Physiopathology and Diagnosis of Congestive Heart Failure: Consolidated Certainties and New Perspectives

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Abstract: Volume overload and fluid congestion are a fundamental issue in the assessment and management of patients with heart failure (HF). Recent studies have found that in acute decompensated heart failure (ADHF), right and left-sided pressures generally start to increase before any notable weight changes take place preceding an admission. ADHF may be a problem of volume redistribution among different vascular compartments instead of, or in addition to, fluid shift from the interstitial compartment. Thus, identifying heterogeneity of volume overload would allow guidance of tailored therapy. A comprehensive evaluation of congestive HF needs to take into account myriad parameters, including physical examination, echocardiographic values, and biomarker serum changes. Furthermore, potentially useful diagnostic tools include bioimpedance to measure intercompartmental fluid shifts, and evaluation of ultrasound lung comets to

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detect extravascular lung water. (Curr Probl Cardiol 2021;46:100691.)

Background

Acute heart failure (AHF) is a clinical syndrome characterized by the presence of a tissue congestion due to fluid retention because of an initial myocardial dysfunction (cardiac pathway) associated with renal dysfunction, and redistribution of the circulating volume as a consequence of vascular dysfunction.[1] On a pulmonary level, congestion is an indicator of hypertension in the pulmonary venous circulation, marked by increased pulmonary capillary wedge pressure (PCWP), causing interstitial and alveolar edema, with subsequent dyspnea. System congestion, which to a limited extent is correlated with increased central venous pressure, manifests with jugular turgor, peripheral edema, and/or gradual weight gain.[2] AHF requires hospitalization and IV diuretic treatment, which, however, is effective for the resolution of the congestion in only 50% of cases. The literature reports a hospitalization rate of approximately 50% after 6 months due to a new episode of cardiac decompensation, according to the data reported in the ADHERE Registry.[3] The target of depletive treatment is often limited to the amount of fluid overload, which, though responsible for acute symptoms (clinical congestion), represents only a small proportion, or, as it was well described, ". . . just the tip of a congestion iceberg," with a prevailing, but submerged, element, hemodynamically detectable but paucisymptomatic and, therefore, only partially treated[4] (Fig 1). As a consequence, resolution of clinical congestion is often associated with persistent hemodynamic congestion and, since it gradually develops over the weeks before hospitalization, the use of hemodynamic[5] congestion markers would allow early treatment to prevent transition from a stable/chronic to unstable/acute stage of HF.[6] Data on the use of implantable devices provided with sensors for hemodynamic monitoring have shown how some pulmonary hemodynamic congestion markers (eg, increased PCWP, and intrathoracic impedance) can lead to early intervention strategies, with an effective reduction of rehospitalization rate after 6 months.[7] The most frequently requested therapeutic option is escalation of diuretic treatment. Aggressive diuretic treatment, necessary in the setting of AHF, can cause a progressive worsening of renal function (WRF). Nevertheless, WRF as described in the setting of AHF is not only related, as historically known, to renal arterial hypoperfusion (low stroke volume, dehydration due to excessive diuretics), but is associated principally with the presence of

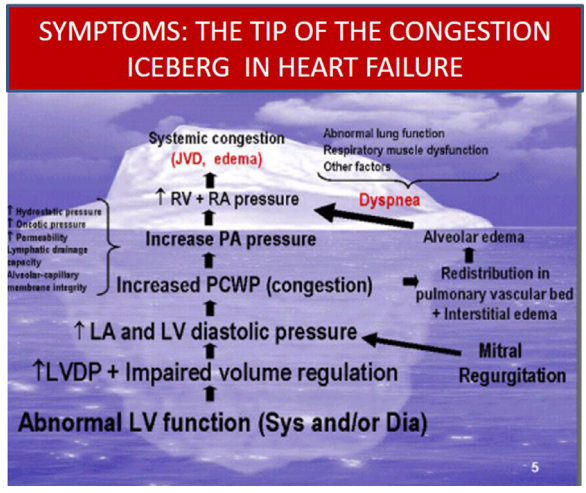

FIG 1. "The congestion iceberg" in acute heart failure. Adapted from Gheorghiade M. et al.[4]

