Ventilation/perfusion SPECT: One more promising resource to fight the medical Hydra

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According to World Health Organization, cardiovascular diseases are the leading cause of death not only in the United States, but also around the world.¹ Heart failure (HF) represents the natural evolution of many primary cardiac and extracardiac disorders. Nearly 5 million currently live with chronic HF in the United States with approximately 550,000 new diagnoses annually and an incidence approaching 10/1000 person-years after age 65.² In Europe, the incidence of chronic HF is around 5/1000 person-years in adults and the prevalence of HF appears to be 1%-2% of adults.³ As studies only usually include recognized/diagnosed HF cases, the true prevalence is likely to be higher.

Cleland⁴ equated HF to Hydra, the mythological, terrifying, multi-headed monster. He pointed out the many shared characteristics, including the assonance of the term “hydrops”, anciently used to describe HF, underlying one of the most impressive hemodynamic derangement of the disease, salt and water retention.

Indeed, the definition of HF is made difficult by the considerable variability of the etiologies, pathogenetic and pathophysiological mechanisms, symptoms and clinical signs of this syndrome. Many attempts have been made in order to identify adequate criteria to define HF.^{5,6} These criteria include clinical, epidemiological, pathogenetic and pathophysiological aspects, the latter related to hemodynamic responses to exercise and therapeutic treatments. The need for a precise definition

of HF reflects the opportunity to introduce criteria to stratify the groups of patients according to the severity of the disease and the peculiarity of the pathophysiological picture, to reveal HF in its initial stage and to implement optimal therapeutic strategies, for the purposes of therapy personalization. The history of medicine teaches that the nosographic identification of a disease, that is to say the knowledge of its clinical profile (symptoms, signs, course, prognosis), very often preceded the discovery of its etiology and the identification of its etiology by centuries, its pathogenetic and pathophysiological mechanisms. The considerable diversity of the definitions of HF proposed so far probably derives not only from the variability of the etiopathogenetic and pathophysiological mechanisms and the clinical pictures, but also from the prevalent clinical or pathophysiological aspect that was intended to emphasize in the definition of the disease. For many years, the most well-known definitions of HF refer above all to the pathophysiology and in particular to a pathological condition characterized by insufficient capacity of the heart to pump quantities of blood adequate to the metabolic needs of the organism during exercise and, in the most serious cases, even in conditions of rest. Very widely cited is the definition proposed by Braunwald,⁷ according to which “HF is the pathophysiological state in which an anomaly of the cardiac function is responsible for the heart’s failure to pump blood in an amount commensurate with the metabolic demands of the tissues, or to do so only through a high ventricular filling pressure”.

Another definition, also widely adopted, is that of Packer,⁸ according to which “congestive HF represents a complex clinical syndrome characterized from anomalies of the function of the left ventricle and of the neurohormonal regulation, which are accompanied by tolerance to effort, to conservation of hydro saline and reduced life”. However, while both definitions refer to clinical pathophysiological aspect that characterize the

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disease, they are unable to specify the “common denominator” that underlies all forms of chronic HF, regardless of their etiology, pathogenetic and pathophysiological mechanisms, clinical pictures and their evolutionary stage.⁹ Recently, the Writing Committee of the Universal Definition of Heart Failure¹⁰ defined HF a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.

Heart and lungs are closely linked in their function of transporting O₂ and CO₂. Hence, impairment of the lungs often affects the heart and the other way around. In patients with chronic HF, exertional dyspnea is a common symptom, and the ventilation effort increases at a given exercise workload despite normal arterial blood gases. It is well known that in most body positions, with the exception of prone position, a vertical gradient exists in transpulmonary pressure so that the upper lung regions are more expanded than the lower.¹¹ As a result, alveoli are less expanded and have higher compliance at the base, resulting in a more substantial increase in volume on inspiration for increased ventilation. Also, perfusion is greater at the base of the lung due to gravity pulling blood down toward the base. Overall, perfusion increases more than ventilation at the base of the lung, resulting in lower V/Q ratios in the base of the lung compared to the apex. In a healthy individual, in sitting position the V/Q ratio is 1 at the middle of the lung, with a minimal spread of V/Q ratios from 0.3 to 2.1 from base to apex. Lying in supine position the V/Q ratio becomes more homogenous among different parts of the lung. It is also well known that in patients with HF a high ventilation (VE) with respect to CO₂ production (VCO₂) is associated with a poor prognosis, also if in the recent years the peak VO₂ and VE/VCO₂ slope cut-offs identifying a definite risk progressively decreased and increased, respectively, due to the improvement in the HF prognosis over time.¹² It has been hypothesized that the major source for an abnormally steep VE/VCO₂ slope in chronic HF is increased non-uniformity of ventilation-perfusion ratios (V/Q), causing increase in physiological dead space, and inefficient gas exchange.¹³ In chronic HF, the dead space to tidal volume ratio (VD/VT) is both elevated at rest and during exercise compared with normal subjects, suggesting the presence of areas of high V/Q ratios or alveolar dead space due to under perfusion.¹⁴ In fact, in chronic HF, there is flow redistribution with relatively more blood flow to the apical regions of the lungs due to raised pulmonary venous pressure and other pulmonary structural changes. This has been shown radiographically,¹⁵ and for the first time in 1966 by Friedman and

