



The potential role and limitations of echocardiography in acute respiratory distress syndrome

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Abstract: Bedside use of Doppler echocardiography is being featured as a promising, clinically useful tool in assessing the pulmonary circulation in patients with acute respiratory distress syndrome (ARDS). The present review is aimed at summarizing the available evidence obtained with echocardiography on right ventricle (RV) function and pulmonary circulation in ARDS and to highlight the potential of this technique in clinical practice (only articles in English language were considered). According to the available evidence on echocardiographic findings, the following conclusions can be drawn: (a) echocardiography (transthoracic and transesophageal) has a growing role in the management ARDS patients mainly because of the strict interactions between the lung (and ventilation) and the RV and pulmonary circulation; (b) there may be a continuum of alterations in RV size and function and pulmonary circulation which may end in the development of acute cor pulmonale, probably paralleling ARDS disease severity; and (c) the detection of acute cor pulmonale should prompt intensivists to tailor their ventilatory strategy to the individual patient depending on the echocardiography findings. Bearing in mind the clinical role and growing importance of echocardiography in ARDS and the available evidence on this topic, we present a flow chart including the parameters to be measured and the timing of echo exams in ARDS patients. Despite the important progress that echocardiography has gained in the evaluation of patients with ARDS, several open questions remain and echocardiography still appears to be underused in these patients. A more systematic use of echocardiography (mainly through shared protocols) in ARDS could help intensivists to tailor the optimal treatment in individual patients as well as highlighting the limits and potential of this methodology in patients with ALI.

Keywords: acute respiratory distress syndrome, echocardiography, pulmonary systolic arterial hypertension, right ventricle

Introduction

In acute respiratory distress syndrome (ARDS), the treatment of lung injury is based mainly on supportive therapy with lung-protective ventilation; but pulmonary vascular injury associated with this condition is being considered as yet another therapeutic target, together with its effects on the right ventricle (RV) and on systemic hemodynamics. In this context, bedside use of Doppler echocardiography is being featured as a promising, clinically useful tool [Mayo *et al.* 2015] in assessing the pulmonary circulation and RV function (as well as

biventricular function) in ARDS patients [Repešé *et al.* 2015; Chiumello and Pesenti, 2013; Vieillard-Baron, 2009; Khrishnan and Schmidt, 2015]. Since the first report in 1985 [Jardin *et al.* 1985] describing the RV and left ventricle (LV) functions with echocardiography in a small subset of patients with acute respiratory failure, an increasing number of papers have been published on this topic, but the available evidence mainly concerns the prevalence and the prognostic impact of acute cor pulmonale (ACP) in ARDS [Repešé *et al.* 2015; Chiumello and Pesenti, 2013; Vieillard-Baron, 2009].

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The present review is aimed at summarizing the available evidence obtained with echocardiography on RV function and pulmonary circulation in ARDS and to highlight potentials of this technique in clinical practice.

A PubMed search was conducted combining the words ‘acute lung injury and/or ARDS’, and ‘echocardiography’, and ‘adult’, and ‘pulmonary vascular dysfunction and/or right ventricle’. Only articles in English language were considered and case reports were excluded.

The term ‘pulmonary vascular dysfunction’ was first introduced by Zapol and Snider in 1977 [Zapol and Snider, 1977] when describing ARDS patients with elevated pulmonary vascular resistance, an increase in RV stroke-work index and progressive RV dysfunction resulting in cor pulmonale and refractory circulatory failure after several days on respiratory support.

Three elements, which can be investigated by echocardiography, characterize the pulmonary vascular alterations and their effects on the RV in ARDS: (a) pulmonary systolic arterial hypertension (sPAP); (b) RV dimension and function; and (c) septal dyskinesia. Using echocardiography, Boissier and colleagues [Boissier *et al.* 2013] stratified ARDS patients with pulmonary circulatory system dysfunction into three groups as follows.

1. No dysfunction [pulmonary systolic arterial pressure (sPAP) of more than or equal to 40 mmHg with normal right RV size and normal interventricular septum kinetics].
2. Moderate dysfunction (sPAP more than 40 mmHg or dilated RV but without cor pulmonale).
3. Severe dysfunction (ACP). Cor pulmonale is defined as an alteration in the structure and function of the RV caused by a primary disorder of the respiratory system. RV impairment can quickly turn into ACP due to an increase in RV afterload. Common causes of ACP in the ICU are ARDS, ‘aggressive’ mechanical ventilation and massive pulmonary embolism [Bouferrache and Vieillard-Baron, 2011; Repessé *et al.* 2015].