systemic venous congestion (PVC> 8 mmHg).[8] Persistent systemic venous congestion upon discharge is a negative prognostic factor for adverse events and rehospitalization, likely because this is an indicator of reduced efficacy, namely inadequate diuretic treatment.[9] The prognostic value of WRF in the setting of AHF is controversial because it varies according to the physiopathology mechanism to which it is mainly related, and its subsequent reversibility: persistent WRF, which can be determined by a prolonged low renal hypoperfusion, is generally an indicator of permanent kidney damage, not only of kidney hypoperfusion adjustments (indicated by variation of creatinine levels), and has a clear negative prognostic value. On the other hand, a temporary WRF (defined as pseudo-WRF), due to a reduced systemic venous congestion during diuretic therapy, and associated with hemoconcentration,[10] is considered a positive prognostic indicator, likely because it expresses a therapeutic susceptibility margin, and generally leads to an improvement of the general clinical picture.[11,12] The trend of renal functions during hospitalization for AHF is at the foundation of statistical models used for the prognostic stratification of our patients.[13]

Physiopathology: cardiorenal syndrome and intercompartmental fluid distribution

Cardiorenal syndrome (CRS) is a physiopathological disorder in which both cardiac and renal dysfunctions coexist. It was described for the first

time, in 2008, by Ronco,[14] who classified 5 different types of CRS according to the syndrome's primum movens organ. Prevalence is high: one-third of patients with cardiac decompensation also suffer from renal failure, and more than 40% mortality of patients with chronic renal dysfunction is associated with cardiovascular diseases.[15] The physiopathology of CRS is complex and includes hemodynamic and neurohormonal mechanisms: peripheral hypoperfusion determines chronic activation of the renin-angiotensin-aldosterone axis, responsible for increased pre- and post-load, and production of pro-inflammatory mediators and oxygen-derived free radicals. The sympathetic nervous system (SNS) is also activated, with a subsequent peripheral vasoconstriction, and an increased post-load and myocardial oxygen consumption.[16] From a physiopathology standpoint, CRS is also associated with increased central venous pressure, responsible for the congestion of patients with decompensation and, as a consequence, the dysfunction of abdominal organs. Congestion in cardiac decompensation manifests with increased abdominal pressure, and subsequent dysfunction of abdominal organs including kidneys. This correlation has been analyzed in some studies, in which a reduction of abdominal pressure in patients with HF was associated with an improvement of renal functions.[12,17]

Right ventricle (RV) cardiac decompensation is a complex clinical syndrome caused by any cardiovascular disorder that damages the RV function. Right HF is caused by all pathological conditions responsible for RV overload (eg, pulmonary embolism), diseases causing RV volume overload (eg, tricuspid insufficiency, intracardiac shunt), and conditions responsible for RV reduced contractility (eg, right ventricular infarction).[18] There is still a significant lack of data in the literature regarding the disorders of the RV, likely because of its anatomy, which is completely different from the left ventricle, and makes diagnostic assessment much more complex. Even today, transthoracic echocardiogram (TTE) is one of the most used approaches for the study of RV longitudinal function by means of tricuspid annular plane systolic excursion and for lung pressure sampling, which gives an indirect estimate through tricuspid regurgitation.[18,19] The mortality rate for this disease is very high, and RV dysfunction is a powerful predictor of adverse prognosis, independent of the presence and extent of a left ventricular (LV) dysfunction.[20] The main clinical signs of cardiac decompensation include symptoms secondary to peripheral congestion (eg, peripheral edema, hepato- and splenomegaly, ascites, anorexia, and decreased effort tolerance).[21] Frequently, cardiac decompensation patients (with or without LV dysfunction) show signs and symptoms of congestion. This means

