

## REVIEW

# Diastology in the intensive care unit: Challenges for the assessment and future directions

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## Abstract

Myocardial dysfunction is common in patients admitted to the intensive care unit (ICU). Septic disease frequently results in cardiac dysfunction, and sepsis represents the most common cause of admission and death in the ICU. The association between left ventricular (LV) systolic dysfunction and mortality is not clear for critically ill patients. Conversely, LV diastolic dysfunction (DD) seems increasingly recognized as a factor associated with poor outcomes, not only in sepsis but also more generally in critically ill patients. Despite recent attempts to simplify the diagnosis and grading of DD, this remains relatively complex, with the need to use several echocardiographic parameters. Furthermore, the current guidelines have several intrinsic limitations when applied to the ICU setting. In this manuscript, we discuss the challenges in DD classification when applied to critically ill patients, the importance of left atrial pressure estimates for the management of patients in ICU, and whether the study of cardiac dysfunction spectrum during critical illness may benefit from the integration of left ventricular and left atrial strain data to improve diagnostic accuracy and implications for the treatment and prognosis.

## KEYWORDS

critically ill, diastolic dysfunction, echocardiography, intensive care, left atrial strain, myocardial dysfunction

**Abbreviations:** ASE/EACVI, American Society of Echocardiography/European Association of Cardiovascular Imaging; DD, diastolic dysfunction; EDP, end-diastolic pressure; EF, ejection fraction; FP, filling pressure; GLS, global longitudinal strain; ICU, intensive care unit; LA, left atrium; LV, left ventricle; MV, mechanical ventilation; PALS, peak atrial longitudinal strain; RV, right ventricle; TDI, tissue doppler imaging; TRV, tricuspid regurgitant jet velocity; VEXUS, venous excess ultrasound.

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## 1 | INTRODUCTION

Myocardial dysfunction is a common finding in patients admitted to the intensive care unit (ICU).<sup>1</sup> Patients with cardiogenic shock have profound cardiovascular compromise and consequently high mortality. However, also other critically ill patients frequently suffer from cardiac dysfunction; for instance, this is the case of patients with septic shock. Importantly, sepsis represents the most common cause of admission

to ICU with mortality further increasing when cardiac dysfunction develops.<sup>2</sup>

Cardiac involvement in patients admitted to ICU has been typically classified as left, right or biventricular systolic function. However, recently, the association between left ventricular (LV) diastolic dysfunction (DD) has received more attention, being increasingly recognized for its association with poor outcomes. Such observation was primarily seen in the context of septic patients,<sup>3</sup> but the negative effects of DD on outcomes have also been found in other circumstances, such as the weaning process from mechanical ventilation (MV).<sup>4</sup>

Our review will focus on introducing the importance of DD in the ICU with particular attention to the septic critically ill patients, leaving apart the cardiogenic shock and the cardiac surgery setting. We will summarize first the challenges in the current classification of DD on critically ill patients, despite its recognized impact on prognosis and mortality. Then, we will describe new tools for the assessment of DD with a focus on strain echocardiography.

## 2 | MYOCARDIAL DYSFUNCTION IN ICU-SYSTOLIC DYSFUNCTION

Several factors influence myocardial function in the general ICU population, and sepsis is probably the best example as it is one of the most encountered causes of admission; moreover, in terms of research on the impact of myocardial dysfunction in ICU patients, sepsis is also the most explored setting. Circulatory compromise is a hallmark of the disease, and even more, if septic shock develops.<sup>5</sup> The reduction in venous and arterial tone is a well-known factor leading to a reduction in preload and afterload in septic patients with consequent hypotension and hypoperfusion. However, the clinical scenario can be additionally complicated by the occurrence of cardiac dysfunction, which further increases the risk of death.<sup>6</sup> Nonetheless, its characteristics and frequency, as well as its long-term consequences, remain very unclear. Indeed, while it has been widely accepted that the occurrence of myocardial involvement in the context of sepsis, and particularly in patients with septic shock- septic cardiomyopathy, has not yet found an accepted definition since its clinical manifestations may variably involve the LV, the right ventricle (RV), or both, as well as simultaneously affecting systolic and/or diastolic function.<sup>7</sup> Not only may sepsis grossly influence myocardial dysfunction in the ICU, but other factors, such as MV with positive pressure and other clinical conditions, may have a significant clinical impact. Indeed, other populations of critically ill patients have been explored, but the consistency of the results and the grade of evidence reported is very low, as in the case of cardiac dysfunction in patients affected by subarachnoid hemorrhage.<sup>8</sup>

Recently, DD was associated with poor outcomes in sepsis, whilst the association is more unclear when looking at LV systolic dysfunction. Before entering the discussion on the clinical impact of DD, we believe it is important to have a preliminary summary of the most recent findings regarding the influence of LV systolic function on patients' outcomes.

Recently, a clustering approach was developed using the multicenter French cohort of septic shock patients (4); based on clinical and echocardiographic parameters, the authors characterized five different cardiovascular phenotypes, as summarized in Table 1.

