39.1 – 43.9)	41.2 (39.1 – 44.0)	41.2 (39.0 – 43.8)	41.0 (38.9 – 43.5)	5	ns
Hemoglobin (g/dl.)	13.7 (12.7 – 14.6)	13.7 (12.7 – 14.6)	13.2 ± 1.7	11.9 (11.3 – 13.5)	5	<0.01 #
Creatinine (mg/dl)	1.2 (1.0 – 1.5)	1.2 (1.0 – 1.5)	1.2 (1.1 -1.3)	1.4 (1.1 – 1.6)	6	ns
eGFR MDRD (ml/min/1.73m^2)	57 (46 – 73)	58 (47 – 77)	56 (48 – 65)	55 (46 – 66)	6	ns
NTproBNP pg/ml	944 (237 – 1755)	716 (192 – 1548)	1361 (764 – 2172)	2116 (1111 – 4945)	24	ns
Sodium (mEq/l)	141 (139 – 143)	141 (140 – 143)	142 (141 – 143)	141 (138 – 144)	17	ns
Potassium (mEq/l)	4.5 (4.2 – 4.9)	4.5 (4.2 – 4.8)	4.5 (4.4 – 4.8)	4.5 (4.3 – 4.9)	9	ns
ePlasma Vol (ml)	2640 (2428 – 2879)	2633 (2417 – 2860)	2684 (2499 – 3002)	2653 (2522 – 3010)	6	ns

(#) = (1) Vs (3) Student-Newman-Keuls test for all pairwise comparisons p < 0.05

Table 2: blood sample results of the enrolled patients divided into subgroups under comparison. Group "Non-Cong": patients without clinical signs of peripheral congestion nor echographic signs of congestion. Group "SubC" (Sub Clinical congestion): patients with echographic signs of congestion without peripheral clinical congestion. Group "Edema": patients with peripheral congestion irrespective of echographic findings.

Mean eGFR was 57 ml/min/1.73m2 (46 – 73 ml/min/1.73m2); an eGFR between 20 and 30 ml/min/1.73m2 was observed in 8 patients. Median plasma NTproBNP was 944 ng/l (237 - 1755 ng/l). No significant differences in blood chemistry were observed except for the hemoglobin parameter,

which was significantly reduced in the group with clear signs of congestion ($p < 0.01$). The inter-rater agreement analysis showed a significant correlation between the circulating levels of NTproBNP and inferior vena cava diameters and collapsibility (IVC minimum diameter: correlation coefficient r 0.342, $p < 0.01$; IVC maximum diameter: correlation coefficient r 0.233, $p < 0.05$; IVC collapse: correlation coefficient r 0.338, $p < 0.01$).

Physical examination and ultrasound analysis

Results of PE and TTE evaluations are summarized in Table 3.

Population characteristics	Total Pop (n 104)	Non-Cong (n 77)	SubC (n 12)	Edema (n 15)	Missing	p value
Vital signs						
Heart rate (bpm)	69 ± 13	70 ± 12	69 ± 10	69 ± 16	-	ns
Systolic blood pressure	127 ± 17	129 ± 16	123 ± 13	125 ± 21	-	ns
Diastolic blood pressure	75 ± 10	76 ± 10	72 ± 7	74 ± 12	-	ns
Physical examination						
Pulmonary congestion	8 (8%)	1 (1%)	2 (17%)	5 (33%)	-	<0.001
Peripheral congestion	15 (14%)	0 (0%)	0 (0%)	15 (100%)	-	<0.001
Elevated CVP	30 (29%)	11 (14%)	6 (50%)	13 (87%)	-	<0.001
Ultrasound parameters						
LVEF (%)	40 ± 11	40 ± 11	40 ± 12	42 ± 13		
TAPSE (mm)	20 ± 5	21 ± 5	18 ± 7	18 ± 6	-	<0.05
PAPS (mmHg)	35 ± 11	26 ± 5	47 ± 14	47 ± 11	7	<0.001 *
TAPSE/PAPS	0.63 ± 0.26	0.71 ± 0.23	0.43 ± 0.24	0.40 ± 0.16	7	<0.001 *
S'VD (cm/sec)	10.6 ± 2.8	11.0 ± 2.7	8.9 ± 3.2	10.0 ± 3.1	3	= 0.05
RV end-diastolic area (cm2)	19.1 ± 4.6	18.7 ± 5.0	20.1 ± 3.8	20.0 ±2.6	2	ns
RV end-systolic area (cm2)	11.5 ± 3.7	10.9 ± 3.7	13.4 ±4.0	13.0 ±2.5	2	< 0.05 #
RV FAC	0.40 ± 0.13	45 ± 13	33 ± 16	35 ±11	2	<0.05
RA end-diastolic area (cm2)	14.8 ± 6.7	12.4 ± 4.5	20.5 ±8.9	21.5 ± 7.0	3	0.001 *
RA end-systolic area (cm2)	19.6 ± 6.8	17.4 ± 5.1	24.8 ±8.5	25.7 ±6.9	2	0.001 *
IVC Min (mm)	11 ± 5	8 ± 3	19 ± 4	22 ±5	6	<0.001°
IVC Max (mm)	17 ± 5	15 ± 4	24 ± 3	16 ±4	2	<0.001 *
IVC collapse (%)	40 ± 16	45 ± 13	22 ± 12	25 ± 11	6	<0.001 *

(#) = (1) Vs (3) Student-Newman-Keuls test for all pairwise comparisons p < 0.05
(*) = (1) Vs both (2) and (3) Student-Newman-Keuls test for all pairwise comparisons p < 0.05
(°) = (1) Vs (2) Vs (3) Student-Newman-Keuls test for all pairwise comparisons p < 0.05

Table 3: main PE and echographic characteristics of the enrolled patients divided into subgroups under comparison. Group "Non-Cong": patients without clinical signs of peripheral congestion nor echographic signs of congestion. Group "SubC" (Sub Clinical congestion): patients with echographic signs of congestion without peripheral clinical congestion. Group "Edema": patients with peripheral congestion irrespective of echographic findings.

