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Estimation of left ventricular systolic function by single transpulmonary thermodilution

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Abstract *Objective:* The single-indicator transpulmonary thermodilution technique (PiCCO system) provides two derived indices of cardiac systolic function: the cardiac function index and the global ejection fraction. We used transesophageal echocardiography to compare theses indices with left ventricular fractional area of change only for patients with no isolated right ventricular dysfunction. (The global cardiac systolic function may be decreased despite preserved left ventricular function in this situation.) *Design:* Prospective, open, clinical study. *Setting:* Intensive care unit (ICU) in a university hospital. *Patients:* Thirty-three mechanically ventilated patients. *Intervention:* Left ventricular fractional area of change (LVFAC) was measured using transesophageal echocardiography. The cardiac function index (CFI) and the global ejection fraction (GEF) were determined from transpulmonary thermodilution-derived cardiac output and thoracic volumes. *Measurements and main results:* Transesophageal echocardiography identified 3 patients with isolated right ventricular failure (PiCCO underestimated LVFAC in this situation). Significant correlations were established between LVFAC and CFI (r=0.87, n=30, p<0.0001) or GEF (r=0.82, n=30, p<0.0001). The mean differences between measured LVFAC and LVFAC estimated with CFI or GEF were 0.8±8.5% (range: –17 to 14%) and 0.8±9.0% (range: –21 to 19%), respectively. Area under the receiver operating characteristics curves for the estimation of LVFAC $\geq$40% using CFI or GEF was 0.92. CFI >4 and GEF >18% estimated LVFAC $\geq$40% with respective sensitivities of 86 and 88% and specificities of 88 and 79%. Significant correlations were established between changes of LVFAC and CFI/GEF over time. *Conclusions:* In mechanically ventilated ICU patients, PiCCO-derived cardiac function index and global ejection fraction provide reliable estimations of LV systolic function but may underestimate it in the cases of isolated right ventricular failure.

Keywords Ventricular function · Echocardiography · Transesophageal · Transpulmonary thermodilution · Cardiac function index · Global ejection fraction

Introduction

Cardiovascular monitoring is essential for the diagnostic and therapeutic management of critically ill patients. The pulmonary artery catheter has been the gold standard for 2 decades, but concerns have been raised about its safety [1] and the clinical usefulness of the data it provided [2, 3]; thus, alternative monitoring methods have been evaluated. Doppler echocardiography, a non-invasive method of hemodynamic monitoring, enables accurate estimation of

cardiac index, volume status and ventricular function of intensive care unit (ICU) patients [4]; however, the use of this technique for routine and/or continuous cardiac monitoring in the ICU setting is limited by the availability of equipment and/or experienced echocardiographic examiners.

Recently, the PiCCO system (Pulsion Medical System, Munich, Germany), based on the transpulmonary thermodilution technique with a single thermal indicator, was proposed as a "minimally invasive" monitoring system for ICU patients. The system provides intermittent (transpulmonary thermodilution-derived) and continuous ("pulse contour"-derived) assessment of cardiac output and estimations of intrathoracic volumes (intrathoracic blood volume, global end-diastolic volume, extravascular lung water). Accuracy of cardiac output calculation using the PiCCO system has been demonstrated in several clinical studies [5, 6, 7, 8, 9] and intrathoracic blood volume (blood volume contained in the heart and in intrathoracic vessels) and global end-diastolic volume (the largest blood volume contained in the four chambers of the heart) have been shown to provide reliable and more sensitive estimates of cardiac preload than pulmonary artery catheter-derived filling pressures [10, 11, 12, 13, 14, 15, 16, 17]. The PiCCO system also provides two transpulmonary thermodilution-derived indices of cardiac systolic function: the cardiac function index (CFI) and the global ejection fraction (GEF) which are automatically calculated by the monitor. The CFI is defined as the ratio of cardiac output to the global end-diastolic volume and GEF is defined as the ratio of the stroke volume to the quarter of the global end-diastolic volume. Both indices are therefore global ejection phase indices since they are the ratio of cardiac output or stroke volume to the global end-diastolic volume of the heart and are physiologically close to LV fractional area of change (LVFAC), which is the ratio of LV stroke area to LV end-diastolic area (an index of LV preload). Additionally, these new indices are obtained very easily by the intensivist at the bedside, while only an experienced operator can get similar information using echocardiography; however, no assessment of the validity of theses indices have been published to date.

