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Review article

The "CHEOPS" bundle for the management of Left Ventricular Diastolic Dysfunction in critically ill patients: an experts' opinion

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ABSTRACT

The impact of left ventricular (LV) diastolic dysfunction (DD) on the outcome of patients with heart failure was established over three decades ago. Nevertheless, the relevance of LVDD for critically ill patients admitted to the intensive care unit has seen growing interest recently, and LVDD is associated with poor prognosis. Whilst an assessment of LV diastolic function is desirable in critically ill patients, treatment options for LVDD are very limited, and pharmacological possibilities to rapidly optimize diastolic function have not been found yet. Hence, a proactive approach might have a substantial role in improving the outcomes of these patients. Recalling historical Egyptian parallelism suggesting that Doppler echocardiography has been the "Rosetta stone" to decipher the study of LV diastolic function, we developed a potentially useful acronym for physicians at the bedside to optimize the management of critically ill patients with LVDD with the application of the bundle. We summarized the bundle under the acronym of the famous ancient Egyptian pharaoh CHEOPS: **C**hest Ultrasound, combining information from echocardiography and lung ultrasound; **HE**modynamics assessment, with careful evaluation of heart rate and rhythm, as well as afterload and vasoactive drugs; **OP**timization of mechanical ventilation and pulmonary circulation, considering the effects of positive end-expiratory pressure on both right and left heart function; **S**tabilization, with cautious fluid administration and prompt fluid removal whenever judged safe and valuable. Notably, the CHEOPS bundle represents experts' opinion and are not targeted at the initial resuscitation phase but rather for the optimization and subsequent period of critical illness.

Abbreviations: AFA, trial fibrillation; ASE, American Society of Echocardiography; CCE, critical care echocardiography; DO_2, delivery of Oxygen; DAP, diastolic arterial pressure; EACVI, European Association of Cardiovascular Imaging; EDP, end-diastolic pressure; ESP, end-systolic pressure; ESPVR, end-systolic pressure-volume relationship; HR, heart rate; ICU, intensive care unit; LA, left atrial; LUS, lung ultrasound; LV, left ventricle; LVDD, left ventricular diastolic dysfunction; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; POCUS, point of care ultrasound; RV, right ventricle; SVR, systemic vascular resistances; TDI, tissue Doppler imaging; TR, veltricuspid regurgitation peak velocity; US, ultrasound; VExUS, venous excess ultrasound; VO_2, oxygen consumption.

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Contents

Background

Since the late seventies, it became evident that abnormalities of left ventricular (LV) diastolic function play a major role in patients with heart failure [1,2]. Over 25 years ago, Nishimura and Tajik compared the importance of the introduction of Doppler echocardiography for the study of LV diastolic function to the discovery of the "Rosetta stone", the granodiorite stele on which an ancient decree was transcribed in three languages allowing to finally decipher the Egyptian scripts [3]. Nowadays, Doppler echocardiography had become the turnaround for the daily non-invasive understanding of LV diastolic function [4,5], reducing the need for invasive cardiac catheterization.

In this manuscript, to help a holistic approach to LV diastolic dysfunction (LVDD) we first summarize the complexities of its assessment in the intensive care unit (ICU), with the current guidelines and their intrinsic limitations. Hence, we propose a bundle for screening and management of critically ill patients with impaired LV diastolic function.

We are aware that suggesting a bundle for ICU patients with LVDD has limitations considering the profound heterogeneity of this population. Indeed, "*one-size-fits*" approaches in ICU are unlikely to work, and a bundle is no exception to this. Nevertheless, generalized approaches might help ICU physicians to initiate treatments and diagnostic pathways that could later leave the pace to a more personalized management. Considering the relevance of LVDD for the outcome of ICU patients, we are convinced that it is worth providing basic guidance for the optimization of such patients, while clinicians with advanced competencies may apply a more personalized approach. Our bundle represents experts' opinions targeted on the optimization of ICU patients after the initial resuscitation when for instance shock occurs.

LV diastolic function: diagnosis and grading

One of the preliminary considerations in the assessment of LVDD is that it does not rely on a single number/variable but rather on a complex interplay of variables related to the deterioration of LV relaxation, the compensatory rise in left atrial (LA) pressure, and the reduction of LV compliance [6]. Moreover, these variables do not show a linear trajectory with worsening of dysfunction as it happens for changes in LV ejection fraction to describe systolic function. Such non-linear change in the variables is due to the activation of compensatory mechanisms (*i.e.*, "pseudo-normalization") [7,8].

