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Thoracic fluid content: a new marker of congestion with prognostic value in acute heart failure

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Investigação realizada no Serviço de Medicina Interna do Hospital de S. João e Serviço de Higiene e Epidemiologia da Faculdade de Medicina da Universidade do Porto, sob orientação da Prof. Doutora Ana Azevedo e co-orientação do Prof. Doutor Paulo Bettencourt.

A abrigo do Artigo 8º do Decreto-Lei nº 388/70 esta dissertação teve como base um manuscrito, em que colaborei activamente na recolha, armazenamento e análise da informação, tendo sido responsável pela análise dos dados que reporta, bem como pela versão inicial do manuscrito.

I. Thoracic fluid content assessed by impedance cardiography predicts medium-term prognosis in acute heart failure patients

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Contents

1. Introduction

Definitions

Heart failure is a syndrome composed of many symptoms and clinical signs of fluid overload and/or low cardiac output. Establishing a definitive diagnosis requires confirmation of an abnormality of the structure or function of the heart at rest, if possible using echocardiography.[1]

Heart failure can be classified in heart failure with left ventricular systolic dysfunction and with preserved left ventricular systolic function or diastolic heart failure. These definitions have implications on diagnosis, therapeutic interventions and prognosis[1]. This syndrome can also be classified according to the severity and duration of signs and symptoms in acute and chronic heart failure. Acute heart failure can be theoretically subdivided into new-onset or gradually or rapidly worsening of heart failure symptoms and signs that require urgent therapy.[2]

Prevalence and incidence of heart failure

Heart failure is a major cause of morbidity and mortality in developed countries and one of the most costly conditions to health care systems.[3-5] In developing countries, an epidemiological transition is taking place, whereby the increase in wealth is associated with western lifestyle and the acquisition of risk factors for cardiovascular diseases, which are becoming an important cause of morbidity and mortality.[6-9]

Over the last decades, several population-based studies were conducted that contributed to knowledge on the prevalence, incidence and risk factors for heart failure. The earliest studies defined heart failure based on clinical criteria. The Framingham Heart Study set up a new definition of this syndrome using a clinical score of signs and symptoms of fluid overload. Heart failure was found to be more common in older persons and affected approximately 2.5% of the population aged over 45 years.[10] Similar results were reported by the National Health and Nutritional Examination Survey, with a prevalence of 1.1% in the adult population, using self-report, and 2%, using clinical criteria.[11] More recent population-based studies included echocardiographic evidence of cardiac dysfunction in the definition of heart failure according to the European Society of Cardiology.[1] In the Glasgow MONICA project the prevalence of left ventricular systolic dysfunction was 2.9% (symptomatic in 1.5% and asymptomatic in the others 1.4%).[12] In the cohort of Olmsted County the prevalence of a diagnosis of heart failure in the participants' medical record was 2.6%, among which 2.2% fulfilled the Framingham criteria.[13] Even more recently the American College of Cardiology guidelines for the diagnosis of heart failure proposed a new concept of heart failure stages to reflect the whole spectrum from a healthy heart to overt heart failure.[14] In a population-based study reporting the prevalence of heart failure stages in a population aged ≥ 45 years resident in Porto, Portugal, the prevalence of stage A (high risk for heart failure) was 54%, stage B (asymptomatic cardiac structural or functional abnormalities) 21.6% and stage C (heart failure symptoms plus objective evidence of cardiac structural or functional abnormalities) 5.1%.[15] In the cohort of Olmsted County, aged ≥ 45 years, the prevalence of stages A, B, C and D were 22%, 34%, 12% and 0.2%, respectively. [16]

Other studies were described in different settings, namely in primary care centers. In west midland England the prevalence of heart failure was 3.9%, including heart failure from all causes and symptomless systolic dysfunction.[17] In Portugal, the

EPICA Study reported an estimated prevalence of all heart failure types of 4.36% in patients over 25 years old attending primary care.[18]

The multiple studies that included echocardiography and clinical assessment brought valuable information regarding the best estimate of heart failure prevalence, including symptomless and symptomatic systolic dysfunction, which were underestimated in previous studies. Differences between studies can be mostly attributed to diverse methodologies rather than to differences in populations.

Despite a decline of coronary heart disease incidence and mortality, the prevalence of heart failure is increasing because myocardial infarction survival is improving and heart failure therapies that modify prognosis extends patients' life.[19]

The incidence of heart failure is also increasing. However, there is much less information about incidence than prevalence of heart failure. Data from large population-based studies report incidence rates ranging from 1.0 to 5.0 cases per 1000 population per year, increasing with age.[3] The main recent studies for incidence estimation were the Hillingdon and the Rotterdam Studies, both population-based. The Hillingdon study reported a crude incidence of 1.3 cases per 1000 population per year, increasing with age (0.02 cases per 1000 population per year in those aged 25-24 to 11.6 in those aged over 85 years).[20] The Rotterdam study also reported an increasing incidence with age: 2.5 per 1000 population per year for those aged 55-64 years to 44 per 1000 population per year over 85 years.[21] In both studies the incidence was higher in men than in women. Based on over 40 years of follow up of the Framingham study cohort, the life-time risk of heart failure, the cumulative risk of developing heart failure during the remaining lifetime, is around 20% at 40 years of age.[22]

Prognosis of heart failure

Heart failure is a lethal condition. The majority of patients with heart failure die from cardiovascular causes,[23] but the exact cause of death is often difficult to determine. Sudden death is reported as a major cause of death in some studies. In the ATLAS study, including 3164 heart failure patients randomized to high versus low-dose lisinopril, New York Heart Association functional class II to IV, 44% died and, of these, 43% due to sudden death.[23] In the Rotterdam Study a total of 131 participants (2.5%) died from cardiovascular causes, during the follow-up period, among whom 43.7% of sudden death. The incidence rate of sudden death among heart failure participants was 24.9 per 1000 person-years and the risk increased fivefold after diagnosis of heart failure.[24] Information is lacking concerning risk factors for sudden death. Some studies indicate that younger patients die predominantly due to arrhythmias and the older ones mainly due to ventricular dysfunction[25].

The Framingham Study and the National Health and Nutritional Examination Survey were the core population-based studies reporting mortality. The former study reported 1- and 5-year survival rates of 57% and 35% for men and 68% and 38% for women, respectively.[10] In the latter, the 15-year risk of death was 39.1% in women and 71.8% in men, for ages higher than 55 years old.[11] In both population-based studies mortality was higher in men than in women even when age-adjusted. Recently, the Rotterdam study reported a 5-year cumulative survival of 35% in patients with first heart failure diagnosis, higher than the survival rate reported in Framingham.[21] In the Echocardiographic Heart of England Screening Study (ECHOES), a primary care practice population was followed and 53% of heart failure patients with left ventricular

systolic dysfunction were alive five years after the diagnosis. Patients with heart failure without left ventricular systolic dysfunction, patients with asymptomatic left ventricular systolic dysfunction and the general population had 5-year survival rates of 62%, 69% and 93%, respectively.[26] There is considerable difference in mortality in older and more recent studies, with the latter reporting better prognosis. This can be related to the definition of heart failure and to the widespread use of therapies that modify prognosis. Earlier studies were based on clinical criteria alone and therefore only symptomatic patients were considered to have heart failure. On the other hand, angiotensin-converting enzyme inhibitors and beta blockers were only in use in more recent studies, after evidence on their effectiveness was available.

Additional information about prognosis comes from hospital-based registries. The EuroHeart Failure Survey program reported a high risk of death and readmission, 13.5% and 24%, respectively, 12 weeks after discharge from an episode of acute heat failure.[27] More recently, an American registry, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure, reported rates of death and readmission of 9.6% and 29%, respectively, within the same follow-up period, after an episode of acute heart failure.[28] Some hospital-based studies have presented data on in-hospital mortality, which was similar in ADHERE[29] and in OPTIMIZE-HF[28] (4% and 3.4%, respectively).