Thus, the aim of this study was to evaluate the accuracy of CFI and GEF for the estimation of left ventricular (LV) systolic function for patients with no isolated right ventricular (RV) dysfunction, since the global cardiac systolic function may be decreased despite preserved LV function in such clinical situations. For that purpose, we used transesophageal echocardiography to assess left and right ventricular function and to compare CFI and GEF with LV fractional area of change (LVFAC), a well-recognized echocardiograhic index of LV systolic function, which is the ratio of LV stroke area to LV end-diastolic area [18, 19].

Methods

Study population

This prospective study was conducted in an 18-bed ICU in a university hospital. The investigational protocol was approved by the Ethics Committee of the Société de Réanimation de Langue Française. All consecutive patients on mechanical ventilation hospitalized in our ICU and meeting the following criteria were studied: a PiCCO catheter had been inserted to monitor hemodynamics for acute respiratory distress syndrome (ARDS); hemodynamic failure; septic shock and/or multiorgan failure; and transesophageal echocardiography had been scheduled to guide diagnosis and therapeutics. Exclusion criteria included: age <18 years; non-sinus rhythm; segmental wall-motion abnormalities predominantly at the LV apex; abdominal aortic aneurysm and transesophageal echocardiography; or experienced transesophageal echocardiography examiner not available at the time of hemodynamic measurements. All patients were on continuous IV sedation and temporarily paralyzed during hemodynamic and transesophageal echocardiography measurements. In addition, the following data were recorded: age; sex; simplified acute physiology score (SAPS II) [20]; acute physiology and chronic health evaluation (APACHE II) score [21]; primary reason for ICU admission; and infusion of vasoactive drugs at the time of hemodynamic measurements.

PiCCO monitoring, CFI, and GEF calculations

A 5-F thermistor-tipped catheter (Pulsiocath PV2015L20A, Pulsion Medical Systems) was placed in the femoral artery and connected to the PiCCO System (version 4.1). Cardiac output (CO) and volumetric variables were measured with the single indicator transpulmonary thermodilution technique. Measurements were obtained by injections of 20 ml of cold saline solution, at a temperature of <8°C, via the distal port of the central venous catheter placed in the internal jugular or subclavian veins with subsequent detection by the thermistor embedded in the wall of the femoral artery catheter. The CO was calculated from the thermodilution curves according to the Stewart-Hamilton principle. The mean of three consecutive CO measurements was used.

The PiCCO, using only one cold indicator, calculates the mean transit time (MTt) and the exponential downslope time (DSt) of the thermodilution curve. The result of the product of CO times MTt is the intrathoracic thermal volume (ITTV), whereas the product of CO times DSt is the pulmonary thermal volume (PTV). The difference between ITTV and PTV is the global end-diastolic volume (GEDV), which represent the volume of blood contained in the four heart chambers:

$$\mathrm{GEDV} = \mathrm{ITTV} - \mathrm{PTV} = \mathrm{CO} \times (\mathrm{MTt} - \mathrm{DSt})\ (\mathrm{mL}) \quad (1)$$

Importantly, the PiCCO monitor automatically calculates and permanently displays on its screen two transpulmonary thermodilution-derived indices of cardiac systolic function, the cardiac function index (CFI), and the global ejection fraction (GEF).

