Global end-diastolic volume an emerging preload marker vis-a-vis other markers - Have we reached our goal?

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ABSTRACT

A reliable estimation of cardiac preload is helpful in the management of severe circulatory dysfunction. The estimation of cardiac preload has evolved from nuclear angiography, pulmonary artery catheterization to echocardiography, and transpulmonary thermodilution (TPTD). Global end-diastolic volume (GEDV) is the combined end-diastolic volumes of all the four cardiac chambers. GEDV has been demonstrated to be a reliable preload marker in comparison with traditionally used pulmonary artery catheter-derived pressure preload parameters. Recently, a new TPTD system called EV1000™ has been developed and introduced into the expanding field of advanced hemodynamic monitoring. GEDV has emerged as a better preload marker than its previous conventional counterparts. The advantage of it being measured by minimum invasive methods such as PiCCO™ and newly developed EV1000™ system makes it a promising bedside advanced hemodynamic parameter.

Key words: EV1000; Global end-diastolic volume; Hemodynamic; PiCCO; Transpulmonary thermodilution

INTRODUCTION

Hemodynamic monitoring is paramount importance for the early identification and management of critical changes in hemodynamic parameters to optimize tissue oxygen delivery. A reliable estimation of cardiac preload is helpful in the management of severe circulatory dysfunction. The assessment of central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), pulmonary capillary wedge pressure (PCWP), and end-diastolic volume (EDV) indices as preload markers has been the mainstream of advanced hemodynamic monitoring for years. The estimation of cardiac preload has evolved from nuclear angiography, pulmonary artery catheterization to echocardiography, and transpulmonary thermodilution (TPTD). TPTD has emerged as a less invasive bedside method to obtain accurate cardiovascular parameters. In addition to cardiac output (CO) measurements, TPTD also provides advance volumetric parameters such as global EDV (GEDV) and extravascular lung water (EVLW).

STATIC VERSUS DYNAMIC PARAMETERS

The stroke volume increases with fluid loading till both ventricles are on steep portion of Frank–Starling’s Curve. Once the ventricles reach the flat portion of curve, fluid infusion has little effect on CO. Therefore, it is important not only to measure the patient’s preload...
but also to assess whether the patient will respond to fluid therapy or not. Most of the conventionally used parameters (CVP and PAOP) fail to predict fluid responsiveness of the patient. However, in patients undergoing positive-pressure mechanical ventilation, heart–lung interactions can be used to reliably determine response to fluid infusions using dynamic parameters. These parameters can be determined using continuous beat-to-beat CO monitoring devices and echocardiography [Table 1].

**CONVENTIONAL PRELOAD MARKERS AND TECHNIQUES**

**Pulmonary artery catheterization**

The introduction of pulmonary artery catheter (PAC) in the 1970s revolutionized the field of hemodynamic monitoring. However, the therapeutic usage of PAC has been questioned based on the studies which failed to demonstrate its beneficial effect. In 1996, Connors et al. demonstrated that right heart catheterization may increase mortality in critically ill patients in intensive care. Despite these controversies, PAC-derived parameters such as CVP and PAOP has been used as a pressure estimate of ventricular preload. Nonetheless, these parameters have also been questioned as they failed to correlate with EDV in critically ill and postcardiac surgery patients.

As per Frank–Starling Law, the preload is determined by end-diastolic left ventricular fiber length. Hence, instead of these widely used cardiac filling pressures (CVP and PAOP), EDV indices of the left ventricle are better indicators of preload.

Kumar et al. demonstrated that neither CVP nor PAOP correlated with EDV index and stroke volume index. Hence, it cannot be used as a predictor of ventricular preload with respect to optimizing cardiac performance.

**Pulmonary artery thermodilution**

Pulmonary artery thermodilution technique can be used to derive right ventricular EDV index (RVEDVI). In various studies, RVEDVI has shown a better correlation with cardiac performance than cardiac filling pressures. A modified version of conventional pulmonary artery thermodilution catheters allows the continuous determination of RVEDVI in form of continuous EDV index (CEDVI).

Wiesenack et al. observed that an increased cardiac preload is more reliably reflected by CEDVI than by CVP, PCWP, or left ventricular end-diastolic area (LVEDA) index in cardiac surgery. However, CEDV index failed to be a variable of fluid responsiveness.