Pulmonary congestion was revealed by PE in 8% of enrolled patients; 14% showed clinical signs of peripheral OED; in 29% clear signs of elevated central venous pressures were present (JVD and/or HJR). Among the patients in the "Edema" group, 33% showed signs of pulmonary congestion and almost all of them had signs of elevated central venous pressure. PE revealed a statistically significant

difference in pulmonary congestion and signs of elevated central venous pressure between the compared groups ($p < 0.001$).

Regarding right ventricular function, a TAPSE <17 mm was found in 29% of patient, 31% showed a value of S' <9.5 cm/s, 33% a FAC value <35%. Assuming RVD as the presence of at least two of these parameters, RVD was found in 29% of the population. The mean estimated RAP was 7.4 ± 4.2 mmHg. PH was found in 42% of the patients; the TAPSE/PAPS lower tertile represented 14% of the whole population; 46% of patients presented TAPSE/PAPS values <0.57. The "Non-Cong" group showed significantly higher values of TAPSE, S' and FAC (respectively $p < 0.05$; $p = 0.05$; $p < 0.05$).

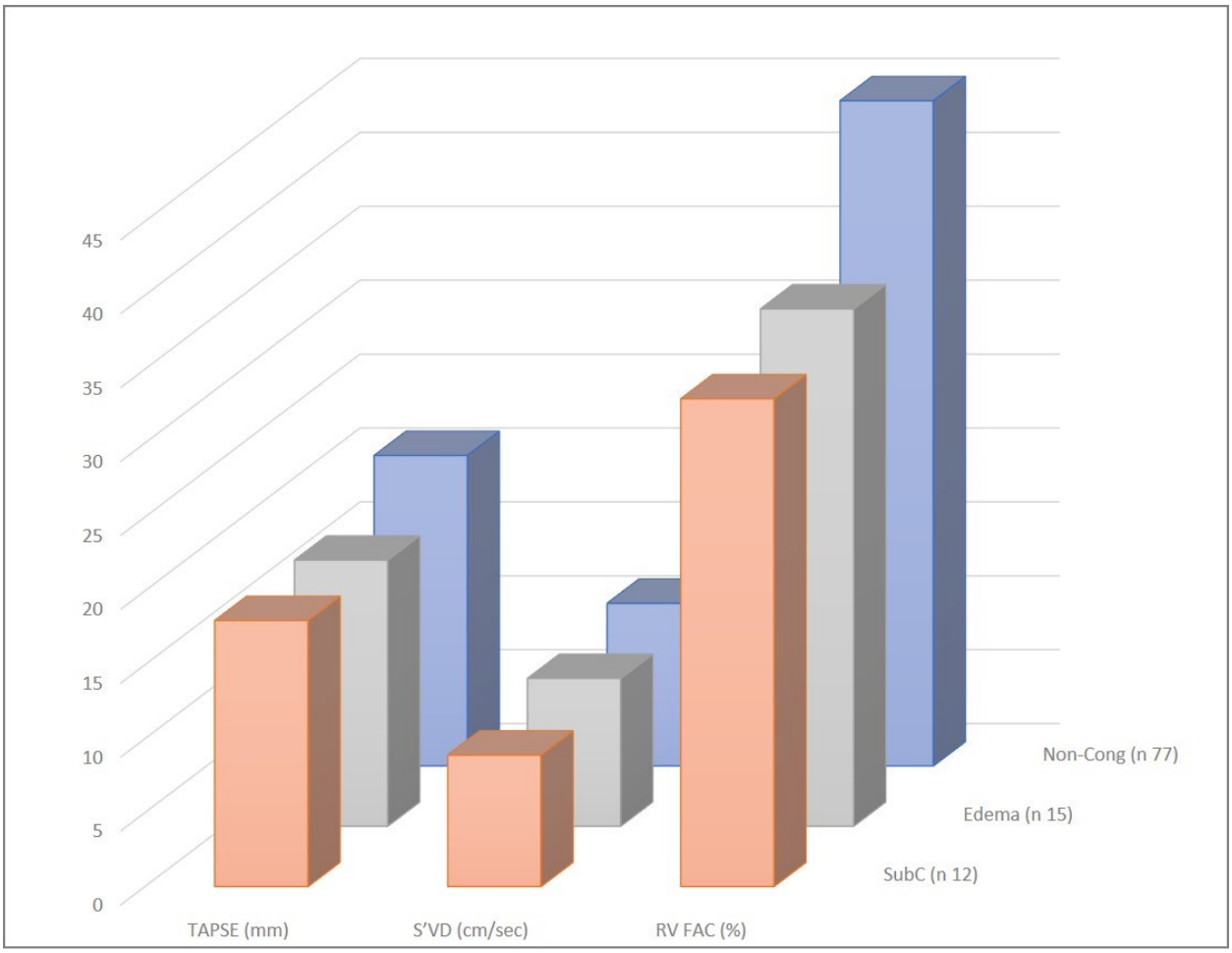


Figure 3: right ventricle functional parameters, comparison between groups.

The values of TAPSE ($p < 0.001$) and FAC ($p < 0.05$) were significantly reduced in the congested groups compared to the group without instrumental and clinical congestion; the parameter S ' was found to be close to statistical significance.

Comparing the three groups, significant differences emerged in terms of cavity size and systolic function parameters of the left ventricle. The end-systolic and end-diastolic areas of the right atrium were significantly higher in the congested groups compared to the group without instrumental or clinical congestion ($p = 0.001$). The end-systolic area of the right ventricle was increased in the congested groups compared to the "Non-Cong" group, reaching statistical significance only in the "Edema" group ($p < 0.05$).

