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Right ventricular function in pulmonary (arterial) hypertension

In the past decade, the right ventricle and right ventricular (RV) function have become the focus of increased scientific interest and the RV is no longer "the forgotten chamber". Right ventricular function is the main determinant of symptomatology and outcome in patients with pulmonary arterial hypertension (PAH; [73]). The response of the RV to the increasing afterload in pulmonary circulation is a complex process and maladaptation or RV failure predominantly determines the prognosis of patients with PAH [73]. Right heart failure in pulmonary hypertension (PH) is caused by increased afterload and therefore a description of the cardiopulmonary unit is indispensable. This is best described as the interplay between RV contractility, ventricular elastance (Ees), and arterial elastance (Ea), a measure of afterload [72].

However, in the current literature there are several measures of RV contractility and its relation to the load it faces (Ees/Ea). The present review focuses on existing measures of RV contractility and measures of the RV–pulmonary artery (PA) unit and summarizes the existing noninvasive measures of RV function.

Adaptation and maladaptation

Right ventricular failure can be described as a clinical syndrome, consisting of dyspnea, fatigue, and congestion, which is characterized by a decrease in RV function, leading to elevated filling pressures and reduced cardiac output [34]. However, there is currently a debate about accessible bedside tools for assessing RV function and physiological parameters describing the relation of RV contractility to its load. In certain states of the adaptational process to increased afterload, the RV ejection fraction (EF) might be decreased, whereas Ees might be elevated [54]. This fact emphasizes the current dilemma of, firstly, adequately describing RV function and, secondly, how to cope with the existing data on physiological parameters derived from pressure–volume loops in daily clinical practice.

In the course of disease, and owing to increasing afterload in PAH, RV contractility (Ees) increases in order to maintain RV–PA coupling (Ees/Ea). At a certain point, "the point of uncoupling," Ea significantly exceeds Ees, leading to a significantly reduced Ees/Ea relationship. At this point, the RV dilates to maintain stroke volume (SV).

Recently it was shown that the coupling of RV contractility to increased afterload in PH has considerable reserve, as Ees/Ea has to decrease from normal values of 1.5–2 to below 0.8 before an increase in volumes and a decrease in EF below the critical value of 35% occur [59].

The onset of RV dilatation due to uncoupling and eventual RV failure are not entirely clear. It appears that the homeometric (contractile) adaptation of the RV to afterload buffers the Ees/Ea ratio in the presence of significant worsening of PH [73]. In animal models, the RV dilated when the Ees/Ea ratio decreased to 0.7–1.0 [13, 19], and the Ees/Ea ratio was not sensitive to interventions that effectively decreased Ea because Ees decreased proportionally to Ea [49]. Experimental work on isolated canine hearts showed that maximal stroke work (volume × pressure) occurs at Ea/Ees = 0.80 ± 0.16, whereas ventricular efficiency (stroke work/myocardial oxygen consumption) is maximal at Ea/Ees = 0.70 ± 0.15. This suggests that optimal RV–arterial coupling might occur at values lower than the range of 1.5–2 predicted by mathematical models [10]. Recently, Axell and coworkers defined the Ees/Ea threshold below which SV or cardiac output decreased in either animal models or patients with chronic thromboembolic PH as around 0.7 [2], which is lower than the cut-off defined by Tello and coworkers [59].

Patients with PAH receiving targeted therapies may remain stable for several years but may present with increased RV dimensions and decreased EF, heralding clinical deterioration and decreased survival [66, 67, 73]. As increased RV dimensions and decreased EF can only be the consequence of RV–PA uncoupling, a definition of the Ees/Ea ratio—the gold standard measure of RV–PA coupling—at which relevant RV maladaptation begins is crucial for linking physiological measurements to noninvasively assessed measures of RV function.