The prevalence and clinical significance of each grade of pulmonary circulatory system dysfunction has not been completely elucidated to date,

even if previous investigations assessed the prognostic impact of ACP (that is severe pulmonary dysfunction) on mortality in ARDS patients [Boissier *et al.* 2013, Jardin *et al.* 1997, 1999; Lhéritier *et al.* 2013; Vieillard-Baron *et al.* 2001, 2002, 2013].

Pulmonary systolic arterial hypertension

Pulmonary hypertension (PH) is defined as a condition characterized by an increase in mean arterial pulmonary pressure more than or equal to 25 mmHg measured at rest with right heart catheterization [Galié *et al.* 2009], which typically coincides with pulmonary systolic arterial pressure more than 40 mmHg. [McQuillan *et al.* 2001]. This definition mainly reflects chronic PH, which is further classified in five categories [Simonneau *et al.* 2009]. To date there is no specific agreement in the definition of PH in the acute setting of acute lung injury (ALI) or ARDS, in which other factors such as RV dysfunction and mechanical ventilation play a pivotal role.

Boissier and colleagues [Boissier *et al.* 2013] considered an sPAP cut off of 40 mmHg in defining the presence of moderate pulmonary vascular dysfunction in ARDS patients using echocardiography.

sPAP can be calculated with echocardiography from the tricuspid regurgitant velocity [Howard *et al.* 2012; Portnoy and Rudski, 2015; Rudski *et al.* 2010]. However, this value may be underestimated due to an insufficient Doppler envelope or eccentric tricuspid regurgitation jet and it should be interpreted with caution because pulmonary systolic artery pressure also depends on right ventricular systolic function [Rudski *et al.* 2010; Caille and Vieillard-Baron, 2010; Jardin and Vieillard-Baron, 2007]. The gold standard for the diagnosis of PH is right-heart catheterization, whose main disadvantage is that it is an invasive test, associated with increased morbidity and mortality even in experienced centers. In a systematic review and meta-analysis only a modest correlation between sPAP estimated from echocardiography was reported compared with that measured by right-heart catheterization from mild-to-moderate sPAP. This can be related to the potential limitations of echocardiography itself, including the technical difficulties in detecting a tricuspid regurgitant jet of good quality [Fisher *et al.* 2009, Janda *et al.* 2011]. However, in ARDS patients, right heart catheterization is

more often quite difficult to perform, while echocardiography can be performed at the bedside and can provide more information on anatomical and functional cardiac abnormalities. Bearing in mind the potential limitations of echocardiography, especially in ventilated patients [Fougeres *et al.* 2010], serial measurements of PH and cardiac function can be performed using echocardiography, therefore allowing the monitoring of therapies and ventilatory strategy.

In ARDS, pulmonary arterial pressure has been investigated, mainly invasively, with pulmonary arterial catheterization [Squara *et al.* 1998; Ryan *et al.* 2014; Beiderlinden *et al.* 2006; Osman *et al.* 2009; Bull *et al.* 2010], and only a few reports assessed pulmonary systolic arterial pressure with echocardiography in patients with ALI with or without ARDS [Jardin *et al.* 1985; Boissier *et al.* 2013; Vieillard-Baron *et al.* 2001; Cepkova *et al.* 2007; Mekontso-Dessap *et al.* 2010] (Table 1). Clinical interpretation of these data is challenging, since definition of ARDS has changed over time [Murray *et al.* 1988; Bernard *et al.* 1994; Force *et al.* 2012], as well as the standard of care in ARDS with the introduction of lung-protective ventilation [The Acute Respiratory Distress Syndrome Network, 2000] and conservative fluid management [Wiedemann *et al.* 2006].

Fougeres and colleagues [Fougeres *et al.* 2010] used both echocardiography and pulmonary arterial catheterization to assess the hemodynamic impact of increasing positive-end expiratory pressure (PEEP) when tidal volume and the plateau pressure were limited in 21 ARDS patients. Pulmonary arterial pressure (mean) was measured invasively and it was not affected by increasing PEEP while this maneuver induced an increase in RV and diastolic area, and pulmonary vascular resistance.