Over the last decades, the guidelines for diagnosis and grading of LVDD have evolved in algorithms allowing a more precise and complete classification of LV diastolic function [5,9]. The present manuscript is based on the last 2016 guidelines that report two major changes in comparison with the previous releases [5]. Firstly, LVDD is already diagnosed "by definition" in patients with impaired LV systolic function, with the latter determined by a depressed ejection fraction; this concept is closely related to the observation that diastolic function is an active and highly energy-dependent process. Indeed, during myocardial ischemia, the worsening of LV relaxation precedes the reduction of systolic function [10]. Hence, the latest guidelines separate the assessment of LVDD in patients with normal or abnormal LV systolic function [5]. Secondly, the 2016 guidelines present an algorithm (reproduced in Fig. 1) that makes the diagnosis of LVDD easier with the use of only four variables: left atrial (LA) volume, tricuspid regurgitation jet velocity (TRvel), e' wave velocity (septal or lateral wave measured by means of the Tissue Doppler Imaging - TDI) and E/e' ratio (usually average value between septal and lateral e' waves). The diagnosis is made on a "democracy ground" according to the number of normal vs abnormal values. Once the diagnosis is made (majority of variables are abnormal, or due to pre-existing LV systolic impairment), the subsequent grading of LVDD is based on the integration of values from the trans-mitral flow: E wave velocity and E/A ratio. Importantly, each variable describes changes in one or more physiological aspects of LV diastolic function. Although a simplification is not without drawbacks, the e' velocity is influenced by the LV relaxation process; the LA-to-LV pressure gradient and the LV compliance largely influence the E wave velocity and the E/A ratio; finally, the E/e' ratio is usually adopted as a surrogate of an increase in LV filling pressure, whilst long-standing pulmonary congestion due to LVDD usually determines an increase in LA volume and in the TRVel. Furthermore, it should be considered that, in the assessment of

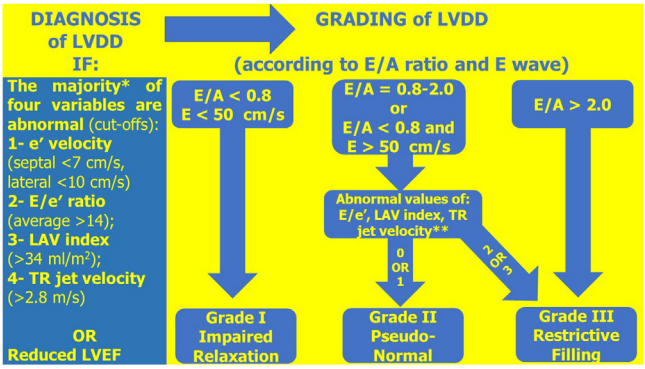

Fig. 1. Algorithm for the diagnosis and grading of left ventricular diastolic dysfunction (LVDD) according to the 2016 American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines. LAV: left atrial volume; LVEF: left ventricular ejection fraction; TR: tricuspid regurgitation.
*In a patient with normal LVEF, if 2 variables are normal and 2 are abnormal, the LV diastolic function remains indeterminate. **when grading LVDD and only 2 of the 3 parameters (E/e', LAV index and TR jet velocity) are available, if one is normal and the other abnormal, the LVDD remains of indeterminate grade.

Table 1
Limitation in the application of cardiology guidelines for the diagnosis and grading of left ventricular diastolic dysfunction (LVDD) in patients admitted to intensive care unit (ICU). LA: left atrial. RV: right ventricle.

Limitations of guidelines in ICU patients	Practical considerations
Echocardiographic variables have been tested in cardiology setting	Until guidelines specific for the ICU population are developed, clinicians should rely on validated algorithms
Cut-offs for each variable are developed from the outpatients	Awareness that reliability of the cut-off used could be different and that different values may apply in ICU
Guidelines are not designed to identify acute changes of LV diastolic function	Repeated daily assessment may identify progression and acute changes in LVDD
The premorbid diastolic function is unknown in most cases for the treating physicians	Estimate the pre-existence of LVDD according to the risk factors (age and comorbidities).
Whether the LV filling (and LA) pressures are increased or not is of utmost importance in ICU	Use E/e' (lower cut-off than outpatients) to gauge the impact on pulmonary congestion and RV function

LVDD, such parameters should be contextualized to population-derived age-specific criteria [11].