Predicting prognosis is an everyday challenge for a physician. Numerous studies have used different populations, diverse statistical methods for risk estimation and variable outcomes and follow-up periods, limiting their comparability.[30] Many prognostic models were elaborated to estimate individual risk of death.[31, 32]

The New York Heart Association functional classification was evaluated in several studies as a predictor of prognosis. [33, 34] Dyspnea is a subjective experience of breathing discomfort and is the most common presenting symptom in patients with heart failure. However, it is not specific of this syndrome but is present in other

conditions as obesity, lung disease, myocardial ischemia and poor physical condition.[35] In heart failure dyspnea reflects pulmonary congestion and increased left ventricular filling pressure, but there is no standardization of dyspnea measurement.[36] In a recent trial, treatment success in dyspnea relief was associated with better outcomes, shorter in-hospital stay and lower 60-day mortality.[37]

Age is a non-modifiable and not preventable prognostic factor in cardiovascular disease and particularly in heart failure. Population and hospital-based studies have reported increasing age to be associated with higher mortality in patients with heart failure.[10, 11, 38-40]

Women with heart failure are older, and more frequently diabetic, hypertensive and with preserved left ventricular systolic function than their male counterparts. Fewer have coronary heart disease.[41] However, there are conflicting results concerning prognosis. Some studies reported better outcomes in women[42], which can be explained by the difference in risk factors such as hypertension and coronary heart disease, and left ventricular systolic function in both genders. At the same chronological age women's bodies are biologically younger than men's and more able to cope with poor pump function.[43] Other studies failed to report any difference in prognosis between genders.[44]

Hypertension carries a huge burden worldwide and is a risk factor for both systolic and diastolic heart failure. Once heart failure develops, low systolic blood pressure becomes an adverse prognostic marker reflecting the loss of myocardial reserve or the ability to maintain blood pressure and the limited use of drugs that modify prognosis.[29, 43, 45, 46] Hypercholesterolemia and obesity are other examples of the reverse epidemiology in heart failure. Despite their role as etiologic factors for cardiovascular disease, and therefore to heart failure, once the diagnosis of heart failure is established these factors became associated with better prognosis. A

complex syndrome of malnutrition, with cachexia and low cholesterol levels, and inflammation worsens the survival of heart failure patients.[47, 48]

Besides blood pressure, other relevant signs in the physical examination of a heart failure patient are jugular venous distension and S3 gallop, as measures of right and left side filling pressures. Both signs are important prognostic predictors of progression of heart failure.[49]

Comorbidities are very common in heart failure patients, both in the acute and chronic setting. Coronary heart disease,[50] anemia,[50, 51] renal dysfunction,[52-54] obstructive sleep apnea,[55] chronic pulmonary disease,[39, 40, 56] diabetes mellitus[24, 42, 50] and depression[57] coexist with heart failure and unfavorably affect prognosis. The association between progressive renal dysfunction and cardiac failure has been termed cardiorenal syndrome. The definition of this entity is still controversial and several parameters of renal function have been explored as possible markers of this syndrome.[58] The levels of blood urea,[39, 54, 59] creatinine[54, 60] and cystatin C[61] and worsening renal function,[59, 62] estimated using different equations, were reported as strong predictors of adverse outcomes.

Other biomarkers were extensively studied as potential prognostic markers in heart failure. These biomarkers are representative of several mechanisms involved in the pathophysiology of heart failure: hyponatremia[40, 50] (representing electrolyte disturbances), elevated troponin I level[63, 64] (representing myocardial death), increased C-reactive protein[65] (as a marker of inflammatory activation), and natriuretic peptides levels[66-68] (markers of volume congestion and rennin-angiotensin-aldosterone and sympathetic nervous systems activation). Natriuretic peptides are hormones synthesized in heart chambers in the setting of volume expansion and pressure overload and have many biological actions, promoting vasodilation, diuresis and natriuresis, counterbalancing the effects of the rennin-angiotensin-aldosterone and sympathetic nervous systems.[69, 70] Numerous studies have shown that natriuretic

peptides levels in acute[66, 71, 72] and chronic heart failure[73-75] patients are predictive of future outcomes. At least as important as the prognostic value of elevated natriuretic peptide levels at admission and discharge is the reduction of over 30% during hospitalization.[66-68]

Left ventricular systolic dysfunction is associated with poor prognosis in most studies[76-78]. However, there are conflicting results concerning prognosis in heart failure with preserved systolic function. Some studies reported that prognosis of patients with preserved systolic function is better,[28] equal[79, 80] or worse[81] than in patients with left ventricular systolic dysfunction. There are some issues regarding this diagnosis. In the presence of normal systolic function we may possibly be overestimating heart failure diagnosis by misclassifying patients with obesity, low exercise tolerance and with other non-cardiac causes of dyspnea. This misclassification likely contributes to the apparently contradictory results on the prognosis of heart failure with preserved left ventricular systolic function.

Acute heart failure syndromes and hemodynamic monitoring

Acute heart failure, including chronic decompensated and new-onset heart failure, is responsible for a huge number of hospital admissions all over the world. In the main registries, the proportion with chronic decompensated heart failure among all acute heart failure cases ranges from 56%[27] to 75%.[29]

Congestion is the dominant feature in acute heart failure syndromes.[28, 29] Volume overload is one of the most complex pathologic processes confronting physicians in the daily management of acute heart failure patients. Increased filling pressures, reduced cardiac output, excessive peripheral vasoconstriction and impaired

natriuresis and diuresis are the hallmarks of acute heart failure. Arterial underfilling, consequent to low cardiac output, is sensed in arterial baroreceptors leading to increased adrenergic discharge from the central nervous system and activation of the rennin-angiotensin-aldosterone system, which stimulate sodium and water resorption and consequently increase preload. Simultaneously, arginine vasopressin is released. The activation of V2 receptors in the collecting ducts promotes antidiuresis. Activation of V1a receptors causes increased protein synthesis in cardiac myocytes, coronary constriction, systemic arteriolar constriction and venoconstriction leading to myocardial dysfunction. The production and release of natriuretic peptides work as a counter-regulatory mechanism by promoting smooth muscle relaxation, natriuresis and diuresis. However, these beneficial effects are quickly overwhelmed by the continued neurohormonal activation causing renal resistance to natriuretic peptides.[82]

Hemodynamic congestion, that is, elevated filling pressures, precedes clinical congestion. Clinical signs and symptoms of fluid overload occur mostly in the form of pulmonary congestion, which is caused by fluid redistribution, rather than fluid accumulation. This redistribution is caused by vascular mechanisms (constriction of venous and arterial beds), and neurohormonal activation, described above. [83]

At first sight, the most obvious approach to deal with congestion is to remove volume. There are several therapeutic options to achieve this aim. Diuretics are the most commonly employed drugs. They cause relief of symptoms and signs of pulmonary and systemic congestion.[1] Large randomized clinical trials on diuretic therapy are lacking. Evidence from the few studies on the benefit of diuretics is contradictory. In one randomized controlled trial, including 110 patients presenting to the emergency unit with pulmonary edema, the efficacy and safety of nitrates and furosemide were compared. The endpoints evaluated were death, need for mechanical ventilation and myocardial infarction. High-dose nitrate after a low dose of furosemide

was safe and more effective than high-dose diuretic with low-dose nitrate.[84]. Another study included 48 male patients with acute heart failure secondary to myocardial infarction admitted to a coronary care unit and monitored with pulmonary catheter. Furosemide, compared with the use of a venodilator, an arteriolar dilator and a positive inotropic agent, was associated with a reduction in filling pressures without affecting cardiac output.[85] Data from other studies suggest increased mortality with both acute and chronic diuretic therapy.[86, 87] Advanced heart failure patients had frequently to be managed with high-dose diuretics due to diuretic resistance. These patients had severe symptoms, hypotension and renal dysfunction and, as a result, low glomerular perfusion. The poor prognosis associated with diuretic use could be due to patients' characteristics, with more advanced heart failure, and also to diuretic adverse effects, additional neurohormonal activation, electrolyte depletion and worsening renal function.[88] The combination of different diuretic classes might offer advantages, concerning both efficacy and safety, but it has not been tested.[89]

Another therapeutic option to remove fluid overload is to antagonize the arginine vasopressin V2 receptor. This blockage causes a rapid and profound water diuresis, with little or no electrolyte depletion. Tolvaptan is a selective V2 antagonist available in the United States for euvolemic and hypervolemic heart failure patients with hyponatremia.[89] The Everest trial, a large randomized controlled trial, tested the hypothesis that tolvaptan added to conventional therapy would affect the outcomes by producing significant fluid removal. The patients in the tolvaptan arm had significant weight loss, maintained normal sodium levels, but had modest improvement of symptoms and no effect on mortality or readmission due to heart failure.[90, 91]

Ultrafiltration is an alternative method of sodium ant water removal that safely improves hemodynamics in patients with heart failure[92]. Ultrafiltration bypasses the kidney and there is no neurohumoral stimulation or electrolyte deplection.[89] Indeed, the

application of this technique is limited due to the need for a central venous line.[92] The UNLOAD trial compared ultrafiltration with intravenous diuretic therapy in acute heart failure patients and showed that ultrafiltration was a safe procedure that produced significant fluid loss, with a reduction in hospitalization days and in the risk of readmission due to acute heart failure. However the dyspnea relief, quality of life, functional status and biomarkers were not significantly different between the two arms.[93] Further studies would be valuable to explore the benefits of this technique.