The CFI is defined as the ratio of cardiac output to the global end-diastolic volume:

$$\mathrm{CFI} = \mathrm{CO}/\mathrm{GEDV},\ \text{expressed in } \mathrm{min}^{-1}. \quad (2)$$

The GEF is defined as the ratio of the stroke volume to the quarter of the global end-diastolic volume:

$$\mathrm{GEF} = \mathrm{SV}/(\mathrm{GEDV}/4),\ \text{expressed as a percentage}. \quad (3)$$

Both indices are therefore global ejection phase indices since they are the ratio of CO or stroke volume to the global end-diastolic volume of the heart.

The reproducibility (of three consecutive measurements) of CFI and GEF was (mean±SD) 4±3 and 4±2%, respectively.

Echocardiographic study

Transesophageal echocardiography was performed with an Acuson Sequoia Model S-256 (Siemens, Mountain View, Calif.). The multiplane transducer was set at 0° and the transgastric midpapillary short-axis view was obtained. The end-diastolic (EDA) and end-systolic (ESA) areas were measured by tracing the endocardial border including the papillary muscles and averaging three consecutive beats. The fractional area of change (LVFAC), which is an estimation of ejection fraction (normal: 50–55%) was calculated using the following equation:

$$\mathrm{LVFAC} = \{(\mathrm{EDA} - \mathrm{ESA})/\mathrm{EDA}\} \times 100, \quad \text{expressed as a percentage.} \tag{4}$$

The reproducibility (of three consecutive measurements) of LVFAC was (mean±SD) 7±7%. Additionally, RV function and pulmonary artery systolic pressure were evaluated.

Statistical analyses

Continuous variables are expressed as means±SD and compared with Student's *t* test or the Mann-Whitney U test where appropriate. Categorical variables are expressed as percentages and were compared with the chi-square or Fisher's exact test, as appropriate. For patients with no isolated right ventricular (RV) dysfunction (global cardiac systolic function may be decreased despite preserved LV function in such clinical situations), correlations between LVFAC and PiCCO parameters (CFI and GEF) were established using linear regression analysis and are expressed as correlation coefficients; Bland-Altman analysis was used to evaluate the agreement between transesophageal echocardiography-measured and PiCCO-estimated LVFAC [22]. The PiCCO-estimated LVFAC was calculated using the linear regression equation. Receiver-operating characteristics curves were constructed to evaluate the abilities of CFI and GEF to estimate LVFAC $\geq$40%. Thereafter, for patients with no isolated right ventricular (RV) dysfunction and multiple hemodynamic evaluation, variable changes (Δ) at two different times were calculated by subtracting the first from the second measurement, the second from the third, and so on. Correlations between changes of LVFAC and CFI or GEF were established using linear regression analysis and are expressed as correlation coefficients. All statistical analyses were performed using the StatView 5.0 software package (SAS Institute Inc., Cary, N.C.). Statistical significance was defined as $p<0.05$.

Results

Characteristics of the 33 consecutive patients studied are listed in Table 1. Isolated right ventricular failure was diagnosed by transesophageal echocardiography in 3 patients (2 with ARDS and 1 with chronic pulmonary hypertension); therefore, 30 patients were included in the analyses comparing PiCCO and echographic indices. Seventy-seven measurements were obtained in the 30 patients (1, 2, 3, and 4 measurements in 3, 13, 8, and 6 patients, respectively, with at least 12 h between two consecutive measurements).

Table 1 Patients' characteristics

Variable	Value
Patients (*n*)	33
Men (*n*)	25 (76)
Age (years, mean±SD)	58±15
SAPS II (mean±SD)	53±20
APACHE II score (mean±SD)	24±7
Reason for ICU admission (*n*)	
Septic shock	16 (48)
Postoperative multiple-organ failure	7 (21)
Cardiogenic shock	5 (15)
Primary respiratory failure	5 (15)
Patients on catecholamines (*n*)	28 (85)