Hence, as it can be observed, the highest mortality was reported in those with LV systolic dysfunction, followed by RV failure and persistent hypovolemia, while the LV hyperkinetic profile did not seem associated with an increase in mortality. However, this is a controversial matter since a recent retrospective study conducted on over 3,000 patients showed a U-shape association between LV ejection fraction (EF) and in-hospital mortality in septic patients; indeed, both severe systolic dysfunction (LVEF < 25%) and hyperdynamic conditions (LVEF ≥ 70%) were independently associated with higher mortality.<sup>10</sup> Hence, the latter study confirms the poor outcomes of patients with severe LV systolic dysfunction but also highlights the impact of a hyperdynamic profile. Further, meta-analyses conducted so far have not shown an association between LVEF and mortality in sepsis.<sup>3,11</sup> Similarly, the prognostic role of s' wave obtained with Tissue Doppler Imaging (TDI) has not shown an association with mortality,<sup>12</sup> whilst data on mitral annular plane systolic excursion is growing but yet scarce in the literature.<sup>13</sup>

## 3 | DIASTOLIC DYSFUNCTION-THE PREVIOUSLY FORGOTTEN PHENOTYPE

Diastolic function in critically ill patients has been receiving more attention only in the past decade. Assessing LV diastolic function is more complex and requires advanced echocardiography competencies as compared to evaluating LV systolic function.<sup>14</sup> A recent meta-analysis demonstrated a strong association between the diagnosis of DD and mortality in septic patients and confirmed no association between LV systolic dysfunction and mortality.<sup>3</sup> Subsequently, another meta-analysis showed that worse TDI diastolic-related parameters (lower  $e'$  and higher  $E/e'$  ratio) are associated with mortality in septic patients<sup>15</sup>; later, the same findings were reported for the weaning from MV, where DD was associated with greater risk of weaning failure.<sup>15</sup> Also, another study reported in a group of cardiac surgery patients that any grade of diastolic dysfunction was associated with greater all-cause morbidity compared with patients with normal diastolic function.<sup>16</sup> So, these findings suggest the overall importance of properly assessing DD in critically ill patients.

## 4 | DIASTOLIC DYSFUNCTION ASSESSMENT AND THE CHALLENGES IN THE ICU PATIENTS

Echocardiography is essential for the noninvasive evaluation of LV diastolic function. The term diastolic function comprehends several mechanisms and measurements, including active myocardial relaxation (which significantly influences early ventricular filling), LV compliance, which is related to the ability to accept volume (filling) from the left atrium (LA) depending on "LV stiffness," and finally the estimation of

**TABLE 1** Prevalence and mortality of the patients included in the analysis according to cluster partition on the French cohort.<sup>9</sup>

Cluster and characteristics	Prevalence	Day 7 mortality	ICU mortality
1-well resuscitated with no LV systolic dysfunction, RV failure or fluid responsiveness	16.9%	9.8%	21.3%
2-LV systolic dysfunction	17.7%	32.8%	50.0%
3-LV hyperkinetic profile	23.3%	8.3%	23.8%
4-RV failure	22.5%	27.2%	42.0%
5-Persistent hypovolemia	19.4%	23.2%	38.6%

Abbreviations: ICU: Intensive Care Unit; LV: Left Ventricular; RV: Right Ventricular.

LA pressures as a pathophysiological consequence of worsening LV diastolic function.<sup>17</sup>

Over the years, there has been an evolution in the diagnosis and grading of DD. The 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines were the latest published document and have proposed a new algorithm for diagnosis and grading of DD (reported in supplementary material), for the first time separating patients with depressed LVEF from those with normal systolic function.<sup>18</sup> This algorithm relies on four diastolic variables for the diagnosis of DD, and it is mostly dependent on expert consensus-based categorization schemes, with an overall accuracy of 67%–75% but with higher specificity for detecting elevated LV filling pressure (FP) than the previous 2009 guidelines.<sup>19</sup> Although it is not the focus of our review to enter details of the value of each variable, we think that the four parameters used by the latest guidelines for the diagnosis of DD<sup>18</sup> deserve some brief considerations on their value for critically ill patients:

- A. The  $e'$  values (where  $e'$  is the TDI of mitral annulus early diastolic velocity) are sampled at basal myocardial segments. The hemodynamic determinants of the  $e'$  wave are LV relaxation, the restoring forces and the FP and are affected by several conditions, including the presence of mitral valve disease (i.e., calcifications) and myocardial ischemia (acute or chronic),<sup>18</sup> but more importantly it may be modified by the increase in heart rate,<sup>20</sup> especially in the ICU population where heart rate may reach extreme values in certain circumstances.
- B. The mitral  $E/e'$  ratio, which seems one of the best parameters to estimate LA pressure, is influenced by the conditions affecting both the E (arrhythmias, age, mitral and coronary artery disease, to name a few) and the  $e'$  waves (see above); in general, this parameter is useful as it corrects the E wave for the effect of LV relaxation. The  $E/e'$  ratio relates directly to LA pressure, but the cut-off in the ICU may be different from those in other settings.
- C. The LA volume gained importance in the recent guidelines, but ICU physicians must be aware that it provides more useful indications regarding a chronic elevation of LA pressure,<sup>18</sup> hence its usefulness in critically ill patients to describe acute changes of LA pressure is doubtful.
- D. The tricuspid regurgitation jet velocity (TRV) has been introduced because it delivers information on the impact of increased LA pres-

