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Right heart failure in left heart disease: imaging, functional, and biochemical aspects of right ventricular dysfunction

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Abstract
For decades, cardiologists have largely underestimated the role of the right heart in heart failure due to left heart disease. Nowadays, the importance of evaluating right ventricular (RV) structure and function in left heart failure is well documented and this concept has been emphasized in the most recent heart failure guidelines. However, several relevant questions remain unanswered such as the following: (a) which imaging technique (standard or 3D echocardiography or strain imaging or cardiac magnetic resonance) and, more, which parameters should be used to grade the severity of RV dysfunction? (b) do less widespread and less applied diagnostic tools such as cardiopulmonary stress testing and bioelectrical impedance analysis play a role in this field? (c) are there specific biochemical aspects of RV failure? (d) why notion of pathophysiology of heart and lung interaction are so well appreciated at an academic level but are not applied in the clinical setting? The present review has been prepared by the Heart Failure (HF) working group of the Italian Society of Cardiology and its main objective is to improve our understanding on RV dysfunction in heart failure.

Keywords Right heart function · Echocardiography · Cardiac magnetic resonance · Right heart catheterization · Strain · Bioelectrical impedance analysis

Imaging the right ventricle

Imaging the right ventricle is crucial in heart failure patients for many reasons: to reach a precise diagnosis, to stratify prognosis, to tailor pharmacological and non-pharmacological treatment. However, whichever imaging technique is used, it remains a very challenging task, mainly due to the complex anatomy of this heart chamber. Anatomically, the right ventricle can be divided into two components: the sinus which extends from the tricuspid valve (inflow region) and includes the trabeculated apical portion of the ventricle and the conus (outflow region) which is usually free of muscular trabeculations and extends from the septomarginal band to the pulmonary valve. The sinus and the conus regions are separated by the parietal band and the infundibular septum which make up the crista supraventricularis; the moderator band extends from the base of the anterior papillary muscle to the ventricular septum [1]. In addition, the complex anatomy is associated with a peculiar position immediately beneath the sternum. As a consequence, the basic measurements which are the cornerstones of the morpho-functional evaluation of the left ventricle for all clinicians and researchers, i.e., chamber volumes and ejection fraction, are difficult to obtain for the right ventricle.

Cardiologists are therefore left with difficult choices to study the right ventricle, both as regards the imaging technique and the parameter to be used (i.e., to favor a simpler examinations or the completeness of the gold standard technique, to seek precise volumetric measurements of the right ventricle or more simple morpho-functional surrogates). Table 1 outlines main advantages and limitations of various techniques in imaging the right ventricle.

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Table 1 Main advantages and limitations of various techniques and parameters in imaging the right ventricle

Technique/Parameter	Advantages	Limitations
Standard Echocardiography		
TAPSE	• Fast and easy to measure • Reproducible • Prognostically relevant	• Angle and load dependent • Reflects only longitudinal function • Neglects contribution of apical and outflow tracts
S′ velocity	• Fast and easy to measure • Reproducible • Prognostically relevant	• Angle and load dependent • Reflects only basal lateral longitudinal function • Neglects contribution of apical and outflow tracts
RVFAC	• Fast and easy to measure • Reflects longitudinal and radial function • Prognostically relevant • Good correlation with CMR-derived RVEF	• Poor reproducibility • Neglects contribution of the RVOT • Load dependent
RV MPI	• Provide information on global RV function • Prognostically relevant • Does not require geometrical assumptions	• Unreliable in case of elevated RAP or irregular rhythms
Strain Imaging Echocardiography	• Less angle and load dependent • Less confounded by RV geometry and passive motion • Reproducible • Prognostic value	• Requires good 2D image quality • Neglects contribution of outflow tract • Requires post-processing • Limited availability • Vendor dependency
3D Echocardiography	• Does not require geometrical assumptions • Validated against CMR • Superior prognostic value to other RV echo parameters	• Load dependency • Requires good 2D image quality • Need for patient's co-operation and regular R–R intervals in case of multi-beat acquisition • Limited availability • Requires post-processing
CMR	• Gold standard imaging modality for assessment for RV volumes and EF • Excellent image quality • Free from acoustic window limitations • Independent of geometric assumptions • Prognostic value	• Costly and time consuming • Limited availability • Use limited to clinically stable patients • Need for patient's co-operation • Impaired image quality/accuracy in patients with intracardiac leads • Challenging positioning of basal slice during post-processing

(a) Standard echocardiography

Echocardiography is the mainstay of the assessment of right ventricular (RV) function [2]. Recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging advocate quantitative assessment of global RV function by at least one of the following parameters: right ventricle fractional area change (RVFAC); tricuspid annular plane systolic excursion (TAPSE); Doppler tissue imaging-derived systolic S velocity of the tricuspid annulus; or RV myocardial performance index (RV MPI) [3] (Table 2).

