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EDITORIAL

Cardiac congestion assessed by natriuretic peptides oversimplifies the definition and treatment of heart failure

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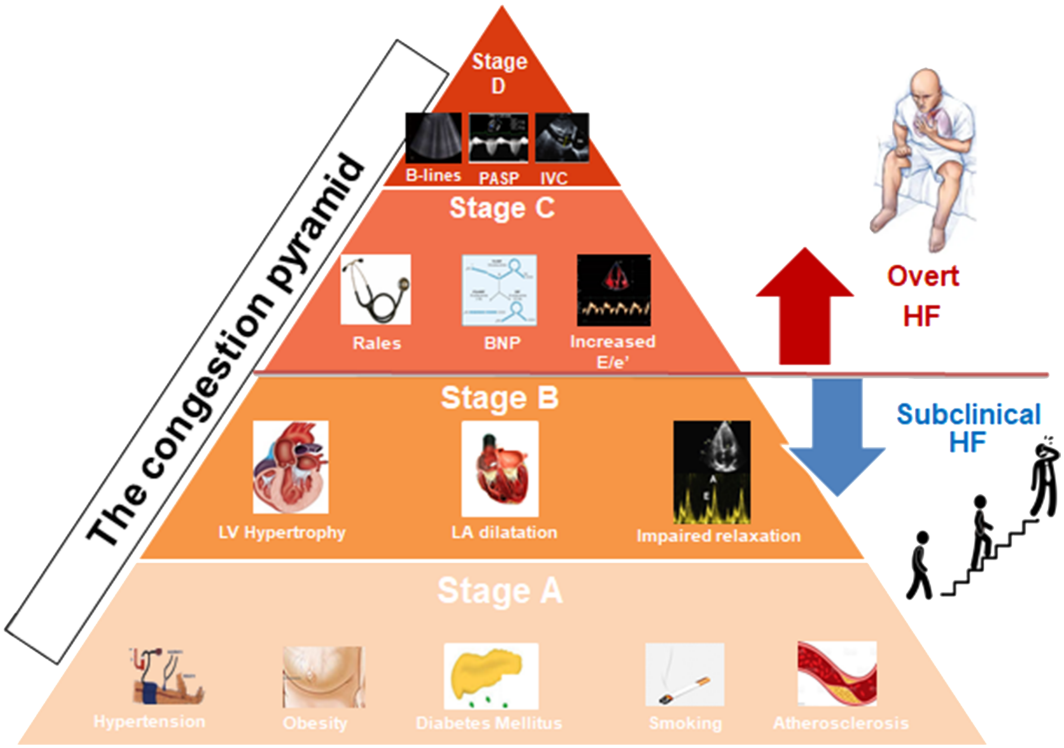
Introduction

The lack of a clear definition and classification of heart failure (HF) impairs the screening, detection and management of this devastating disease. In order to simplify the HF diagnosis, it has been proposed by Cleland et al. in a recent viewpoint that natriuretic peptide (NP) levels should not only be used to 'rule out' but also as an almost sole criterium to 'rule in' the diagnosis of HF. The authors further divide HF in five different phases based upon the presence of congestion, leading to different degrees of intra- and extravascular volume overload.[1] Surely, if these hypotheses were correct, it would simplify diagnosis of HF tremendously and would overcome a lot of the different classification schemes currently used. However, this viewpoint partially contradicts a recent joint consensus document of several HF societies in which HF should be defined based upon symptoms and/or signs caused by a cardiac abnormality and corroborated by elevated NP levels and/or objective evidence of pulmonary or systemic congestion.[2] Additionally, an oversimplification does not take into consideration how complex the syndrome congestion actually is.