As we have seen so far, fluid accumulation does not play a pivotal role in acute heart failure, but pulmonary congestion and the mechanisms that cause redistribution of fluid are critical. To control congestion we need therapies that act on neurohumoral mechanisms beyond the direct removal of fluid.[89]

Assessment of fluid status is critical to initially establish the patient's profile in risk stratification and to monitor the efficacy of therapeutic interventions.

Symptoms are the main therapeutic target in acute heart failure. Their rapid resolution, which does not faithfully reflect the reduction in volume overload, limits their usefulness to guide therapy. Dyspnea, orthopnea and paroxysmal nocturnal dyspnea are indicative of elevated left-side filling pressure, but orthopnea is the most sensitive.[94, 95] Other symptoms as abdominal discomfort, early satiety, nausea and vomiting reflect right-side elevated filling pressure.

Signs of congestion in physical examination are also important in guiding diagnosis and monitoring initial therapy, but alone they do not allow an accurate hemodynamic classification. Jugular venous pressure remains the most reliable test for evaluation of elevated filling pressure, but still misclassified a large proportion of patients.[95-97] Positive hepatojugular reflux showed good correlation with pulmonary capillary wedge pressure in chronic heart failure patients.[96] Pulmonary rales may be

indicative of fluid overload but had poor negative predictive value.[98] Peripheral edema is specific but not sensitive to detect elevated filling pressure.[94] Some patients without signs of congestion had elevated filling pressures.[94] The combination of history and physical examination findings could enhance their sensitivity and specificity in the determination of cardiac hemodynamics. Forrester et al have demonstrated that four clinical profiles, defined by clinical examination, could be able to identify four hemodynamic profiles, determined using right-side heart catheterization, among patients with acute myocardial infarction. These profiles were predictive of prognosis[99]. Similarly, Stevenson et al applied these clinical profiles to heart failure patients. Congestion was assessed by the presence of orthopnea, jugular venous distension, pulmonary rales, hepatojugular reflux, ascites, peripheral edema, leftward radiation of the pulmonic heart sound or a square-wave blood pressure response to Valsalva maneuver. Compromised perfusion was assessed by the presence of a narrow proportional pulse pressure, pulse *alternans*, symptomatic hypotension, cool extremities and/or impaired mentation. These clinical profiles reflected invasive monitoring measurements and predicted outcomes.[100]

In summary, congestion can be clinically silent in heart failure patients and its assessment could be a challenge. Therefore, patients are frequently discharged with some degree of increased filling pressures leading to early readmissions.[101]

Acute heart failure syndromes are medical emergencies and hemodynamic monitoring is crucial in this setting, mainly for patients whose symptoms and physical signs are discordant, who are not responding as expected to conventional therapies or who are hemodynamically unstable. The gold standard for hemodynamic monitoring is right-sided heart catheterization using a pulmonary artery catheter.[1] The clinical value and safety of this procedure has been the subject of considerable debate. The most

relevant studies, PAC-Man and ESCAPE trial, reported no survival benefits and a slight increase in the incidence of procedure-related events.[102, 103]

A non-invasive method of hemodynamic monitoring would be useful. Chest x-ray remains the most widely used screening test for the detection of pulmonary edema and to evaluate other cardiac and non-cardiac conditions.[1] Echocardiography provides reliable information regarding heart failure etiology, systolic and diastolic function and also provides useful information about cardiac chamber dimensions. Ultrasound provides information on hemodynamic and pulmonary congestion by cardiac and chest sonography. However, it requires an adequate acoustic window and demands expertise and it cannot provide continuous monitoring.[1, 83]

Impedance cardiography has emerged as a non-invasive method of hemodynamic monitoring. This technique uses four external electrodes, two applied in opposite sides at the base of the neck and the other two at the level of xyphoid process in the midaxillary line (Figure 1).

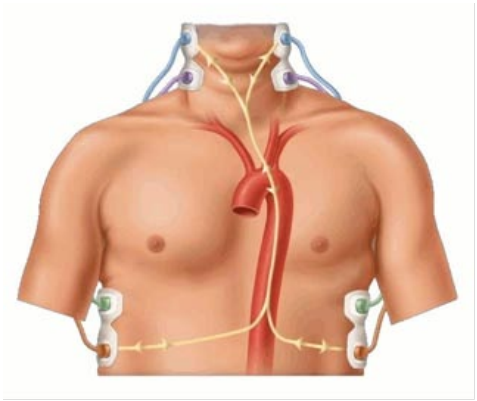

Figure 1: Impedance cardiography electrode placement. Reprinted with permission of Medizinische Messtechnik GmbH, Ilmenau, Germany.

A high-frequency (60-100 kHz) and low amplitude (1 mA) current is applied to measure electric resistance changes in the thorax. The impedance changes are generated by variations in blood volume and flow velocity in the ascending aorta during the cardiac cycle, and are detectable as alterations in conductivity. Baseline thoracic impedance (Zo), pulsatile impedance/time changes (dZ/dt) and electrocardiogram (ECG) are used to calculate stroke volume, cardiac output and contractility parameters. The monitor software uses the Smarek-Bernstein equation to calculate stroke volume (Figure 2). Cardiac output is calculated using stroke volume and heart rate.[104-106]

$$SV = (0.17ht)^3/4.2 * LVET * (dZ/dt)_{max}Z_0)$$

Figure 2. The Smarek-Bernstein equation. SV - stroke volume; ht - height; LVET – left ventricular ejection time, dZ/dt – the maximum absolute rate of change in the impedance signal for a given beat (ohms per second); Z0 – baseline impedance.

Figure 3 shows the relation of impedance signals with systole and diastole. Several positive and negative wave forms are identified including the B wave, representing the opening of the aortic valve, the X and Y waves that coincide with aortic and pulmonic valve closure, respectively. The C wave occurs after ventricular depolarization and represents the maximal acceleration (dZ/dt) of blood in the aorta. The O wave corresponds to a small positive deflection and corresponds to an early diastolic event linked to diastolic blood flow in the central veins. The A wave is associated with atrial systole and coincides with P wave on ECG.[104]

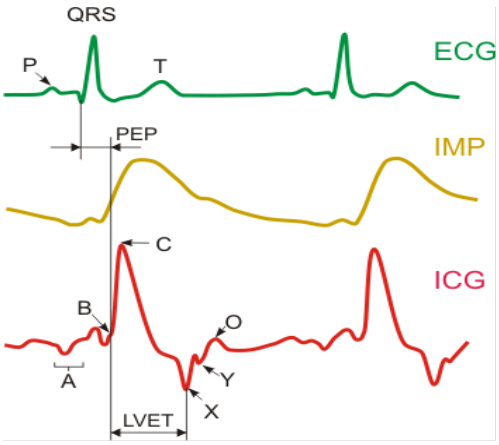

Figure 3: Typical impedance wave (yellow) and the first derivation (red) with typical curve points. A-wave- contraction of atrium; B- opening of aortic valve; C- maximum systolic flow; X- closing aortic valve; Y- closing of pulmonary valve; O-opening of mitral valve; PEP- pre-ejection period; LVET- left ventricular ejection time. Reprinted with permission of Medizinische Messtechnik GmbH, Ilmenau, Germany.

Impedance cardiography allows continuous acquisition of several parameters: cardiac output, stroke volume, systemic vascular resistance, thoracic fluid content, pre-ejection period, ventricular ejection time, systolic time ratio, acceleration index, velocity index and left cardiac work index. The impedance cardiography measurements demonstrated both intra- and inter-day reproducibility in stable coronary heart disease patients and in stable heart failure patients treated in an outpatient clinic.[107, 108]

However, this technique has several limitations. It cannot be applied to patients using respiratory controlled pacemakers if the pacemaker also uses impedance technique to detect respiration. The accuracy of impedance cardiography measurements is reduced in severe or moderate aortic valve disease, prosthetic valves, deviation from standard body *habitus (*height <120 cm and >230 cm, weight <30 Kg and >155 Kg), bradycardia (heart rate <40 beats per minute) and tachycardia (heart rate>250 beats per minute) and recent cardiac or pulmonary surgery.[104, 106]

Several studies have assessed the accuracy of impedance cardiography to estimate hemodynamic parameters. Most comparisons between impedance

cardiography and the gold standard, right-sided heart catheterization, were performed for cardiac output or cardiac index determinations. Impedance cardiography was validated against both the Fick and thermodilution methods in different settings. Cardiac output measurements were significantly correlated between impedance cardiography and thermodilution method in critically ill patients[109] and in acute heart failure, with correlation coefficient ranging from 0.64 to 0.89.[110, 111]