Numbers in parentheses are percentages

Linear regression analyses between the first measurements of CFI or GEF and LVFAC in the 30 patients studied, and Bland-Altman analysis of agreement between transpulmonary thermodilution-estimated and transesophageal echocardiography-measured LVFAC are shown in Fig. 1. Significant correlations were established between LVFAC and CFI (r=0.87, $p<0.0001$) or GEF (r=0.82, $p<0.0001$; Fig. 1). The mean differences between estimated and measured LVFAC were 0.8±8.5% (range: –17 to 14%) and 0.8±9.0% (range: –21 to 19%) for CFI and GEF, respectively. As anticipated, PiCCO underestimated LVFAC (>20% difference) in the 3 patients with RV failure (open circles in Fig. 1).

The area under the receiver-operating characteristics curves for the estimation of LVFAC $\geq$40% using CFI or GEF was 0.92 for both indices (Fig. 2). CFI >4 and GEF > 18% estimated LVFAC $\geq$40% with respective sensitivities of 86 and 88% and specificities of 88 and 79%. The likelihood ratio of CFI >4 and GEF >18% for predicting LVFAC $\geq$40% were 6.88 and 4.10, respectively.

Significant correlations were established between changes of LVFAC and CFI (r=0.79, n=47, $p<0.0001$) and changes of LVFAC and GEF(r=0.76, n=47, $p<0.0001$; Fig. 3).

Discussion

Our working hypothesis in this study was that the CFI and the GEF would provide reliable surrogate estimations of LV ejection fraction in mechanically ventilated ICU patients with no isolated right ventricular dysfunction. Our results indicate that in this situation, robust relationships exist between left ventricular fractional area of change (LVFAC) measured using transesophageal echocardiography and the transpulmonary thermodilution-derived indices, and that the observed changes of LVFAC over time closely parallel the estimated changes of LV function calculated with the PiCCO system.

The validity of CFI and GEF calculation relies on accurate transpulmonary thermodilution determination of LV output, stroke volume, and global end-diastolic vol-