In the context of ICU patients, it is worth emphasizing that a crucial aspect closely related to LVDD is the question of whether LV filling pressures are increased or not, with an understanding of the repercussions on pulmonary circulation and respiratory function. For the assessment of the LV filling pressures, the 2016 guidelines [5] represent an advancement as compared to the 2009 ones [9], as shown by the Euro-Filling study [12], where the 2016 algorithm was superior to the previous guidelines for the prediction of invasively measured LV filling pressures. However, the same study showed that there is only a marginal correlation between the LV filling pressures and any of the single parameters included in the 2016 guidelines [12]. Regarding the ICU setting, the greater ability of the 2016 guidelines in classifying LV diastolic function has been elegantly shown by Clancy *et al.* in a cohort of septic patients, and this finding yielded for both subgroups of patients with normal or abnormal systolic function [13].

Guidelines and their limitations

Even if guidelines are necessary to classify LV diastolic function, the 2016 algorithm settled for the cardiology outpatients has significant drawbacks when applied in the ICU (Table 1).

First, all the proposed variables have been derived from investigations performed in outpatients [5], rather than from critically ill patients. These variables may be influenced by ventricles' loading condition (preload and afterload) during critical illness. A typical example is the change in right ventricular (RV) pressures under the influence of mechanical ventilation (MV) with repercussions on the TRvel [14].

Second, even accepting these echocardiographic variables, the cut-off adopted may be profoundly different in ICU, as compared to those in the stable outpatients. For instance, the E/e' ratio has repeatedly shown a fair correlation with pulmonary artery occlusion pressure both in outpatients [15,16] and in mechanically ventilated ICU patients [17,18]. However, in the ICU patients, a value of E/e' ratio $\sim$ 8 seems the best cut-off in predicting an increase in LA pressures, a rather lower value from the one (range 13–15) found in the outpatients' [17,18]. Therefore, even if one would accept to use the same echocardiographic variables for the assessment of LVDD, the reference values could be very different in the ICU population as compared to the outpatient setting [19].

Third, cardiology guidelines are not designed to identify acute changes in LV diastolic function, as it may happen in the course of sepsis or other critical illnesses [20]. For instance, the LA size is unlikely to change acutely as a response to the deterioration of diastolic function, while it rather represents a chronic pathophysiological mechanism to compensate for the increase in LV filling pressure [19].

Fourth, pre-ICU patients' diastolic function is unknown in a vast majority of cases, and in most patients, some degree of LVDD may be already present before critical illness develops. Moreover, there is no convincing evidence that LVDD is fully or partially reversible with the control of critical illness. However, irrespectively from its origin, the presence of LVDD appears an increasingly important prognostic factor in the general population; for instance, E/e' is associated with cardiovascular events [21].

Fifth, a crucial aspect when clinically approaching LVDD in the ICU setting is whether the LV filling (and LA) pressures are increased or not, as this will influence pulmonary congestion, RV function, and gas exchanges. For such reason, Lanspa *et al.* proposed to simplify the approach to diastolic function assessment in the ICU, using two TDI variables only, the e' wave velocity (for diagnosis) and the E/e' ratio (for LVDD grading) [22]. Although not yet validated, the authors found that such a simplified protocol categorized a greater number of septic ICU patients as compared to previous guidelines [9]. However, a recent study [23] showed marked discrepancies in the diagnosis and grading of LVDD between the "Lanspa protocol" and the full assessment according to recent guidelines [5].

LV diastolic function: impact on clinical outcome

The association between LVDD in the context of critical illness and poor patients' outcomes is widely accepted. Meta-analyses suggest high mortality in septic ICU patients with LVDD, both in adults [24,25] and in pediatric setting [26]. A meta-analysis failed to identify a clear association between LV systolic dysfunction and mortality of septic patients [27,28]; however, new evidence suggests a U-shaped association between values of LV ejection fraction and mortality in septic patients, with both severely depressed ($<$25%) and hyperdynamic LV systolic function ($\geq$70%) being poor prognostic factors [29].