sure on the right-side circulation in the absence of precapillary pulmonary hypertension. However, exacerbation of chronic pulmonary disease and the effects of MV with positive pressure have a profound influence on TRV, and this parameter cannot differentiate the overload on pulmonary circulation from pre- or postcapillary origin.

## 5 | WHAT SHOULD YOU QUESTION ABOUT THE BEDSIDE MANAGEMENT OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN THE ICU?

ICU clinicians understanding the relevance of LV diastolic function for the outcome of their patients should consider two main questions that could influence their decision-making:

1. Can I use the parameters and cut-offs suggested by the current recommendations in the ICU setting to reach a diagnosis and a grading?
2. Are the LA and LVFP of my patients elevated?

To answer the first question, it should be considered that parameters used for the assessment of DD become even more challenging when applied to critical illness due to fluid shifts with variation in preload, changes in afterload and use of vasoactive drugs, the influence of sedation and of MV, just to name a few. Hence, a fair amount of patients may remain in a grey zone between normal and abnormal LV diastolic function. The most recent 2016 ASE/EACVI guidelines<sup>18</sup> represent an improvement, which has also been confirmed when applying these recommendations to the ICU setting. For instance, in a population of septic patients, Clancy et al.<sup>21</sup> compared the assessment obtained with the most recent guidelines (2016) to the previous ones (2009) and demonstrated a significant difference in the prevalence of DD (for instance, on the first day the authors found 60% with the 2016 guidelines as compared to 21% with the older 2009 recommendations). Furthermore, the authors found a much lower prevalence of indeterminate LV diastolic function (23%) as compared to a three times higher with previous guidelines (74%). Cavefors et al. found that general ICU patients with indeterminate LV diastolic function (2016 guidelines) had the same four-fold increased risk of death as those who had fulfilled the criteria for isolated DD.<sup>22</sup> On reflection, it is likely that

a significant proportion of patients classified as indeterminate had indeed DD that could not be verified with current criteria; consistently, increased mortality has also been seen in patients with indeterminate DD in other cohorts.<sup>23,24</sup>

The second clinically oriented question for ICU clinicians is to estimate if DD has resulted in an increase in LA and LVFP. Addressing such questions is far more complex with noninvasive methods, but the answer has significant clinical implications in the management of critically ill patients, with consequences on the interpretation of hemodynamic and respiratory parameters, on the appropriateness of performing fluid challenges, or to apply a more restrictive approach.<sup>25</sup> Also, in this regard, the newest guidelines (2016) seem an improvement. According to the Euro-Filling study,<sup>26</sup> the latest guidelines<sup>18</sup> have represented a simplification and improvement<sup>19</sup> for the prediction of invasively measured LVFP.

Considering the challenges of DD assessment in critically ill patients and the influence of several conditions on each of the echocardiographic parameters used, a simplified definition for DD in ICU was proposed, using only two parameters (septal  $e' < 8$  cm/s for diagnosis of DD; values of  $E/e'$  for DD grading).<sup>27</sup> In this study, such a simplified definition categorized more septic patients than the ASE 2009 definition, but without differences in clinical outcome or comorbidities. Notably, after the publication of the 2016 guidelines,<sup>18</sup> the authors subsequently explored their simplified definition of septic patients and showed that it guaranteed a characterization of a significantly higher number of septic patients with respect to their LV diastolic function (78%), as compared to the 2016 and 2009 guidelines (71% vs. 34%, respectively). Moreover, they highlighted that ASE/EACVI 2016 guidelines designate many patients with normal LV diastolic function despite having an elevated  $E/e'$  ratio, hence with a high likelihood of increased LA pressure.<sup>28</sup> Such discrepancy has been confirmed in patients with COVID-19, where a fair proportion of patients with normal LV diastolic function (2016) had grade II or grade III DD according to the simplified definition.<sup>29</sup> In another COVID-19 cohort, cardiac dysfunction was detected by speckle tracking echocardiography in 73% of patients, 60% of which with DD that correlated with immuno-inflammatory biomarkers.<sup>30</sup>

From the above literature summary, it seems apparent that there are several concerns in applying the guidelines for the assessment of DD in the ICU setting, which could be summarized as follows.