Thoracic fluid content, the inverse of Zo, is a unique parameter of thoracic fluid status measured by impedance cardiography. This marker of reduced impedance reflects interstitial, intravascular and intra-alveolar fluid within the thorax. There are few studies, with small sample sizes, comparing thoracic fluid content with symptoms and clinical signs of congestion. One study, including 89 patients complaining of shortness of breath in the emergency department, showed higher thoracic fluid content levels in heart failure patients than in patients with other causes for dyspnea.[112] Impedance cardiography evaluation also changed the diagnosis in 13% of patients and the therapeutic options in 39% compared with clinical assessment alone.[112] Another study, including 131 emergency patients, showed that Zo, the inverse of thoracic fluid content, was lower in patients with signs of congestion in the chest x-ray.[113] Controversy surrounds the accuracy of thoracic fluid content to estimate elevated filling pressure, measured using right-sided heart catheterization. One study, including 29 patients admitted to an intensive care unit due to acute heart failure, reported a correlation of 0.39 ($p=0.02$) between thoracic fluid content and left ventricular diastolic pressure.[110] Drazner et al, in a study with 50 patients with advanced heart failure who had indication to right-sided heart catheterization, reported that thoracic fluid content was not correlated with pulmonary capillary wedge pressure ($r=0.05$, $p=0.71$).[111] Similar results were reported by Kamath et al in the BIG trial, including 82 patients hospitalized due to acute heart failure, with a correlation coefficient ranging from 0.18 to 0.52, on consecutive days.[114]

Limited information has been published concerning the prognostic value of thoracic fluid content. In a sample of patients followed in a heart failure clinic, after an episode of acute heart failure. Packer et al assessed the value of thoracic fluid content in the prediction of the risk of heart failure decompensation. Increased thoracic fluid content was found to be a powerful predictor of death or worsening heart failure symptoms.[115] Hemodynamic congestion was present before its clinical manifestations became apparent and impedance cardiography identified those high risk patients. An additional study, the multicenter BIG trial, assessed the predictive value of thoracic fluid content in patients hospitalized due to acute heart failure randomized to right-sided heart catheterization. This study included 170 patients, with severe left ventricular systolic dysfunction, who underwent impedance cardiography monitoring at admission and discharge. Eighty two patients were treated according to hemodynamic determinations assessed by right-sided heart catheterization and the other 88 were treated based on clinical findings. Thoracic fluid content, both at admission and at discharge, failed to predict 6-month death or readmission.[114] The differences in treatment decisions could confound the association between impedance variables and prognosis. Additional studies are needed to evaluate the predictive value of this method of hemodynamic monitoring.

Impedance cardiography is a non-invasive method of hemodynamic monitoring that allows continuous assessment of many hemodynamic parameters. It is reliable, safe and reproducible and can be used across the whole spectrum of heart failure severity, both in hospitalized and in outpatients. We hypothesize that it may be useful in the evaluation of congestion adding valuable information to other clinical and laboratorial variables.

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2. Aims

The specific aims of this study were:

1. To evaluate the independent prognostic value of thoracic fluid content, as a marker of volume overload status, in predicting 3-month all-cause death or readmission due to cardiovascular cause, after an episode of acute heart failure.

2. To assess the association between thoracic fluid content and physical examination signs of congestion as well as BNP, as an argument for its added value in classification of volume overload status.

3. Paper

Thoracic fluid content assessed by impedance cardiography predicts medium-term prognosis in acute heart failure patients

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ABSTRACT

Aims The purpose of the present study was to determine the prognostic value of thoracic fluid content, assessed by impedance cardiography, to predict 3-month all-cause death or readmission for a cardiovascular cause, after an episode of acute heart failure.

Methods and results We included 212 patients (median age 74 years, 64.6% men) admitted to the hospital due to acute heart failure. Blood samples were collected at admission and discharge for the measurement of several biomarkers. Impedance cardiography was performed at discharge to assess hemodynamic parameters and

thoracic fluid content. Patients were treated at the discretion of the attending physician. During the 3-month follow-up period, 52 patients were readmitted and 15 died. The combined end-point was observed in 56 patients. Thoracic fluid content and B-type natriuretic peptide (BNP) levels were not strongly correlated (Spearman´s correlation: $\rho=0.35$, $p<0.001$) and they had very similar discriminative power to predict the outcome (area under the receiver-operating characteristic curve of 0.645 and 0.662, respectively). In multivariate Cox regression analysis, patients in the upper third of thoracic fluid content had higher hazard of death or readmission, independently of BNP levels and adjusted for other confounders (hazard ratio: 2.51, 95% confidence interval: 1.14-5.56).

Conclusion Thoracic fluid content provides incremental prognostic information to that obtained from BNP levels in patients discharged after an episode of acute heart failure. This marker can be used to complement physical examination and BNP in identifying patients at high risk.

INTRODUCTION

Heart failure is a major and growing public health problem in industrialised countries and has a large impact on health care systems.[1-3] Management of heart failure patients is complex and requires specific training. Despite advances in clinical stratification and therapies that modify prognosis, the daily management of individual patients with heart failure remains challenging. Although recent guidelines have focused on patients with acute heart failure,[4] there are no scoring systems to help clinicians in the decision to discharge patients from the hospital. Multiple individual

variables have been associated with morbidity and mortality, including co-morbidities, symptoms, clinical evidence of fluid overload, hemodynamic parameters, renal dysfunction, anaemia and cardiac biomarkers.[4, 5]

Symptoms of congestion, rather than low cardiac output, are the leading cause of admission due to acute heart failure.[6-8] Fluid status, assessed by the search for elevated jugular venous pressure in patients with heart failure, was associated with adverse outcomes and progression of disease.[9] However, the reliability of physical examination findings in estimating cardiac hemodynamics is not well established.[10, 11] The invasive nature of right-sided heart catheterization and the risks associated with this technique led to the development of a non-invasive method of hemodynamic monitoring. Impedance cardiography estimates several hemodynamic parameters through measurements of the change in conduction (impedance) of an alternating current as a function of fluid shifts in the thoracic cavity and the great vessels during the cardiac cycle.[12] The inverse of impedance is a measure of fluid status called thoracic fluid content, reflecting intravascular, intra-alveolar and interstitial fluid in the thorax. Higher thoracic fluid content was identified as a predictor of acute heart failure episodes in outpatients.[13] One study has reported on the prognostic value of thoracic fluid content in acute heart failure, although only very severe cases with indication for invasive hemodynamic monitoring by right-sided heart catheterization were included and no consideration for putative confounders was taken.[14]

We aimed to study the added prognostic value of thoracic fluid content as a marker of fluid status to predict 3-month all-cause death or readmission due to a cardiovascular cause after an episode of acute heart failure.

METHODS

Patients

We studied a sample of 212 patients admitted to the Department of Internal Medicine of Hospital de São João, Porto, between October 2006 and February 2008, due to acute heart failure, including new-onset or decompensated chronic heart failure. Hospital de São João is a university hospital that serves a population of 500,000 inhabitants; a catheterization laboratory and cardiac surgery are available. Patients with acute heart failure are evaluated at the emergency department and the decision to admit a patient is made by the attending consultant after proposal by an emergency physician. Most patients are admitted to the internal medicine department, except for patients with acute heart failure due to acute coronary syndromes or acute valvular heart disease requiring urgent surgery, who are admitted to the cardiology department. The internal medicine department has a team specialized in heart failure composed by five internists and a varying number of residents of internal medicine and cardiology. The authors of this study belong to this team. Upon admission, patients are sequentially distributed among all attending physicians of the internal medicine department including heart failure specialists. For the purpose of this study, we asked all clinicians to report to the research team when a patient with acute heart failure was admitted under their care. Then, recruitment and data collection was made by the research team members.

The diagnosis of heart failure was established by the attending physician and reviewed by the investigators, based on the European Society of Cardiology criteria.[15]

Patients with acute coronary syndromes, defined as rise and/or fall of troponin I, with at least one value above the upper reference limit (99th percentile of a normal population), together with symptoms or electrocardiographic signs of myocardial ischemia, and with moderate-to-severe aortic valve disease or prosthetic aortic valves were excluded. Patients who died during the index hospitalization were also excluded. Only the first hospitalization of each patient during the study period was considered. All patients consented to participate.

Study procedures

History of coronary heart disease, diabetes mellitus, hypertension and atrial fibrillation were considered according to registered diagnoses by the attending physicians. New York Heart Association functional class was assessed by the research team using standard definitions.[15]

Left ventricular systolic function was classified by echocardiogram as preserved, mildly, moderately or severely depressed.

