EDITORIAL

# Left Ventricular Diastolic Dysfunction in the Critically Ill: The Rubik's Cube of Echocardiography

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Left ventricular diastolic dysfunction (LVDD) is frequently encountered in the intensive care unit (ICU). The incidence in septic cohorts varies from 20 to 67% and is highly dependent on the case mix studied.[1–3] The importance of LVDD stems from the fact that its presence predicts worse clinical outcomes in critically ill cardiac and vascular surgery patients, independent of other variables and even in the absence of left ventricular systolic dysfunction (LVSD).[3,4] It also predicts weaning failure.[5,6] Left ventricular diastolic dysfunction in the ICU is routinely assessed non-invasively by Doppler echocardiography. Critical care physicians have struggled for decades to elucidate an easily elicitable, highly reproducible parameter to diagnose LVDD in the ICU. This ideal parameter should have minimal confounding factors, therapeutic potential, and a high correlation with morbidity and mortality. The challenges of defining LVDD in the ICU are profound, and we need to understand them before interpreting an echocardiography report in the ICU.[7]

Left ventricular diastolic dysfunction is physiologically identified by impaired relaxation, followed by a compensatory increase in left atrial pressure, and thereafter by an increased stiffness of the left ventricle. These changes are picked up by different echocardiographic variables. It is implicit that these variables will be influenced by the age of the patient besides preexisting comorbid conditions, especially hypertension, diabetes mellitus, coronary artery disease, heart failure with preserved ejection fraction, chronic kidney disease, mitral valve disease, and aortic valve disease, even in the absence of LVSD. It is presumed that all patients with LVSD will have LVDD and hence the American Society of Echocardiography (ASE) 2016 guidelines recommend separate methods for assessment of diastolic function in patients with and without LVSD.[8] The incidence of LVDD in the ICU is consequently highly influenced by the case mix studied and varies in an unpredictable way across medical, surgical, and trauma units. A baseline echocardiography report may not be available for all patients getting admitted to the ICU, and hence, after diagnosing LVDD based on an echocardiogram done in the ICU it is difficult to differentiate between patients who had preexisting LVDD from those who acutely developed LVDD in the ICU. This distinction may not be so important in a functional aspect because what matters to the critical care physician is the net impact of LVDD on the patients physiology rather than the grade of LVDD, this is assessed by left atrial pressure (LAP), which is a surrogate for left ventricular filling pressure or left ventricular end diastolic pressure (LVFP/LVEDP). These terms are used interchangeably, but the LAP is more relevant when evaluating pulmonary congestion, whereas LVFP is a better marker of left ventricle (LV) preload. However, patients with similar LVFP can have different LAP depending on left atrium (LA) compliance. Left atrium compliance in the ICU can vary with fluid loading and changes in ventilator settings, in addition to an elevation of LVFP.

There are a plethora of interventions in the ICU that impact LVDD and, therefore, LAP. These include fluid loading and removal, use of vasoactive agents, mechanical ventilation, tachycardia, atrial fibrillation, left ventricular systolic function, right ventricular systolic and diastolic function, the dynamic phenomenon of ventricular interdependence, and heart-lung interactions.[7] Critical care physicians should also appreciate the so-called physiological entity of pseudo LVDD, which is a term explaining the development of LVDD-like physiology in a setting of acute cor pulmonale where the LV is compressed by the pressure-overloaded right ventricle, thereby interfering with LV filling and giving the echocardiographic impression of a stiff LV.[7] It is therefore imperative that once we diagnose LVDD in the ICU, whether preexisting or of ICU origin, the value we derive from the echocardiographic assessment of LAP be interpreted in the context of the above-mentioned confounding factors. This is not easy because most of the listed confounding factors will keep changing frequently in the critically ill patient.

Left ventricular diastolic dysfunction and sepsis share a dynamic relationship. A typical septic shock scenario is characterized by relative or absolute hypovolemia, worsening vasodilation, and the presence of sepsis-related myocardial dysfunction. Sepsis-related myocardial dysfunction can involve the left and/or right ventricles producing systolic and/or diastolic dysfunction in any combination.[7] These pathophysiologic alterations will be managed by fluid, and vasopressor agents, with or without mechanical ventilation.