The transition from adaptation to maladaptation and failure is progressive and cut-off values on volumes are difficult to define. An RVEF of <35% has consistently been shown to be associated with decreased survival in severe PH [5, 7, 66, 69] and is easily modeled to be associated with rapid increases in end-diastolic

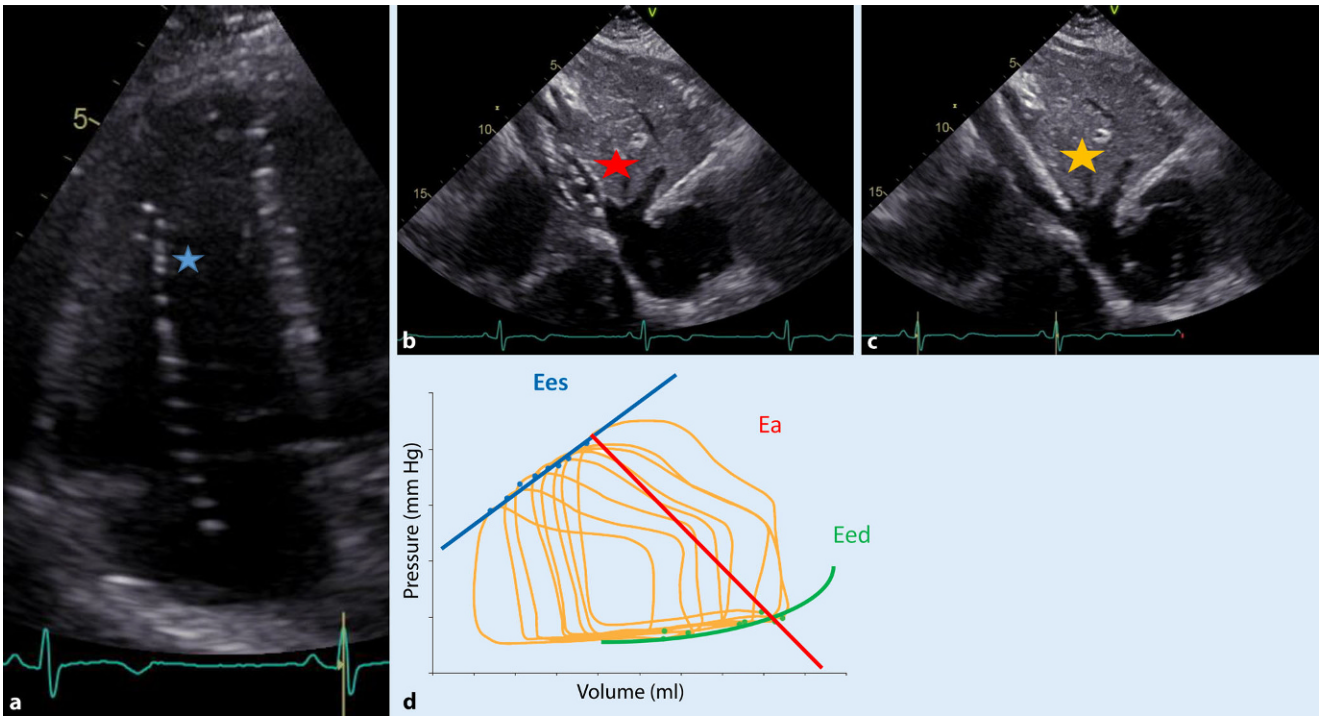

Fig. 1 ▲ Assessment of right ventricular (RV) contractility and RV–pulmonary artery (PA) coupling with the gold standard multi-beat approach (original measurement). **a** Ultrasound-guided insertion of pressure–volume (PV) catheter (*blue asterisk*). **b** Balloon occlusion of the inferior vena cava (IVC; *red asterisk*). **c** Deflation of the IVC balloon (*yellow asterisk*). **d** Original PV–loop measurement, with load-independent contractility (end-systolic elastance, *Ees*), arterial elastance as a measure of afterload (*Ea*), and end-diastolic elastance (*Eed*) as a measure of diastolic function

volume (EDV) and end-systolic volume (ESV) when SV is to be preserved [70].