that the current strategies for managing HF are based on the classic principle, according to which fluid retention is responsible for intravascular volume expansion and congestion. Nevertheless, an altered intercompartmental fluid distribution plays a significant role in the development of decompensation.[22] Indeed, in many patients with HF, episodes of decompensation are not preceded by body weight gain.[23] Supporting evidence is provided by the analysis of the body volume through the radio-labeled-albumin dilution technique. Androne et al found that a state of hypervolemia is frequently present in nonedematous OPC patients with chronic HF.[24] Miller et al found that almost 10% of patients with HF had normal intravascular blood volume, whereas a wide homogeneity of total volume distribution, 9.5%-107%, was present in all the other patients.[25] In advanced cardiac decompensation, the interstitium, which is normally a low-compliance area, becomes capable of containing excess fluids, with a progressive development of pathological hypervolemia, contributing to the volume overload and organ congestion. Fluid excess in these patients can be several liters, and often this is only marginally treated with standard diuretic therapy.[26] Redistribution of blood volume in various vascular areas is another mechanism involved in the evolution of congestion and decompensation in patients with HF.[27] In fact, most blood volume is within the veins, compliance vessels, and particularly in the splanchnic veins, remarkably more compliant than extremity and skin veins.[28] The splanchnic vascular system is the largest blood reservoir that can accept or release, actively and passively, most of the circulating blood volume (Fig 2). The SNS causes venous constriction by releasing adrenalin and noradrenalin, therefore reducing the splanchnic capacity - adrenergic receptor density along the walls of splanchnic veins is 5 times larger compared with adrenergic nerve endings of the arteries[28] and recruits effective circulating volume. A reduced vascular or intracardiac filling pressure is perceived by baroceptors, with an increase of the sympathetic tone and blood recruitment from splanchnic and peripheral areas towards the heart. When these mechanisms work regularly, an increase of intracardiac filling pressure inhibits the sympathetic outflow, with an increase of the splanchnic reservoir. On the contrary, in advanced HF sympathetic activation continues uncontrollably, maintaining elevated filling pressures (sympathetic-adrenergic stimulation can cause acute translocation of up to 1 L of blood in a few seconds from the splanchnic reservoir to the central circulation, with no change in the body weight). Furthermore, elevated filling pressures maintained by the chronic volume overload and chronic activation of SNS[29] can cause, over time, gradual increase of the peripheral venous pressure and lead to a status of progressive abdominal

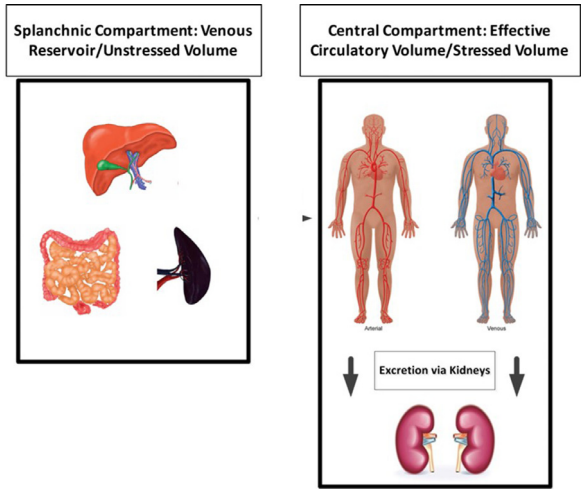

FIG 2. Two-compartment model of the human blood pool. Adapted from Fudim M. et al.[27]

congestion, and eventually ascites and consequent organ dysfunction (eg, kidney, liver, gastroenteric system; Fig 3). Abdominal pressure in patients with HF and abdominal congestion can be measured with a urinary catheter provided with a pressure transducer. In fact, some studies have shown how mechanical fluid removal through ultrafiltration or paracentesis in case of ascites could reduce endo-abdominal pressure and improve the functions of all abdominal organs. A rapid reduction of