TAPSE is commonly used to assess the global RV systolic function. It is both highly specific and easy to measure. It measures the apical displacement of the lateral portion of the tricuspid valve annulus during systole from an M-Mode recording. According to the guidelines, a value of TAPSE < 16 mm indicates RV systolic dysfunction (Table 2). In patients affected by chronic HF, literature data clearly demonstrate that a poor TAPSE is associated with worse prognosis, regardless of etiology of HF and regardless of the severity of left ventricular dysfunction [4–7]. Importantly, improvement of TAPSE after therapy optimization improves prognosis [8]. However, assessing the RV function without pulmonary artery pressure is inappropriate if not a real mistake being the right ventricle highly afterload dependent despite that the RV morphology is prone to adapt to major volume and pressure adaptations. In fact, a further refinement in prognostic stratification can be obtained TAPSE with pulmonary artery pressure [9, 10]. S′ velocity of the tricuspid annulus (RV S′) is derived by tissue Doppler echocardiography (TDE) and it corresponds to maximum systolic tricuspid valve lateral annular velocity. In patients with HF and atrial fibrillation (AF), RV S′ can be an independent predictor of outcomes. In stable patients with LV systolic dysfunction, RV S′ may add prognostic information over RVEF and TAPSE [11, 12]. The limit of TAPSE and RV S′ is that both measures are angle dependent and only reflect the longitudinal function of the basal portion of the RV, not considering

Table 2 Normality thresholds of imaging parameters describing right ventricular dimensions and function

Methods	Parameters	Cutoff value for RV dysfunction
Standard echocardiography	Right ventricle fractional area change (RVFAC)	< 35%
	Tricuspid annular plane systolic excursion (TAPSE)	< 17 mm
	Doppler tissue imaging-derived systolic S velocity of the tricuspid annulus	< 9.5 cm/s
	RV myocardial performance index (RV MPI)	> 0.43 using PW Doppler > 0.54 using TDE
	RV End-Diastolic Volume indexed to BSA	> 87 mL/m^2 (men) > 74 mL/m^2 (women)
	RV End-Systolic Volume indexed to BSA	> 44 mL/m^2 (men) > 36 mL/m^2 (women)
Strain imaging Echocardiography	RV Free Wall Longitudinal Strain (RVFWLS)	< 20%
	RV Global Longitudinal Strain (RVGLS)	< 20%
3-dimensional Echocardiography	3D-RVEF	< 45%
	RV 3D Global-Free-Wall Longitudinal Strain (3DGFW-RVLS)	−17%
	RV End-Diastolic Volume indexed to BSA	Age 30–39 > 77 mL/m^2 (women) > 85 mL/m^2 (men) Age 40–49 > 65 mL/m^2 (women) > 78 mL/m^2 (men) Age 50–59 > 69 mL/m^2 (women) > 76 mL/m^2 (men) Age 60–69 > 64 mL/m^2 (women) > 86 mL/m^2 (men)
	RV End-Systolic Volume indexed to BSA	Age 30–39 > 38 mL/m^2 (women) > 38 mL/m^2 (men) Age 40–49 > 27 mL/m^2 (women) > 37 mL/m^2 (men) Age 50–59 > 29 mL/m^2 (women) > 36 mL/m^2 (men) Age 60–69 > 26 mL/m^2 (women) > 36 mL/m^2 (men)
Cardiac magnetic resonance imaging (CMR)	RVEF	< 51%
	End-Diastolic Volume/End-Diastolic Volume indexed to BSA	> 201 mL/ < 112 mL/m^2
	End-Systolic Volume/End-Systolic Volume indexed to BSA	> 84 mL/ > 52 mL/m^2

BSA body surface area, *RV* right ventricle, *TDE* tissue Doppler echocardiography, *PW* power Doppler

the contribution of the apical and outflow tract components. RVFAC is another index of global RV systolic function (normal value is > 35%), which accounts for both the longitudinal and radial components of the RV contraction but neglects outflow tract contraction. It showed a good correlation with the measurement of the right ventricular ejection fraction (RVEF) derived by magnetic resonance imaging [13]. Lower values of RVFAC were found to be associated with an increased risk of all-cause mortality, cardiovascular (CV) death, sudden death, HF, and stroke [14]. It is load dependent and potentially difficult to acquire in the case of poor endocardial definition, which limits its value in current clinical practice. Assessment of RVEF based on two-dimensional echocardiography is not recommended, as the limits found in the measurement of the RVFAC are enormously amplified in the calculation of RVEF. RV MPI or Tei index, calculated by dividing the total isovolumic time (isovolumic contraction plus isovolumic relaxation) by the ejection time, is a parameter of global RV function, which is associated with the risk of cardiac events in HF [15]. The proposed cutoff values for abnormal RV MPI are > 0.43 using pulsed-wave Doppler and > 0.54 using tissue Doppler

echocardiography (TDE) (Table 1). The advantage of RV MPI is that it may overcome the limitations of the complex RV geometry, as it is only derived from time intervals and it does not require assumptions on RV shape, but it may be unreliable in patients with elevated right atrial pressure and irregular rhythms.

(b) Strain imaging

The analysis of myocardial deformation (i.e., "strain") of RV ventricular walls using speckle-tracking echocardiography (STE) allows to obtain feasible and reproducible measures of RV systolic function which overcome most limitations of M-Mode or tissue Doppler techniques [16] (Fig. 1). Strain analysis is less dependent on imaging plane angle and discriminates active myocardial deformation from passive movement of dyssynergic myocardium [17]. RV free wall longitudinal strain (RVFWLS) can be calculated averaging the three segments (basal, medial, apical) of RV free wall, or including the interventricular septum (RVGLS) [18, 19]. Both measures have shown good correlation with RVEF measured by cardiac magnetic resonance imaging (CMR) but require an optimal acoustic window and complete RV free wall visualization [20].