### Table 1: The dynamic parameters of fluid responsiveness

| Dynamic parameter | Description | Method | Remarks |
|-------------------|-------------|--------|---------|
| SVV: Stroke volume variation during the respiratory cycle | SVV (%)=(SV\text{max}−SV\text{min})/SV\text{mean} | PICCO, LiDCO, Vigileo | Measured by pulse contour analysis An SVV threshold of 12%, indicates fluid responsiveness |
| PPV: Pulse pressure variation during respiratory cycle | PPV (%)=(PP\text{max}−PP\text{min})/PP\text{mean} | LiDCO, Vigileo | Correlates equally well as SVV for volume responsiveness A PPV threshold of 13% differentiates between responders and nonresponders to fluid administration |
| SPV: Systolic pressure variation | SBP\text{max}−SBP\text{min}/SBP\text{mean} | LiDCO, Vigileo | Less specific indicator of LV stroke volume and less useful in predicting fluid responsiveness |
| Aortic blood velocity (ΔV\text{peak}) | Expressed in percentage | Doppler echocardiography | Threshold value of 12% discriminates responders and nonresponders |
| IVC distensibility index | Maximum diameter at inflation-minimum diameter at expiration/maximum diameter | Transthoracic or transesophageal echocardiography | IVC distensibility index above 18% predicts fluid responsiveness. Major limitation is intra-abdominal pressure |
| Plethysmographic variability index | Respiratory cycle induced variation in plethysmograph waveform | Modified pulse oximeter (radical 7) | A threshold of 19% suggests fluid responsiveness |

SVV: Stroke volume variation, PPV: Pulse pressure variation, SPV: Systolic pressure variation, IVC: Inferior vena cava
Imaging techniques
Radionuclide ventriculography, cardiovascular computed tomography, and magnetic resonance imaging have been used in the past to assess cardiac dimensions; however, these procedures are laborious, noncontinuous, and nonpractical in various clinical settings. Bellenger et al. compared the agreement of left ventricular volumes and ejection fraction (EF) by M-mode echocardiography (echo), two-dimensional echo, radionuclide ventriculography, and cardiovascular magnetic resonance in patients with chronic stable heart failure. They found that cardiovascular magnetic resonance imaging is the preferred technique for volume and EF estimation in heart failure patients because of its three-dimensional approach for nonsymmetric ventricles and superior image quality.\[12\]

Echocardiography
Echocardiography can be done to assess EDV and area as a marker of preload. Cheung et al. demonstrated that transesophageal echocardiography was sensitive to detect even 5% of the blood volume change by measurement of LVEDA.\[13\]

In addition, echocardiographic-derived E/e’ has emerged as a surrogate of left ventricular diastolic pressure (LVDP). In a study done by Ommen et al., E/e’ ratio was found to be the best tissue Doppler imaging parameter to correlate with mean LVDP ($r = 0.64$). The author observed that this correlation was better in patients with EF $<50\%$ ($r = 0.64$) than those with EF $>50\%$ ($r = 0.47$).\[14\]

However, expertise in performing echocardiography is not widely available among intensive care staff. One of the major drawbacks of echocardiography is that it gives only a snapshot of ventricular functions at a single point of time. It lags behind in continuous monitoring of hemodynamic parameters.

Transpulmonary thermodilution
TPTD is an evolving technique in the field of hemodynamic monitoring which does not require invasive PAC. In addition to intrathoracic blood volume (ITBV), it can also yield pulmonary blood volume and EVLW as a predictor of pulmonary edema.\[15-17\]

Technique of transpulmonary thermodilution measurements
The technique of thermal dye dilution (indocyanine green [ICG]) to assess ITBV was introduced by a German Company (Pulsion Medical Systems, Munich, Germany). In this method, a cold indicator (ICG dye) is injected into the central vein, and after transpulmonary passage, it is detected by a special thermistor-tipped femoral arterial catheter for computation of TPTD curve.\[15\] This double-indicator TPTD technique has evolved into a single thermal indicator TPTD technique which has been found to be as accurate as the former.\[16\] The TPTD technique has been used to derive various hemodynamic parameters such as ITBV, GEDV, a volumetric marker of cardiac preload, and EVLW, a marker of pulmonary edema [Figure 1].\[15-17\]

Global end-diastolic volume
GEDV is a hypothetical volume that assumes the situation that the four heart chambers are simultaneously in the diastolic phase [Figure 2]. GEDV is the combined EDVs of all the four cardiac chambers. In addition, it also includes volume of central vein and aorta from point of injection of injectate to site of measurement. It is calculated as the difference between the intrathoracic thermal volume (ITTV) and pulmonary thermal volume (PTV).\[20-22\] It has been found to be a reliable indicator of cardiac preload in critically ill patients.\[21\]

Mathematical analysis of transpulmonary thermodilution hemodynamic parameters
There are two different systems to assess TPTD hemodynamic parameters. The well-known PiCCO™ system (Pulsion Medical Systems, Munich, Germany) is based on the mathematical analysis described in the 1950s.\[20-22\] However, recently, a new TPTD system called EV1000™ has been developed and introduced into the expanding field of advanced hemodynamic monitoring.\[23,24\] It consists of a specific thermistor-tipped arterial catheter, the VolumeView™ catheter, and EV 1000™ monitoring system (Edwards Lifesciences, Irvine, CA, USA). It uses a unique
algorithm for the mathematical analysis of the thermodilution curve [Figure 1].