With regard to PAPS values, a significant difference was observed between the congested groups compared to the group with no signs of instrumental or clinical congestion ($p < 0.001$). Consistently, the TAPSE/PAPS values identified a significant difference between the congested groups and the "Non-Cong" group ($p < 0.001$).

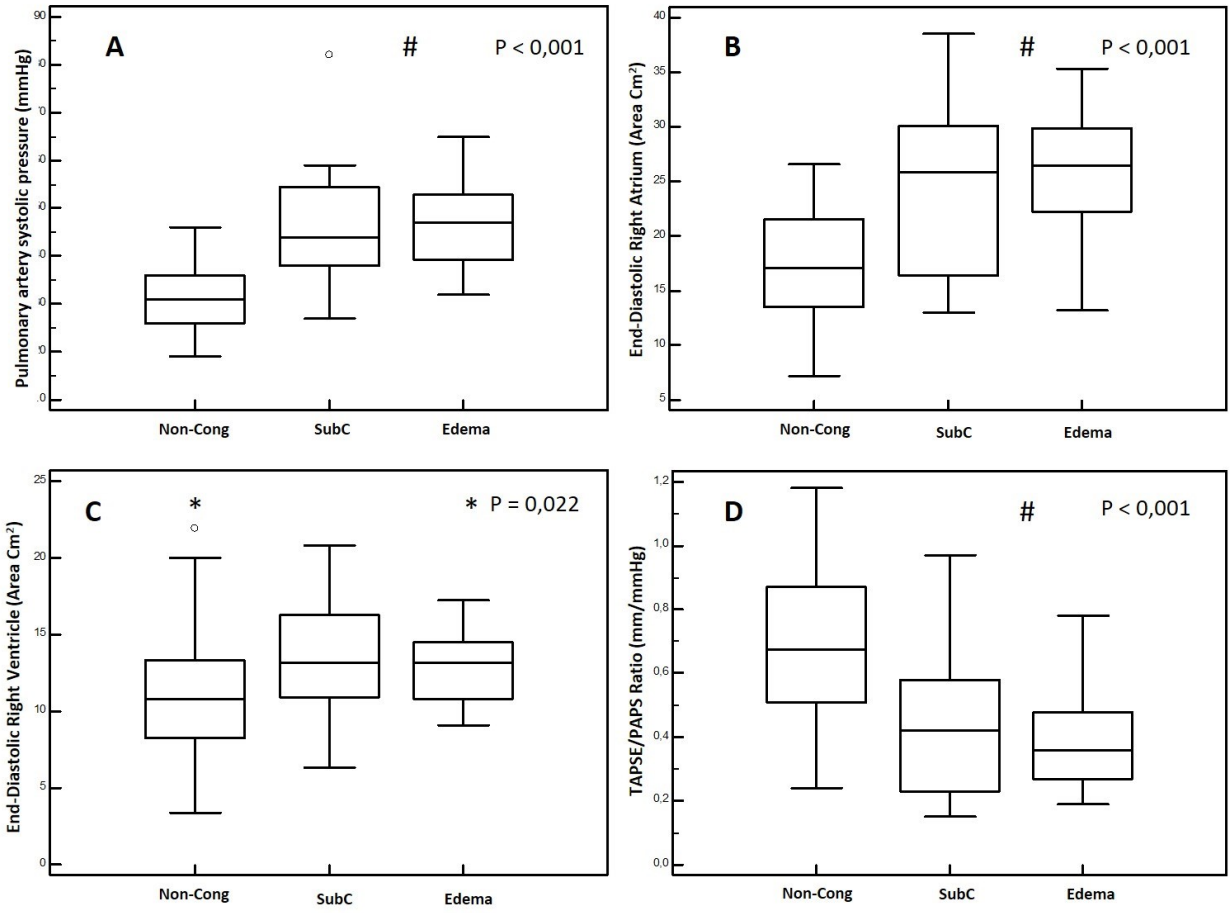


Figure 4: ultrasoud findings: comparison between groups. A: pulmonary artery systolic pressure. B: end-diastolic right atrium area. C: end-diastolic right ventricle area. D: TAPSE/PAPS ratio. #: p value for congested patients Vs Non-Cong. *: p value for selected groups.

Considering the whole cohort, 72 patients did not have any clinical signs of congestion or elevated central venous pressures; in this subgroup, 12 had clear signs of subclinical congestion with an estimated RAP 13 mmHg, 22 had evidence of PH without clinical signs of elevated central venous pressure. The ROC area under the curve (AUC) of combining OED/HJR/JVD as a predictor of echographic overt congestion was 0.727 (p = 0.001) with a specificity of 77% (Kappa coefficient = 0,360); considering peripheral OED alone, specificity rise to 92% and sensitivity drops to 42% (p <

0,001) with an AUC of 0,669 (Kappa coefficient = 0,369). The specificity of JVD/HJR in identifying PH resulted in 86% with an AUC of 0,681 (Weighted Kappa coefficient = 0,332).