RV strains are impaired in HF patients, and in small single-center studies, they have been associated with outcome and exercise capacity, showing an incremental prognostic power to that derived from conventional echocardiographic parameters. In addition, RVFWS may be impaired even in the presence of a normal TAPSE, possibly documenting subtle abnormalities of RV contractility associated with increased risk of adverse cardiac events [21]. On the other side, assessment of RV longitudinal strain also proved to be the strongest echocardiographic predictor of RV failure in most advanced HF patients after left ventricular assist device (LVAD) implantation [22].

In summary, the strength of strain is the possibility to measure shortening rather than motion, thus better reflecting function. The limitations of RVFWS include a great variability between different software analysis systems, and a relative dependence on the quality of 2D image.

(c) 3D echocardiography

Because of its peculiar shape and geometry, RV volume assessment is challenging and is not recommended using 2D measurements. CMR is currently the gold standard for quantitative assessment of RV volumes and RV EF. However, CMR is not widely available and is time consuming. Echocardiographic 4D (semi-)automated volume quantification tools for the RV are now available and provide more objective and accurate measurements than those

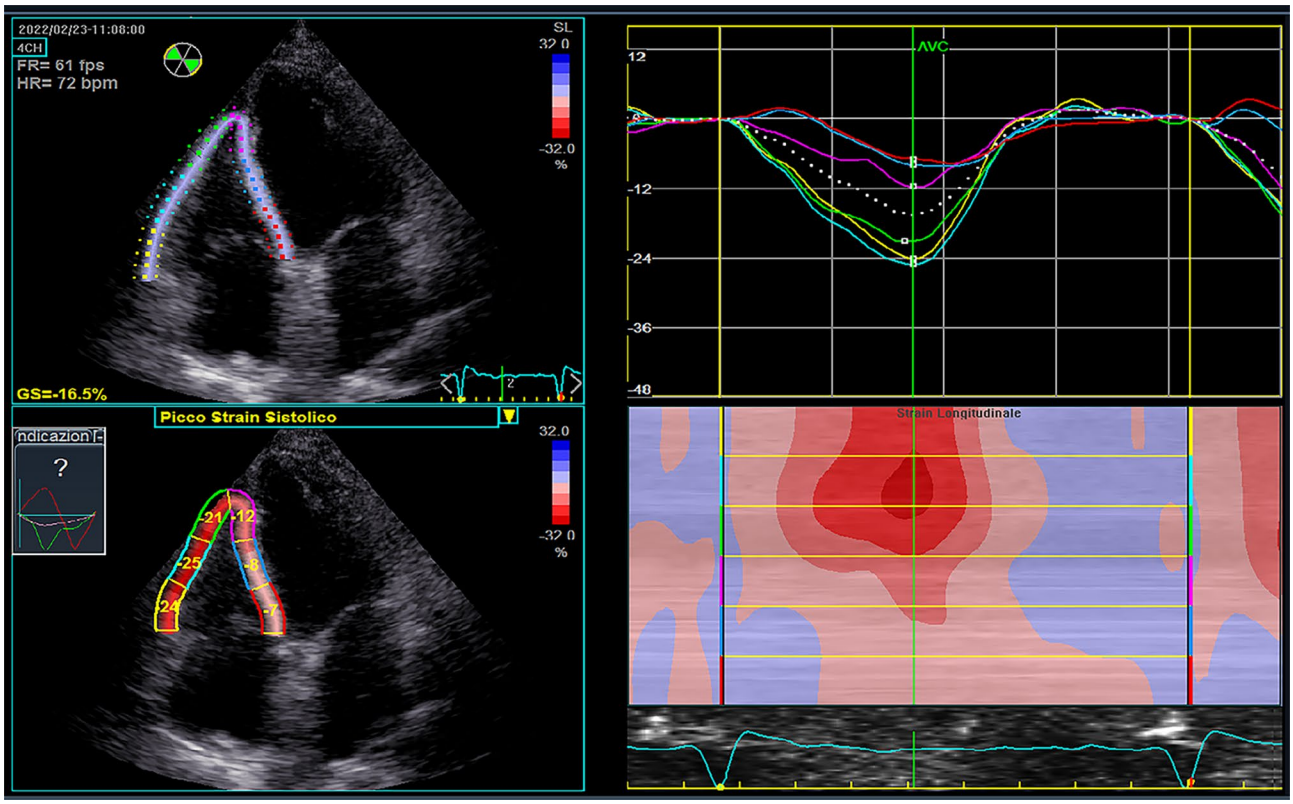


Fig. 1 2D speckle-tracking right ventricular strain

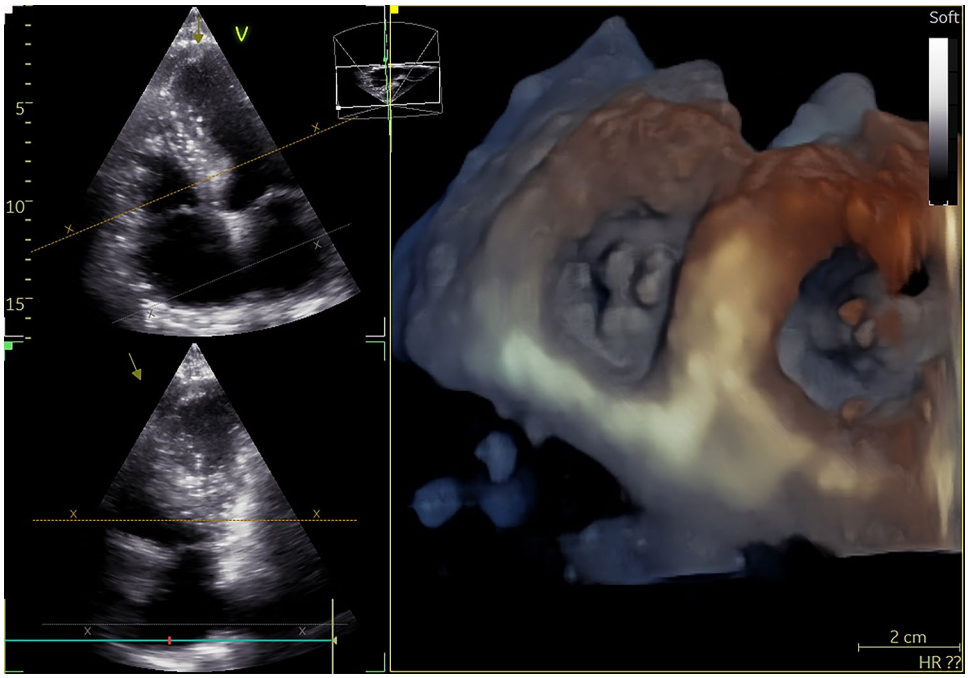


Fig. 2 3D echocardiographic imaging of the right ventricle

derived from 2D echo, overcoming the geometric assumptions used in 2D echo [23]. From apical RV-focused view, images are acquired with 3D probe by means of a full-volume data set and a multi-beat acquisition (Fig. 2), and data set analyzed with a dedicated software after tracing the RV endocardial border, allowing reconstruction of the RV geometry and calculation of RV volumes and EF. 3D-RV volumes and EF have been validated against CMR in normal subjects and in patients with dilated RV, showing good accuracy and reproducibility [23]. Receiver operating characteristic curves showed that the thresholds offering an adequate compromise between sensitivity and specificity for detecting hemodynamic signs of RV failure were 39% for 3D-RVEF (AUC 0.89) and −17% for 3DGFW-RVLS (AUC 0.88) [23] (Table 2). Impaired 3D-RVEF is also an independent predictor of RV failure after LVAD implantation [24]. The main limitations of 3D echocardiography are load dependency (as for TAPSE and RVFAC) and challenges in acquiring adequate images and in correctly tracing the endocardial borders of the RV chamber.