Reports of Ees and Ea measured with gold standard pressure volume–loop catheters in patients with PH are scarce. Kuehne et al. used high-fidelity catheters in 2004 [33]. The authors measured RV pressures in animals and reported an approximately threefold increase in Ees in the presence of a sixfold increase in Ea, resulting in a substantially decreased Ees/Ea ratio (on average from 2 to 1) in PH. Subsequent studies showed similarly increased Ees but decreased Ees/Ea in idiopathic PAH [54, 57], PAH associated with systemic sclerosis [28, 57], and chronic thromboembolic PH [40, 54]. Two of the studies also reported measurements during exercise, showing decreased Ees/Ea even in patients with PAH who had persistently normal values at rest [28, 54], in contrast to controls who maintained their Ees/Ea ratio during exercise. Decreased Ees/Ea during exercise in PAH was associated with increased RV ESV and EDV [28].

With gold standard high-fidelity pressure–volume technology for the measurement of RV volumes, Ees and Ea measurements have relied either on a multiple-beat method allowing for elastance calculations on a family of pressure–volume loops generated during a decrease of venous return ([28, 57]; ◘ **Fig. 1**) or a single-beat method with Pmax calculations and measurement of relative change in volume on just one pressure–volume loop [33, 54]. The single-beat method has been validated in normotensive dogs with or without acute hypoxia-induced PH [8]. Most recently, Inuzuka and coworkers demonstrated an association of the aforementioned single-beat estimation with the multi-beat approach [31]. The single-beat method was tightly correlated with the multiple-beat method for assessment of RV–PA coupling in patients with and without PH [31]. In that study, the "standard" single-beat method assuming linearity of the Ees curve was less well correlated with the multiple-beat method for assessment of RV–PA coupling.

Methods to measure function of RV–PA unit

Right ventricular function can be characterized by the pressure–volume loop relation. The gold standard for measurement of ventricular contractility is the construction of multiple pressure–volume loops as described by Suga et al. [55] for the left ventricle and adopted for the RV by Maughan et al. in the canine ventricle and by Redington et al. in the human RV ([38, 48]; ◘ **Fig. 1**). To measure Ees, a linear regression is set through the end-systolic pressure–volume relationship (ESPVR) of each one of several cardiac cycles during load alterations [55].

With the development and the validation of the conductance catheter for the volume measurement [11], research in RV pressure–volume loops has become more widespread, as the assessment is simpler to perform than with previous methods.

The conductance catheter (◘ **Fig. 1**) measures pressure and volume simulta-

neously. Volume is measured by setting up an electrical field between the proximal and distal electrodes of the catheter when positioned (via echocardiography (**Fig. 1**) or radiography) in the RV apex. Electrical conductivity is measured by the electrodes, and changes in conductivity reflect segmental volume changes. The catheter is mostly volume-calibrated via cardiac magnetic resonance imaging (CMRI) as the gold standard for measurement of volume.

There are several clinical studies in which conductance catheters were used to assess contractility and/or RV–arterial coupling. The studies included patients with idiopathic PAH, systemic sclerosis-associated PAH [28, 57], systemic sclerosis without PH [57], chronic thromboembolic PH and chronic thromboembolic disease without PH [2, 39].

The main difference between these studies is the method used to assess RV–arterial coupling. Tedford et al. [57] and Tello and coworkers [60] measured Ees using a multi-beat method (**Fig. 1**) with preload reduction either by balloon occlusion of the inferior vena cava (IVC) or through the Valsalva maneuver [75]. By contrast, Tello and colleagues [59, 61, 62]and McCabe et al. [39], for instance, used the conductance catheter to measure precisely the end-systolic pressure (ESP) as one of the essential values required for determination of coupling via the single-beat method described by Brimioulle et al. [8]. In the single-beat method, Ea is calculated as ESP/SV and Ees is calculated as (Pmax – ESP)/SV, while Pmax is estimated as the maximal theoretical pressure that would build up through clamping of the pulmonary valve. Some groups used a right heart catheter-based approach, in order to avoid pressure–volume loop measurement [63]. In that approach, ESP is replaced by mean PA pressure [63] and Pmax is calculated using the sine wave extrapolation [8]. However, recently this approach has been shown to be misleading as especially in higher pressures ESP is significantly underestimated by mPAP [62].