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It is therefore imperative that the diagnosis of LVDD with a raised LAP be interpreted in the appropriate context. Left ventricular diastolic dysfunction in sepsis correlates with poor prognosis and outcomes in patients with sepsis, even in the absence of left ventricular systolic dysfunction.[4]

The question of which now arises is how to measure LVDD using echocardiography in the ICU. It is impossible for a single parameter to accurately diagnose LVDD since there are so many confounding factors. There is also no single gold standard of measure for LVDD. The ASE guidelines are not applicable for the perioperative or critically ill patients. The ASE 2016 guidelines include E (early diastolic velocity at mitral inflow), E/A (ratio of early to late diastolic velocity at mitral inflow), e' (early diastolic mitral annular velocity), E/e' (ratio of early diastolic velocity at mitral inflow to early diastolic mitral annular velocity), LAVI (left atrial volume index), and TR Vmax (maximum velocity of tricuspid regurgitation jet).[8] The e' velocity is influenced by the LV relaxation process, restoring forces (reflecting diastolic suction), LAP at the start of mitral opening, mitral annular calcifications, myocardial ischemia, and heart rate; the E/A ratio is influenced by the LA to LV pressure gradient, and LV compliance, age, arrhythmias, mitral valve disease, and coronary artery disease; E/e' is a surrogate for LAP/LVFP and is affected by increased LV preload (septal unchanged and lateral reduced), increased by increased LV after load, increased by conduction blocks, and is unreliable during arrhythmia; the LAVI and TR jet Vmax reflect long-standing elevated LVFP. These guidelines are derived from cardiology outpatients, and do not capture acute changes in LVDD and hence are not applicable in the ICU. However, until ICU guidelines are developed, clinicians should rely on validated algorithms and appreciate the fact that ICU cutoffs may be different from outpatient cutoffs.[9] An example in this regard is the E/e' ratio which correlates fairly with pulmonary artery occlusion pressure in both outpatients and mechanically ventilated patients, but E/e' = 8 is the best cutoff for ICU patients as compared to E/e' of 13–15 for outpatients for predicting elevated LAP/LVFP.[10,11]

A simplified assessment definition proposed by Langspa is extracted from the ASE 2009 guidelines for LVDD and uses e' (septal mitral annulus velocity measured by Tissue Doppler) <8 cm/sec as a marker of LVDD. If LVDD is present, then LAP/LVFP is assessed by E/e' (ratio of early mitral inflow velocity to septal mitral annulus velocity measured by Tissue Doppler) ≤8 – Grade I, 9–12; Grade II, ≥13 as Grade III LVDD.[12] This definition was studied in a cohort of septic patients. This definition is based on the premise that the above parameters are easy to measure, reproducible, and relatively less affected by changes in preload and afterload. They have done away with E/A as A velocity cannot be measured because of fusion during sinus tachycardia and in the presence of atrial fibrillation. The Left atrial volume index (LAVI) is also misleading since it takes time for the left atrium to enlarge in the presence of elevated LVFP, and hence an increased LAVI is suggestive of chronically elevated LAP/LVFP and does not reflect an acute rise in LAP/LVFP. The maximum velocity of the tricuspid regurgitation jet (TR Vmax) is dependent on right ventricular function, which in turn is altered by the settings of the ventilator during mechanical ventilation. The predictive value of these two variables from the simplified definition – E/e' and e', is the same as that of the full definition of the ASE 2009 guideline for LVDD-related clinical outcomes. The advantage is that it takes easily measurable parameters and avoids discordance by omitting unimportant parameters. It categorizes a greater number of septic ICU patients into those with and without LVDD as compared to the ASE 2009 and subsequently, with ASE/EACVI 2016 guidelines. They pointed out that the ASE/EACVI 2016 guidelines designate many patients with normal LV diastolic function despite having an elevated E/e' ratio, and hence a high likelihood of having elevated LAP/LVFP. The limitations include the use of only select criteria as compared to all criteria of the ASE 2009 definition for comparison, the non-inclusion of patients on mechanical ventilation, and no adjustment for the dose of fluid and vasopressors. Based on other studies using this definition, LVDD is classified as septal e' <8 cm/sec and an elevated LAP/LVFP as E/e' (average) >14.[13]