Cardiac magnetic resonance

Cardiac magnetic resonance imaging (CMR) allows to obtain dynamic images of the cardiac chambers with high spatial and temporal resolution, with excellent definition of the endocardial borders and without the need for geometrical assumptions (Fig. 3). These technical characteristics are perfectly suited for the assessment of structure and function of the right ventricle (Table 2), because of its complex anatomy and mechanics and its unfavorable location within the chest (i.e., behind the sternum) [25].

The direct assessment of RV systolic dimensions and function with cine imaging is a powerful marker of poor prognosis in patients with advanced heart failure, regardless of the degree of left ventricular dysfunction [26–29]. The evaluation of RV function can be easily combined with phase contrast imaging of the main pulmonary artery with the possibility of obtaining both morphological and functional information on pulmonary circulation (including cyclic changes in vessel size, flow volume, and flow rates); the clinical usefulness of this information in heart failure is yet to be determined. Late gadolinium enhancement (LGE) sequences may allow the detection of areas of myocardial damage induced by chronic ventricular overload (typically observed at the level of the RV insertion points). Ongoing large population studies will ascertain the prognostic relevance of RV scar detection which has been suggested in smaller single-center studies [30]. Literature data on clinical and prognostic usefulness of non-invasive assessment of RV-arterial coupling in heart failure patients using CMR-derived parameters is limited but it is extremely promising, given the importance of the adequacy of RV functional adaptation to afterload in patients with pulmonary hypertension [31]. The identification of early changes in RV function by feature tracking CMR analysis on cine images has also the potential to be of interest to clinicians [32].

In general, it must be acknowledged that most of the data regarding the clinical usefulness of CMR in the evaluation of patients with RV dysfunction have been produced in selected