Blood samples were collected at admission and discharge. B-type natriuretic pepide (BNP) was measured using a chemiluminescent immunoassay kit (Abbott AxSYM). The normal range is <100 pg/ml. Other biochemical analyses were performed at the hospital laboratory using standard methods. Glomerular filtration rate (eGFR) was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation and renal failure was defined as eGFR<60 ml/min/1.73 m^2.[16] Anemia was defined as hemoglobin ≤13 g/dl for men and ≤12 g/dl for women.[17]

Impedance cardiography was performed immediately before discharge by one of three members of the research team using Niccomo® monitor (Medis. Medizinische Messtechnik GmbH, Ilmenau, Germany). A high frequency and low voltage current is

applied across the thorax and produces a waveform signature of voltage changes, produced by varying resistances and sensed by two pairs of electrodes placed on the edges of the chest. Voltage changes (delta Z) are the consequence of fluid alterations within the thorax (changes in the intra-alveolar and interstitial thoracic compartment) and volume alterations and velocity changes in aortic blood flow.[18, 19] Patients were placed on supine position and four dual sensors were applied on the neck and thorax (two paired electrodes placed 180° apart at the base of the neck and another two at the mid-axillary line at the level of xyphoid process). The outer electrodes of the sensors transmit a low-amplitude (1mA), high frequency current (60-100 kHz) and the inner electrodes detect thoracic voltage changes. The blood pressure cuff was applied to the right arm. Height and weight were previously measured and their values inserted in the monitor for indexation of hemodynamic parameters. In the current study, we assessed thoracic fluid content (normal range from 30 to 50/KOhm for men and from 21 to 37/KOhm for women) and other hemodynamic parameters: cardiac index (normal range from 2.5 to 4.7 l/min/m^2), stroke index (normal range from 30 to 65 ml/m^2), systemic vascular resistance index (normal range from 1700 to 2600 dyne/sec/m^2) and systolic time ratio (normal range of systolic time ratio from 30 to 50%).[20]

A standardized physical examination was performed by the research team before discharge. Pulmonary rales, peripheral edema, jugular venous distension (assessed with the patient at 45º supine) and hepatojugular reflux were recorded as present or absent. This procedure was included in the study protocol only in October 2007; therefore, only the last 52 patients were assessed with physical examination.

All patients received standard treatment at the discretion of the attending physicians, who had access to BNP values. Impedance cardiography was performed only after decision to discharge and therapeutic prescriptions for ambulatory care were made.

Patients were followed up for three months after discharge. Surveillance was made by direct contact with patients or next of kin and review of electronic medical records. The primary end point was all-cause death or hospital readmission for a cardiovascular cause.

Statistical analysis

Data storage and analysis were performed using SPSS 17.0 (SPSS Inc, Chicago, IL).

Descriptive data are expressed as median and interquartile range (IQR) for numeric variables and as counts and proportions for categorical variables. Thoracic fluid content was categorized in thirds according to gender. The chi-square test was used to compare proportions and differences in continuous variables between thoracic fluid content thirds were tested using the Kruskall-Wallis test. Paired differences in BNP from admission to discharge were tested using the non-parametric Wilcoxon test.

Spearman correlation (ρ) was used to quantify the association between thoracic fluid content and BNP. A receiver-operating characteristic (ROC) curve and the area under the curve (AUC) were estimated for prediction of death and readmission by thoracic fluid content and BNP levels at discharge.

The association of independent variables with time to outcome was assessed by Cox regression and is expressed as hazard ratio (HR) and 95% confidence interval (CI).The variables presenting a significant association with survival on univariate analysis were considered for a multivariate Cox regression to adjust for the effect of confounders. Survival curves by thoracic fluid content thirds were estimated by the Kaplan-Meier method and compared by the log rank test, according to BNP level (< 700 pg/ml and ≥ 700 pg/ml),[21] and thoracic fluid content (1st-2nd third and 3rd third).

A significance level of 5% was used.

Ethics

The study was approved by the local Ethics Committee and patients gave informed consent.

RESULTS

A total of 212 patients were evaluated. The baseline characteristics of the study sample are presented in Table 1. The patients' median age was 74 years and 65% were men. Most patients met criteria for decompensated chronic heart failure and 50% had severe left ventricular systolic dysfunction. The prevalence of renal failure and anemia was 56.6% and 53.1%, respectively. Hemodynamic parameters at discharge showed low cardiac and stroke index, and high systemic vascular resistance index. Most patients had thoracic fluid content within the normal range proposed by the equipment's manufacturer for each gender. BNP levels were higher at admission than at discharge [median (IQR): 1093 (635-1971) pg/ml *versus* 605 (253-1971) pg/ml, $p<0.01$], and decreased more than 30% in 128 (61.8%) patients.

Thoracic fluid content increased with increasing levels of BNP at discharge, but the rank correlation between these two variables was not strong ($\rho=0.35$, $p<0.001$) (Figure 1). Signs of congestion at the physical examination were in general also associated with higher thoracic fluid content but a quarter of patients without jugular venous distension, hepatojugular reflux or peripheral edema and 38.5% of those

without pulmonary rales were at the highest third of thoracic fluid content. One out of each five patients with none of these clinical signs of congestion had thoracic fluid content in the upper third (Table 2).

Fifty two patients were re-admitted to the hospital due to a cardiovascular cause and 15 died during the 3-month follow-up period. The combined end point of death or readmission was observed in 56 patients.

BNP and thoracic fluid content had very similar discriminative power to predict events within 3 months, with areas under the ROC curve of 0.662 and 0.645, respectively (Figure 2). Patients at the upper third of thoracic fluid content had a 2.5-fold significantly higher hazard of death or readmission, independently of BNP and other confounders of the association (Table 3).

When stratifying by B-type natriuretic peptide levels at discharge, the upper third of thoracic fluid content was associated with higher hazard of 3-month death or readmission in both groups (Figure 3).

DISCUSSION

Thoracic fluid content, measured by impedance cardiography to assess fluid status at discharge from an acute episode of heart failure, is a strong predictor of 3-month death or readmission for a cardiovascular cause independently of other robust prognostic markers, including BNP. It provides information for classification of fluid status beyond that conveyed by physical examination.

Congestion, rather than low cardiac output, is the dominant feature in

populations with acute heart failure.[7] Symptoms and physical examination findings are important but do not provide enough information to comprehensively assess the severity of a case or to monitor the efficacy of therapies during hospitalization and after discharge. The gold standard for hemodynamic monitoring in acute heart failure is right-sided heart catheterization. Conflicting results emerged from several studies concerning the agreement in the assessment of status of fluid overload by clinical examination and based on hemodynamic parameters from right-sided heart catheterization.[5, 10, 11, 22, 23] Butman et al studied 52 patients, awaiting heart transplantation, with severe heart failure (average NYHA class III), and reported that, among several physical examination findings, jugular venous distension had the best sensitivity and specificity in assessing left heart filling pressure, but still misclassified a large proportion of cases.[11] Stevenson et al assessed 50 patients with heart failure and severe left ventricular systolic dysfunction (mean ejection fraction of 18%) and found that many patients without rales, edema or elevated mean jugular venous pressure had elevated left heart filling pressures.[10] The disagreement between clinical signs and hemodynamic status lead to the concept of hemodynamic congestion, reflecting elevated filling pressure preceding clinical congestion (dyspnea, orthopnea, pulmonary rales, jugular venous distension and peripheral edema).[24] The best way to estimate filling pressures using clinical assessment is to combine findings from symptoms, physical examination, electrocardiogram and chest radiograph in profiles,[25, 26] but clinical assessment alone does not allow a good classification.

Impedance cardiography has emerged as a promising non invasive method of hemodynamic monitoring. Intra- and inter-day reproducibility were acceptable in stable coronary heart disease patients and in stable heart failure patients treated in an outpatient clinic.[27, 28] Several studies have assessed the accuracy of impedance cardiography to estimate hemodynamic parameters. Cardiac output estimated by impedance cardiography was strongly correlated with the termodilution method in

critically ill patients[29] and in acute heart failure,[30-32] with correlation coefficients ranging from 0.64 to 0.89. The correlation between thoracic fluid content and hemodynamic parameters of filling pressure measured using right-sided heart catheterization was not so strong. One study, including 29 patients admitted to an intensive care unit due to acute heart failure, reported a correlation of 0.39 between thoracic fluid content and left ventricular diastolic pressure.[31] In another study of 50 patients with advanced heart failure with indication for cardiac catheterization, the correlation between thoracic fluid content and pulmonary capillary wedge pressure was 0.05.[32] Recently, in a subsample of 82 patients from the BIG trial who underwent right-sided heart catheterization, the correlation coefficients between thoracic fluid content and pulmonary capillary wedge pressure ranged from 0.18 to 0.52 on consecutive days.[14] These modest correlations could result from the fact that thoracic fluid content is not only a measure of intravascular volume but also intra-alveolar and interstitial fluid within the thorax.[33] Cardiac catheterization is an invasive procedure that cannot be used routinely. The PAC-Man and ESCAPE trials failed to show survival benefit of treatment guided by right-sided heart catheterization and had a slight increase of adverse effects related to this procedure.[34, 35] Assuming that impedance cardiography could be used as an alternative to non-invasively evaluate hemodynamics and fluid overload status, we assessed whether it was concordant with congestion evaluated by physical examination. Similarly to hemodynamic assessments by the gold-standard, in the current study, patients without any clinical sign of congestion had thoracic fluid content on the second and third thirds reflecting some degree of hypervolemia that was not clinically apparent.