Diagnosis of congestion

Congestion plays a central role in the pathophysiology, presentation and prognosis of HF. In 95% of acute HF hospitalizations, congestion, and not low cardiac output, is the main reason for presentation to the clinic.[3] Additionally, subclinical congestion is an important driver of symptoms and disease progression in HF, and residual fluid overload assessed by clinical exam has been clearly linked to worse outcome. However, congestion does not equal volume overload, and often, pressure and volume changes diverge, which complicates the identification and treatment of HF. Therefore, it is not surprising that the assessment of congestion through current clinical assessment correlates at best only moderately with the 'gold standard' of an invasive assessment.[4,5] Therefore, Harjola et al.[6] purposed a congestion score related to organ injury assessed through an integrated ultrasonographic assessment evaluating cardiac, lung and abdominal districts. Importantly, a more accepted algorithm to detect congestion has been first purposed by Gheorghiade and recently adopted by several HF societies.[2,7] This comprises not only the traditional clinical signs and symptoms of congestion but also objective evidence of pulmonary or systemic congestion assessed by technical exams. Nevertheless, previous ESC and US HF guidelines give to ultrasonographic examination only a minor recommendation in HF patients presenting with dyspnoea, and diagnostic examinations remain confined to chest radiography and NP measurement.[8,9] However, new ultrasound methods for the detection of elevated intracardiac pressures and/or fluid overload have been developed, which are more sensitive and specific, thereby enabling earlier and more accurate diagnosis and facilitating treatment strategies.[10] In these echographic assessment, inferior vena cava and internal jugular vein allow to assess central congestion; intrarenal venous flow can facilitate detection of elevated venous pressures, which might help to assess diuretic responsiveness, whereas lung ultrasound enables detection and quantification of extravascular lung fluid.[11] Additionally, a comprehensive analysis of echocardiographic variables allows a non-invasive assessment of intracardiac pressures (*Figure 1*). As such, a more widespread adoption of non-invasive techniques will complement clinical skills, which should allow for improved diagnosis and management of patients with known or suspected HF.

FIGURE 1 Diagnostic algorithm including different clinical echography and laboratory variables for distinguish heart failure stages: During subclinical HF, cardiovascular risk burden and echocardiographic features may predict HF development. After HF occurrence, clinical examination and detailed ultrasonographic assessment became priority to recognize cardiac congestion. BNP, B-type natriuretic peptide; IVC, inferior cava vein; LA, left atrium; LV, left ventricle; PASP, pulmonary artery systolic pressure



NPs as HF hallmark

A universal accepted threshold for NP's to include and/or exclude HF is far from being achieved.[12,13] Although NPs surely have diagnostic and prognostic importance in acute and advanced HF, they are of limited help to guide HF therapies.[14,15] In addition, the role of NPs to diagnose patients at risk for HF and those with structural heart disease without clinical evidence of congestion (Stages A and B) is questionable.[16] Atrial enlargement and left ventricular dilatation/hypertrophy are a natural attempt to avoid intracardiac pressure elevation in accordance with Laplace law. Therefore, NPs are not necessarily elevated, and HF diagnosis could be delayed and even missed if based only on laboratory test.[17] Additionally, clinicians should take into consideration different cut-offs for heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) before they can rule out patients from having HF.[18,19] Moreover, several cardiac conditions such as atrial fibrillation, pulmonary hypertension and elevated E/e1 ratio are associated with increased NP levels, whereas mitral regurgitation and pericardial constriction diuretic/decongestion treatment may decrease NP levels.[20,21] Finally, many other non-cardiac diseases, such as chronic kidney disease (CKD), anaemia, obesity, endocrine–pulmonary diseases and inflammatory disorders, differently impact NP levels. Therefore, the comparison of NPs in HF with troponin (TnT) in myocardial infarction does not appear to be reliable enough (*Table 1*).