In the era of protective ventilation, ARDS patients with ACP showed significantly higher sPAP [Vieillard-Baron *et al.* 2001] when compared with those without ACP (even if an adequate measurement of this parameter was easily obtained only in 22 out of 56), while no difference in sPAP was detected in patients who survived compared with those who did not [Cepkova *et al.* 2007]. Interestingly, in this investigation, values of sPAP reported in ACP patients (47 ± 8 mmHg) were comparable with those of ALI patients (42.1 ± 9.1 mmHg) [Cepkova *et al.* 2007], despite discrepancies in number consistency of the two

groups (19 ACP patients *versus* 42 ALI patients). Similar results were reported a few years later by Boissier and colleagues [Boissier *et al.* 2013] who observed that sPAP was significantly higher in patients with ACP than in those without (ACP, 44 ± 20 mmHg *versus* no ACP, 31 ± 15 mmHg). However, in this paper RV function was not investigated, even if ACP patients showed a higher incidence of RV dilatation. In a large series of 203 ARDS patients, Mekontso-Dessap and colleagues [Mekontso-Dessap *et al.* 2010] observed that patients with a patent foramen ovale (PFO) [detectable in the about 20% of their population with contrast transesophageal echocardiography (TEE) as the reference method] showed a significantly higher pulmonary systolic arterial pressure in respect to those without a PFO (PFO, 43 ± 17 mmHg *versus* no PFO, 35 ± 18 mmHg, $p = 0.04$). Systolic arterial pressure was available only in 133 patients (65.5%). However, in 257 ARDS patients, Zhang and colleagues [Zhang *et al.* 2014] documented that echocardiography tended to overestimate pulmonary systolic arterial pressures in respect to right-heart catheterization in patients with atrial septal defect. Nevertheless, since the presence of PFO may worsen hypoxemia in ARDS patients, the echocardiographic assessment should rule out the presence of PFO and whenever detected (especially if moderate to severe), serial echocardiograms should be performed in order to assess sPAP and RV function in these patients.

On the other hand, in moderate-to-severe ARDS, evaluated using echocardiography within the first 48 hours after admission, sPAP was not significantly different in ACP patients (irrespective of associated PFO) when compared with the patients without PFO. This finding may be related to the fact that ACP patients showed an altered systolic RV function (as indicated by median RV fractional area contraction). These data strongly suggest that, in clinical practice, the measurements of sPAP should always be associated with the assessment of RV function. Interestingly, in the same investigation, sPAP significantly correlated with PaCO₂, a finding in agreement with the effect of PaCO₂ on pulmonary vascular bed [Balanos *et al.* 2003].

When clinically interpreting the echocardiographic values of sPAP obtained at bedside, intensivists should also bear in mind that pulmonary arterial pressure is influenced by several factors [Price *et al.* 2012] which are related to the severity of

Table 1. Echocardiography in ARDS.

	Number of patients	Study design	TTE/TEE	Echocardiographic findings	
Jardin <i>et al.</i> [1985]	23 patients requiring mechanical ventilation for acute respiratory failure	Prospective observational study	TTE	Right ventricular dysfunction (RV enlargement with abnormal contractile pattern) in 5/23 (21.7%)%	In all patients, LV function was normal
Jardin <i>et al.</i> [2007]	352 patients	Prospective observational study	TTE and TEE	Incidence of acute cor pulmonale: 56% with plateau pressure > 35 cm H ₂ O; 32%, when plateau pressure was between 27 and 35 cm H ₂ O; 13% when plateau pressure was < 27 cm H ₂ O	A clear interaction between plateau pressure and cor pulmonale was documented
<i>Lung protective ventilation</i>					
Vieillard-Baron <i>et al.</i> [2001]	75 patients	Prospective open clinical study	TEE	ACP was present in 19/75 25%	ACP was associated with pulmonary artery hypertension
Page <i>et al.</i> 2003	150 patients	Retrospective study	TTE and TEE	Incidence of ACP 18% (no differences between survivors and nonsurvivors)	RVF reversible in survivors PaCO ₂ level as the sole factor independently associated with ACP
Cepkova <i>et al.</i> [2007]	42 patients with ALI mechanically ventilated	Prospective observational cohort study	TTE	7% had RV dysfunction	No differences in sPAP between patients who survived and those who did not.
Vieillard-Baron <i>et al.</i> [2007]	42 severe ARDS patients treated with prone positioning	Prospective study	TEE	ACP was detected in the 50%	RV and sPAP dysfunction not predictive of increased mortality Prone positioning, applied for 18 h, was associated with a reduction in RV dilation

(Continued)

Table 1. (Continued)