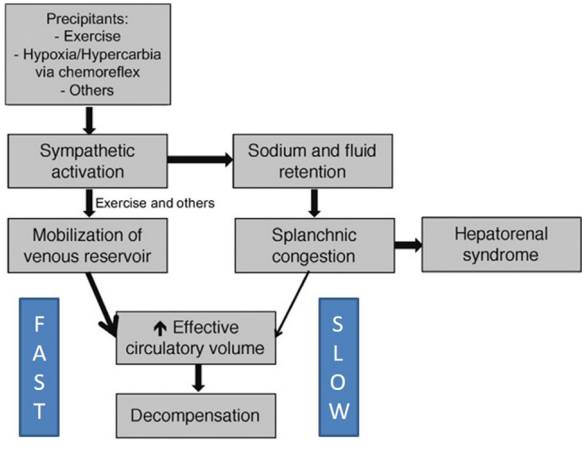

FIG 3. Proposed mechanism of transition from chronic compensated to acute decompensated heart failure. Adapted from Fallick C. et al.[22]

abdominal pressure in such patients, who often are diuretic-resistant, can improve renal functions and any hemodynamic variable.[17,30]

Symptoms reported by patients with advanced-stage heart failure (HF) and abdominal congestion include malabsorption, abdominal discomfort, sense of fullness, and loss of appetite leading to cachexia.[31] The physiopathology of cachexia with cardiac origins is multifactorial and depends on neuro-hormonal chronic activation, persistent oxidative stress, and reduced food supply due to hyporexia. Cachexia in advanced-stage cardiac decompensation is most frequently associated with right ventricular dysfunction rather than with LV systolic dysfunction, and is an unequivocal indicator of adverse prognosis.[31]

How to identify congestion values and limits of physical examination

Clinical congestion, an overload status associated with symptoms and physical signs, is different from hemodynamic congestion, which is characterized by an increased cardiac filling pressure. Indeed, the lack of objective signs of congestion does not rule out volume overload, and the resolution of clinical signs after diuretic therapy does not always imply the resolution of hemodynamic congestion.[5] Physical examination remains crucial for the assessment of a patient with HF, especially in the evaluation of his/her congestion status. All congestion signs must be detected (pulmonary rales, peripheral edemas, jugular vein distension, third tone) to monitor the patient's stability over time, and assess his/her response to treatment.[32]

While the relation between physical signs and hemodynamic characteristics has been confirmed with sound observations in the diagnosis of AHF, the chronic status is characterized by a series of decompensation mechanisms with no evidence of pulmonary rales and peripheral edemas.[33]

Butman et al found that jugular venous distension (JVD) is characterized by a better combination of sensitivity (81%), specificity (80%), and predictive accuracy (81%) in correlation with increased PCWP and, together with the third tone (SIII), was a significant independent predictor of increased PCWP (JVD: $P = 0.0067$; SIII: $P = 0.0232$). Furthermore, for diagnostic purposes, it has been found that additional research of abdominal-jugular reflex was useful, compared with JVD exams alone,[34] as the latter is often limited by physical factors (eg, obese patients).

Contrary to the above mentioned signs, pulmonary rales and edemas are characterized by lower sensitivity. While in acute decompensation a

sudden increase of pulmonary venous pressure causes transudation of fluids into the interstitium, in chronic decompensation an increased lymphatic drainage is observed so that alveoli are relatively "dry." This mechanism explains the frequent absence of lung rales in the case of chronic volume overload.[33] In a study by Stevenson et al, pulmonary rales were present in only 19% of patients with PCWP >22 mmHg, and in only 11% of patients with PCWP >35 mmHg could it be identified.[33] Drazner et al conducted a post-hoc SOLVD analysis, and found that JVD and SIII are independently associated with a more unfavorable prognosis in terms of hospitalization for HF and death.[35] The main limits of physical examination, which can make it quite difficult, include poor reproducibility, physical characteristics, and co-morbidities of the patient. A diagnosis based on physical examination alone can result in an inadequate treatment. Therefore, though physical examination is an inevitable and essential step in the diagnostic work-up of a patient with HF, a multiparametric evaluation with an integration of several parameters deriving from instrumental and lab tests becomes necessary.