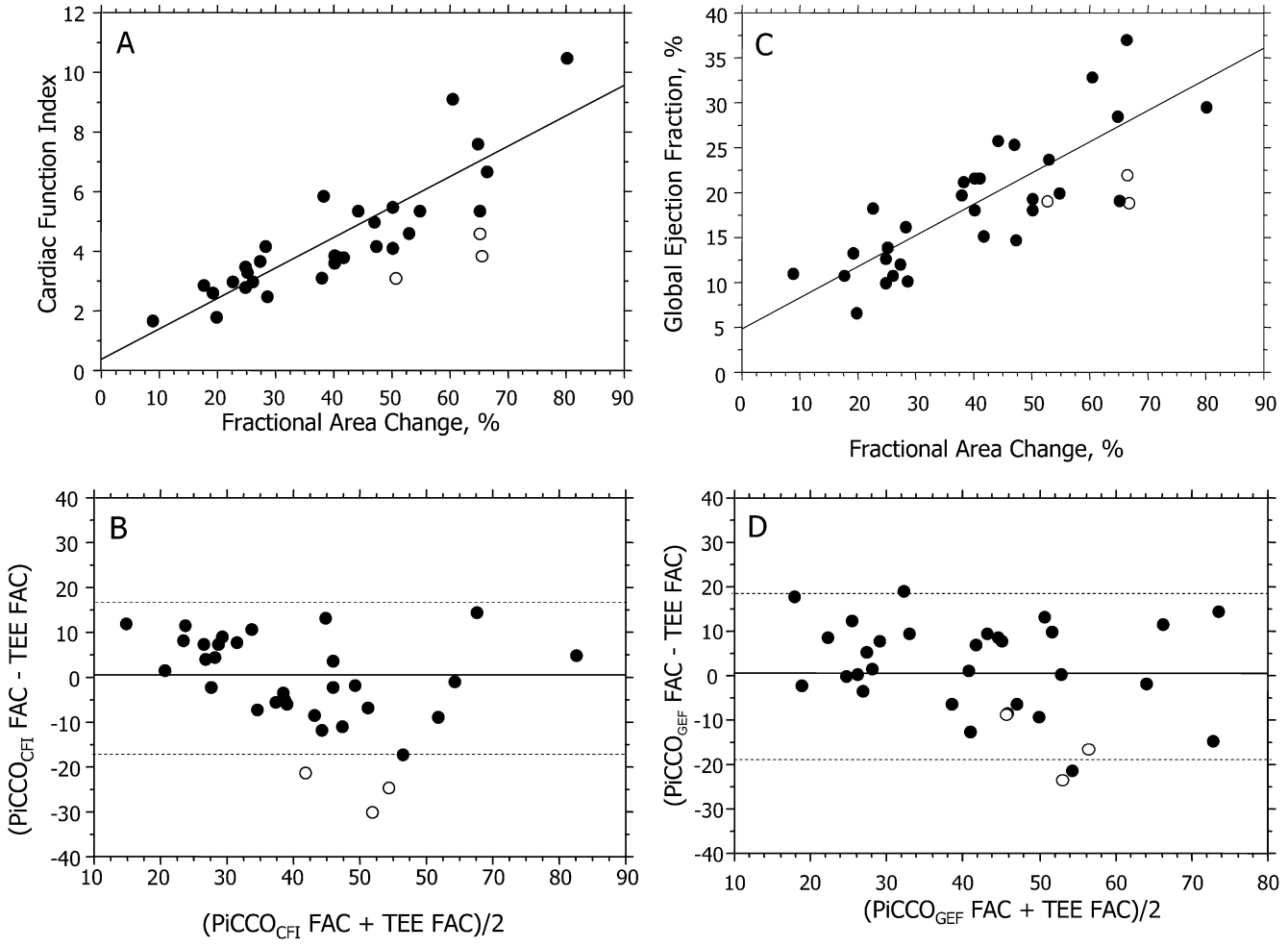

Fig. 1A–D Linear regression analysis between LV fractional area of change (LVFAC) and cardiac function index (*CFI*; **A**) or global ejection fraction (*GEF*; **C**). Bland-Altman analyses of agreement between PiCCO-estimated LVFAC using CFI (**B**) or GEF (**D**) and transesophageal echocardiography (*TEE*)-measured LVFAC. The *central unbroken line* is the mean difference (bias) between the two methods, whereas the *outer dotted lines* represent the two SD limits of agreement. *Open circles* represent the 3 patients with right ventricular failure (patients not included in the regression and Bland-Altman analyses)

ume. Previous studies demonstrated the accuracy of thermodilution-derived volumes and flow [5, 6, 7, 8]. Moreover, good correlations were found between the transpulmonary thermodilution technique and thermodilution using a pulmonary artery catheter, with both methods applying the Stewart-Hamilton principle to calculate CO from the obtained curves. A similar correlation was described between transpulmonary thermodilution and the direct Fick method [9]. Furthermore, transpulmonary thermodilution-derived intrathoracic blood volume and global end-diastolic volume have been proven to be reliable indices of cardiac preload. Intrathoracic blood volume was significantly associated with transesophageal echocardiography determination of end-diastolic area in ten anesthetized patients [10] and intrathoracic blood volume and global end-diastolic volume were more reliable indicators of cardiac preload than central venous pressure or pulmonary artery occlusion pressure in several studies on medical and surgical patients [11, 12, 13, 14, 15, 16, 17]. Finally, since calculation of intrathoracic blood volume and global end-diastolic volume mathematically rely on CO, concerns have been raised as to the validity of these measurements based on the mathematical coupling of data; however, no evidence of such a coupling was found in three recent studies in which CO was either decreased by esmolol [23] or increased by dobutamine [17, 24].