	Number of patients	Study design	TTE/TEE	Echocardiographic findings
Fougeres <i>et al.</i> [2010]	21 ARDS patients ventilated with a tidal volume of 6.0 +/- 0.5 mL/kg of predicted body weight	Prospective study	TEE	Increasing PEEP did not affect mean arterial pulmonary pressure
Mekontso-Dessap <i>et al.</i> [2010]	203 ARDS patients	Prospective study	TEE performed within 3 days after diagnosis	sPAP was higher in patients with a patent foramen ovale
Boissier <i>et al.</i> [2013]	226 moderate to severe ARDS	Prospective observational study	TEE performed within 3 days after the diagnosis of ARDS	ACP in 49 patients (22.5%) The 28-day mortality rate was significantly higher in the group with cor pulmonale (60 versus 36 %, p=0.01) ACP was an independent risk for 28-day mortality
Lhéritier <i>et al.</i> [2013]	200 patients with moderate-to-severe ARDS	Prospective multicenter study	TTE and TTE	ACP was detectable in the 22.5% (TEE) pCO2 was strongly associated with ACP
Legras <i>et al.</i> [2015]	195 moderate-to-severe ARDS	Prospective observational study	TEE performed within 48 hours after admission	sPAP did not differ among subgroups sPAP significantly correlated with PaCO2 ACP: 36 patients PFO: 21 patients ACP and PFO: 8 patients No ACP no PFO: 130 patients

ACP, acute cor pulmonale; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; PEEP, positive-end respiratory pressure; PFO, patent foramen ovale; Pplat, plateau pressure; RVF, right ventricular failure; sPAP, systolic pulmonary arterial pressure; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Table 2. Main factors influencing pulmonary arterial pressure.

Factor	Mechanism	Effect
Endothelial dysfunction/ imbalance of vasoactive mediators	Initiation of inflammation and intravascular coagulation. Intravascular microthrombi, fibrin, and intravascular sequestration of cells lead to pulmonary capillary occlusion, and clots	Increased PVR
Hypoxia	Increased vascular tone in muscular arterioles and veins	Increased PVR
Atelectasia, reduction in lung volume, high PEEP	Extrinsic vessel compression	Increased PVR
Hypercapnia/acidosis	Increase vascular tone	Increased PVR
Increased LA pressure and or LV dysfunction	Pulmonary vein constriction	Post capillary pulmonary hypertension

PEEP, peak expiratory pressure; LA, left atrial; LV, left ventricle; PVR, pulmonary vascular resistance.

lung disease (that is, changes occurring within the pulmonary vasculature, the degree of hypercapnia and hypoxia) as well as to RV function and contractility (Table 2). Moreover, mechanical ventilation itself (PEEP, tidal volume and plateau pressure) is able to influence pulmonary arterial pressure directly via changes in RV after load and indirectly via alterations in pCO₂ and pH. Mekontso-Dessap and colleagues [Mekontso-Dessap *et al.* 2009] assessed the effects of different PEEP on RV function in patients with severe ARDS and observed that high PEEP values (which were associated with more severe hypercapnia and acidosis) were related to a lower RV stroke index. However, a multivariate analysis on changes in pH (and not in PEEP) were correlated with impaired RV function. The authors hypothesized that the reduction in RV function was due to an increase in pulmonary vascular resistance but, unfortunately, pulmonary systolic pressures were not measured; the finding of increased pulmonary arterial pressures would have supported the hypothesis that RV dysfunction was caused by RV overload.

RV dilatation

Assessment of RV dimension with echocardiography is mainly qualitative (due to the peculiar, complex anatomic shape of RV chamber), using a focused approach mainly based on the four-chamber and short-axis views in the transthoracic approach. [Lang *et al.* 2015]. Since in mechanically ventilated patients normal values for RV dimension with echocardiography have not been

established [Rudski *et al.* 2010], it is accepted that comparison with LV size furnishes a good estimated of RV size. RV dilatation is defined as moderated when the ratio between right (RVEDA) and left-ventricular end diastolic area (LVEDA) is more than 0.6, and severe when this ratio is more than 1.0 [Boissier *et al.* 2013; Jardin *et al.* 1999; Vieillard-Baron *et al.* 2001; Portnoy and Rudski, 2015].

Cepkova and colleagues [Cepkova *et al.* 2007] assessed RV size qualitatively, according to their 'laboratory protocol' and, among the 42 patients with ALI included in their investigation, RV dilatation was observed in 26% (11 out of 42).