Another clinical condition where LVDD has a significant influence is the weaning from MV. During the separation from MV, a shift from positive to negative pressure ventilation occurs. Although the hemodynamic impact of such a shift is not always straightforward, in most patients it increases both LV preload and afterload, with the chance to increase LV filling pressures, especially in patients with impaired relaxation [30]. Evidence from pooled results confirms that worse TDI values (e' velocity and E/e' ratio) are associated with weaning failure [31].

The impact of LVDD has been explored also in the perioperative period, with the majority of studies conducted in cardiac surgery, where LVDD is again associated with poor outcomes [32,33]. Similar results have been reported in the case of major vascular surgeries [34,35]. Contrarywise, uncertainties remain on the effects of LVDD on outcomes after non-cardiac non-vascular surgery. Unfortunately, the quality of the evidence in this setting is

rather low, as most patients do not undergo a preoperative assessment of LV diastolic function. A small study showed that elevated E/e' ratio was significantly associated with postoperative cardiovascular events (pulmonary edema and arrhythmias), as well as with longer ICU and hospital stays [36]; however, a much larger (but retrospective) study showed opposite findings: Willingham *et al.* included data from echocardiograms performed within 6 months of a non-cardiac surgical procedure and found that LVDD was not associated with in-hospital mortality, acute kidney injury, nor hospital stay [37]. As discussed, the assessment of LVDD is complex and seldomly performed in the perioperative period of non-cardiac non-vascular surgery, but it is possible that the implementation of artificial intelligence may increase the quality and the amount of data available in this regard [38].

How to optimize lv diastolic dysfunction: the CHEOPS bundle!

As mentioned, a parallelism was made between the study of LV diastolic function and the "Rosetta stone", the stele allowing researchers to subsequently decipher Egyptian scripts [3]. In particular, the authors suggested that the clinical implementation of Doppler echocardiography was the "Rosetta stone" for the study of diastolic function. Indeed, at that time Doppler echocardiography became essential (and still is) for the diagnosis and grading of LV diastolic function. Apart from the LA volume, all currently used variables for the assessment of LV diastolic function are based on Doppler echocardiography [5].

Recalling this elegant parallelism, we decided to suggest an acronym that could be useful for clinicians at the bed space to optimize the LV diastolic function in critically ill patients by applying a dedicated bundle. The bundle with its aspects is summarized under the acronym of CHEOPS, the famous ancient Egyptian Pharaoh (also known as Khufu) of the Fourth Dynasty living in the first half of the 26th century before Christ. The CHEOPS bundle is summarized in Table 2 and graphically reported in Fig. 2. As Pharaoh Cheops commissioned the Great Pyramid of Giza (one of the Seven Wonders of the Ancient World), we graphically show the CHEOPS bundle in a pyramidal shape. For a matter of practicality, the bundle is briefly explained in short paragraphs with a summary of reasons why each component could be important for the management of patients with LVDD. The interested reader should go into details elsewhere for each of these.

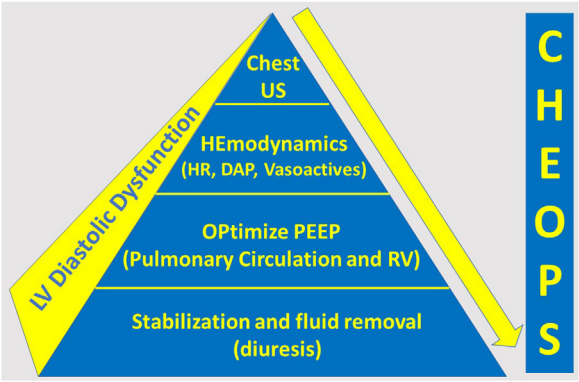

Fig. 2. The CHEOPS bundle for the management of left ventricular (LV) diastolic dysfunction. US: ultrasound; PEEP: positive end-expiratory pressure; RV: right ventricle.

Items of the CHEOPS bundle

C - chest ultrasound

The use of both critical care echocardiography (CCE) and of Lung Ultrasound (LUS) is becoming widespread and the use of Chest Ultrasound is becoming part of the physical examination like a stethoscope. The use of CCE has grown over the recent decades as a tool for hemodynamic optimization [39], with several training pathways and accreditations being available [40,41]. With regards to Chest Ultrasound, we think that three aspects are particularly relevant for patients with LVDD, namely assessment of LV diastolic function and LV filling pressure, estimation of pulmonary edema with LUS, and evaluation of RV function.