The Eed of the ventricle is a load-independent representation of the diastolic function. The clinical relevance of RV diastolic function in patients with PH is a new area of interest in our understanding of RV function. Recent studies in patients with pulmonary hypertension have shown that increased RV diastolic stiffness is significantly associated with outcomes including mortality and lung transplantation [64, 69]. Patients on PAH-specific therapy for 3 months showed a significant decrease in RV diastolic stiffness compared with pretreatment values [68]. On the left side of the heart, it has long been recognized that diastolic dysfunction and stiffening of the left ventricle are major contributors to heart failure, and an integral part of the routine evaluation of patients presenting with heart failure is the assessment of left ventricular diastolic dysfunction using echocardiography [42]. Recent studies have started to develop clinical methods to assess RV diastolic stiffness. Tello et al. recently showed that RV diastolic stiffness is highly associated with impaired RV strain measured with feature tracking [61] and they introduced a novel parameter (RV longitudinal strain/EDV [BSA]) to estimate Eed in chronic pressure overload.

Right ventricular diastolic function is typically quantified from the end-diastolic pressure–volume relationship

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Abstract

The right ventricle (RV) is the main determinant of prognosis in pulmonary hypertension. Adaptation and maladaptation of the RV are of crucial importance. In the course of disease, RV contractility increases through changes in muscle properties and muscle hypertrophy. At a certain point, the point of "uncoupling," the afterload exceeds contractility, and maladaptation as well as dilation occurs to maintain stroke volume (SV). To understand the adaptational processes and to further develop targeted medication directly affecting load-independent contractility, an accurate and precise assessment of contractility and RV–pulmonary artery (PA) coupling should be performed. In this review, we shed light on existing methods to assess RV function, including the gold standard measurement of contractility and RV–PA coupling, and we evaluate existing surrogates of RV–PA coupling.

Keywords

Contractility · Right heart failure · Pulmonary hypertension · Coupling · Right heart function

Rechtsventrikuläre Funktion bei pulmonaler (arterieller) Hypertonie

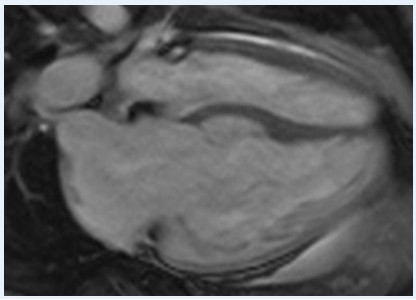
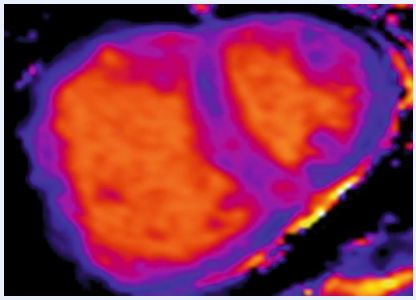
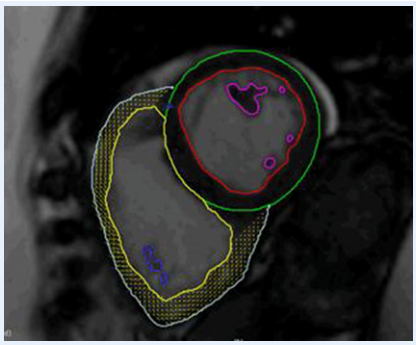
Zusammenfassung