The analysis implemented in the PiCCO™ System is based on CO, mean transit time (Mtt), and downslope time (Dst) of TPTD curve [Figure 1].\cite{20,22}

\[
\text{ITTV} = \text{CO} \times \text{Mtt} \\
\text{PTV} = \text{CO} \times \text{Dst} \\
\text{GEDV} = \text{ITTV} - \text{PTV} \\
\text{GEDV PiCCO} = \text{CO} \times (\text{Mtt} - \text{Dst}).
\]

In comparison, the EV1000™ system uses a novo algorithm, which is based on maximum up-slope (S₁) and down-slope (S₂) of the TPTD curve [Figure 1].\cite{23,24}

\[
\text{GEDV EV1000} = \text{CO} \times \text{Mtt} \times (S_1/S_2)
\]

The algorithm for analysis of EVLW is same for both systems; however, it is based on GEDV which is derived differently by the two systems.

\[
\text{EVLW} = \text{CO} \times \text{Dst} \times (\text{GEDV} \times 0.25)
\]

Nicholas Kiefer et al. compared the volume View EV1000™ measurements to those by PiCCO2™ in 72 critically ill patients. They found that in a mixed Intensive Care Unit (ICU) population, and in a wide range of clinical situations, CO, GEDV, and EVLW values assessed with the new VolumeView™/EV1000 system are interchangeable with the current PiCCO™ method. However, for GEDV, the VolumeView Method has a higher precision.\cite{24}

GEDV and ITBV has been demonstrated to be a reliable preload marker in comparison with traditionally used PAC-derived pressure preload parameters such as CVP and PAOP.\cite{25,26} Godje et al. compared these conventional preload markers (CVP and PCWP) with ITBV and GEDV in patients undergoing CABG. The authors demonstrated that changes of CVP, PCWP, and RVEDVI do not correlate with changes of cardiac index and stroke volume index (coefficients ranged from −0.01 to 0.28). In contrast, intrathoracic and GEDV indices with coefficients from 0.76 to 0.87 show a good correlation to cardiac function indices.\cite{25,26} GEDV has found to be as equivalent reflector of preload as echocardiographic-derived preload indices.\cite{27,28} Hofer et al. observed that GEDV index (GEDVI) assessed by the PiCCO system gives a better reflection of echocardiographic changes in left ventricular preload, in response to fluid replacement therapy, than CEDVI measured by a modified PAC.\cite{27}

To compare individual patients, GEDV and EVLW are indexed to body surface area, yielding GEDVI and EVLW index. The numerical values of GEDVI and echocardiographic volume indices show only a moderate correlation.\cite{27,28} The latter can be explained in part by different techniques used for echocardiographic volume calculation.\cite{29} GEDVI has been found to be a helpful parameter in monitoring fluid responsiveness and nonresponsiveness.\cite{30,31}

The reference range for GEDVI as proposed by expert opinion is 680–800 ml/m². Wolf et al. found that GEDV and ITBV depend on age and gender. The age and sex dependence of GEDV and ITBV was persistent after indexing to body surface area. Therefore, targeting resuscitation by fixed ranges of GEDVI or ITBVI without concern for age and gender is not appropriate.\cite{32} GEDVI has been successfully used in goal-directed therapy. Goepfert et al. demonstrated that guiding therapy by an algorithm based on GEDVI leads to a shortened and reduced need for vasopressors, catecholamines, mechanical ventilation, and ICU stay in cardiac surgery patients.\cite{33}

**CONCLUSION**

GEDV has emerged as a better preload marker than its previous conventional counterparts. The advantage of it being measured by minimum invasive methods such as PiCCO™ and newly developed EV1000™ system makes it a promising bedside advanced hemodynamic parameter. The effective use of GEDV in goal-directed therapy can ease the management of circulatory dysfunction and guide the appropriate use of inotropes and vasopressors.
However, further studies regarding utility of GEDV as preload markers in major cardiac surgeries such as valve repair, CABG, aortic dissections, congenital heart diseases, and noncardiac surgeries are required. Finally, the novel method of GEDV analysis (EV1000™) should further be validated in perioperative field, and research on development of completely noninvasive techniques for preload assessment should be encouraged.

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Conflicts of interest
There are no conflicts of interest.

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