Conversely, RV dilatation was quantitatively assessed and detected in patients with ACP, indicated as RVEDA alone [Vieillard-Baron *et al.* 2001] or as the ratio RVEDA to LVEDA [Mekontso-Dessap *et al.* 2009]. In ARDS patients with a PFO, when compared with those without, Mekontso-Dessap and colleagues [Mekontso-Dessap *et al.* 2010] observed significant higher values of RVEDA to LVEDA ratio associated with higher sPAP and similarly, Legras and colleagues [Legras *et al.* 2015] reported that ARDS with ACP and PFO exhibited the highest RVEDA to LVEDA ratio, associated with RV dysfunction. Interestingly, Boissier and colleagues [Boissier *et al.* 2013] observed that moderate RV dilatation (defined as RV to LDVEDA ratio more than 0.6 and less than 1.0) was detectable in the 49% of patients without ACP, thus suggesting that RV dilatation may precede ACP development.

Table 3. Main echocardiographic parameters for the right ventricle.

View	Normal values
RV dimensions	
RV-focused four apical chamber view	Base: < 41 mm Midlevel: < 35 mm
RV area	
Manual tracing of RV endocardial border from the lateral tricuspid annulus along the free wall to the apex and back to medial tricuspid annulus, along the interventricular septum at end-diastole and at end-systole	RV EDA indexed to BSA (cm ² /m ²) Men <i>normal range</i> 5–12.6 Women <i>normal range</i> 4.5–11.5 RV ESA indexed to BSA (cm ² /m ²) Men <i>normal range</i> 2.0–7.4 Women <i>normal range</i> 1.6–6.4
RV wall thickness	
Linear measurement of RV free wall thickness performed at end-diastole, below the tricuspid annulus at a distance approximating the length of anterior tricuspid leaflet, when it is fully open and parallel to the RV free wall.	Normal value: < 5 mm
TAPSE tricuspid annular plane systolic excursion	
Tricuspid annular longitudinal excursion is measured by M-mode by proper alignment of M-mode cursor with the direction of RV longitudinal excursion from apical view	24 ± 3.5 mm Abnormal < 15 mm
Systolic (S') wave velocity	
It is obtained by pulsed wave DTI (cm/s), from the apical approach, in the view that achieves parallel alignment of Doppler beam with RV free wall longitudinal excursion	14.1 ± 2.3 cm/s Abnormal: < 9.5 cm/s
Right ventricle outflow tract acceleration time	
By positioning the sample volume at the center of the pulmonary artery (ideally at the annulus) in the short-axis view	Abnormal < 105 ms
DTI, Doppler tissue imaging; RV, right ventricle.	

Septal dyskinesia

Septal dyskinesia is present when the interventricular septum shows a paradoxical motion, characterized by its displacement leftward at the onset of left ventricular diastole followed by a sudden return rightward when the LV resumes contraction. This phenomenon is related to interventricular dependence and is due to the fact that right ventricular systolic overload increases the duration of RV systole, which occurs when the LV begins to relax, thus reversing the left-to-right pressure gradient at end systole or onset diastole. As the interventricular septum flattens and progressively loses its convexity during diastole, the LV assumes a progressively more *D-shaped* cavity [Rudski *et al.* 2010]. The detection of paradoxical septal motion is qualitative [Repressé *et al.* 2012] and it is part of the definition of ACP [Jardin *et al.* 1997]. Speckle-tracking echocardiography can allow the assessment of the local rate of wall deformation (strain rate) and the degree of deformation (strain). However, this parameter, which describes

RV function in relation to both its preload and its afterload, has not been investigated in patients with RV dysfunction and ARDS yet.

The incidence and the prognostic impact of ACP in ARDS patients has been extensively addressed in previous papers [Jardin *et al.* 1997; Vieillard-Baron *et al.* 2001, 2002, 2007; Mekontso-Dessap *et al.* 2009; Boissier *et al.* 2013; Lhéritier *et al.* 2013; Legras *et al.* 2015] so will not be discussed extensively in the present review. ACP is defined as the association of RV dilatation with a paradoxical septal motion at end systole [Repressé *et al.* 2015]. Briefly, in the era of protective ventilation, ACP occurs in the 20–25% of ARDS patients and its development seems to be especially related to plateau pressure, driving pressure and pCO₂ [Repressé *et al.* 2015]. The presence of ACP may cause or precipitate circulatory failure and it seems to have an impact on prognosis since it presented as an independent risk factor for 28-day mortality in moderate-to-severe ARDS patients [Boissier

<u>What to measure</u>	<u>When</u>
<ul style="list-style-type: none"> ➤RV dimensions/function ➤RV wall thickness ➤sPAP ➤IVC ➤Septal dyskinesia ➤LV ejection fraction 	<ul style="list-style-type: none"> •On ICU admission •Serial exams during ICU stay •Closer echo monitoring In presence of development of RV dilation/Dysfunction An increase in sPAP

Figure 1. Flow chart.