We acknowledge several limitations to the present study. Firstly, because the global end-diastolic volume is used as the preload index for CFI and GEF calculations, we anticipated that some specific clinical situations may give rise to erroneous estimations of LV systolic function with this technique. Specifically, in case of isolated right ventricular failure, e.g., in massive pulmonary embolism

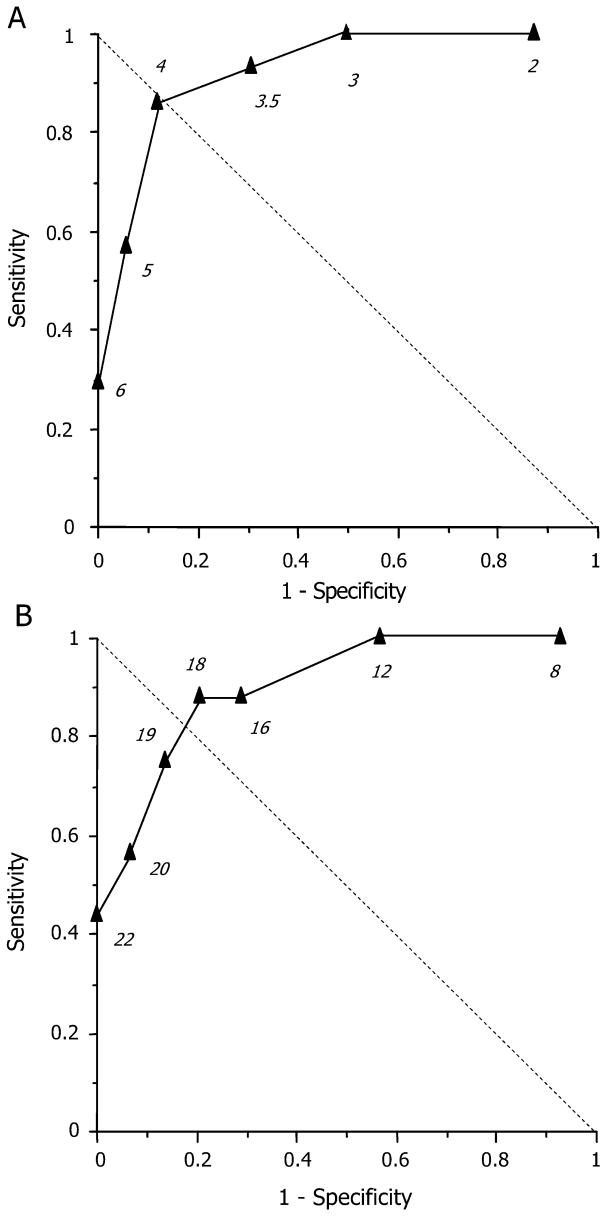

Fig. 2A,B Receiver operating characteristics curves for estimation of LVFAC ≥40% using PiCCO-derived CFI (**A**) or GEF (**B**). Area under the curve=0.92 for both indices