First, the CCE is essential for the diagnosis and grading of LVDD, being also the tool for subsequent follow-up of changes in LV filling pressure. We think that ideally, all patients should receive an advanced CCE within the first few days of ICU admission: patients found to have LVDD and/or increased LV filling pressure may enter the pattern of the CHEOPS bundle. Second, in addition to CCE the use of LUS is certainly invaluable to confirm the presence of pulmonary edema and to estimate its degree in different clinical settings [42,43], but scores are variables according to the number of sectors that are scanned by the operator. With recent advances

Table 2
The CHEOPS bundles for the management of the critically ill patients with left ventricular (LV) diastolic dysfunction. AF: Atrial Fibrillation; DO2: delivery of Oxygen; DAP: Diastolic Arterial Pressure; HR: Heart Rate; LUS: Lung UltraSound; MV: Mechanical Ventilation; POCUS: Point of Care UltraSound; RRT, renal replacement therapy; RV: Right Ventricle; SVR: Systemic Vascular Resistances; VExUS: Venous Excess UltraSound; VO2: oxygen consumption.

Items of CHEOPS bundle	Practical considerations
Chest ultrasound	The use of echocardiography is mandatory for the evaluation of LV diastolic function and for the non-invasive evaluation of LV filling pressure. Echocardiograms may be repeated frequently to evaluate changes in diastolic function and filling pressure; it should also focus on optimization of RV function; the additional use of LUS can be very valuable.
HEmodynamics (HR, DAP, Vasoactives)	Assessment of hemodynamic should consider to: 1) keep HR as low as reasonable (to guarantee diastolic time and to reduce myocardial VO_2); 2) prevent AF (to ensure atrial contribution to LV filling); 3) maintain adequate afterload balancing the importance of DAP (to secure LV coronary perfusion and myocardial DO_2) and of reducing SVR (to decrease the LV end-systolic pressure and increase atrio-ventricular gradient during diastole). If vasoactive drugs are needed, vasopressors (*i.e.* norepinephrine) are generally favored over those with predominant inotropic effects, as most of the latter have negative lusitropic effects. If inotropic effect is needed, levosimendan can be considered case by case for its potentially positive effects on lusitropy.
OPtimize PEEP (Pulmonary circulation and RV)	Ensure positive effects of MV and PEEP on both the LV and RV function; to set PEEP in order to facilitate LV ejection and decrease LV preload, to favor alveolar recruitment with beneficial effects on pulmonary vascular resistances. Avoid RV dilatation, which in turn would compromise the LV filling. Critical care echocardiography may be coupled with LUS with a holistic approach balancing the effects of MV on alveolar recruitment and oxygenation, as well as on RV function and pulmonary circulation.
Stabilization and fluid removal (diuresis)	For the clinical stabilization consider fluid administration cautiously, due to the high risk of congestions. Once stabilized, start personalized fluid removal (diuretics or RRT in case of diuretic resistance) as soon as feasible to reduce LV filling pressure and congestion, facilitating the weaning from MV. The LUS and the VExUS may be valuable for the quantification of congestion and monitoring effects during de-escalation

in technology, LUS has been confirmed to be a rapid, non-invasive, and reproducible bedside tool to estimate the extra-vascular lung water [44], although with limited ability to predict LV filling pressure [45,46]. This parameter correlates clinically with pulmonary edema [47] and with its resolutions during fluid removal [48]. Notably, high values of extra-vascular lung water have been independently associated with poor outcomes [49,50]. Hence, we pooled together CCE and LUS at the top of the pyramid in Fig. 2 under the "Chest US" item, the first aspect of the CHEOPS bundle. Third, also the evaluation of RV function can be done during Chest US; however, it necessitates high expertise, and the subjective RV assessment is prone to errors even for experienced operators [51]. Moreover, CCE research does not show a consistent pattern in RV assessment and definition of RV dysfunction [52–54]. Anyway, a preliminary evaluation of signs of RV dilatation is part of the basic skills in CCE, and RV dilatation and paradoxical septal motion would determine mechanical compression of the LV cavity with a subsequent compromise in LV filling. In this context, CCE should serve as a monitoring tool to guide the management of patients in regard to the modulation of vasoactive drugs and the setting of MV.