RV, right ventricle; IVC, inferior vena cava; sPAP, pulmonary systolic arterial pressure; LV, left ventricle; ICU, intensive care unit.

et al. 2013]. In 226 ARDS patients, ACP was associated with lower systolic and mean arterial pressures, a higher heart rate and a higher incidence of shock [Boissier *et al.* 2013]. In another study including 200 ARDS patients, 64% of patients with ACP required norepinephrine infusion, compared with 49% of patients without ACP [Lhéritier *et al.* 2013]. Based on the echocardiographic findings on ACP in ARDS patients and its clinical meaning, it has been proposed as an approach to protect the RV by setting or adapting the ventilatory strategy in the presence of the echocardiographic finding of RV overload [Jardin *et al.* 1997; Vieillard-Baron *et al.* 2001, 2002, 2007; Mekontso-Dessap *et al.* 2009, 2011; Boissier *et al.* 2013; Lhéritier *et al.* 2013; Legras *et al.* 2015; Repessé *et al.* 2015]. Though this ‘protective RV approach’ (avoidance of intrinsic PEEP, limiting plateau pressure, PEEP and permissive hypercapnia as feasible, without compromising protective lung ventilation strategy) has to be validated in a randomized controlled trial, it seems to protect both the lung and the ventricle by an individual patient-tailored strategy. In this context, in ARDS patients, it is now recommended to perform at least one echocardiographic examination per day during the first three days to evaluate RV function and to adapt the ventilator.

Overall, according to the available evidence on echocardiographic findings in patients with ALI/ARDS, the following considerations can be drawn.

1. Echocardiography (transthoracic and transesophageal) has a growing role in the management ARDS patients, mainly because of the strict interactions between the lung (and ventilation) and the RV and pulmonary circulation. These two techniques are not completely interchangeable. The choice of one instead of the other is usually made on the acoustic windows (i.e.

TEE is performed because of the absence of transthoracic windows) as well as on the clinical needs (i.e. TEE is needed for the detection of a PFO). However, both techniques should be performed together in peculiar clinical settings such as venovenous extracorporeal membrane oxygenation implantation to optimize echocardiographic views [Peris *et al.* 2015].

2. The detection of ACP should make intensivists critically evaluate the possibility of tailoring their ventilatory strategy to the individual patient depending on the echocardiography findings.
3. It may be suggested that there is a continuum of alterations in RV size and function and pulmonary circulation which may end in the development of ACP, probably paralleling ARDS disease severity. The findings by Boissier and colleagues [Boissier *et al.* 2013] strongly support this assumption. In fact, in their paper, moderate pulmonary dysfunction (defined as the presence of pulmonary dysfunction or isolated RV dilatation without ACP) was detected in 48% of patients and a progressive increase in mortality was observed with an increase in pulmonary dysfunction severity.

Bearing in mind the clinical role and growing importance of echocardiography in ARDS and the available evidence on this topic, we present a flow chart (mainly based on the protocol used at our institute [Peris *et al.* 2015; Cianchi *et al.* 2011], including the parameters measured at echocardiography examination (*What to measure*) and the timing of echo exams (*When*) in ARDS patients (Table 3).

What to use

The choice of the modality of echocardiography (transthoracic *versus* transesophageal) strictly depends on the clinical condition of individual patients as well as on the clinical inquiry. In ventilated patients, TEE is to be preferred since it overcomes technical problems with acoustic views and measurements can usually be easily performed [Jardin *et al.* 1997; Vieillard-Baron *et al.* 2001, 2002, 2007; Mekontso-Dessap *et al.* 2009, 2011; Boissier *et al.* 2013; Lhéritier *et al.* 2013; Legras *et al.* 2015; Repessé *et al.* 2015]. Whenever the patient is spontaneously breathing with or without noninvasive ventilation, transthoracic echocardiography (TTE) is more feasible and in

many cases can provide enough information to meet the clinical inquiries [Joseph *et al.* 2004; Howard *et al.* 2012].