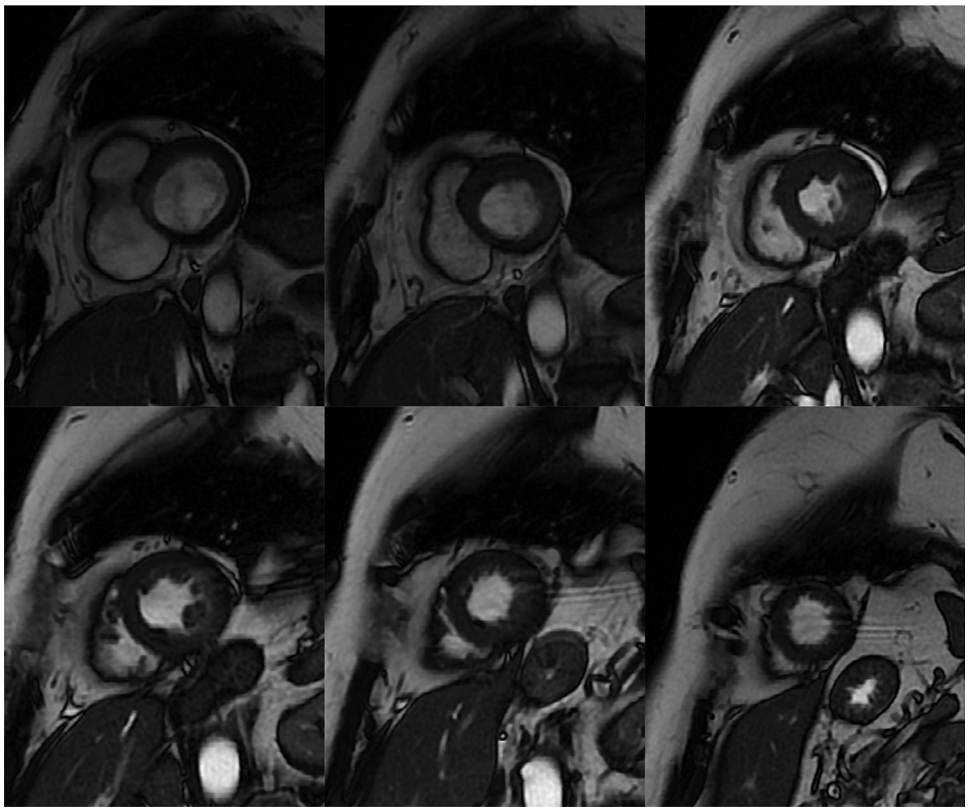


Fig. 3 Cardiac magnetic resonance imaging of the right ventricle

specialized centers. In clinical practice, high costs and lack of trained operators still contribute to prevent a more diffuse use of CMR. It must be recognized that the possibilities for the future development of CMR are so wide that it is difficult not to imagine an exponential growth in the use of this technique in patients with heart failure**.**

Right ventricular reserve

As for the left cardiac disease, the evaluation of RV may be performed not only at rest but also during stress. Indeed even in patients with impaired RV function at rest, who by definition have a poor prognosis, there may be the necessity to unmask phenotypes with different levels of risk. To this aim, an interesting hypothesis is to assess the role of contractile reserve of the right ventricle albeit stress echocardiography (whether physical or pharmacological) has been focused almost exclusively on the left ventricle. More recently, the impact of RV contractile reserve on exercise intolerance has been investigated in 67 high-risk HF patients [33]. The change in RV s′ velocity during the test correlated with peak oxygen consumption (VO2) and was a robust predictor to determine exercise intolerance [33]. In another study, the simple increase in TAPSE above a threshold of 15.5 mm during exercise was associated with a greater ventilatory efficiency in a population of 97 HF patients who could undergo maximal exercise stress echocardiographic and cardiopulmonary exercise testing [34]. Further studies are warranted to validate the hypothesis that RV contractile reserve has a predictive value in patients with advanced HF.

Another simple and practical method to disclose the presence of functional reserve of the right ventricle in patients with heart failure and high pulmonary artery pressure is the evaluation of the changes in RVEF after an acute afterload reduction; the rationale is the strong dependence of RV systolic function to the afterload imposed on this cardiac chamber. This hypothesis has been tested in 76 patients with advanced heart failure and pulmonary hypertension (PH) under evaluation for potential heart transplant listing [35]. During right heart catheterization, the hemodynamic measurements, including thermodilution-derived right ventricular ejection fraction, were repeated after an intravenous bolus of nitroglycerin (NTG). During a median follow-up period of 8.2 months, 47 patients had a cardiac event (death or urgent heart transplantation). At survival analysis, a multivariate model that included the New York Heart Association class and the hemodynamic variables obtained after NTG administration allowed a better assessment of the short-term prognosis of the patients than a model including the baseline variables. In particular, the improvement of RVEF in response to the acute pulmonary vasodilation identified patients at lower risk [35].

Similar conclusions were obtained in a retrospective analysis of 402 heart failure patients with pulmonary hypertension who underwent right heart catheterization and a pulmonary vasodilator challenge. A lower increase in cardiac index (CI) and stroke volume index (SVi) and (with a borderline statistical significance) a lower increase of RVSWi were all associated with poorer prognosis [36].

Right heart catheterization

Characterization of pulmonary hemodynamics cannot rely only on non-invasive methods. In fact, Doppler echocardiography allows for accurate measurements of the pulmonary circulation (little bias), but with moderate precision (large limits of agreement), explaining why the non-invasive measure is valid for population studies but cannot be used for the individual diagnosis of pulmonary hypertension [37].

According to the recommendations of European HF guidelines, right heart catheterization (RHC) is mandatory in patients listed for heart transplantation (HT), since high pulmonary vascular resistance remains a major contraindication to transplant listing (Table 3). In addition, according to the recommendations of European guidelines on pulmonary hypertension, the invasive measurement of pulmonary artery wedge pressure is pivotal in discriminating between pulmonary arterial hypertension from PH due to left heart disease in those cases in which neither clinical, biomarkers, nor echocardiographic variables have been able to define the diagnosis [38]. Nevertheless, a single measure of pulmonary artery wedge pressure might be misleading since this measure is highly volume dependent. For this reason, it might be appropriate to perform a fluid challenge test in those having a clinical profile consistent with heart failure with preserved ejection fraction (HFpEF, elderly, several comorbidities), albeit an invasively assessed wedge pressure < 15 mmHg [39].

Besides diagnosis, RHC is likely to provide important prognostic information in HF patients. Contrary to expectations, the direct assessment of RV function at RHC (measuring the RV stroke work or the RV stroke volume) has a limited role in the clinical scenario of HF patients. There is only one exception: a RV stroke work index < 300 mmHg × mL/m^2 is an independent predictor of RV failure after implantation of LVAD, and thus, this parameter has to be calculated to plan a correct strategy in advanced HF [40].