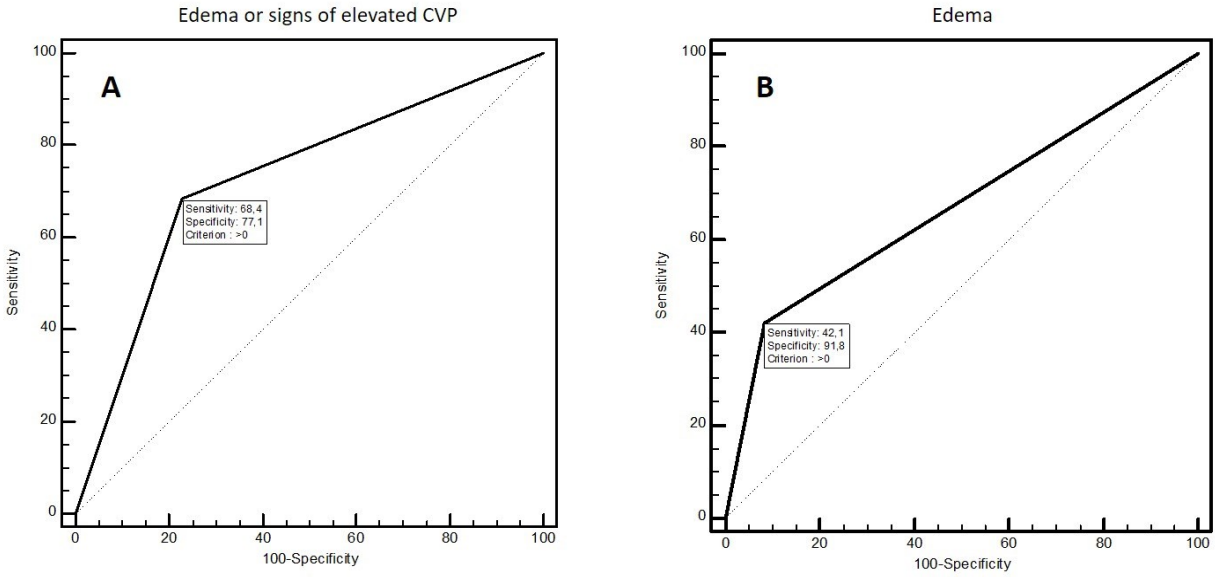


Figure 5: accuracy of PE expressed by ROC curves. A: signs of edema or elevated central venous pressure compared to the gold standard (echographic signs of congestion or pulmonary hypertension). B: clinical signs of edema compared to the gold standard (echographic signs of congestion). CVP: Central Venous Pressure.

The inter-rater agreement analysis showed a strong correlation between both right cambers size and coupling with echographic congestion. Right atrium size and TAPSE/PAPS resulted in the most significant correlation with IVC diameters and collapse ratio.

The main findings are summarized in the distribution graphs below (Figure 6).

Right ventricular-arterial coupling and right atrial dimensions showed a strong linear correlation with IVC diameters and collapsibility ($p < 0.001$); the end-systolic area of the right ventricle also showed a correlation with the degree of congestion, although less significant ($p < 0.05$).

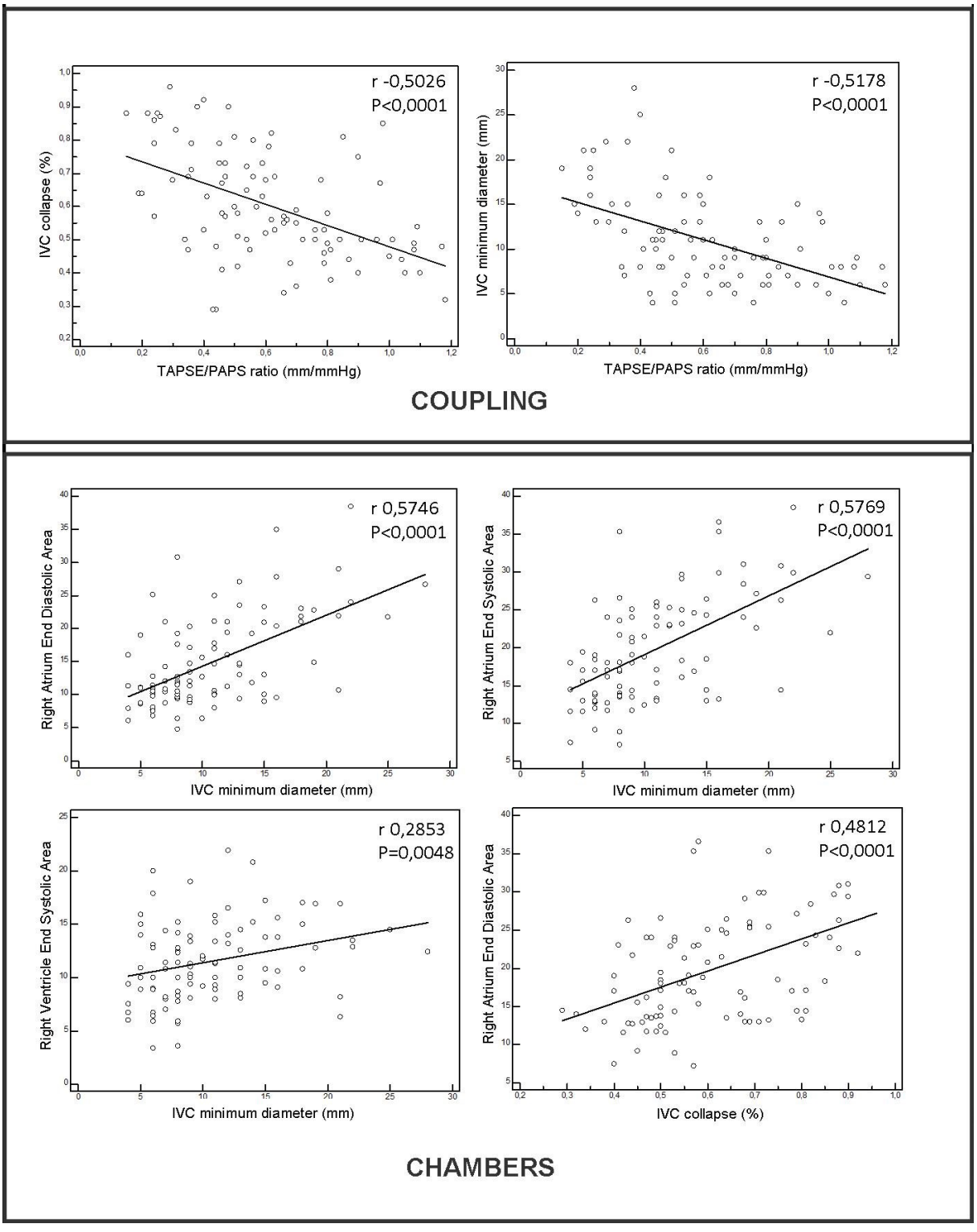


Figure 6: correlations between echographic signs of coupling and chambers volumes Vs. congestion. IVC: Inferior Vena Cava.