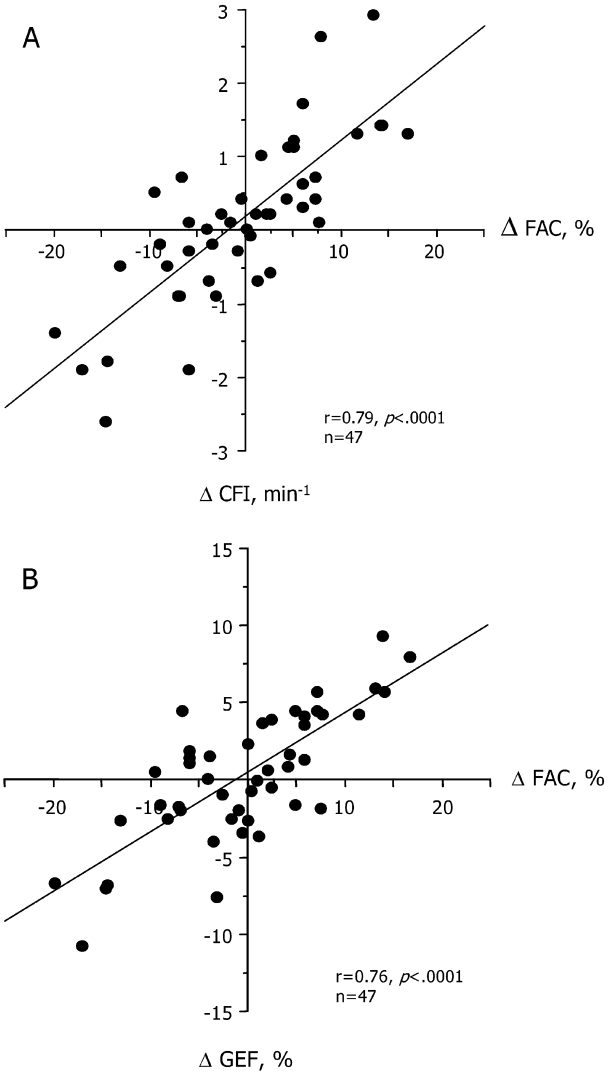

Fig. 3A,B Linear regression analysis between changes (Δ) of LVFAC and CFI (**A**) or GEF (**B**)

or in ARDS patients with acute cor pulmonale, the global end-diastolic volume may not reflect LV end-diastolic volume or area, and CFI and GEF might underestimate the true LV systolic function. Indeed, we confirmed that PiCCO markedly underestimated LVFAC (>20% difference) for our 3 patients with significant right ventricular failure. This point might be considered as a weakness of the technique but also as a strength, since the PiCCO monitor can be used to detect either a right or a left ventricular dysfunction; therefore, a low CFI or GEF might be considered as an indication to perform a "diagnostic" echocardiography to discriminate between a right and a left ventricular dysfunction. Furthermore, CFI and GEF could be used to monitor changes of cardiac function during the treatment of both right (pulmonary vasodilators, inotropes, changes in ventilator settings) or left ventricular dysfunction (inotropes, systemic vasodilators). Secondly, it might be argued that the performance of CFI and GEF (as assessed by sensitivity, specificity and likelihood ratios) might not be strong enough for an accurate prediction of LV systolic function. Indeed, CFI/GEF changes over time might provide more information than isolated values, particularly when interpreted in the light of a clinical situation. This point could be more extensively tested in future studies. Thirdly, conflicting data exist about the accuracy of thermodilution-derived measurement of cardiac output in pa-

tients with severe (grade 3) tricuspid regurgitation, studies reporting underestimation [25], overestimation [26], or accurate estimation [27] of the actual output; however, no tricuspid regurgitation greater than grade 2 existed in the 30 patients included in the regression analyses. Finally, in the case of marked atrial dilatation (patients with mitral stenosis or permanent atrial fibrillation), the global end-diastolic volume might also not be a true reflection of LV end diastolic volume or area and, thus, PiCCO may also underestimate LVFAC.

Conclusion

In conclusion, we demonstrated that, in addition to accurately estimating CO [5, 6, 7, 8] and preload [11, 12, 13, 14, 15, 16, 17], hemodynamic monitoring using the PiCCO system provides a reliable evaluation of LV systolic function in mechanically ventilated ICU patients with no isolated right ventricular dysfunction. As anticipated, CFI and GEF might underestimate the actual LV systolic function in the case of right ventricular failure, since the global cardiac systolic function may be decreased despite preserved LV function in this particular clinical situation. Low CFI or GEF might therefore be considered as an indication to perform an echocardiography to discriminate between a right and a left ventricular dysfunction. This simple, easy to repeat, operator-independent, and minimally invasive technique will not replace the invaluable information provided by Doppler echocardiography, but it may assist intensivists in defining diagnostic and treatment strategies, especially when the use of Doppler echocardiography for hemodynamic monitoring is limited by the availability of equipment and/or experienced echocardiographic examiners.

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