HE- HEmodynamics

Hemodynamic assessment is an essential part of the daily evaluation of critically ill patients, with management focused on optimizing organ perfusion. This target is achieved by adequately balancing the use of fluids and inotropic/vasoactive drugs. As both fluids and inotropic/vasoactive drugs have side effects, their optimization is relevant for the outcome of critically ill patients [55–58]. In the case of patients with LVDD, some relatively simple concepts valid for all critically ill patients should be further emphasized for hemodynamic optimization.

Tachycardia not only increases myocardial oxygen consumption but also worsens LV filling by decreasing diastolic time. In truth, healthy individuals compensate for the decrease in LV diastolic time occurring during episodes of tachycardia with a "frequency-dependent acceleration of relaxation", a sort of physiologic improvement of diastolic properties [59]. However, such phenomenon is impaired in experimental models of sepsis [60], as possibly could be during critical illness. Control of heart rate can become particularly important in the context of compromised LV relaxation as it happens in patients with LVDD, and clinicians should perform a careful assessment to decide whether pharmacological options to control heart rate are appropriate. If so, the use of beta-blockers may be considered for their ability to reduce heart rate, prolong the duration of diastole, and for their anti-arrhythmic properties [61]. A recent meta-analysis found that ultrashort-acting β-blockers (esmolol and landiolol) significantly reduce 28-day mortality in septic patients with persistent tachycardia after initial resuscitation [62]; however, the use of beta-blockers in this context is not yet mentioned in the guidelines [63]. Whether the benefit is greater or not in patients with LVDD remains to be established. Moreover, it is clear that only a portion of ICU patients may benefit from beta-blockade during the acute phase of critical illness, and the selection of these patients can be complex [64]. Ivabradine could be another option if control of the heart rate is needed but in a small study, it did not change LV diastolic function, though global strain improved [65]. Another intriguing option for heart rate control could be the use of dexmedetomidine, considering it seems to counteract alpha-receptors down-regulation, positively modulating vascular responsiveness to norepinephrine [66].

Proactive prevention of tachy-arrhythmias (namely atrial fibrillation, AF) is always important [67], and new-onset AF in ICU patients is associated with poorer short- and long-term outcomes [68]. Avoidance of AF becomes even more relevant in patients with impaired LV diastolic function. Indeed, in these patients, the LA contribution to LV filling has an increased hemodynamic relevance, and consequently, its loss has greater consequences in terms of cardiac output reduction in patients with LVDD. Hence, non-pharmacological interventions to reduce arrhythmogenicity and the risk of AF can be particularly valuable in patients with LVDD [69]. However, if an acute arrhythmic event occurs, restoring sinus rhythm is likely to be very valuable for these patients, either with the use of amiodarone or with electric cardioversion.

Pharmacological modulation of the afterload is usually performed to guarantee a target mean arterial pressure. It should be kept in mind that in patients with impaired LV diastolic function, an unnecessarily high LV afterload with a higher mean arterial pressure (possibly causing ventriculo-arterial decoupling) should be avoided as much as possible. Indeed, an excess of systemic vascular resistances would negatively affect the LV stroke volume with a consequent increase in LV end-systolic volume and pressure. Such higher pressure into the LV cavity, in turn, would decrease the atrio-ventricular gradient during the next diastole, impairing LV filling (Supplementary material 1). Whilst selecting an appropriate degree of afterload and mean arterial pressure, clinicians dealing with a patient with LVDD should consider that the diastole is an energy-dependent process; hence, it is important to maintain myocardial oxygen supply by ensuring optimal values of diastolic blood pressure, coronary perfusion, and adequate arterial oxygen content. In short, in patients with LVDD and increased LV filling pressure, vasopressors use should be targeted to reasonable values of mean arterial pressure over higher targets as suggested by the latest sepsis guidelines [63], but also considering that diastolic arterial pressure is enough to ensure adequate myocardial perfusion.

Vasopressors are certainly the most commonly administered vasoactive drugs in critically ill patients, but in a proportion of these, a positive inotropic effect may be desirable. Most inotropes have also positive chronotropic effects, but some have negative effects on diastolic properties (lusitropism). This seems the case with epinephrine and dobutamine [70–72]. When positive inotropism is needed in patients with advanced LVDD a better option might have been the administration of phosphodiesterase inhibitors or levosimendan. While it seemed that LV diastolic function remains grossly unchanged with milrinone and similar [72,73], the evidence seems rather in agreement on the beneficial effects of levosimendan on LV diastolic function [70,74,75]. However, evidence from a large randomized trial does not support the use of levosimendan in septic shock, even in the subgroup analysis of patients with biochemical evidence of cardiac dysfunction [76,77]. Again, the patient's selection based on a personalized approach is likely to be the key.