In the outpatient setting, thoracic fluid content was a predictor of death or hospital readmission in patients followed at a heart failure clinic after a recent episode of clinical decompensation.[13] The prognostic value of thoracic fluid content was also studied in the acute heart failure setting. The BIG trial included 170 patients

hospitalized due to acute heart failure that were randomized to right-sided heart catheterization. All of them underwent an impedance cardiography assessment at admission and discharge and the attending physicians were blinded to impedance cardiography measurements. The thoracic fluid content at admission and discharge, and its change from admission to discharge, failed to predict 6-months death or readmission.[14] The difference in prognostic value of thoracic fluid content between our study and the BIG trial can be attributed to several factors. The latter study only included severe heart failure patients, with ejection fraction under 30%, with at least one hospitalization due to heart failure in the previous year and previously treated with more than 160 mg of furosemide, while our sample included a broad spectrum of heart failure patients, with left ventricular systolic function ranging from preserved to severely depressed. In the BIG trial, treatment was not guided by impedance cardiography measurements. Instead, in 82 patients treatment was guided by right-sided heart catheterization determinations and in the other 88 treatment was guided by clinical findings.[14] These treatment strategies may confound the association between impedance cardiography measurements and the outcomes. The multicenter design of the BIG study introduced some variability in the impedance measurements, which could affect the reproducibility, while in our study all measurements were performed by the same three members of the investigation team. Another important difference is the length of follow-up. In the current study we used a medium-term follow-up period, instead of 6-months, to evaluate the prognostic value of volume overload status. Conceptually, a longer term follow up would reflect not only volemia but several other factors including neurohormonal activation and its blockage by therapeutic agents, such as angiotensin-converting enzyme inhibitors and beta blockers. Furthermore, the impact of volume overload on outcomes is probably related to diuretics use and dosage. Information on diuretic dosage and thoracic fluid content during follow up would be very important to elucidate this issue.

The prognostic value of natriuretic peptide levels at admission and discharge from an episode of acute heart failure, and their change during in-hospital treatment, is well established.[36] In our sample, thoracic fluid content and BNP had similar discrimination power as assessed by the area under the ROC curve for prediction of death or readmission within three months. Similar results were obtained by Maisel et al, with an area under the curve of 0.606 for all-cause death and 0.593 for hospitalization, both within three months.[37] To assess the magnitude of the effect of thoracic fluid content and BNP independently of each other, and to distinguish them in the prediction of future events we performed a multivariate Cox regression model to achieve more accurate risk stratification. We found that thoracic fluid content is a powerful predictor of death or readmission independent of other well known predictors including BNP level at discharge. Median values of BNP across thoracic fluid content thirds were not different, both in patients with BNP at discharge below and above 700pg/ml (data not shown), meaning that this observation does not result from residual confounding by BNP.

Some limitations have to be addressed. The use of the combined end-point did not allow the distinction of important differences in what determines death or readmission. Readmission could reflect health care system factors, social support or treatment compliance, beyond patients' clinical characteristics. We cannot control for the treatment interventions performed within these three months. Overall the sample size was not large enough to allow for the control of additional prognostic markers. Another limitation is the lack of data on physical findings in the whole sample for comparison with thoracic fluid content.

This study adds information concerning prognosis of heart failure patients, by demonstrating the predictive power of thoracic fluid content in patients with a large spectrum of heart failure severity and not only the more critical. This is particularly

useful since right-sided heart catheterization cannot be used in such a setting and the results are generalizable to a large population of heart failure patients. Thoracic fluid content assessed by impedance cardiography allowed the identification of patients at high risk whose congestion could not be detected by physical examination. Thoracic fluid content maintained the predictive power independently of BNP levels, which are among the most powerful predictors of adverse outcomes in heart failure. Our results support that knowledge of fluid status measured using thoracic fluid content may help physicians to selectively use diuretics, reducing the neurohormonal activation, electrolyte depletion and worsening renal function induced by their use.

CONCLUSION

Thoracic fluid content can be used as a prognostic factor in acute heart failure. It is safe, easy to perform, noninvasive, acceptable and identifies patients at risk of decompensation additionally to clinical signs and to other well-known prognostic markers.[38] In the future thoracic fluid content could be included in models of identification of high risk patients discharged from a hospitalization due to acute heart failure.

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Table 1. Baseline characteristics of the study sample.

Gender, n (%)	
Male	137 (64.6)
Female	75 (35.4)
Age (years)¥	74 (64-80)
Male	71 (59-79)
Female	77 (69-82)
Admission criteria, n (%)	
Decompensated chronic HF	171 (81.4)
New onset HF	39 (18.6)
Coronary heart disease, n (%)	103 (48.6)
Atrial fibrillation, n (%)	111 (52.6)
Diabetes mellitus, n (%)	88 (41.5)
Hypertension, n (%)	133 (63.0)
LV systolic function, n (%)	
Preserved	43 (25.4)
Mildly depressed	10 (5.9)
Moderately depressed	31 (18.3)
Severely depressed	85 (50.3)
NYHA functional class III-IV at discharge, n (%)	29 (14.4)
Hemodynamic parameters at discharge¥	
Systolic blood pressure (mmHg)	113 (99-130)
Heart rate (beats/min)	73 (63-84)
Thoracic fluid content (/kOhm)	31.9 (27.8-36.4)
Cardiac index (L/min/m^2)	2.18 (1.87-2.60)
Systemic vascular resistance index (dyne/sec/m^2)	2663 (2154-3275)
Systolic time ratio (%)	41 (33-50)
Stroke index (ml/m^2)	30.7 (26.0-37.0)
Serum hemoglobin at discharge (g/dl) ¥	12.3 (10.9-13.8)
Serum creatinine at discharge (mg/dl) ¥	1.16 (0.95-1.51)
Creatinine clearance at discharge (ml/min) ¥	55.9 (40.7-71.3)
Plasma BNP at discharge (pg/ml) ¥	605 (253-1292)

¥ Results presented as median (interquartile range).

BNP: B-type natriuretic peptide; HF: heart failure; LV: left ventricular; NYHA: New York Heart Association.

Table 2. Physical examination at discharge according to thoracic fluid content thirds (N=52).

	Thoracic fluid content*			
	1st third	**2nd third**	**3rd third**	**P**
Jugular venous distension, n (%)				
Yes	4 (26.7)	4 (26.7)	7 (46.7)	0.358
No	16 (43.2)	11 (29.7)	10 (27.0)	
Hepatojugular reflux, n (%)				
Yes	5 (26.3)	6 (31.6)	8 (42.1)	0.361
No	15 (45.5)	9 (27.3)	9 (27.3)	
Pulmonary rales, n (%)				
Yes	7 (26.9)	12 (46.2)	7 (26.9)	0.021
No	13 (50.0)	3 (11.5)	10 (38.5)	
Peripheral edema, n(%)				
Yes	3 (16.7)	6 (33.3)	9 (50.0)	0.047
No	17 (50.0)	9 (26.5)	8 (23.3)	
Any signs of congestion, n (%)				
Yes	10 (27.0)	13 (35.1)	14 (37.8)	0.028
No	10 (66.7)	2 (13.3)	3 (20.0)	

* Thirds of TFC according to gender: male (1st 19.3 to 30.2; 2nd 30.2 to 35.5; 3rd 35.5 to 56.7); female (1st 20.4-27.6; 2nd 27.6-32.0; 3rd 32.0 to 62.3).

Table 3. Association between thoracic fluid content and all-cause death or cardiovascular-cause hospital readmission after a hospitalization for acute heart failure.

	Crude HR (95% CI)	Adjusted HR¥ (95% CI)
Thoracic fluid content (/Kohm)§		
1st third	1	1
2nd third	0.99 (0.46-2.13)	0.92 (0.35-2.35)
3rd third	2.64 (1.38-5.06)	2.51 (1.14-5.56)
BNP at discharge (per 100 pg/ml)	1.03 (1.02-1.04)	1.02 (1.00-1.04)

¥ Adjusted for each other, new-onset heart failure (vs decompensated chronic heart failure), and anemia, troponin I and B-type natriuretic peptide level at discharge.