Die Funktion des rechten Ventrikels (RV) ist für die Prognose der pulmonalen Hypertonie (PH) ein entscheidender Faktor. Dabei spielen adaptive und maladaptive Prozesse eine wichtige Rolle. Ein entscheidender Faktor der Adaptation ist die Erhöhung der nachlastunabhängigen Kontraktilität des RV als Reaktion auf die Nachlast. Diese wird zu Beginn der Erkrankung durch z. B. muskuläre Hypertrophie gesteigert. Am Beginn der Maladaptation kann jedoch die Kontraktilität den Anstieg der Nachlast nicht kompensieren, und es kommt zu einem „Entkoppeln" der Achse zwischen RV und Pulmonalarterien (PA) und zu einer Maladaptation und Dilatation, um das das Schlagvolumen (SV) zu erhalten. Um einerseits diese adaptiven und maladaptiven Prozesse zu analysieren und andererseits therapeutische Strategien zu entwickeln, die auf die lastunabhängige Kontraktilität zielen, sollte die Kontraktilität des RV bestmöglich gemessen werden. In diesem Übersichtsartikel werden Methoden vorgestellt, die nach derzeitigem Stand die Funktion der RV-PA-Achse am genauesten darstellen, und Methoden beurteilt, die als Surrogate dafür verwendet werden.

Schlüsselwörter

Kontraktilität · Rechtsherzinsuffizienz · Pulmonale Hypertonie · Kopplung · Rechtsherzfunktion

Table 1 Important tools in cardiac magnetic resonance imaging for assessment of RV function

	*Conventional functional parameter*	*Examples of studies including MRI and PAH*
	RV-EDV	Swift et al. [54]
	RV-ESV	Badagliacca et al. [4]
	RV-EF	Sanz et al. [50]
	RV-SV	Van de Veerdonk et al. 2017 [63]
	RV-SV/ESV	
	RV mass	
	*Native T1 map*	*Examples of studies including T1 mapping in PAH*
	T1 times in RV free wall	Tello et al. [59]
	RV insertion points	Mewton et al. [41]
	Septum	Garcia-Alvarez et al. [17]
	*MR feature tracking strain*	*Examples of studies including feature tracking strain in PAH*
	Global longitudinal strain	Tello et al. [61]
	Global radial strain	Sato et al. [52]
	Global circumferential strain	

EF ejection fraction, *EDV* end-diastolic volume, *ESV* end-systolic volume, *MRI* magnetic resonance imaging, *PAH* pulmonary arterial hypertension, *RV* right ventricular, *SV* stroke volume

(EDPVR). Under ideal conditions, the EDPVR would be measured from multi-beat pressure–volume loops with preload reduction (**Fig. 1**). The ESV/beginning-diastolic pressure (BDP) and end-diastolic volume (EDV)/end-diastolic pressure (EDP) would be determined from each pressure–volume loop and then fitted to an EDPVR. However, EDPVR has also been determined from single-beat pressure–volume loops (**Fig. 1**). Right ventricular pressure traces from right heart catheterization are used to determine begin-diastolic pressure and end-diastolic pressure, while CMRI is used to determine ESV and EDV. Studies on RV diastolic function have used an exponential fit [$P = \alpha \exp(\beta V) - 1$] to describe RV diastolic stiffness [47, 59, 61, 64, 68, 69]. The derivative of the EDPVR is a measure of chamber stiffness or the change of pressure for a given change in volume.

Surrogates of RV–PA coupling

The description of RV function in relation to its load is of high interest for clinicians. Currently, several methods exist to define Ees/Ea RV–PA coupling in a semi-invasive or even noninvasive approach.

Sanz et al. described a method to simplify measurements of elastance and avoid pressure measurements when assessing contractility and RV–arterial coupling [51]. The method assumed that Emax is defined as ESP/ESV; ESP was replaced by mPAP and Ea was calculated as mPAP/SV. Thus, Ees/Ea was simplified to SV/ESV without validation by the gold standard of Ees assessment (the multi-beat method with preload reduction and simultaneously measured pressure–volume loops). It should be emphasized that SV/ESV is inversely related to RVEF, as demonstrated by the formula SV/ESV = EF/(1 – EF); SV/ESV and RVEF have a prognostic meaning, and should be taken as parameters of functional interaction and of not coupling. Furthermore, RVEF and SV/ESV have been shown to be predictive of outcome in patients with PAH [7]. Cut-off values for RVEF shown to be associated with mortality are 35% [66] and for SV/ESV, 54% [7].