Multiparametric evaluation of congestive heart failure

The role of echocardiography

Echocardiography plays a primary role in the assessment of patients with HF. A short summary of the most useful measurements to assess left ventricle filling pressures (Fig 4) is reported below[36]:

1) Transmitralic flow: Increased E/A ratio and reduced acceleration rate of the E wave (<150 ms) are associated with increased left ventricle filling pressures.
2) Mitral "L" velocity: An L (lambda) wave occurs in mid-diastole in patients with diastolic dysfunction and high left atrial (LA) pressure. This is more evident in the case of bradycardia, whereas it cannot be assessed in the presence of frequent ectopy or tachycardia.
3) Protodiastolic velocity (E') of the mitral annulus by pulsed wave tissue Doppler imaging: This is related to LV relaxation and suction performance, as well as transmitralic pressure. In normal hearts, LA pressure substantially affects this measurement. Furthermore, the main limits include presence of mitral stenosis, significant mitral regurgitation, surgical ring, surgical valve replacement, severe mitral annular calcification, left bundle branch block, and pacemaker stimulation.

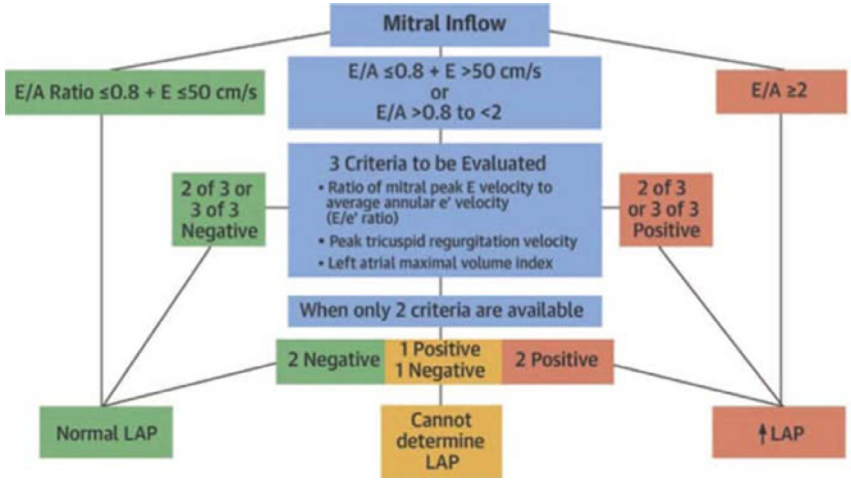

FIG 4. Algorithm currently recommended for estimating left ventricular filling pressure in cardiac disease patients. LAP, left atrial pressure; LVEF, left ventricular ejection fraction. Adapted from Andersen et al.[36]

4) E/E'ratio: Dimensionless parameter directly correlated with LA pressure. It mainly plays a diagnostic role in patients with advanced systolic dysfunction, and is less associated with LV filling pressures in healthy hearts. All E or E' velocity combined limitations analyzed individually are also included.
5) Indexed LA volume: Parameter that reflects the effects of chronically increased LA pressure. It is often increased in particular conditions, such as in the case of athletes, patients with atrial fibrillation, mitral valvulopathy, transplanted hearts, and hyperkinetic syndrome.
6) Pulmonary vein flow: Systolic (S) velocity, diastolic (D) velocity and S/D ratio: both S wave velocity and S/D ratio decrease in the case of increased LA pressure. However, these results are less reliable in patients with normal EF or in patients with at least moderate stenosis or mitral failure.
7) Tricuspid regurgitation peak velocity (TRV): Usually, patients with increased LA pressure have concurrent increased tricuspid insufficiency peak velocity because of the increased systolic blood pressure in the pulmonary artery. Nevertheless, IV contrast agents can be necessary to improve the signal and obtain reliable measurements of the peak velocity. In addition, velocity is less useful in patients with a primary lung disease; therefore, careful examination of the clinical

setting is essential before relying on the IT peak velocity to find interferences on the LA pressure.

