EXPERT OPINION

Limitations of volumetric indices obtained by transthoracic thermodilution

L. M. BIGATELLO [1], E. B. KISTLER [2], A. NOTO [3]

[1]Anesthesiology Service, VA Boston Healthcare System, Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesia, University of California at San Diego, San Diego, CA, USA; [3]Department of Cardiothoracic and Vascular Anesthesia, University of Messina, Policlinico G. Martino, Messina, Italy

ABSTRACT

Transthoracic thermodilution (TTT) measures cardiac output without the need for right heart catheterization. In addition, two volumetric hemodynamic indices have been derived from the mathematical analysis of the TTT curve: the global end diastolic volume (a quantitative measure of cardiac preload) and the extravascular lung water volume (a quantitative measure of pulmonary edema). Despite the undeniable appeal of these two novel parameters, uncertainty exists regarding both the validity of their mathematical derivation and their physiological significance. This concise review attempts to discuss such concerns. *(Minerva Anestesiol 2010;76:945-9)*

Key words: Monitoring, physiologic - Stroke volume - Extravascular lung water.

Pressure-based hemodynamic monitoring has been the basis for assessing cardiovascular performance in critically ill patients for decades. The combined measurement of arterial pressure, central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP) and cardiac output (CO) provides valuable information about the physiological determinants of hypotension: hypovolemia, vasodilation, or myocardial dysfunction.[1-3] However, the interpretation of intravascular pressures in critically ill patients is complex, and their use as the sole guide to therapy has failed to demonstrate beneficial outcomes.[4] Thus, a number of new monitors have been developed as alternatives to the pulmonary artery catheter (PAC) targeting two primary perceived needs: (1) limiting invasiveness and (2) simplifying the interpretation of cardiovascular performance.[5] In this context, transthoracic thermodilution (TTT) provides unique volumetric indices of preload, the global end diastolic volume (GEDV) and of "pulmonary edema", the extravascular lung water (EVLW).[i] Herein, we review the physiological derivation of these two parameters and highlight some conceptual and physiological pitfalls.

Cardiac output measurement by TTT

With both TTT and the PAC, a bolus of cold fluid is injected in the superior vena cava and blood temperature is measured distally, in the pulmonary artery for the PAC or the distal aorta for TTT. The change in temperature is a function of flow, *i.e.*, CO. As with any indicator, thermal dilution must satisfy the restrictions of conservation of mass, including complete mixing of the indicator, homogeneous distribution, no loss, no addition, and no recirculation.[6] Of all these factors,

[i] The volumetric hemodynamic indices illustrated in this review are available in the PiCCO2™ monitor, manufactured by Pulsion Medical Systems AG, Munich, Germany.

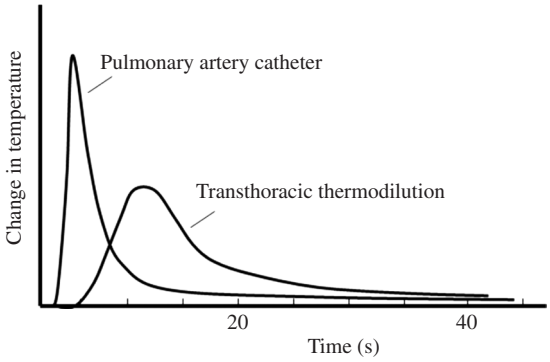

Figure 1.—Comparison of time course between the pulmonary artery catheter and transthoracic thermodilution temperatures after fluid bolus of cold saline used for the calculation of cardiac output.

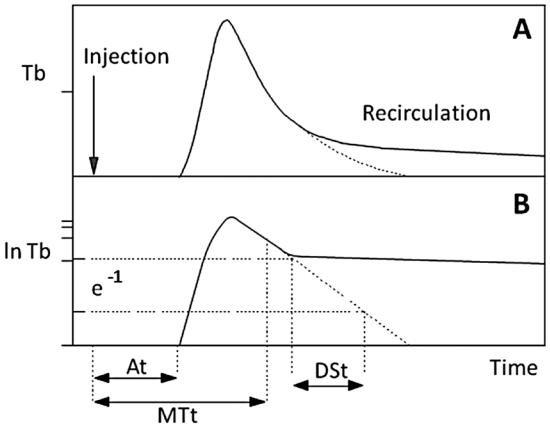

Figure 2.—A) Schematic of change in temperature seen by sensing thermistor after bolus of cold saline used in calculation of cardiac output; B) Method of obtaining Mean Transit time (MTt) and Downslope time (DSt) from the cardiac output thermodilution curve after delay time At. Note semi-log axis in lower plot.

recirculation is one that is essentially unavoidable, and its influence is minimized by extrapolating a monoexponential decay of the temperature-time curve before the point when indicator recirculation is projected to occur.[7] With TTT, the inclusion of the pulmonary circulation in the volume of distribution of the indicator results in a lower-peaked, broader curve than with the PAC (Figure 1), which exposes the CO measurement to errors due to baseline drift in the addition to recirculation. Practically, baseline drift is minimized when using a larger and colder bolus, while the lengthened circulation time may be beneficial because it reduces the influence of respiratory- related variation.[8, 9] However, two sources of concern remain that will be further discussed in the last section of this review. First, any error in measurement of CO will be propagated through multiple subsequent calculations. Second, there is an inherent conflict between the measurement of CO, which ought to occur without the loss of the thermal indicator,[6] and the measurement of EVLW, which is based on the loss of the same indicator.