Kuehne et al. were the first to describe assessment of pressure–volume loops in patients with PAH ($n = 6$). They measured volume using CMRI and synchronized this with pressure measurements from a fluid-filled catheter [33]. The

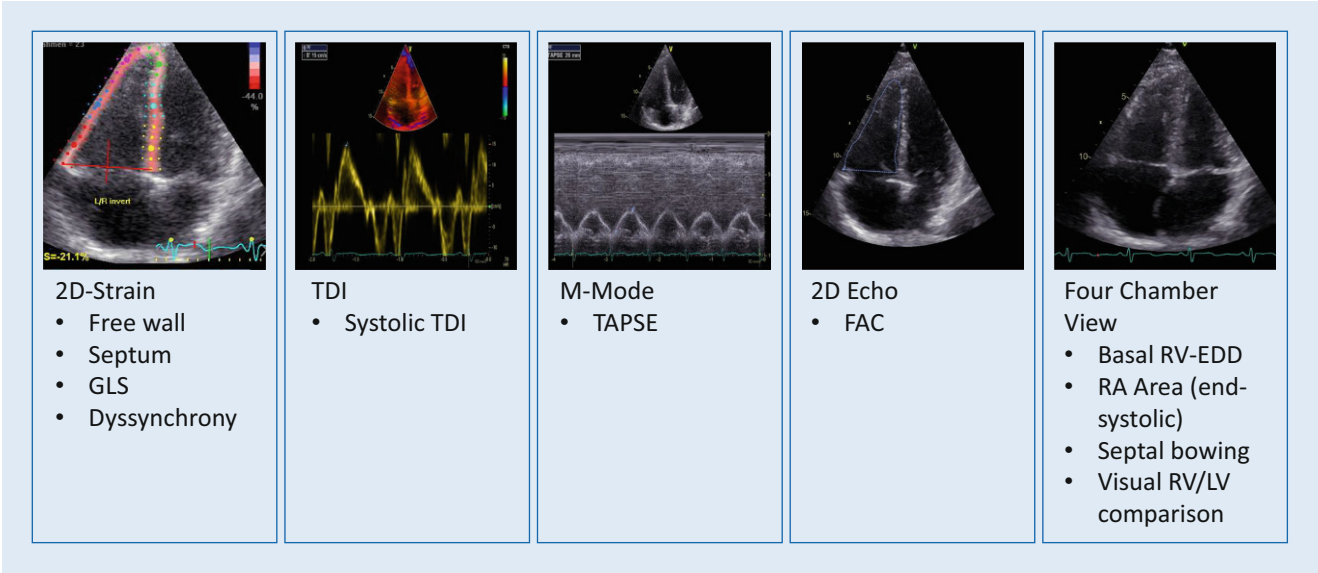


Fig. 2 ▲ Echocardiographic functional parameter of the right ventricle. *GLS* global longitudinal strain, *TDI* tissue Doppler imaging, *TAPSE* tricuspid annular plane systolic excursion, *FAC* fractional area change, *RV-EDD* right ventricular end-diastolic diameter, *RA* right atrium, *RV* right ventricle, *LV* left ventricle

Ees was calculated using the single-beat method described before [8].

Other surrogates of RV–PA coupling rely solely on echocardiographic data [25]. Since measuring Ees and Ea via pressure–volume loops is invasive and expensive, simpler noninvasive surrogates are being sought. One of these is the Doppler echocardiography measurement of the ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary artery pressure (PASP; [25]). The TAPSE/PASP ratio has been shown to be a potent independent predictor of pre-capillary PH and prognosis in heart failure [6, 18, 20, 25–27], with a defined prognostic cut-off value of 0.36 mm/mm Hg [24]. The TAPSE/PASP ratio has also been shown to be an independent predictor of outcome in PAH [58]. Initially thought of as an indirect assessment of the ventricular length–tension relationship [25], TAPSE/PASP has been considered a surrogate of Ees/Ea, based on the assumption that TAPSE estimates contractility and PASP estimates afterload [6, 18, 20, 24, 26, 27, 58]. Other suggested echocardiographic surrogates are the ratios of RV fractional area change (FAC) to mean pulmonary artery pressure (mPAP, invasively measured; [45, 46, 50]) RV area change to RV end-systolic area (ESA; [15]) TAPSE to pulmonary artery acceleration time (PAAT; [36]) and SV to ESA (derived by dividing PASP/ESA as a surrogate of Ees; [9, 44] by PASP/SV as a surrogate of Ea). None of these parameters has been validated against pressure–volume loop-derived parameters yet.