Bioelectrical impedance analysis

Body fluid can be assessed by bioimpedance vector analysis (BIVA). This method measures the ability of biological tissue to oppose electric current administered by four surface electrodes, two on the wrist and two on the ankle [41]. Bioelectrical impedance consists of two components: resistance (Rz) and reactance (Xc). Rz is inversely related with the amount of total body water, while the Rz is proportional to body mass. It only requires few seconds to give the results of body tissue impedance that is inversely proportional to fluid overload.

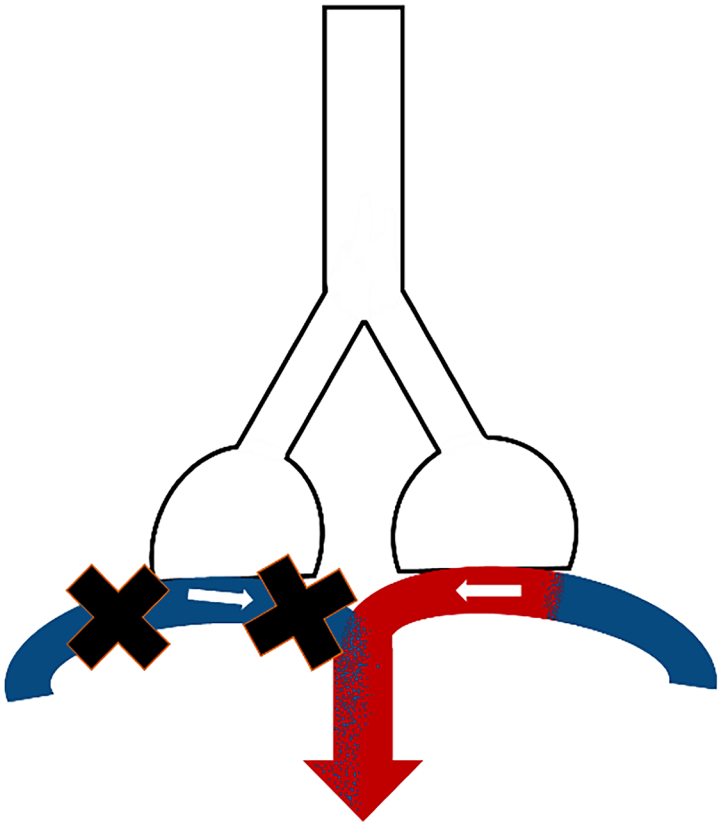
BIVA can be applied in every clinical setting due to its favorable characteristics of noninvasiveness, accuracy, and portability. Total body water assessment by BIVA produces a measure of body congestion. This method has been used to assess congestion. It has been shown in severe heart failure patients that the higher the hydration state evaluated by BIVA, the longer the hospital length of stay [42]. In addition, a prospective observational study showed that BIVA can predict cardiovascular events at 90 days in acute decompensated heart failure (ADHF) [43].

In addition to ADHF, BIVA has shown a good diagnostic performance in chronic heart failure (CHF) patients. BIVA was more accurate than brain natriuretic peptide (BNP) in detecting peripheral congestion in CHF in a retrospective study [44]. Of note, in a small preliminary study of ambulatory patients with HF, BIVA also distinguished between stable and unstable heart failure patients: patients with stable HF had significantly lower impedance measured fluid

Table 3 Indications to right heart catheterization in HF patients

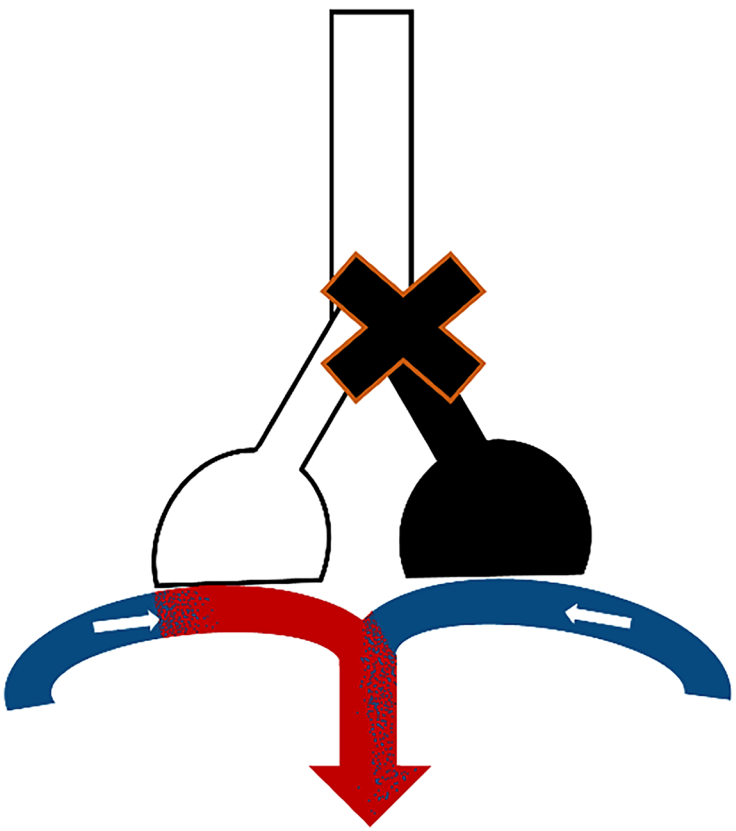
Indication	Class of recommendation	Level of evidence
Patients with severe HF listed to HT and/or MCS	I	C
Patients in which HF is thought to due constrictive pericarditis, restrictive cardiomyopathy, congenital heart disease, and high output states	IIa	C
Patients with probable PH at echo to be confirmed before correction of valve/structural heart diseases and eventually its reversibility	IIa	C
In selected patients with HFpEF to confirm diagnosis	IIb	C