§ Thirds of TFC according to gender: male (1st 19.3 to 30.2; 2nd 30.2 to 35.5; 3rd 35.5 to 56.7); female (1st 20.4-27.6; 2nd 27.6-32.0; 3rd 32.0 to 62.3).

BNP: B-type natriuretic peptide ; CI: confidence interval; HR: hazard ratio.

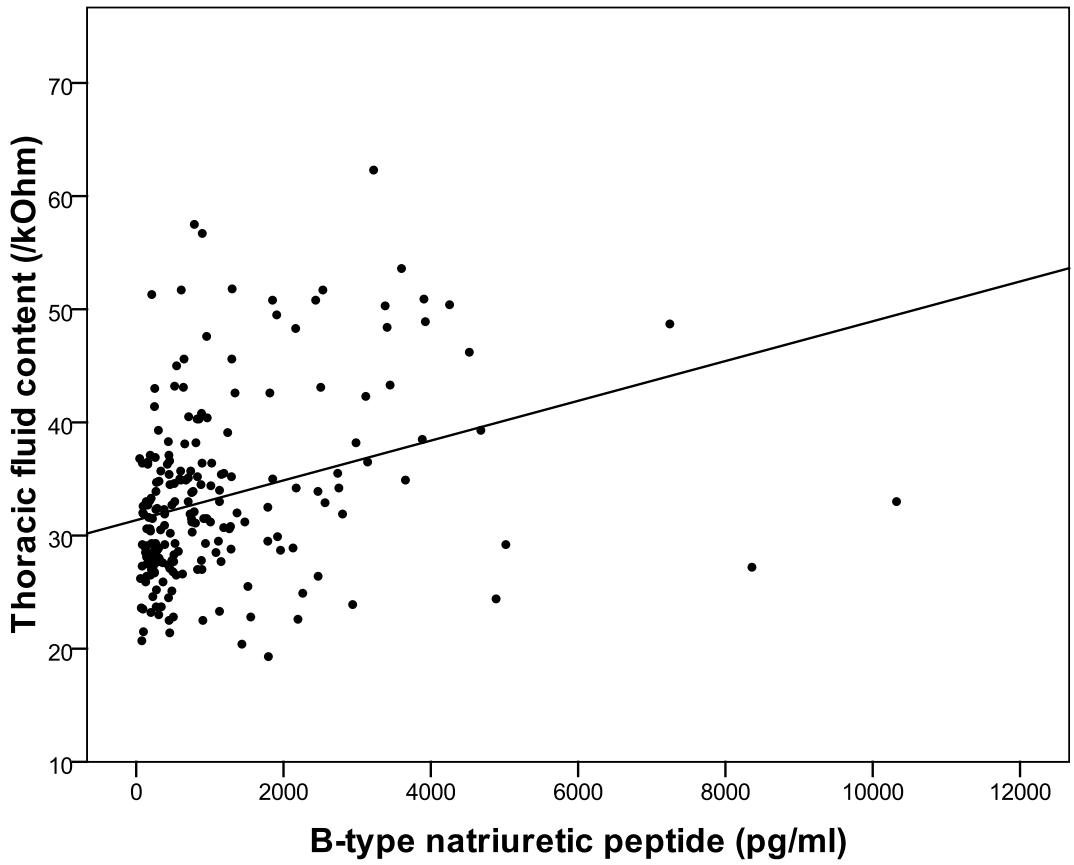

Figure 1. Thoracic fluid content plotted against B-type natriuretic peptide at discharge.

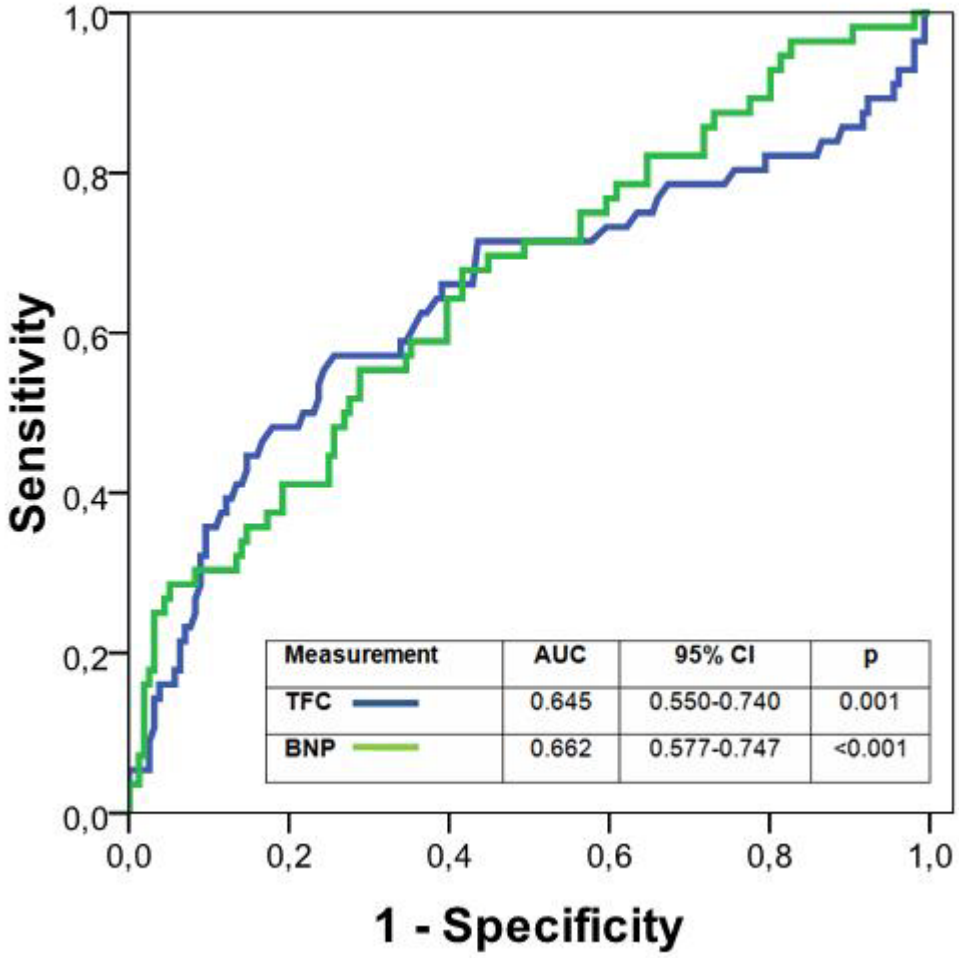

Figure 2. Receiver-operating characteristic curves for thoracic fluid content (TFC) and B-type natriuretic peptide (BNP) in predicting 3-month all-cause death or readmission for cardiovascular cause. AUC - area under the curve; 95% CI - 95% confidence interval