During recovery from critical illness, a therapeutically reasonable option for patients with LVDD could be the introduction of angiotensin-converting enzyme inhibitors for their activity on LV remodeling and lusitropy [78,79]; however, their positive effects are usually seen in the long-run whilst amelioration of diastolic properties in the acute setting is not demonstrated yet.

OP - OPtimization of PEEP and pulmonary circulation

Increased LV filling pressures lead to pulmonary congestion, with extravasation of fluids in the alveolar space resulting in pulmonary edema (increased extravascular lung water) and poor gas exchanges. After a proper echocardiographic assessment and hemodynamic optimization, clinicians should consider that patients with LVDD may have potentially negative repercussions of MV. Hence, it could be particularly important to optimize MV settings in these patients, in order to decrease pulmonary

congestion. As a preliminary and simplified consideration, positive end-expiratory pressure (PEEP) produces positive effects on the LV function, reducing both preload and afterload, whilst opposite effects are often imposed on the RV. In principle, it seems possible that a slight increase in the levels of PEEP may be beneficial in patients with LVDD, facilitating the LV ejection (for the decrease in afterload) and reducing the LA pressure, as long as the pulmonary circulation is not affected. In truth, the effects of PEEP should be evaluated according to the change in pulmonary vascular resistances. Basically, when PEEP produces alveolar recruitment with the opening of extra-alveolar vessels (''rectilinearization'' of the peri-bronchial vasculature), the overall pulmonary vascular resistances will be decreased, and the RV function may improve. Conversely, when PEEP causes alveolar overdistension and ''squeezing'' of alveolar vessels, it increases pulmonary vascular resistances. With such background, whilst several ventilatory maneuvers and evaluation of gas exchanges can be performed to find the ''best PEEP'' level, we suggest that particularly in patients with increased LV filling pressures, a good clinical approach to the titration of PEEP will include also an evaluation at hemo- and echo-dynamic level. Hence, setting PEEP and MV targeting a decrease in LV preload and afterload remains valuable as long as such settings do not produce RV dilatation; as mentioned, RV failure would also cause mechanical compression of the LV cavity compromising LV filling. Whenever possible, MV settings should not harm causing cardiovascular dysfunction [80].

A separate important consideration when discussing the impact of MV on LV diastolic function should be made during the patient's recovery. When approaching the transition from positive to negative pressure ventilation, the venous return to the heart increases with a higher risk of weaning failure for patients with LVDD and preload unresponsiveness. Indeed, such an extra amount of blood returning to the heart with the transition to negative pressure ventilation may not be accommodated in case of significant LVDD, with a consequent risk of pulmonary congestion and edema [31]. This concept has been elegantly shown in a large study by Liu *et al.* where weaning failure was of cardiac origin (''weaning-induced pulmonary edema'') in almost 60% of all failures [81]. Such cardiac origin seemed related to LV filling pressure (higher E/e' ratio) whilst the LV ejection fraction was similar between failures and cases without weaning-induced pulmonary edema. Interestingly, in a sub-group analysis, the authors showed that fluid responsiveness was present in only 6.7% of the patients with weaning-induced pulmonary edema, as compared to 100% in those with weaning success [81]. When clinicians are facing a patient with established LVDD and increased LV filling pressure, it seems clinically reasonable to approach the weaning process under conditions of fluid responsiveness to decrease the risk of failure.

S – Stabilization and fluid removal (diuresis)

The association between positive fluid balance and poor outcome is well-established for critically ill patients [82,83] and in the postoperative period [84]. Hence, the approach to a more thoughtful fluid resuscitation has been the subject of intense study but two recent randomized controlled trials (CLASSIC and CLOVERS) [85,86] did not suggest differences between restrictive and liberal fluid resuscitation, highlighting again the importance of a personalized approach guided by clinical assessment, and that the modern approach to ''liberal'' is much less ''liberal'' than in the past.