HF heart failure, *HT* heart transplant, *MCS* mechanical circulatory support, *PH* pulmonary hypertension, *HFpEF* heart failure with preserved ejection fraction



A:

$PetCO_2$ ↓
$PaCO_2$ ↔
$Pa\text{-}etCO_2$ ↑
sVE/VCO_2 ↑
Y-INTER ↓
$r\ VE/VCO_2$ ↑
Normoxia



B:

$PetCO_2$ ↔
$PaCO_2$ ↑
$Pa\text{-}etCO_2$ ↑
sVE/VCO_2 ↔
Y-INTER ↑
rVE/VCO_2 ↑
Hypoxia

◂**Fig. 4** Ventilation/perfusion mismatch. *Panel A*. Ventilation/perfusion mismatch: ventilated lung areas not or poorly perfused. *Panel B*. Ventilation/perfusion mismatch: lung areas perfused but not ventilated. For abbreviations see text

load ratio (R/H) and cardiac stress biomarkers, such as NT-proBNP, than patients with unstable HF. A variable composed of a bioimpedance component related to fluid overload (R/H) and a biomarker of cardiac stretch (NTproBNP) was developed and named HF-impedance index [(R/H)/log 10(NTproBNP)]. This index was significantly lower in non-stable HF patients as compared to stable patients [45].

In addition to these findings, there is evidence that fluid assessment with BIVA correlates with mortality. In a retrospective study enrolling consecutive ADHF and CHF patients, Kaplan–Meier analysis indicated a significant increase in all-cause mortality rate when the values of the markers of congestion, including BIVA hydration index, were above the calculated cutoff, namely plasma volume status > 5.3 dL/g, BNP > 441 pg/mL, hydration index evaluated by BIVA > 73.8%, and blood urea nitrogen/creatinine ratio (BUN/Cr) > 25. In the multivariate analysis, BIVA hydration index remained an independent predictor of all-cause mortality [46].

In conclusion, BIVA appears to be a promising but so far poorly studied method for the assessment of congestion in RV failure patients.

Cardiopulmonary exercise testing

During exercise, in patients affected by impaired RV function in the context of left CHF, the functional limitation may be assessed by the use cardiopulmonary exercise test (CPET).

RV function in patients with CHF is an important determinant of exercise capacity, in terms of VO2 peak and minute ventilation/carbon dioxide production (VE/VCO2) relationship slope, as expression of ventilatory efficiency during maximal efforts. VE/VCO2 slope provides an indirect assessment of RV in the left-sided HF population [47] and the ventilatory inefficiency may be a marker of more advanced right-sided HF in patients with severe LV systolic dysfunction [48].

In patients with HF, higher pulmonary arterial systolic pressure (PASP) by echocardiography was associated with worse percent predicted peak VO2 and this association was more robust in patients with LVEF ≥ 45% vs < 45%. Lower RVFAC derived by echocardiography was associated with both worse percent predicted VO2 and higher VE/VCO2 slope [49].

Pulmonary hypertension may be a consequence of left-sided HF and impairs exercise performance. CPET could be considered a diagnostic tool for the detection of left-sided PH in HF and for the assessment of its clinical impact on patients' symptoms. A VE/VCO2 slope ≥ 36.0 was the best predictor of a PASP ≥ 40 mmHg. Peak end-tidal CO2 (PETCO2) ≤ 34 mmHg and the presence of exercise oscillatory ventilation (EOV) could help diagnose [50]. Other authors showed that VE/VCO2 slope (> 41), change in PETCO2 on exercise (< 1.2 mmHg), and EOV were independently associated with reactive PH [51].

In patients with PH due to left-sided HF, some CPET parameters are different in presence of combined post- and pre-capillary PH (PPC-PH) compared with patients with isolated post-capillary PH (IPC-PH) or no PH. PETCO2 and arterial oxygen saturation (SaO2) were greater in no-PH and IPC-PH versus PPC-PH patients. Dead space ventilation (VD/VT) and VE/VCO2 ratio were lower in no-PH and IPC-PH versus PPC-PH patients [52]. Lowest percentage of VE/VCO2 predicted value is the single best predictor of PPC-PH. Moreover, the parameters related to VE/VCO2 have a moderate positive correlation with pulmonary vascular resistance (PVR) [53].

Special attention should be dedicated to the intercepts on the *Y*-axis of the ventilation to VCO2 relationship, i.e., to the value of ventilation at VCO2 = 0. This value is highly influenced by dead space and its development during exercise so that a value exceeding or below the normal range (4.9 ± 1.4 L/min) implies high dead space at rest and development of dead space during exercise [54]. Poor right ventricular-arterial coupling (RV-PA) is also associated with more severe HF, reduced exercise capacity (peak oxygen uptake, peak oxygen consumption), and less efficient ventilation (steeper VE/VCO_2 slope) [55]. Thus, the use of CPET may help clinicians in clarifying the causes and the degree of dyspnea on efforts in patients with RV failure associated with left-sided HF and to better assess the presence, the degree, and the type of PH in such context.