The role of biomarkers

Among the different molecules evaluated as possible biomarkers in HF, the natriuretic peptide (NP) family, in particular the B-type natriuretic peptide (BNP) and its N-terminal propeptide (NT-proBNP), has become an integral part of the algorithms for a diagnosis of HF. Since the 1990s, several studies have evaluated the use of BNP and its terminal N fragment in the differential diagnosis of acute dyspnea,[37,38] agreeing on their high negative predictive value, which allows ruling out the diagnosis of HF in patients arriving at the emergency room for acute dyspnea, as well as the significant correlation between their circulating values and the NYHA class. While considering that NP values increase with aging, studies on NT-proBNP show that decision values, differentiated by age, significantly increase the accuracy of the test for the diagnosis of decompensation.[39] In addition to the differential diagnosis of acute dyspnea, NPs are used as prognostic indicators in all stages of the disease. In this context, what we need to think about most is whether the single value of BNP or its variations over time is more important for prognostic purposes. In line with the results of a recent survey on the management of patients with HF, which involved several Sicilian hospitals, heterogeneous results were obtained regarding the timing of NP dosing in patients admitted for acute heart decompensation.[40] It should be clarified that BNP levels in decompensated patients are the sum of 2 components: the basal one, also called optivolemic, which correlates more with the NYHA class and with patient prognosis, and is an expression of the disease stage; the other "wet" component is linked to the increase in pressure and volume overload, ie, 25%-50% above baseline values, and decreases more rapidly with depletive therapy. Several studies in the literature agree that between the absolute levels of NP upon admission (expression of the acute severity of the decompensation), those upon discharge, and the percentage of variation of them, a 30% reduction correlates with a greater survival and a lower rate of readmission for HF.[41] Failure to achieve this result should lead to a reconsideration of the patient's clinical conditions and therapy.

Another potential application of NPs within HF is their role in guiding the therapy. The current scenario is based on a "one size fits all" approach: drugs that are the same for all at the maximum dose tolerated

by the patient as indicated in current European guidelines. In this context, though the results of recent meta-analyses[42] show the advantage of the "BNP-guided" therapeutic approach compared with the "usual therapy, " it is still not recommended, and this is partly due to the high heterogeneity of these small studies (different end points, different peptides, short temporal follow-up). The results of the very recent Guide-IT study[43] found no statistically significant differences between the "usual care" and "BNP guided" approaches. However, it seems still early to completely rule out the usefulness of the BNP-guided strategy in the management of patients with HF; moreover, the use of NPs in these patients is of significant importance as an early warning sign of cardiovascular events thanks to the integration with other diagnostic methods in the scope of a multiparametric approach.

The study of thoracic comets

In the assessment of the state of congestion, a role now validated is that of the thoracic ultrasound study in search of "comets" or, more modernly, the "B lines" (which can be searched for using the cardiological phased array probe). The presence of the B lines can be focal or diffused throughout the entire chest: only in this last case does it take on a meaning related to the congestion, adopting the definition of interstitial ultrasound syndrome (Fig 5). Over the years, a correlation of the B lines with NYHA class, BNP, extravascular fluid content, ejection fraction, and PCWP has