A. First, the cut-off validated for self-breathing patients cannot be easily translated into the typical ICU patients supported with inotropes and/or vasopressors, sedated and ventilated, and eventually exposed to large fluid shifts.<sup>31</sup> In critically ill patients supported by MV, the cut-off values of  $E/e'$  ratio to predict an increase in LA pressure have consistently differed from those suggested in outpatients, and a ratio of 8 seems the most likely appropriate threshold in predicting an increase in LA pressures, rather than the cut-offs ranging between 13 and 15 used for the outpatient population.<sup>32,33</sup> Similarly, even though TRV is an excellent parameter to describe the presence of pulmonary hypertension, it cannot distinguish between pre- and postcapillary increase in vascular

resistances, and in critically ill patients, it is particularly challenging to balance the effects of MV on the values of TRV.<sup>34</sup>

- B. Second, the guidelines are not set for identifying acute deterioration of the LV diastolic function,<sup>35</sup> and ICU patients suffering from acute conditions may experience rapid clinical evolutions (in minutes or hours) that cannot be detected by guidelines developed for patients undergoing follow-up over the years.
- C. Third, premonitory (chronic) LV diastolic function is most often unknown before admission to ICU, making it difficult to value and interpret the worsening or the reversibility of DD in critically ill patients and its potential impact on prognosis.<sup>36</sup>
- D. Finally, it must be acknowledged that neither LVFP nor outcomes have consistently been linked with the four major parameters used to diagnose DD.<sup>12,26,37–39</sup> For instance, the accuracy of  $E/e'$  ratio in predicting elevated LVFP has been questioned in patients with advanced heart failure.<sup>40</sup> However, in critically ill patients, besides the difference in reference values,  $e'$  and  $E/e'$  ratio was associated with mortality.<sup>31</sup>

## 6 | BEYOND CLASSIFICATION! ESTIMATING LA PRESSURE, THE MOSTLY NEEDED DIASTOLIC INFORMATION IN THE ICU

Given the crucial clinical relevance of understanding LA pressure for the estimation of the pathophysiological impact of DD, parameters that provide information about LA properties may be very useful and new parameters of interest have been introduced.

Apart from the four parameters discussed for the diagnosis of LVDD, once the diagnosis of DD is made, the  $E/A$  ratio is still a pivotal variable to classify in grades I, II or III. During isovolumic relaxation, LV pressure falls rapidly, and when it has declined below LA pressure, a positive LA-to-LV gradient is established, the mitral valve opens and the LV fills rapidly, originating  $E$ -velocity. During this passive LV filling (diastasis), LA and LV pressures tend to equilibrate and mitral valve leaflets approach closure. However, the beginning of LA contraction causes an increase in LA pressure with a new LA-to-LV gradient and late diastolic filling occurs, originating  $A$ -velocity.<sup>41</sup> However, the  $E/A$  ratio interpretation may have several pitfalls because it is influenced not only by myocardial relaxation and LV ventricular stiffness but also by the LA pressure itself. The LA pressure is affected by LV properties, and it rises as a physiological adaptation to LV stiffness due to fluid retention. Indeed, the  $E/A$  ratio decreases to values below .8 (depending also on other factors such as age and gender) when LV relaxation is impaired. However, the adaptation to the DD progression involves an increase in LA pressure that restores the “normal” LA-to-LV gradient and the values of  $E/A$  ratio (hence this condition is termed “pseudonormalization,” despite being a relatively advanced DD, grade II). With further progression of the DD and increase in LV stiffness, additional changes in  $E/A$  ratio are observed, with a predominantly early filling pattern and abrupt termination of LV filling even in the presence of active LA contraction—the so-called “restrictive” pattern (grade III). For these reasons, the evaluation of the  $E/A$  ratio cannot be used on its own

to estimate DD and LA pressures, especially in critically ill patients, and this parameter requires contextualization to clinical conditions (i.e., the presence of tachycardia).

To further complicate matters, even though they are frequently used interchangeably, the mean LA pressure and the LV end-diastolic pressure (EDP) do not, from a physiological standpoint, convey the same information. The closest estimate of LV preload serving as a proxy for LV end-diastolic volume is provided by the LVEDP, which also gives information regarding LV operating compliance. Patients with similar LVEDP can experience significantly varying LA pressure, which is also affected by the operating compliance of the LA.<sup>42</sup> This idea is extremely important in the ICU because, for instance, fluid challenges and modifications to MV settings can result in changes to LA compliance. The LA should not be thought of as a passive conduit, and the mean LA pressure integrates the values from both systole and diastole to provide a measurement of the hemodynamic load determined by the LA operating compliance (and indirectly, the LV operating compliance through atrioventricular coupling). Naturally, the pulmonary venous circulation receives a reflection of the mean LA pressure, which affects RV function and gas exchanges.<sup>42</sup> Hence, a more detailed study of the LA function may be desirable to manage critically ill patients.