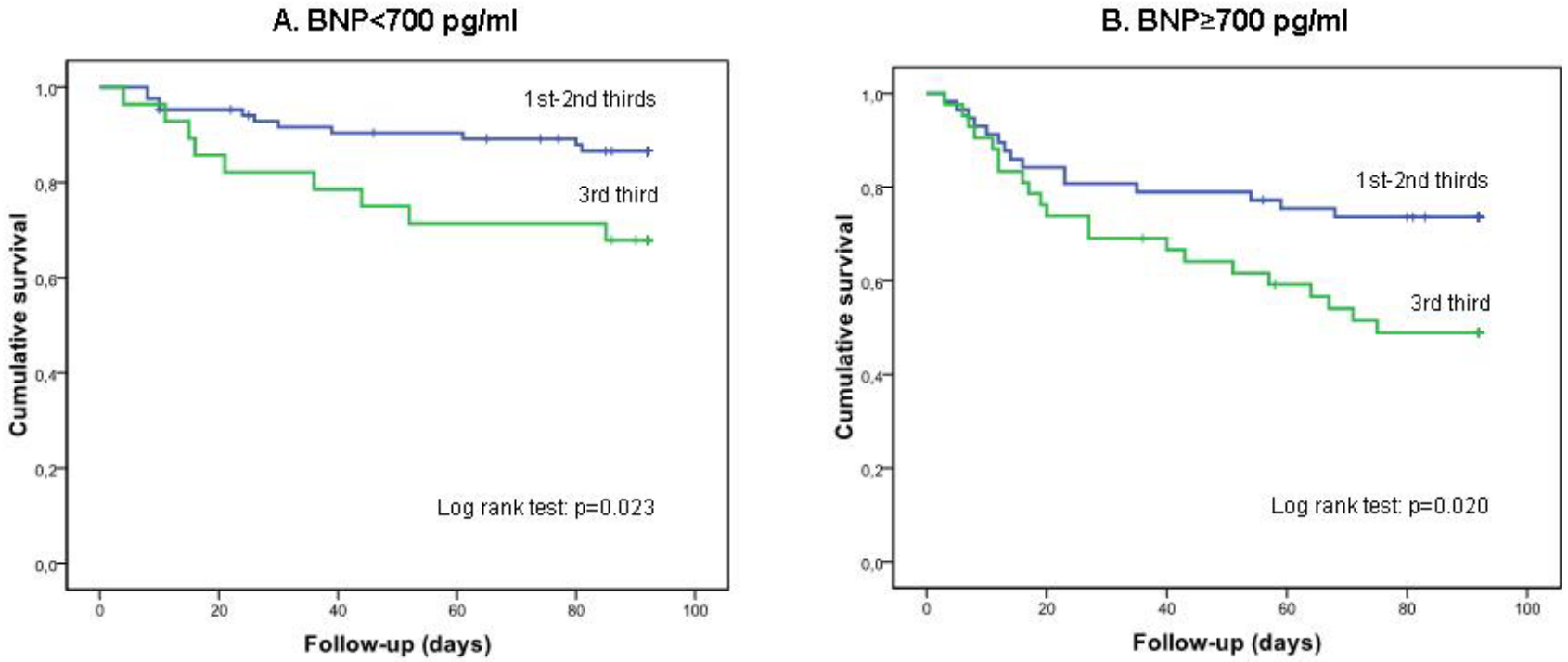

Figure 3. Kaplan-Meier cumulative hospitalization-free survival curves according to thoracic fluid content, stratifying by B-type natriuretic peptide levels at discharge <700 pg/ml (Panel A) and ≥700 pg/ml (Panel B).

4. Conclusions

Signs of congestion at physical examination were, in general, associated with higher levels of thoracic fluid content. Twenty per cent of patients without any sign of congestion had thoracic fluid content in the upper third.

Increasing thoracic fluid content was moderately associated with higher BNP and these markers had similar discriminative power to predict death or readmission within three months, with areas under the ROC curve of 0.645 and 0.662, respectively.

Thoracic fluid content was associated with a 2.5-fold increase in risk of death or readmission, within 3 months, independently of BNP and other confounders.

In summary, impedance cardiography for assessment of thoracic fluid content allowed the identification of patients with some degree of excess thoracic volume that was not clinically manifest and could be used as a safe, easy to perform, non-invasive method to establish prognosis in acute heart failure.

5. Abstract

Heart failure is a major and escalating public health problem with increasing prevalence and incidence. Acute heart failure is associated with great morbidity and mortality. One of the main objectives in the management of these acute patients is to stratify them according to predicted risk in order to optimize treatment and consequently reduce the occurrence of adverse outcomes. Symptoms and physical signs have limited sensitivity, specificity and predictive value for the classification of hemodynamic status. The gold standard for hemodynamic monitoring is right-sided heart catheterization but it is associated with significant procedure-related morbidity and it is not appropriate for the whole spectrum of severity of heart failure patients, but only to the more critical cases. Impedance cardiography emerged as a non-invasive method of hemodynamic monitoring. Thoracic fluid content is a parameter that measures fluid overload within the thorax, including intravascular, interstitial and intra-alveolar compartments.

The purpose of the present study was to determine the prognostic value of thoracic fluid content, assessed by impedance cardiography, to predict 3-month all-cause death or readmission for a cardiovascular cause, after an episode of acute heart failure. Additionally, we intended to assess the association between thoracic fluid content and physical examination signs of congestion as well as BNP, as an argument for its added value in the classification of volume overload status.

We included 212 patients (median age 74 years, 64.6% men) admitted to the hospital due to acute heart failure. Blood samples were collected at admission and discharge for the measurement of several biomarkers. Impedance cardiography was performed at discharge to assess hemodynamic parameters and thoracic fluid content.

In a subsample of 52 patients, a standardized physical examination was performed before discharge. Patients were treated at the discretion of the attending physician.

During the 3-month follow-up period, 52 patients were readmitted and 15 died. The combined end-point was observed in 56 patients. Thoracic fluid content and B-type natriuretic peptide (BNP) levels were not strongly correlated (Spearman´s correlation: ρ=0.35, p<0.001) and they had very similar discriminative power to predict the outcome (area under the receiver-operating characteristic curve of 0.645 and 0.662, respectively). In multivariate Cox regression analysis, patients in the upper third of thoracic fluid content had higher hazard of death or readmission, independently of BNP levels and adjusting for other confounders (hazard ratio: 2.51, 95% confidence interval: 1.14-5.56). Signs of congestion at the physical examination were, in general, associated with higher levels of thoracic fluid content. Twenty per cent of patients without any sign of congestion had thoracic fluid content on the upper third.

Thoracic fluid content provides incremental prognostic information to that obtained from BNP levels in patients discharged after an episode of acute heart failure. Impedance cardiography, with assessment of thoracic fluid content, allowed the identification of patients with some degree of excess thoracic volume that was not clinically manifest. This marker can be used to identify patients at high risk.

6. Resumo

A insuficiência cardíaca é um importante problema de saúde pública cuja prevalência e incidência têm vindo a aumentar. A insuficiência cardíaca aguda está associada a elevada morbilidade e mortalidade. Um dos principais objectivos na abordagem dos doentes com insuficiência cardíaca aguda é a estratificação de risco, com vista a optimizar o tratamento e assim reduzir a ocorrência de eventos adversos. Os sintomas e sinais observados no exame físico não são suficientemente sensíveis e específicos, nem têm elevado valor preditivo, para classificar os doentes em perfis hemodinâmicos. A cateterização cardíaca das câmaras direitas é o *gold standard* para monitorização hemodinâmica. Contudo, é um método invasivo, associado a morbilidade, e só deve ser usado em doentes críticos, não sendo exequível a sua aplicação em todo o espectro de gravidade da insuficiência cardíaca. A bioimpedância eléctrica torácica surgiu como um método de monitorização hemodinâmica não invasivo, permitindo estimar o conteúdo de fluido torácico, um parâmetro que inclui o volume intravascular, intersticial e intra-alveolar.

O objectivo principal deste estudo foi avaliar a associação do conteúdo de fluido torácico, obtido por bioimpedância eléctrica torácica, com o risco de morte ou reinternamento de causa cardiovascular aos 3 meses, após um internamento por insuficiência cardíaca aguda. Adicionalmente, pretendemos avaliar a relação entre o conteúdo de fluido torácico e a presença de sinais de congestão no exame físico, bem como com o peptídeo natriurético tipo B (BNP), como argumento de que complementa estes dados clínicos na classificação do estado de sobrecarga de volume.

Incluímos 212 doentes internados por insuficiência cardíaca aguda. A idade mediana dos doentes foi de 74 anos e 64,6% eram do sexo masculino. Colheu-se uma amostra de sangue para doseamento de vários biomarcadores no dia da admissão e

no dia da alta. Foi efectuada uma avaliação por bioimpedância eléctrica torácica à alta para avaliação de parâmetros hemodinâmicos e do conteúdo de fluido torácico. Numa subamostra de 52 doentes foi realizado exame físico cardiovascular antes da alta. Os doentes foram tratados à discrição do médico assistente.

Durante o período de seguimento foram reinternados 52 doentes e morreram 15. O evento combinado morte ou reinternamento foi observado em 56 doentes. A correlação entre conteúdo de fluido torácico e BNP não era forte (correlação de Spearman: ρ=0,35, p<0,001) e ambos apresentaram uma capacidade discriminativa semelhante na predição do evento em estudo (área abaixo da curva ROC de 0,645 e 0,662, respectivamente). Num modelo de regressão de Cox multivariado, os doentes com conteúdo de fluido torácico acima do 2º tercil apresentavam um risco mais elevado de morte ou reinternamento, independentemente do valor de BNP e ajustando para outros confundidores (*hazard ratio*: 2,51, intervalo de confiança a 95%: 1,14 a 5,56). Globalmente, os doentes com sinais clínicos de congestão apresentavam conteúdo de fluído torácico mais elevado, mas um em cada cinco doentes sem evidência clínica de congestão ainda apresentava conteúdo de fluído torácico elevado.

A avaliação do conteúdo de fluído torácico por bioimpedância eléctrica torácica acrescenta informação àquela obtida pelo BNP na determinação do prognóstico após um internamento por insuficiência cardíaca aguda. A avaliação do conteúdo de fluido torácico por bioimpedância eléctrica permitiu a identificação de doentes com congestão que não era clinicamente evidente. Este marcador pode ser útil para identificar doentes de elevado risco.