The concept of active fluid removal during the recovery from critical illness (''de-resuscitation'') has gained momentum over the past decade. Once the underlying clinical condition is stabilized, it seems reasonable to decrease the burden of congestion by actively removing fluids with diuretics (or in some cases with renal replacement therapy), as long as the risk of precipitating a new shock condition is deemed unlikely. Preliminary results suggest that such approach may speed up the healing process [87], but personalization seems paramount when targeting negative fluid balance [88]. Of course, fluid removal and progressive decongestion might be applied to every ICU condition that determined fluid overload and tissue edema. De-resuscitation should take into account the capacity of the cardiovascular and lymphatic systems to restore the intravascular volume avoiding an excessive drop in mean systemic filling pressure and venous return.

We believe that patients with LVDD and high LV filling pressure are likely to benefit from early consideration of de-resuscitation to decrease the burden of pulmonary congestion. However, these patients may represent a significant clinical challenge, and a multi-parametric approach might be valuable to guide clinicians' decision-making. Non-invasive assessment of congestion can be very valuable in this regard. Importantly, the assessment of congestion goes along with the concept of fluid tolerance that has recently been brought up: clinicians should consider that even patients with characteristics of fluid-responsiveness may be already not fluid-tolerant [89]. Hence, the assessment of signs of congestion is becoming relevant for daily ICU practice. Besides CCE, two other point-of-care ultrasound approaches - LUS and Venous Excess UltraSound (VExUS) [90] - have been implemented for the evaluation of pulmonary and systemic congestion, respectively. The use of LUS has gained further momentum after the recent coronavirus pandemic and has been integrated into the ultrasound skills of intensivists [91]. The findings of diffuse B-lines with LUS in patients with LVDD would support the diagnosis of interstitial lung edema associated with elevated LV filling pressure and also with increased extravascular lung water; indeed, there is evidence supporting the important role of non-invasive evaluation of extravascular lung water with the aid of LUS [92,93]. The use of VExUS is even more novel than LUS. In short, it relies on the assessment of the size of the inferior vena cava coupled with flow interrogation with Doppler at the level of the hepatic, portal, and intra-renal veins. The VExUS score would range from 0 (no congestion) to 3 (severe congestion), but its clinical value is still controversial [94,95].

In general, the feasibility of fluid removal targeting a negative fluid balance should be sought early during the recovery from critical illness. The use of LUS and VExUS in conjunction with the assessment of LV filling pressures may be worthwhile for both quantification of congestion and monitoring the effects of de-resuscitation during fluid removal, but more research is needed. Clinicians should combine point-of-care ultrasound with other considerations such as the trend in hemoglobin, gas exchanges, peripheral edema, and information from hemodynamic monitoring. All these and other aspects might help to personalize the proper rate of fluid removal [96]. We think that a holistic evaluation of the patient with a careful understanding of oliguria/anuria due to non-renal causes is essential in the pathway driving clinicians to start or potentiate fluid removal with diuretics (or with renal replacement therapy).

Conclusions

The study of LV diastolic function has gained interest in the intensive care unit, and an association of LVDD with poor outcomes has been repeatedly shown. Screening for LV diastolic function is desirable in all ICU patients, but the management of critically ill patients with LVDD is complex, and only a multi-faceted proactive approach may produce clinical benefits for this type of patients. We propose a bundle called CHEOPS for the mnemonic optimi-

zation of the management of patients with LVDD. The CHEOPS algorithm includes: the use of **C**hest Ultrasound (CCE and LUS); **HE**modynamics considerations on heart rate and rhythm, as well as on afterload and vasocatives; **OP**timization of mechanical ventilation and pulmonary circulation; **S**tabilization and fluid removal (diuresis) with a personalized approach targeting negative fluid balance. However, whether any dedicated management of patients with LVDD improves outcomes remains an area that deserves further research.

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Authors' contributions

FS developed the idea and the possible acronyms for the bundle. All the authors discussed the options for the best management and optimization of the patients with LVDD. Once agreed the options all authors divided the work in paragraphs. FS, AM, EB and SR drafted the background of LVDD and the paragraph on Chest ultrasound; FS, AM and MC drafted the part on Hemodynamics and vasoactives; FS and GL drafted the part on optimization of ventilation, PEEP, pulmonary circulation and RV; FS, SS and SR drafted the stabilization and fluid removal paragraph. FS, AM, SS and MC created the figures; FS and SR created Table 1; FS, AM, EB and SR created Table 2. All the authors revised the paragraphs produced by the other. All the authors agree on the final version of the manuscript and on its recommendations.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2023.101283.

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