## 7 | NEW PARAMETERS FOR MYOCARDIAL DYSFUNCTION: THE ROLE OF STRAIN

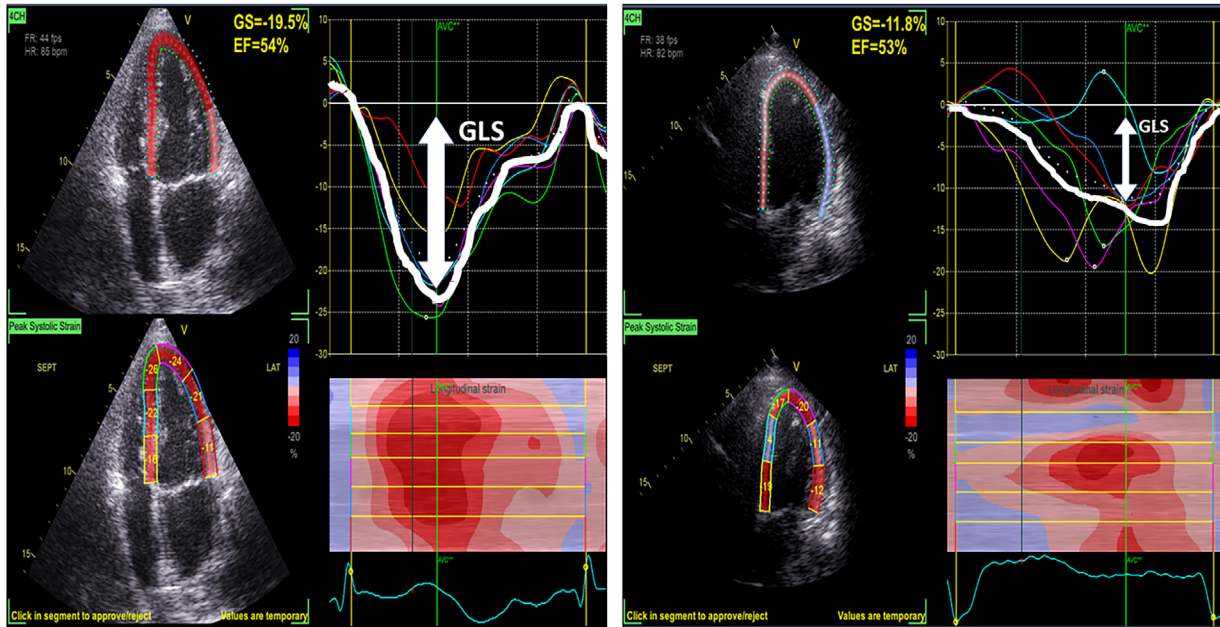
Considering the differences in cut-off seen between the cardiology patient population and the critically ill patients, as well as the complexity of LA function, estimating the bedside mean LA pressure remains a challenge. An alternative echocardiographic modality, speckle-tracking echocardiography, has gradually emerged as a better marker of intrinsic cardiac function with the description of myocardial strain.<sup>43</sup> In the case of the LV, strain represents the difference between the final length of each segment relative to its resting length and can be measured in different planes, mainly longitudinal (from base to apex) and circumferential (rotational short axis). A third form of strain (radial) evaluates inward short-axis movement, but it is less commonly described and infrequently used. The assessment of LV strain can be performed during bedside echocardiography with software-equipped machines, although its clinical feasibility in MV patients seems suboptimal as compared to self-breathing patients.<sup>44</sup> Global longitudinal strain (GLS) is the most commonly reported strain measure and averages the strain values of all segments visualized from the three apical windows. More negative GLS values indicate better LV performance. Interestingly, LV strain's ability to predict prognosis in septic patients has been shown by a meta-analysis,<sup>45</sup> and GLS seems to identify patients with deterioration of LV systolic function earlier than LVEF may do (Figure 1 and Video 1-supplementary material).<sup>44</sup> Further, within the context of sepsis, GLS may better quantify cardiac dysfunction. Indeed, Ng et al.<sup>46</sup> compared patients with septic shock (90-day mortality 41.9%) with a control group of septic patients without shock (90-day mortality 0%), showing a higher degree of myocardial dysfunction in those with sep-

tic shock (GLS  $-14.5\%$ ) as compared with controls ( $-18.3\%$ ); on the contrary, LVEF was similar between groups. Another study compared critically ill adult patients with early severe sepsis/septic shock to a control population of major trauma patients with no sepsis; the authors found that half of the septic patients with preserved LVEF ( $>50\%$ ) had depressed values of GLS, as compared to only 8.7% in the nonseptic trauma group.<sup>47</sup>