Braunwald using radionuclide lung perfusion scans.¹⁶ In a subsequent study, Mohsenifar et al.¹⁷ used ^{81m}Kr and ^{99m}Tc to assess lung ventilation and perfusion in six patients with chronic HF. At rest, the upper lung zones of these patients received significantly higher proportions of the blood flow compared with previously published data in normal volunteers. However, the Authors failed to demonstrate a correlation between pulmonary capillary wedge pressure and the upper zone or the ratio of upper-to-lower zone perfusion counts.

More recently, ventilation/perfusion (V/P) single-photon emission computed tomography (SPECT) has been proposed for the evaluation of pulmonary congestion.¹⁸ V/P scan may be performed using planar or SPECT imaging. However, recognizing ventilation and perfusion defects at the subsegmental level is considerably better with V/P SPECT than planar imaging.¹⁹ The V/P SPECT method was ideated by Palmer et al.²⁰ and modified by Bajc et al.²¹ Noteworthy, it has been reported that perfusion gradients from V/P SPECT are related to left heart filling pressures and have been validated against invasive right-heart catheterization.²²

Several medical, surgical, and non-pharmacological interventions can help to slow the progression of chronic HF and maintain or improve the quality of life in these patients. Among them, cardiac resynchronization therapy (CRT) is a well-established treatment of HF with reduced left ventricular ejection fraction and a wide QRS complex, approved by the US Food and drug Administration since 2001.²³ CRT is delivered alone or combined with implantable cardioverter defibrillators in the same device. Cardiac contractility modulation therapy is an emerging electrical treatment indicated for use in HF patients and left ventricular ejection fraction ranging from 25 to 45%, with no indication for CRT.

In the present issue of the Journal, Al-Mashat et al.²⁴ in a sub study of patients enrolled in a randomized controlled trial²⁵ evaluated if changes in P/V gradients were associated with improvements in HF symptoms after CRT, and if the changes correlated with diagnostic methods currently-used for follow-up of patients with HF after receiving CRT. V/P SPECT imaging was performed according to the guidelines of the European Association of Nuclear Medicine, as a one-day protocol.¹⁹ The study shows that perfusion gradients from V/P SPECT can objectively quantify the improvement of patients with HF after receiving CRT and are better than echocardiography in demonstrating an improvement in New York Heart Association (NYHA) functional class after the treatment. It is interesting to note the same Authors reported that V/P SPECT is a promising method for objective assessment and quantification of treatment effects in patients with HF after heart transplantation.²⁶

The study of Al-Mashat et al.²⁴ is innovative and interesting and has merits. However, it has also some limitations, partly underlined by the Authors in a specific section of the paper. First, only 19 patients could be included from a larger prospective trial and based on the response criteria 13 improved and six did not. Because of the limited patient number, it is hard to draw definitive valid conclusions. Second, to validate the accuracy of V/P SPECT in detecting a favorable CRT response the Authors selected as gold standard the NYHA functional class, a surrogate marker with many limitations.^{27,28} However, changes in perfusion gradients were not associated with changes in Minnesota living with HF quality of life scoring system. Third, the spontaneous day-to-day variations of V/P SPECT perfusion gradients in chronic HF patients are unknown, while quantifying test-retest reliability is essential for to decide the smallest significative difference due to an intervention and to draw evidence-based conclusions.

Another question is if evaluation and monitoring of perfusion gradients by V/P SPECT may be useful in patients with preserved left ventricular ejection fraction, which represent a remarkable proportion of HF patients. It should be also considered that a still debated problem is how accurately select HF patients for CRT and what are the predictors of a satisfactory CRT response. For this aspect, the study of Al-Mashat et al.²⁴ does not provide information. Nevertheless, evaluating V/P SPECT perfusion gradients in HF is of physiological and of pathophysiological interest. Any strategy that could be useful to delay the progression of chronic HF is welcome. Considering the set of available data, the V/P SPECT appears to have the potential to be a non-invasive and user-independent tool to quantitatively evaluate the promise and results of new HF therapy in clinical trials.

Disclosures

A. Cuocolo and M. Petretta declare that they have no conflict of interest.

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