Outcome data

During a follow-up of 370 days (IQR 259-448), 17 events occurred: 3 deaths due to cardiovascular causes and 14 ED admissions/hospitalization for HF. Regarding PE, clinical signs of peripheral OED or elevated CVP significantly affect prognosis ($p < 0.01$). TAPSE/PAPS ratio resulted in a strong predictor of adverse events, with a significant decrease in event-free survival for pathological values < 0.57 ($p < 0.01$). The multiparametric RV evaluation early affected the primary endpoint, doubling the events in the RVD group ($p = 0,05$).

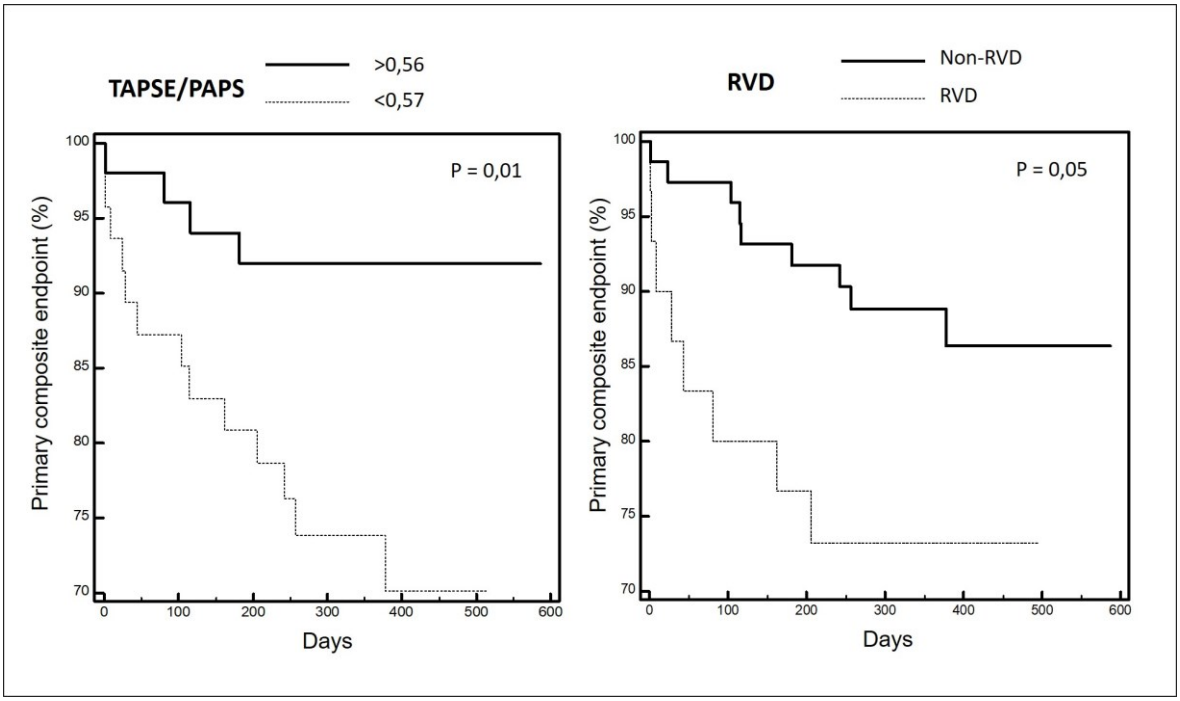
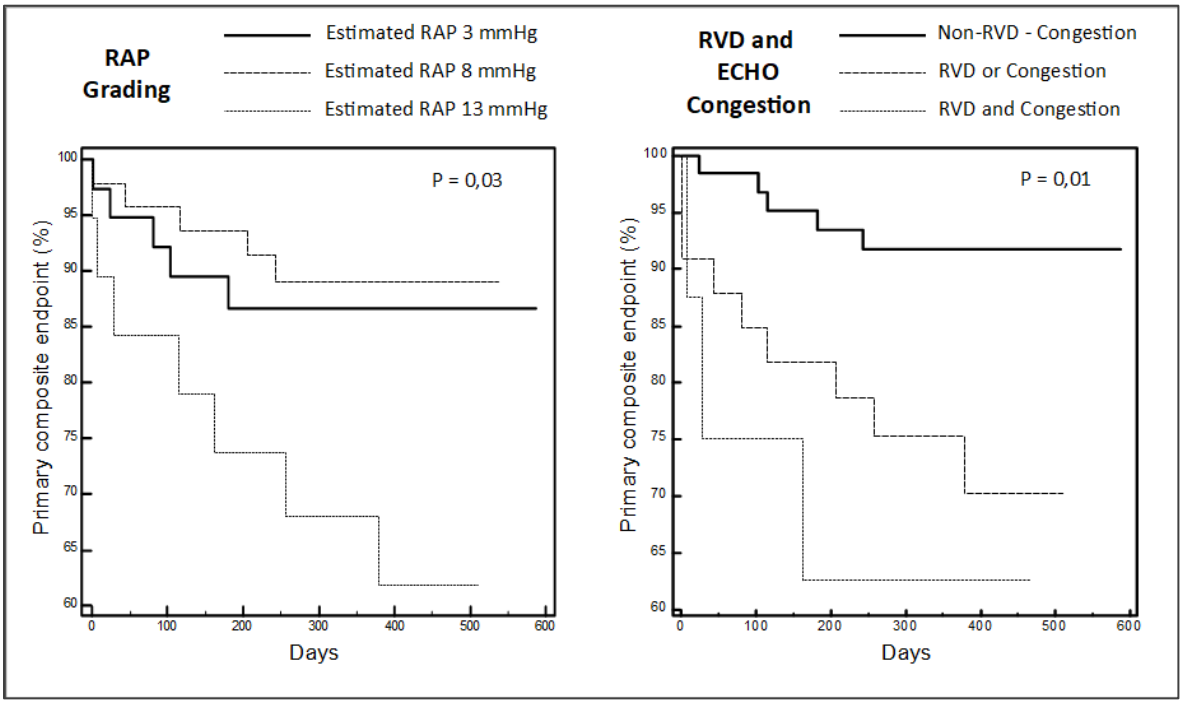