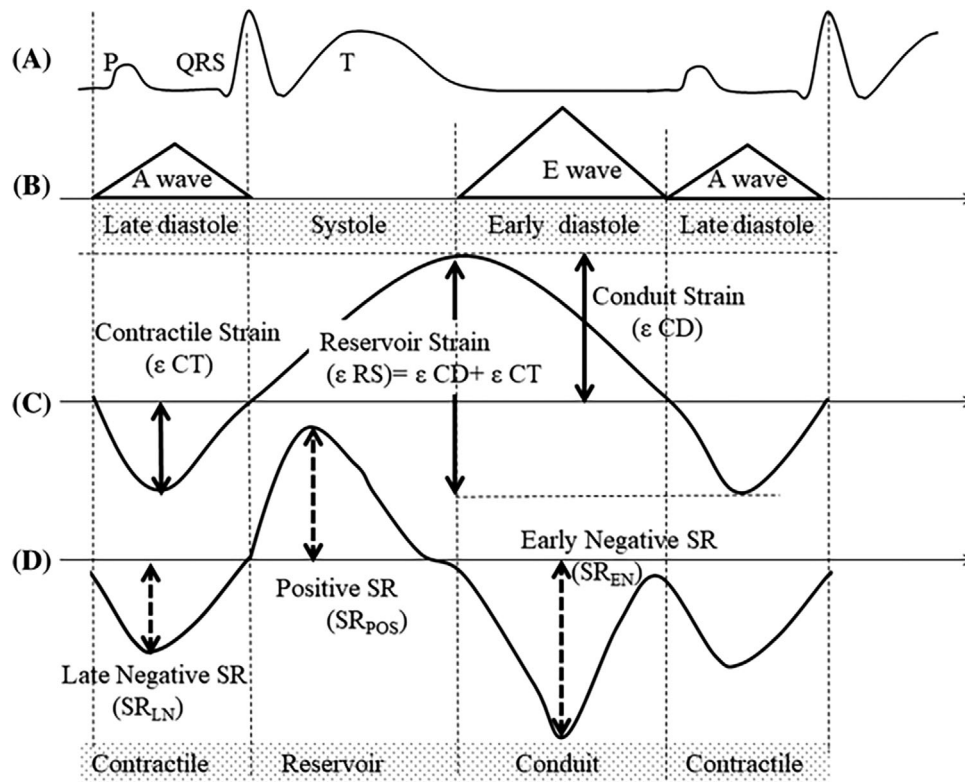
The assessment of LA deformation via strain has been gradually investigated as an accurate and reproducible analysis of the LA function<sup>48</sup> (Figure 2). The better the LA function, the more positive will be the LA strain values (Figure 3 and Video 2-supplementary material). In a multicenter study using invasive hemodynamic monitoring, progressively lower LA strain values were associated with increasingly higher LVFP, and this association was even stronger for patients with reduced LVEF and depressed LV-GLS values.<sup>49</sup> The optimal cut-off to differentiate between normal and elevated LVFP was  $<18\%$  for LA reservoir strain (when using  $>12$  mmHg as a marker of elevated "wedge pressure"); alternatively, a peak atrial longitudinal strain (PALS) cut-off of  $<16\%$  has been identified when referring to a "wedge pressure"  $\geq 15$  mmHg or to an LVEDP  $\geq 16$  mmHg. On the other hand, when PALS exceeds 24% few patients have elevated LV filling pressure. Another study showed striking differences between DD evaluation by classic criteria as compared to the use of LA strain values, namely PALS (28.6% vs. 57.1%,  $p = .0006$ ). Of note, when comparing the classic algorithm for DD assessment with the LA strain, the latter was also able to discriminate patients with worse RV systolic function as evaluated by RV-GLS (21.8% vs. 26.9%) and lower cardiac index (2.5 L/min/m<sup>2</sup> vs. 2.8 L/min/m<sup>2</sup>).<sup>50</sup>