La Via et al. reported a higher incidence of LVDD (81 vs 46%) using the simplified definition as compared to the full definition, with half of the patients diagnosed with normal LV diastolic function according to the ASE/EACVI 2016 having grade II or III LVDD according to the simplified definition in COVID-19 patients.[14] Cavefors et al. reported that patients with indeterminate LV diastolic function as per the ASE/EACVI guidelines had a four-fold increase in mortality, which was comparable to those with isolated LVDD, suggesting that this subset could have had LVDD, which was not diagnosed by the current guidelines.[15]

Neither the full nor the simplified approach are appropriate for measuring LAP/LVFP in patients with atrial fibrillation. A combination of multiple echocardiographic parameters in a two-step method mitral E velocity >100 cm/sec, septal E/e' >11, E wave deceleration time <160 m/sec, and TR velocity >2.8 m/sec in step 1 classify LAP/LVFP as raised if ≥3 criteria are positive and as normal if ≥3 are negative; followed by use of supplementary parameters in step 2 if step 1 is unable to classify LA reservoir strain <16%, pulmonary venous S/D ratio <1, and BMI >30 kg/m$^2$ classify LAP/LVFP as raised if ≥2 criteria are positive and as normal if ≥2 are negative. This two-step algorithm has a sensitivity of 74%, a specificity of 76%, a positive predictive value of 78%, a negative predictive value of 71%, and an area under the curve of 0.75. The study was conducted in patients with suspected heart failure, and echo measures were validated against cardiac catheterization measures.[16]

Sanfilippo et al. have proposed the CHEOPS bundle as a means for optimizing diastolic function in the ICU. Items of this bundle include C (chest ultrasound–lung ultrasound to document extra vascular lung water in addition to advanced critical care ultrasound), HE (hemodynamics–heart rate as low as feasible to optimize diastolic time and reduce myocardial oxygen demand, suggesting beta blockers without strong evidence; to prevent atrial fibrillation; to maintain optimal after load so that diastolic blood pressure is maintained assuring coronary perfusion without an excessive increase in systemic vascular resistance to prevent ventriculo-arterial decoupling; selecting inotropes with minimal chronotropic and lusitropic effect, suggesting levosimendan but without strong evidence), OP (optimize PEEP–adjusting PEEP to optimize LV preload and after load without compromising RV function), S (stabilization and fluid removal – diuresis for preventing/managing elevated LVFP in patients with LVDD).[9]

In this issue of the journal Luitel et al., present their prospective observational study, where they report a prevalence of LVDD of 35% in a cohort of 223 ICU patients who have been mechanically ventilated for more than 48 hours.[17] The admission case mix predominantly includes acute respiratory distress syndrome (ARDS)– 16%, abdominal trauma – 10%, postoperative (excluding cardiac and vascular surgery) – 9%, and meningitis – 8%. They have used the simplified definition of Langspa using a septal e' value

of <8 cms/sec. as the basis for diagnosing LVDD and found an incidence of 35%, which is in range with the incidence reported by other authors using this definition. About 31% of their patients with LVDD had LVSD while 68% had diastolic dysfunction with a preserved ejection fraction. The echo was done only once on day 3 of mechanical ventilation. They found a statistically significant association between the presence of LVDD and 28-day mortality (Odds ratio 7.48) and weaning failure (Odds ratio 5.37) in multivariate logistic regression analysis, which is consistent with the existing literature. Furthermore, they found a statistically significant difference between E/e' in patients with and without LVDD. They did not adjust for the comorbid conditions, dose of vasopressors, fluid shifts, and ventilator settings in the multivariate logistic regression analysis. The echocardiographic parameters collected in the study could also have been used to diagnose LVDD and LAP/LVFP as per the ASE 2016 guidelines, and a comparison could have been made between the full and simplified assessments. One of the biggest limitations of this study is that the cardiac imaging was done by an intensivist with one year of experience in echocardiography, and the images were not reviewed by an expert.

To conclude, the incidence of LVDD in an ICU cohort depends on several variables, premorbid, comorbid, admitting diagnosis, therapeutics, including organ support in the ICU, and dynamic interactions between the above variables. It is not easy to continuously capture and correctly interpret the final outcome of so many static and dynamic variables, along with continuous interactions between them by a single, or few snapshot echocardiographic parameters. Doppler echocardiography, though semi-quantitative, remains the best validated noninvasive measure of LVDD and LAP/LVFP to date. The future may see a greater role for speckle tracking echocardiography in the form of left atrial strain imaging in the evaluation of LVDD. There is an urgent need to frame guidelines for the assessment of LVDD in the ICU.

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