Figure 8: primary composite endpoint expressed by Kaplan-Meier curves. RVD: right ventricular dysfunction.

Instrumental congestion severely affects prognosis, with a 3-fold increase in events when an estimated RAP of 13 mmHg is individuated. Combining the multiparametric evaluation of RVD with echographic signs of congestion, 3 tertiles has been individuated: RVD and congestion significantly affect prognosis, which is even worse when both are present ($p < 0.05$). It is essential to underline

633 that in “RVD or Congestion” subgroup the prevalence of congested patients with normal right
634 ventricular function was 43%.



635

636 **Figure 9: primary composite endpoint expressed by Kaplan-Meier curves. RAP: right atrial pressure. RVD: right ventricular**
637 **dysfunction.**

638

639 Comparing the three main groups, according to the presence of overt congestion and SubC, tertiles
640 identify the increasing risk of events. Clinical congestion is associated with the worse event rate,
641 regardless of the presence of consistent signs of ultrasound congestion; SubC affects prognosis even
642 if signs of clinical congestion are missing at PE ($p < 0,05$). Estimated survival analysis is shown in the
643 figure below (Figure 10).

644

645

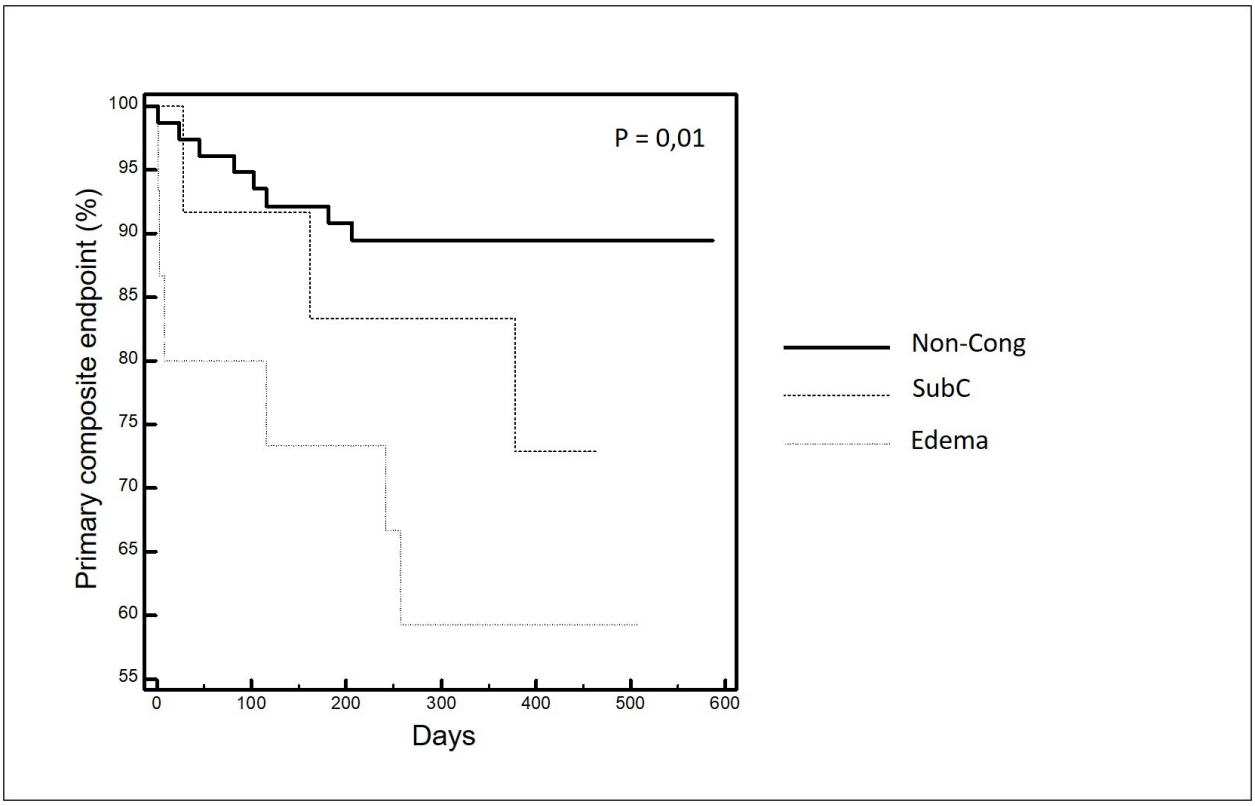
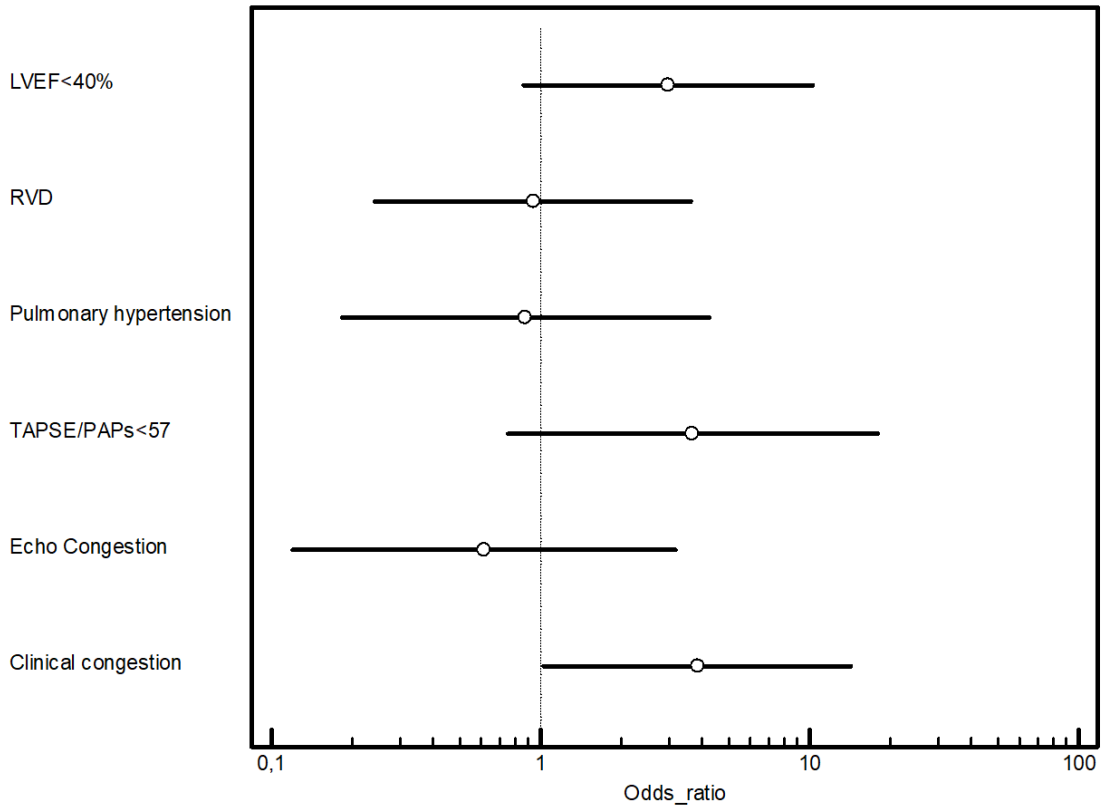