Coupling of ventilation to blood flow

The lung and pulmonary vasculature are vital layers of right ventricular function by contributing to right ventricular afterload. Indeed, ventilation/perfusion mismatch represents a common finding in several cardiorespiratory diseases including, chronic obstructive lung disease, interstitial lung disease, heart failure, and pulmonary hypertension. The term mismatch indicates an erroneous coupling of ventilation and perfusion and it can be characterized by ventilated lung areas not or poorly perfused and/or by lung areas perfused but not ventilated. In Fig. 4, a schema of the two types of ventilation/perfusion

mismatch and the consequences on ventilatory parameters during exercise is reported. The efficiency of ventilation is present when the relationship between ventilation and VCO2 is optimized. Inefficiency of ventilation is present either when for a given VCO2 increase the increase in ventilation is greater than normal or when ventilation does not increase sufficiently and arterial CO2 pressure (PaCO2) rises. The former is associated with low PETCO2 and, therefore, a positive arterial to end-tidal PCO2 gradient (P(a-et)CO2) and elevated ventilation vs. VCO2 slope (sVE/VCO2) with an *Y*-intercept (extrapolation of ventilation to VCO2 = 0) close to 0 or negative. The latter is associated to increase of PaCO2 and systemic hypoxia, while sVE/VCO2 is normal or low but the *Y*-intercept is elevated. Differently from the slope, the VE/VCO2 ratio (rVE/VCO2) is elevated in both cases. The normal value of the sVE/VCO2, i.e., how significant is the increase of ventilation for a given increase in VCO2, is affected, in normal subjects, by age and gender. Indeed, ventilation in women is approximately 1 L/m more than in males at a similar age. Accordingly, it has been reported that the sVE/VCO2 should be reported as a percentage of a normal value [56]. Therefore, an elevated sVE/VCO2 with a low or negative *Y*-intercept means an increase in dead space ventilation during exercise why the presence of an elevated *Y*-intercept demonstrates the existence of increased dead space even at rest. The evaluation of the *Y*-intercept is therefore meaningful when assessing the role of a respiratory co-morbidity in heart failure [57]. Also, the kinetic of the rVE/VCO2 provides relevant information during exercise. Indeed, its value at rest is influenced by resting dead space ventilation while its increase during exercise is suggestive of increase in dead space during exercise as in case of pulmonary hypertension.

A relevant point is why ventilation increases [54]. Three are the major players at sea level: VCO2, the amount of dead space ventilation, and the value of PaCO2 at which even ventilation is settled. The first depends on the amount of exercise, and it is responsible of the normal ventilation increase during exercise. Differently, an abnormal dead space ventilation or PaCO2 set point is responsible of an abnormal ventilation behavior during exercise. From a gas exchange point of view, a high dead space ventilation implies a normal PaCO2 value while an abnormal set point of PaCO2 implies either hypoventilation (high PaCO2) or hyperventilation (low PaCO2).

In brief, ventilation-perfusion mismatch during exercise can be easily evaluated during exercise and provides relevant information in several cardiorespiratory diseases.

Biochemical aspects

The mechanisms by which left ventricular and/or right ventricular cardiomyocytes may release these biologic substances collectively referred to as biomarkers of stress, or of myocyte injury are similar in the left and in the right ventricle. Most, if not all, biomarkers are not RV specific but may be applied in patients with right ventricular failure [58, 59].

For example, in acute pulmonary embolism (PE), the RV faces a rapid rise in afterload which increases wall stress, resulting in higher oxygen demand and a reduced perfusion time with ensuing myocardial ischemia. As a result, circulating troponin (Tn) values often show a rise and fall pattern in PE, as in myocardial infarction. Both standard Tn and high-sensitivity Tn hold a prognostic role in acute PE [60, 61]. In pulmonary arterial hypertension, RV myocyte releases the prohormone pro B-type natriuretic peptide (proBNP), which is then split into the biologically active hormone BNP and the inactive fragment N-terminal proBNP (NT-proBNP), both being independent predictors of mortality [38].

Few studies have investigated the relationship between circulating inflammatory biomarkers and measures of RV geometry and performance in conditions associated with RV failure. In one study on patients with RV failure secondary to ischemic heart disease or idiopathic dilated cardiomyopathy, tumor necrosis factor-α levels positively correlated with the severity of peripheral oedema and showed an inverse correlation with RV ejection fraction calculated though radionuclide angiography [62]. Other studies on patients with pulmonary arterial hypertension have reported a negative association between certain chemokines (CXCL-10, CXCL-12, CXCL-16, or interleuchin-6) and parameters of RV function assessed through echocardiography or cardiac magnetic resonance [63, 64].

In recent years, there have been attempts to identify novel molecules which may more closely reflect RV remodelling and dysfunction. To this purpose, the most promising biomarkers seem to be the following: long non-coding RNA H19, secreted protein acidic and rich in cysteine-like protein 1 (SPARC-like protein 1), and cartilage intermediate layer protein 1 (CILP1) [65]. Notably, CILP1, an extracellular matrix (ECM) protein acting as an antagonist of the profibrotic transforming growth factor β signalling, was found to be increased in PH patients with "maladaptive" RV remodelling not only compared with PH patients with "adaptive" RV remodelling, but also compared to patients with dilated cardiomyopathy or LV hypertrophy due to pressure overload [66]. Moreover, several microRNA associated with RV remodelling have been recently identified, holding the potential to become RV-specific biomarkers or even therapeutic targets [67].

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Declarations

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