## 8 | FUTURE DIAGNOSTIC APPROACHES TO LVDD AND LA PRESSURE IN ICU

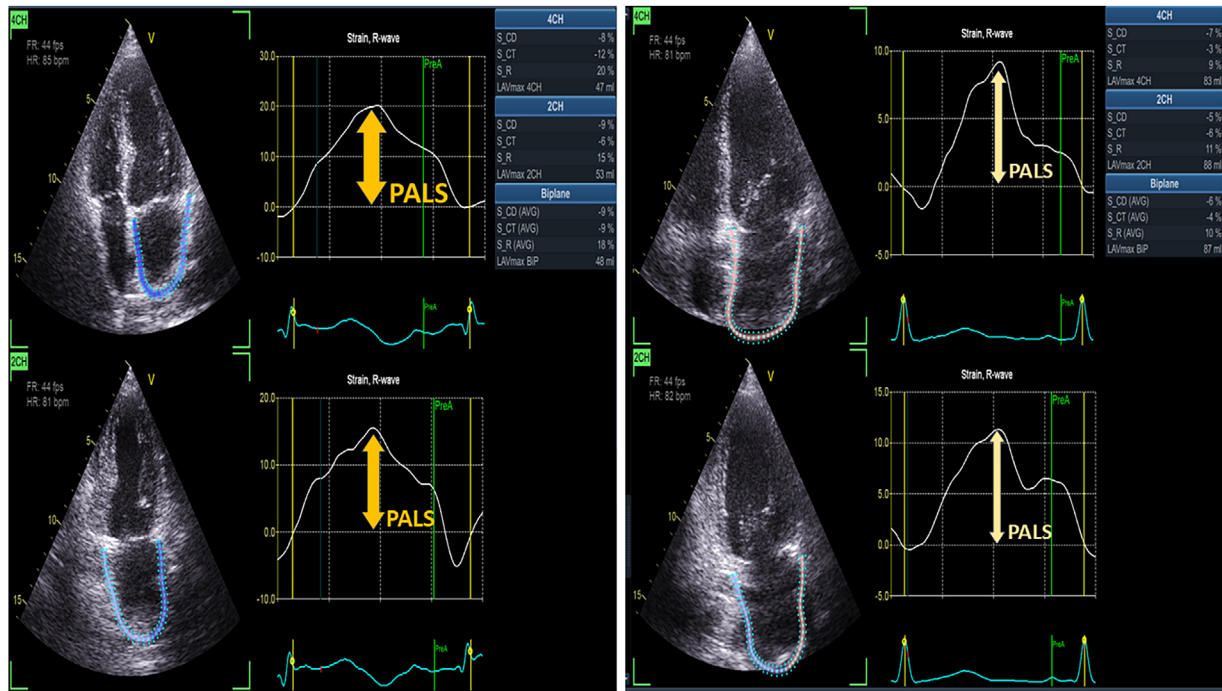
Multivariable models integrating more recent markers, such as the LA strain, seem to outperform other algorithms in terms of prognosis accuracy.<sup>51-53</sup> It has been recently demonstrated that LA strain is a better predictor of LVFP and pulmonary pressure than other conventional indices,<sup>54-56</sup> with a strong association with the severity of DD<sup>57-59</sup> and with prognosis in different clinical scenarios, including heart failure.<sup>51,52</sup> However, PALS has only been recommended in circumstances of ambiguous assessments or inconclusive DD, restricting its clinical usefulness to a relatively small number of instances; hence, it remains unclear its potential benefit for everyday use. In a recent study,<sup>60</sup> in order to identify phenotypes with comparable behavior for forecasting unfavorable outcomes, the authors looked at unsupervised clustering to categorize directly recorded LV diastolic function measures in patients with heart failure, including PALS, only slightly agreeing with the classification determined by the 2016 guidelines.<sup>18</sup> This analysis yielded three separate groups that outperformed guideline-based categorization for forecasting unfavorable occurrences during follow-up (66) and corresponded to greater DD severity. Numerous research that used similar DD variables, PALS, and the 2016 ASE/EACVI classification to compare it to machine



**FIGURE 1** LV GLS image representation in two different settings: first (left), good LV GLS with preserved LVEF; second (right), depressed LV GLS with preserved LVEF, demonstrating that LV GLS can be an earlier marker of cardiac dysfunction than LVEF. LV: left ventricle; GLS: global longitudinal strain; LVEF: left ventricle ejection fraction.



**FIGURE 2** Schematic representation of LA functions during the cardiac cycle. (A) ECG. (B) Transmittal Doppler flow velocity profiles. (C) LA strain curve. (D) LA strain rate curve.  $\epsilon_{CD}$  conduit strain,  $\epsilon_{CT}$  contractile strain,  $\epsilon_{RS}$  reservoir strain, SR strain rate,  $SR_{EN}$  early negative strain rate,  $SR_{LN}$  late negative strain rate,  $SR_{POS}$  positive strain rate.



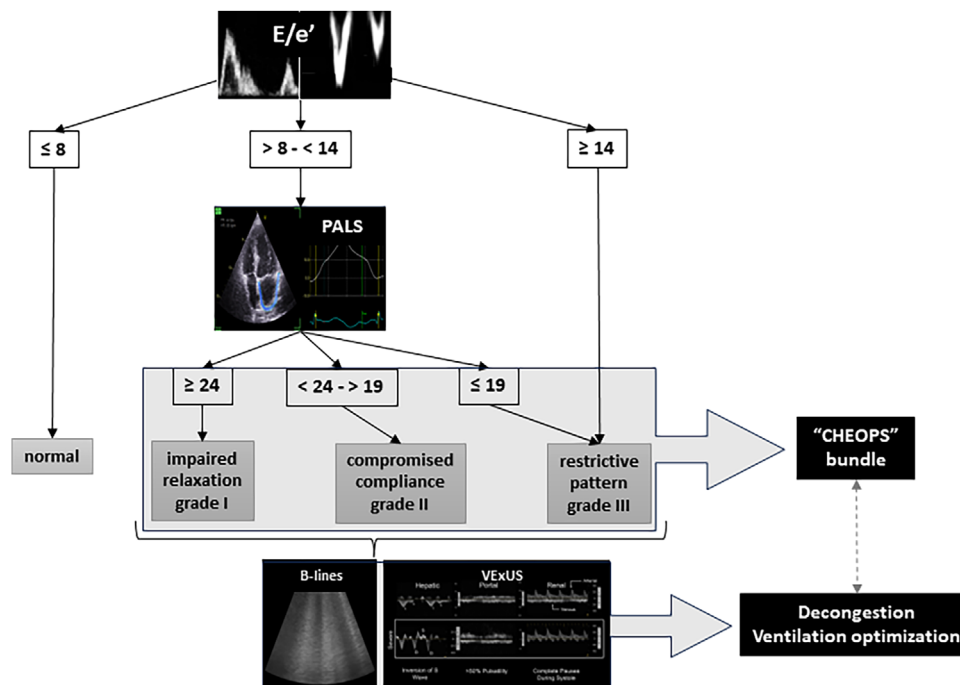
**FIGURE 3** PALS image representation in two different settings: preserved PALS (left) versus compromised PALS (right). PALS: peak atrial longitudinal strain.