Figure 10: primary composite endpoint expressed by Kaplan-Meier curves in the three main groups: Non-Cong; SubC; Edema. RAP: right atrial pressure. SubC: Subclinical Congestion.

In the multivariate analysis comparing the main echographic variables (PH; RVD; TAPSE/PAPS ratio < 57; eRAP ≥ 8 mmHg) with PE, only clinical congestion resulted as an independent factor related to adverse outcome (OR 3.8; p <0.05). However, due to the close relationship between clinical congestion and eRAP, PE loses significance when we consider patients with eRAP 13 mmHg (OR 2.8, p = ns).



660

661 **Figure 11: multivariate analysis of the main ultrasound parameters compared with clinical congestion (OED / HJR / JVD).**
662 **Echo Congestion is defined as eRAP values> 5 mmHg.**

663

Discussion

Our study evaluated an outpatient HF population to analyze the relationship between RVD and congestion, the accuracy of PE and the prognostic impact of clinical and ultrasound variables commonly used to assess congestion in an outpatient setting. The main population characteristics were substantially comparable with previous HF registries[54,55] except for slightly higher mean age and a lower percentage of HFrEF and diabetic patients; among HFrEF patients, 20% were prescribed ARNI, consistent with data from international registries that enrolled patients in the same period[56]. Some population differences emerged when analyzing the three groups regarding mean age, etiology, and history of atrial fibrillation. It is noteworthy that both groups with instrumental or clinical congestion ("SubC" and "Edema") both have a higher prevalence of atrial fibrillation. This result supports the hypothesis of more advanced disease, with a major myocardial structural subversion. Consequently, as already suggested by other authors[46], arrhythmia represents a negative and dynamic prognostic factor, especially when RVD is co-present; consistently it is associated with congestion and worse outcome, regardless of LVEF. Regarding age, patients in the edema group had a significantly higher average age, possibly associated with a worse prognosis and a long history of the disease; however, it should be noted that patients in the "SubC" group did not show significant demographic differences compared with the "Non-Cong" group, making the outcomes comparable and reinforcing the theory of a prognostic role of SubC, as already highlighted in several previous studies[21,57]. Furthermore, congestion being the major cause of symptoms in the patient with HF results in a gradual NYHA class increase in the three groups analyzed.

PE is the cornerstone of outpatient evaluation, however it often lacks in accuracy compared with other instrumental evaluation[21], potentially leading to under/overtreatment, especially regarding

diuretic strategy[16,58]. The benefit of an integrated approach combining natriuretic peptides[59], easily reproducible echographic signs[20,22,57] and implantable device monitoring[13] is still a matter of debate[24].

Several studies described subclinical congestion in outpatients setting: B-lines[20,22], JVD ratio, IVC collapsibility and diameter[21,57] have demonstrated to be affordable and reproducible measures, predicting adverse outcome in chronic HF population, especially when congestion signs are not overt.