What to measure

According to existing evidence and to our experience, the following parameters (mainly focused on RV and pulmonary circulation) should also be measured in a patient with ALI/ARDS. These parameters have been selected on the basis of their feasibility (that is, easy to be measured, even in a short time), and of the existing literature data (that is, clinical significance documented in previous reports).

RV dimensions. RV size can be assessed visually by the ‘eyeball’ method in the short axis and four-chamber views, but it can be quantitatively evaluated by the ratio RV to LV end-diastolic area. The RV to LV area ratio is measured at end diastole by tracing the areas of the two chambers in the apical four-chamber view on TTE or the midesophageal four-chamber view on TEE [Jardin *et al.* 1997; Khrishnan and Schmidt, 2015]. According to recent guidelines [Lang *et al.* 2015], RV dimensions are best estimated by a RV-focused apical four-chamber view and RV dilatation is identified by a diameter of more than 41 mm at the base and more than 35 mm at the midlevel.

RV wall thickness. This measurement is easily performed in diastole, preferably from the subcostal view, using either M-mode or two-dimensional imaging [Rudski *et al.* 2010]. Thickness of more than 5 mm indicates RV hypertrophy. In a patient with ARDS evaluated for the first time on ICU admission, the detection of RV thickness of more than 5 mm may have indicated a chronic RV overload (i.e. in the presence of previously unknown chronic obstructive pulmonary disease). Otherwise, since the RV is able in only a few days to thicken in response to an increase in pulmonary pressure, RV hypertrophy may develop under mechanical ventilation and it may be detected on serial echo exams. In fact, Vieillard-Baron and colleagues [Vieillard-Baron *et al.* 2002] described a moderate thickness of the right ventricular free wall after two days of mechanical ventilation. The detection of severe RV hypertrophy (more than 1 cm) is thought to be related to pre-existing chronic diseases.

Pulmonary systolic arterial pressure. As discussed above, in presence of tricuspid regurgitation, the RV-right atrial pressure gradient can be

estimated by measuring the peak regurgitant jet velocity (v) using continuous-wave Doppler echocardiography and the modified Bernoulli equation (RV systolic pressure = $4v^2$ + right atrial pressure) [Jardin *et al.* 1997; Khrishnan and Schmidt, 2015].

Inferior vena cava diameter. Inferior vena cava (IVC) and its collapse: It can be used as a good estimated of right atrial (RA) pressure in nonventilated patients (in whom central venous pressure is preferred) [Vieillard-Baron *et al.* 2002]. The subcostal view is most useful for imaging the IVC, making it visible in its long axis. IVC diameter of less than 2.1 cm that collapses more than 50% with a sniff suggests a normal RA pressure of 3 mmHg (range, 0–5 mmHg), whereas an IVC diameter of more than 2.1 cm that collapses less than 50% with a sniff suggests a high RA pressure of 15 mmHg (range, 10–20 mmHg) [Brennan *et al.* 2007]. In patients with RV dysfunction, the interpretation of IVC collapsibility is more challenging and it should be interpreted, taking into account its trend and central venous pressure.

Septal dyskinesia. Septal dyskinesia has been discussed previously. In patients with pulmonary embolism, acute RV overload may be associated with a specific pattern, the so called ‘McConnell’s sign’, which is characterized by abnormal regional wall motion with akinesia of the mid-free wall, while simultaneously having normal or increased motion at the apex [McConnell *et al.*, 1996; Vieillard-Baron *et al.* 2002].

Tricuspid lateral annular motion. Tricuspid annular plane systolic excursion (TAPSE) is used as an index of RV function. Since the RV contracts largely along its length, M-mode imaging through the lateral tricuspid valve plane captures this longitudinal motion [Vieillard-Baron *et al.* 2002; Portnoy and Rudski, 2015]. This measurement requires a proper alignment of M-mode cursor with the direction of RV longitudinal excursion from the apical view. Angle dependence is therefore one of its main limitations, together with the fact that TAPSE is not representative of global RV function [Lang *et al.* 2015]. However, this parameter has shown a good correlation with RV fractional area change and radionuclide-derived RV ejection fraction [Kaul *et al.* 1984]. Obviously, interpreting TAPSE as an index of RV function assumes that RV basal segment is representative of global function. A TAPSE of more than 15 mm indicates RV dysfunction [Vieillard-Baron *et al.* 2002; Portnoy