The notion of intravascular and extravascular congestion

In the diagram showing congestion grading, Cleland et al.[1] suggested that for each HF stage, a concomitant and parallel fluid overload occurs. Unfortunately, this too is an oversimplification as congestion does not equal volume overload and often pressure and volume changes diverge, which complicates the identification and treatment of HF.[22,23] In its essence, congestion indicates excessive vascular crowding of the central venous bed due to increased cardiac filling pressures. In HF, both an increase in extracellular volume and a

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Table 1 Scheme of potential advantages and disadvantages related to the extensive and unique natriuretic peptide measurement: blood assay may be supported by integrated ultrasonographic tool

Strength	Weakness
Diagnostic accuracy in AHF	Wide range of grey zone
Useful for prognostic risk assessment	Different threshold for patients screening
Good relationship with E/e1 and invasive measures	Reduced threshold in HFpEF
Relevant predictive positive power	High variability and mild specificity
Significant correlation with NYHA class	Influenced by systemic diseases
Simply and available markers in general population	Reduced in certain cardiac disorders
Reliable biomarker for systemic fluid overload	Unreliable during initial cardiac remodelling and HF stages
High accuracy with pulmonary congestion in AHF	High dependency on BMI sex, age and race
Useful for guiding depletion treatment	Inconsistent results for guiding treatment in CHF

change in the compliance of venous beds can lead to an increase in filling pressure with the former often referred to as volume overload and the latter volume redistribution. Due to a rich innervation of $\alpha 1$ and $\alpha 2$ receptors in the splanchnic system, the compliance state in response to changes of the sympathetic tone can quickly change, thereby meeting preload demands of the heart. This in turn will allow the cardiovascular system to keep meeting the body's metabolic demand by tuning venous return to cardiac output. As such, dynamically increasing the venous return is achieved by the splanchnic system due to the recruitment of passive blood volumes, which normally do not contribute to the effective circulatory volume. Importantly, these changes (i.e. congestion) can occur very fast and without a change in total blood volume. It has long been recognized that central filling pressures often drop spontaneous following right heart catheterization and transfer to a cardiac care unit even before any vasoactive drugs have been administered.[24] Additionally, the fact that only half of the patients exhibit a weight gain of more than 0.9 kg the month preceding hospital presentation for acute HF further indicates that changes in the compliance state of the venous beds are more important drivers of an increase in congestion.[25] Finally, data from direct blood volume analysis indicate that successful reduction in filling pressures after decongestive therapy are often not associated with resolution of blood volume expansion.[26,27]

The authors further argue that HF treatments have the best risk reduction in patients with congestion.[1] In line with that thinking, numerous acute short-working agents have been developed the last decades in an attempt to improve congestion (dobutamine, serelaxin, nesiritide, tezosentan, rolofylline, levosimendan, ularitide, etc.). Whereas most of these drugs have demonstrated faster symptom control and improvement in central haemodynamics, none of these therapies have improved outcome. Therefore, the prospect of improved long-term prognosis with short-term drug therapy only aimed at congestion relief also has shown to be wrong. Although it is clear that the mechanisms contributing to congestion (volume overload or volume misdistribution) overlap and often occur simultaneously in clinical practice, determining to what extent each mechanism contributes is probably needed to direct the emphasis of therapy. Pivotal to understand this process is the fact that the interstitium buffers most of sodium and water and that the kidney is the only organ capable of excreting sodium and water in a regulated fashion.[28] Although sodium is retained iso-osmotically in the extracellular compartment, it is distributed for 1/4th in the plasma compartment and 3/4th in the interstitium.[29] Therefore, small rises in plasma volume are always paralleled with a higher rise in interstitial volume. As such, adequately tackling volume overload not only requires a well-balanced diuretic scheme, but the prerequisite is optimal perfusion of the kidneys while lowering renal venous pressure and strategies to enhance plasma-refill rate.[30,31] When volume misdistribution is driving congestion, the goal of therapy should be to enhance venous capacitance function in order to lower cardiac filling pressures.

In conclusion, a comprehensive diagnostic approach using clinical, laboratory and technical exams will remain important to diagnose and differentiate between signs of congestion and volume overload related to cardiac dysfunction, especially in the preclinical stages of the disease. A better identification is needed to reduce the HF syndrome deterioration and might allow to 'intercept' HF before it is too late.

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Conflict of interest

None declared.

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