Conventional imaging parameters to assess RV function

Cardiac MRI is of crucial importance for imaging in PAH (**Table 1**) and it gives information on RV function and fibrosis (**Table 1**).

Right ventricular dilation has been associated with a worse prognosis [56]. Furthermore, an RVEF below 35% was identified as the leading parameter in predicting mortality in PAH [5]. Badagliacca and colleagues demonstrated more clinical worsening events in patients with an elevated mass/volume ratio [4]. Beside conventional parameters describing volume and mass, delayed enhancement imaging on MRI is well known and established. Magnetic resonance imaging is very important for assessing the impact of drugs on cardiac function, as it is noninvasive. A study by an Amsterdam group included 80 patients with incident PAH (hereditary, idiopathic, or drug-induced). Patients were in functional class II or III. The benefits of either upfront combination therapy with an endothelin-receptor antagonist (ETRA) and a phosphodiesterase-5 inhibitor (PDE5i) or each of these agents given as monotherapy were examined. The authors found that RV volumes, as RV end-diastolic volume, improved in patients with upfront combination therapy but not in patients with monotherapy [65]. The Euro-MR Study [43] found improvements in RV systolic and diastolic volumes as well as in stroke volume.

The RV-insertion point enhancement is strongly associated with elevated PA pressures and showed worse outcomes in patients with PAH [14]. In addition to the link with reduced regional contractility [53], delayed enhancement is an interesting and important tool for the diagnosis of PH patients.

Delayed enhancement imaging reveals regional myocardial abnormalities, whereas T1 mapping, an emerging tool in CMRI identifies diffuse myocardial abnormalities by measuring native RV T1 based on pre- and post-contrast T1 times [41]. T1 mapping (**Table 1**) has the potential to be a marker of fibrosis [17, 30], which has recently been highlighted as part of an adaptive response to prevent cardiomyocyte overstretch and

to maintain RV shape for optimal function, and of a maladaptive response that increases diastolic stiffness [1]. Recently, Tello et al. showed the association of invasively measured pressure–volume loop-derived end-diastolic RV stiffness with T1 mapping, emphasizing its diagnostic value for fibrosis and end-diastolic stiffness [59].

Magnetic resonance imaging strain is an emerging tool for assessing regional myocardial deformation. Myocardial deformation analysis using feature tracking is advantageous as it is applied to bSSFP (balanced steady-state free precession imaging) cine image data, yielding reliable strain data without the need for further image acquisitions. Recently Tello et al. demonstrated that in chronic pressure overload, radial strain is increasingly impaired with increasing RV EDV, which emphasizes the fact that volume overload is one of the central underlying processes that further worsens myocardial deformation [61]. Earlier, Sato and colleagues found that combination therapy was associated with a significant improvement in both RV and LV function, as assessed by CMR-derived feature tracking strain [52].

Echocardiography is one of the key screening tools in the evaluation of PH (**Fig. 2**). Beside conventional and well-established measures of RV function, newer and very interesting nonconventional techniques were introduced in recent years.

Right atrial size as an indirect measure of RV function has proven to be associated with prognosis [21, 22]. Tricuspid annular plane during systolic excursion is mostly taken as a surrogate for RV function (**Fig. 2**). In some studies, a prediction of survival was demonstrated [12] and was introduced in the Guidelines of 2009 [16]; however, it failed to predict mortality [22] in subsequent studies, especially in NYHA III–IV and RV dilation. It predominantly mirrors longitudinal RV function and, furthermore, it is dependent on volume [22]. The longitudinal peak velocity at the basal segment of the free wall measured via tissue Doppler imaging (TDI) is another tool for assessing RV function, and tissue velocity changing at the isovolumic phase has been shown to be load-independent, in contrast to TAPSE [71]. Right ventricular size, assessed at the end-diastole, and fractional area shortening (RV-FAC) have been shown to predict survival [22]. The RV–myocardial performance index (RVMPI) is a composite measure of systolic and diastolic function. An RVMPI above 0.688 or 0.88 was predictive of survival [22, 74].