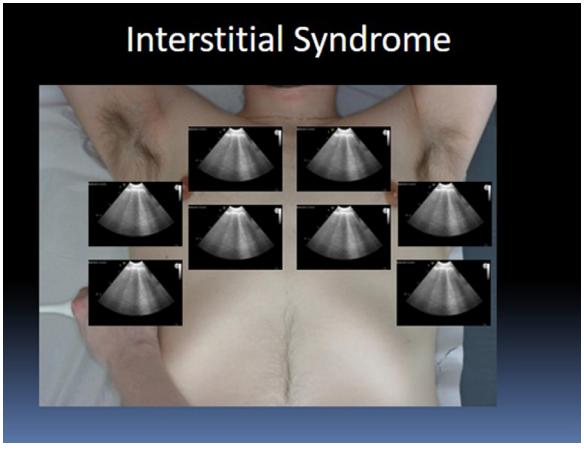

FIG 5. Picture suggestive of interstitial ultrasound syndrome with comets diffused throughout the chest.

been found.[44,45] Furthermore, the link between B lines and dyspnea associated with acute pulmonary edema has also been validated in a meta-analysis.[46] A proportionality between the number of B lines for the field explored by probe and the amount of pulmonary congestion has been demonstrated in various studies by the Picano group.[47] A prognostic role of the B lines has been shown in terms of rehospitalization of patients with HF: a persistent picture of pulmonary congestion before discharge assessed by ultrasound is predictive of rehospitalization for AHF at 6 months. The absence or a reduced quantity of B lines identifies a subgroup at extremely low risk for rehospitalization for AHF.[48] The presence of B lines associated with the study of the inferior vena cava (both in terms of absolute size and variability with respiratory excursions), being related to the pressure in the right atrium, is able to increase the specificity of B lines for a diagnosis of pulmonary congestion and as a cardiogenic cause of dyspnea.[49]

Bioelectrical impedance vector analysis (BIVA)

Detecting congestion in patients with HF is problematic because peripheral edema is often not detected until the interstitial volume increases by about 4-5 L. About a quarter of patients with acute decompensation have no edema upon admission, and only a minority of patients with chronic decompensation show peripheral congestion. BIVA, initially used to evaluate the dry weight in dialysis patients, is a technique used to measure total body water. By placing 2 electrodes on the limbs of the supine patient, an alternating current is administered, the conductivity of which passes through the body, and measures the total impedance, which is the combination of 2 parameters:

1) The total resistance of the body (Rz), defined as the opposition to an alternating current flow through an intra- and extracellular electrolyte solution;
2) The reactance (Xc), ie, the capacitance produced by the interfaces and cell membranes.

Ninety percent of the impedance depends on the soft (lean) tissues of the limbs; therefore BIVA detects above all peripheral congestion. This method has the advantage of being noninvasive, fast, portable, low-cost, and safe, while its limitations are represented by the changes in body temperature and incorrect posture of the patient, which could alter the measurement. Data obtained from the passage of current can be represented in 2 ways:

1) R/Xc Graph, where R and Xc are normalized for the height of the patient and plotted in a nomogram with a bivariate vector (Z). This vector is included in 1 of the 3 ellipses of probability tolerance, which represent the 50th, 75th, and 95th percentile of the normal distribution of the bivariate vectors resulting from a population of healthy people according to gender, age, ethnicity, and BMI. The displacement of the vector parallel to the major axis indicates changes in tissue hydration.
2) The Hydration Index (HI%) expresses the status of hydration as a percentage, and allows quantification of the water overload. The evidence in the literature indicates a role for BIVA in association with BNP for a diagnosis of AHF, as well as a guide for therapy in order to optimize hemodynamic compensation before hospital discharge.[50] Initial data also suggest a possible prognostic role of bioimpedenzometry in predicting cardiovascular events.

Conclusion

Heart failure is a clinical syndrome associated with high rates of morbidity and mortality. The burden of heart failure is likely to increase with time, but effective treatments that improve quality of life and survival are available. Accurate and timely diagnosis is crucial to ensure patients receive appropriate treatment and avoid hospital admissions. However, diagnosing heart failure can be difficult as symptoms and signs commonly overlap with other conditions. A new clinical-decision rule including multiparametric data could help clinicians to achieve a more timely and accurate diagnosis of congestive heart failure to ensure most appropriate therapies.

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