The prevalence of pathological IVC diameter and collapsibility in our population was 47%, similarly to other recent evidences[21], underlining the lack of accuracy of PE in clinical practice and the clinical need of affordable and relevant instrumental signs of congestion in acute and chronic setting[60,61]. Our study confirms the low accuracy of peripheral edema and PE in general in identifying congestion. However, half of our "SubC" patient cohort showed signs of elevated CVP without showing peripheral edema. Therefore, JVD and HJR represent clinical signs with good specificity and, when they are detectable, they must suggest the clinician to investigate signs of subclinical congestion with instrumental methods. Analyzing the morpho-functional parameters of the right ventricle, right atrial dilation is closely associated with congestion, both clinical and instrumental. Pulmonary hypertension, RVD, V-A decoupling represent the triggering and maintenance factors of the right chamber dilation and are to be considered an indirect ultrasound sign of elevated pulmonary pressure and RAP measured invasively, as already noted in previous studies[46,62]. This dynamic condition is associated with further worsening of right ventricular function regardless of LVEF, triggering a vicious circle of "chamber dilation - increased filling pressures - tricuspid insufficiency - arrhythmias" which fully supports the mechanical model transposed by MacIver et al for the left heart[47]. In this context, when comparing non-congested patients with the "SubC" and "Edema" cohorts, we should note that right ventricular function parameters in the three groups analyzed show a significant difference. It is even more important to note that the V-A coupling and RVD parameters are substantially identical in the congested groups, with overlapping values in the "SubC" and

"Edema" groups. These data support the thesis that when subclinical congestion is present this is associated with RVD and V-A decoupling even in the absence of over-fluid clinical signs. The correlation analyzes between the ultrasound signs of congestion and the morpho-functional characteristics of the right heart/pulmonary unit confirm the close relationship between fluid overload and V-A decoupling, showing an almost linear relationship between cavity dimensions, TAPSE/PAPS ratio and the IVC diameters.

Regarding prognosis, several literature data define RVD as a strong predictor of outcome in HF population, irrespective of LVEF[45,63]. Ghio et al. observed that the prognosis of RVD patients without PH was considerably better than that of patients with RVD and PH, assuming that PH and V-A coupling were the main determinants of the prognosis[45]. In this study, TAPSE/PAPS ratio confirms to be a strong predictor of outcome due to its comprehensive evaluation of the right heart/pulmonary unit (OR 4.5 when < 0.57 mm/mmHg; $p = 0.01$) rather than right ventricular function alone, very close to significance in the Kaplan-Meier analysis (OR 2.4 when at least 2 pathologic criteria among TAPSE, FAC, s' are present; $p = 0.05$). When instrumental signs of overt congestion are detectable, the prognosis is dramatically affected. By combining data from right ventricular function and instrumental congestion, when RVD or elevated RAP are detected, we can identify a subset of patients with poor prognosis, irrespective of PE. When both RVD and elevated RAP are present, the long-term prognosis significantly drops to 35% of adverse events at one year follow up (OR 4.3, $p < 0.05$) similarly to the lower TAPSE/PAPS tertiles groups, according to the previous studies[64]. Due to the close interdependence of V-A coupling and congestion, in the multivariate analysis the presence of edema or elevated CVP was the only significant parameter (OR 3.8; $p < 0.05$), confirming the PE sensibility in identifying patients at very high risk of events. Finally, in agreement with previous observations, the presence of subclinical congestion allows us to identify a group of patients at higher risk of events, even in the absence of clinical signs of congestion ($p = 0.01$); this group is identifiable

735 only by instrumental examination, presenting very similar ultrasound characteristics to patients with
736 clinical overt signs of congestion. Due to the poor prognosis of the “SubC” cohort, it is mandatory to
737 implement SubC detection methods in the HF outpatient population.

Conclusion

Despite the fact that congestion represents an important therapeutic target and prognostic factor in HF outpatients, PE has a low sensitivity for identifying congestion, resulting in a significant proportion of subclinical congested patients. Subclinical congestion is a negative prognostic factor, strongly correlated with the right heart structure and ventricular/arterial coupling, amplifying RVD negative outcomes. When congestion coexists with RVD, it dramatically impacts prognosis, even if it is subclinical. An integrated, focused ultrasound approach provides accurate prognostic information and could allow physicians to empower the clinical patient risk assessment, potentially guiding future therapeutic approaches, according to patients' characteristics. Further analyses are necessary to evaluate whether tailored therapy in subclinical congested patients could have a favorable impact on prognosis in an outpatient setting.

Limits

The main limitations of the study are its small sample size, the lack of external validation of the data acquired in the ultrasound laboratory, the lack of a control group without HF and the absence of the invasive validation of ultrasound measurements. Furthermore, the presence of pulmonary congestion has not been systematically evaluated by ultrasound examination.

The sample size was mainly limited by the requirement to enroll patients who had an adequate observation period with a deadline of February 2020, when the Covid-19 pandemic started, as this would have interfered with the primary endpoints. The sample size calculation obtained before starting enrollment estimated the range of patients to be enrolled between 81 and 120; therefore, the 104 enrollments made it possible to obtain a statistically significant result for almost all the data analyzed. The analysis of the literature has shown that the correlation between ultrasound, clinical and hemodynamic data is already well established; for this reason it was not considered necessary to acquire the data of control patients nor to carry out invasive measurements. Moreover, clinical congestion revealed by the PE has not been graded as it has been in recent studies, although it has been identified dichotomously, which could affect the accuracy and the odds ratio analyzes. However, this study aimed to analyze the correlation between instrumental congestion and RVD, both graded in tertiles according to previous studies, which has not been influenced by PE grading. Finally, systematic data on tricuspid regurgitation severity and liver function were insufficient and were therefore omitted from the analysis.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board (Comitato etico dell'Insubria, protocol code 241/2019; report n. 71, date of approval 15 December 2020).

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