Due to the complex RV geometry, two-dimensional (2D) echocardiography cannot capture the inflow and the outflow tract in one acquisition. Real-time three-dimensional (3D) echocardiography is a very promising tool with which to quantitate RV function, as the complex RV structure is captured [23, 37]. Three-dimensional RVEF has been shown to be correlated with hemodynamics and severity in PH [32]. In addition, RV strain, especially RV longitudinal strain, has emerging potential in predicting survival in PH patients [29]. Badagliacca et al. demonstrated that RV dyssynchrony measured via 2D echo-strain had the highest predictive capability of peak V'O_2, even when conventional parameters such as RV FAC were included in the multivariate analyses [3]. Lamia et al. demonstrated an impaired RV strain in borderline PAH, emphasizing the beginning of impaired RV deformation even in borderline PAH in mPAP ranges of 20–24 mm Hg [35]. Recently 3D echo free-wall strain, RVEF, and FAC were shown to serve as outcome predictors in pediatric PH patients [32].

Conclusion

Whether the reported improvements are also a consequence of improved contractility facing the presented afterload cannot be answered. However, to assess the impact of medication on the RV and especially on the load-independent contractility, measures of volume, irrespective of their importance, are misleading as they do not mirror an alteration of the inherent RV performance. Therefore, studies are needed that aim to measure the direct impact of targeted medication on the load-independent contractility, such as our ongoing Right Heart 3 Study (Clinical Trials identifier NCT03362047).

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Compliance with ethical guidelines

Conflict of interest K. Tello, H. Gall, M. Richter, A. Ghofrani, and R. Schermuly declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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Telemedizin - mehr Antibiosen

Fernbehandlung soll Lücken in der Versorgung schließen sowie Praxen und Kliniken entlasten. Doch es gibt auch unangenehme Nebenwirkungen.

Was hierzulande noch neu ist, ist in anderen Staaten seit Jahren gang und gäbe: die ausschließliche Fernbehandlung. In den USA etwa gehören Telekonsultationen fast schon zum Alltag. Allein das auf die Fernbehandlung spezialisierte Unternehmen Teladoc betreut eigenen Angaben zufolge über 20 Millionen Patienten. Dafür beschäftigt das Unternehmen rund 3000 Ärzte. Befeuert wird der Trend zudem von den Versicherern, die mit diesen Dienstleistern zunehmend Verträge abschließen, um sie ihren Versicherten anzubieten.

Anlass sind oft Atemwegsinfekte

Von 2011 bis 2016 ist die Zahl der pädiatrischen Telekonsultationen von 38 auf knapp 25.000 Kontakte pro Jahr gestiegen. Hinter jedem zweiten Anlass steckten – vermeintliche – Infektionen der Atemwege oder Ohren. Nun haben Daten einer Studie des US-Instituts für Kindergesundheit (NICHD) ergeben, dass Telekonsultationen zu deutlich mehr Verordnungen von Antibiotika führen. Kinder bis zum 17. Lebensjahr mit Verdacht auf einen akuten respiratorischen Infekt (Erkältung, Sinusitis, Halsweh) haben nach telemedizinischer Betreuung absolut 21% häufiger Antibiotika erhalten als nach Vorstellung in der Hausarztpraxis (52 versus 31%). Selbst in Notaufnahmen wurden bei diesen Kindern seltener Antibiosen verordnet (42%).

Große Datenbasis

Basis für diese retrospektive Kohortenuntersuchung sind Verordnungsdaten aus einem nationalen Gesundheitsplan für die Jahre 2015 und 2016. Verglichen wurden 4604 Telemedizinvisiten mit rund 38.000 Fällen in Notaufnahmen und fast einer halben Million Fällen in Hausarztpraxen.

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