and Rudski, 2015; Khrishnan and Schmidt, 2015], and it has been associated with a poor prognosis in patients with chronic right-sided heart disease [Forfia *et al.* 2006; Damy *et al.* 2012] and in critically ill patients [Gajanana *et al.* 2015]. A strong relation between TAPSE and LV ejection fraction has been reported in 86 critically ill patients admitted to ICU for acute respiratory failure, circulatory failure or coma [Lamia *et al.* 2007]. In a multicenter, noninvasive hemodynamic study including 195 patients with moderate-to-severe ARDS, ACP was associated with a reduced RV function, as indicated by lower values of TAPSE and RV fractional area change [Legras *et al.* 2015].

Left ventricle. When evaluating patients with ARDS with echocardiography, LV ejection fraction should also be assessed and clinically interpreted taking into account also the dosage of inotropic drugs, if administered. Valvular diseases (mitral and aortic) should also be investigated and, if present, estimated, especially when examining the patient using echocardiography for the first time. The presence of valvular disease (i.e. mitral regurgitation) could influence the course and severity of the lung disease and therefore it will influence treatments (i.e. fluid prescription). Moreover, LV diastolic dysfunction (even in presence of normal ejection fraction) can contribute to increased pulmonary arterial pressures and to the development of RV dysfunction.

When using TEE, the following parameters can also be checked: Superior vena cava collapse (absent or present), filling pressures (low, normal, or high), and shunting across PFO (absent or present). Moreover, since patients with severe ARDS often require prolonged periods of the prone position because of refractory hypoxemia, TEE can thus be safely and efficiently performed.

When to perform echo cardiogram

According to our experience, we suggest that echocardiography should be performed on ICU admission in patients with ALI or ARDS and should be periodically repeated according to the clinical course. On admission, an echocardiogram is able to provide valuable information, not only on the clinical status of that moment but may also highlight clinical elements indicating previous diseases (i.e. severe RV hypertrophy, suggesting pre-existing chronic lung disease). If the clinical course is uneventful, echocardiograms should be done at least

once a week (i.e. to monitor fluid therapy), before weaning off ventilation and after extubation. The patients should be re-evaluated with TTE or TEE any time higher ventilatory parameters are required to maintain adequate oxygenation or any new, undifferentiated state of shock develops, including hyperlactatemia, acidosis, oliguria or other signs of hypoperfusion. In the presence of progressive respiratory failure, the echocardiographic evaluation could help in identifying the reasons (or cofactors) such as increased sPAP, the development of RV dilatation, progressive RV or LV failure and in tailoring the treatment. Whenever RV dilatation or dysfunction is detected (even at an echocardiogram performed routinely), treatments (ventilatory and nonventilatory) should be re-examined; other options (i.e. inhaled nitric oxide and prone position) should be considered and patients should be more closely monitored by use of echocardiography.

Other echocardiographic parameters (such as systolic wave velocity) have thus far not been fully investigated in ALI and ARDS, and therefore they have not been discussed in detail in the present review. Systolic (S') wave velocity is a measure of myocardial contraction (though it cannot be representative of global RV function) and, similarly to TAPSE, it is load dependent. Right ventricle outflow tract (RVOT) acceleration time may be used when the tricuspid velocity cannot be measured and a value of less than 105 msec is suggestive of PH. In an elegant investigation, Arkles documented that the differences the RV Doppler velocity pattern identified marked differences in pulmonary vascular characteristics, and could help in establishing the hemodynamic basis for PH [Arkles *et al.* 2011]. In particular, a 'notched' Doppler signal strongly suggested an increased pulmonary vascular resistance and poor vascular compliance, while the absence of a 'notched' pattern was typically associated with the absence of pulmonary vascular disease, and with PH of pulmonary venous origin. Also, the pulmonary vascular resistance can be calculated with echocardiography, that could be part of the comprehensive assessment in patients with RV dysfunction [Abbas *et al.* 2003] but no data are yet available at this time in ARDS patients.

Overall, the echocardiographic examination is practical and feasible in ARDS patients, and is able to provide valuable information for their management.

However, despite the important progress that echocardiography has made in the evaluation of patients with ARDS, several open questions remain and echocardiography still appears to be underused (or at least not routinely used) in these patients. In other words, a more systematic use of echocardiography (mainly through shared protocols) in ARDS could help intensivists tailor the optimal treatment in individual patients as well as highlight limits and potentials of this methodology in patients with ALI.

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