learning-based methodologies have adequately demonstrated that a cluster-based classification works better than a consensus-based classification.<sup>61–63</sup>

At the same time, the proposed algorithm<sup>60</sup> draws attention to the possible value of PALS in DD grading. According to the 2016 ASE/EACVI consensus, patients with E/A ratios between .8 and 2.0 who are categorized as having DD grade-1 may be able to be identified using PALS. Surprisingly, the TRV (one of the four pillars of current recommendations) was omitted from the classification and regression tree analysis, raising the possibility that this parameter could be a misleading indicator of DD, given that elevated pulmonary pressure may also be associated with other conditions that are not primarily heart-related. Additionally, this is possible with MV patients. The classification and regression tree analysis also revealed that the cut-off values for the pertinent DD factors changed based on the characteristics and combination of features of the patient and other echocardiographic diastolic variables and were also different from that proposed by current consensus documents, especially for LA volume index and PALS.

Hence, we think that it is likely that the current cardiology guidelines will be at some point revised with the chance to introduce PALS or other strain-based parameters describing LA function, and possibly with a contribution from artificial intelligence.<sup>64</sup> Much literature already exists regarding systolic function and fluid status assessment using machine learning algorithms applying automatic measurements of LVEF and left ventricular outflow tract velocity time integral.<sup>65–67</sup> Considering all the pitfalls described for the assessment of DD in critically ill patients, we consider a more holistic approach to the dias-

tolic function in the ICU more valuable. Experienced clinicians should integrate the hemodynamic information (based not only on echocardiographic variables) with other data from like lung ultrasound (LUS), the venous excess ultrasound (VExUS), and the ventriculo-arterial coupling,<sup>68,69</sup> to better stratify critically ill patients according to their pathophysiologic profile and prognostic impact. Briefly, LUS has been confirmed to be a rapid, noninvasive, and reproducible bedside tool to estimate the extravascular lung water,<sup>70</sup> and it is turning into a key component for determining the presence of pulmonary edema and estimating its severity in different clinical contexts<sup>71,72</sup>; hence, it could help to understand whether there is a clinically relevant impact of increased LA pressure. The use of VExUS relies on the measurement of the inferior vena cava's size in conjunction with Doppler flow interrogation at the level of the hepatic, portal, and intrarenal veins, and it may be useful in assessing the systemic venous congestion and directing fluid management,<sup>73</sup> helping the clinical decision-making regarding fluid tolerance. Finally, the ventriculo-arterial “decoupling,” which is present in most septic patients,<sup>74</sup> either from increased vasomotor tone, decreased LV contractility, or both, can lead to heart failure, loss of volume responsiveness and, if sustained, increased mortality.<sup>75</sup> In these patients, knowledge of LV systolic and diastolic function with an estimation of LA pressure may help in tailoring treatment regarding fluids and possibly vasoactive drugs (i.e., beta-blockers). In short, a more integrative approach is needed in critically ill patients, beginning with data gathered from the classic DD guidelines and integrating clinical variables with other more advanced information, including the LA strain, such as the proposed algorithm in Figure 4.



**FIGURE 4** Proposed algorithm for diastolic dysfunction classification and management for the critically ill patient. PALS—peak atrial longitudinal strain; VExUS—venous excess ultrasound; CHEOPS<sup>68</sup> - Chest Ultrasound, combining information from echocardiography and lung ultrasound; HEmodynamics assessment, with careful evaluation of heart rate and rhythm, as well as afterload and vasoactive drugs; OPTimization of mechanical ventilation and pulmonary circulation, considering the effects of positive end-expiratory pressure on both right and left heart function; Stabilization, with cautious fluid administration and prompt fluid removal whenever judged safe and valuable.

## 9 | CONCLUSION

The classification of DD relies on several parameters that are significantly affected by several factors in critically ill patients, and currently we lack standardized DD criteria in the ICU. This can lead to inconsistent diagnoses and possibly inappropriate management strategies. More importantly, the key question on the presence of increased LA pressure remains often unanswered. Therefore, there is a need to develop tailored classification criteria for DD in critically ill patients. We envisage that the gradual integration of the LA strain values as well as the use of artificial intelligence, may both help in the near future with the diastolic assessment in ICU.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

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