Global End-Diastolic Volume (GEDV): an index of preload

The mathematical analysis of the indicator-dilution curve (Figure 2) allows for the extrapolation of volumes (volume=flow x time). The mean transit time *(MTt)* is the volume in which the indicator is distributed:[10]

$$V=CO \times MTt$$

where V can indicate intravascular volume (intrathoracic blood volume, ITBV), in the case of an indicator, that stays within the blood vessels, such as indocyanine green, or it can indicate an intra- and extravascular volume (intrathoracic thermal volume, ITTV) for an indicator that diffuses freely outside the blood vessels, such as temperature. The ITBV includes the blood contained in the heart and pulmonary circulation. In addition, given the preferential diffusion of temperature through water as compared to air, the ITTV also includes water volume in the pulmonary interstitium, in the walls of the heart chambers and blood vessels, in cells such as alveolar and inflammatory cells, and in pleural or pericardial effusions.

Further analysis of the indicator-dilution curve (Figure 2) provides the computation of down-slope time (DS*t*).[11] In a model of the cardiopulmonary circulation as a series of containers with one inflow and one outflow, the time-dilution curve of the largest chamber will have the slowest down-slope of all, which is represented as the overall slope of the indicator dilution curve across all chambers:

$$V=CO \times DSt$$

When measured with an intra- and extravascular indicator, such as temperature, V estimates the overall volume of the lungs (or pulmonary

thermal volume [PTV]), a volume that is sufficiently larger than the other chambers, the right and left heart. By subtracting the PTV from the ITTV, we now obtain a volume of fluid that includes only the heart, both intra- and extravascular. Assuming that the extravascular component of the heart is small, we then obtain an estimate of the intravascular volume of the heart, which is greatest at end diastole:

GEDV=ITTV-PTV

Extravascular Lung Water (EVLW): an index of "pulmonary edema"

As discussed above, the MT*t* of a cold saline bolus can be used to compute the ITTV, and the MT*t* of an indocyanine green dye bolus can be used to compute the ITBV. When these two indicators are injected simultaneously by TTT (Cold Z-021, Pulsion Medical Systems, Munich, Germany), they can provide a measure of extravascular water:

EVLW=ITTV-ITBV

However, the combined thermal/dye dilution method is cumbersome, and its use has remained confined to selected laboratories.[12] A newer and simpler version of TTT offers a measurement of EVLW obtained with just one indicator, cold temperature.[ii] This monitor circumvents the problem of measuring the ITBV by deriving it from the GEDV, based on evidence collected in a cohort of critically ill patients using the thermal/dye dilution technique.[13] In that study, a highly significant linear correlation (r^2=0.92) was found between the ITBV measured by thermal/dye dilution and the GEDV measured by thermodilution alone:

ITBV=1.25*GEDV-28 mls

where the ITBV appears to be consistently and precisely 25% larger than the GEDV (28 mls is a negligible offset).

Methodological and physiological concerns regarding these volumetric indices

A number of studies have indicated a higher accuracy of these volumetric indices over traditional hemodynamic parameters, such as CVP, PAOP, and chest radiograms.[14-16] Other studies have demonstrated validation against experimental models.[17-19] However, some fundamental questions remain about the mathematical analysis of the thermodilution curve and the physiological significance of the two parameters: GEDV and EVLW.

Propagation of errors of CO measurement across repeated mathematical steps

Small errors in the determination of CO by TTT that are unlikely to affect the validity of each individual measurement may acquire substantial weight when repeated in subsequent calculations. For example, determining the ITTV requires the use of three integrals (one from the CO and two from the MT*t*) obtained from the same thermodilution curve.[20] Although the exact degree of error magnification is difficult to quantify, it adds to the uncertainty of the actual physiological equivalent of these indices.

Dependence of the GEDV on the CO

The mathematical derivation of the GEDV intimately ties it with the CO because CO is the "flow" term of both ITTV and PTV calculations (see above) and both MT*t* and DS*t* are calculated based on the same thermodilution curve used for the determination of the CO. Likewise, the concept of GEDV—the volume of blood contained in the heart at diastole—ties it intimately to the stroke volume (SV) because changes in the CO related to changes in the diastolic volume of the heart, by volume loading for example, occur via changes in the SV. Hence, it is somewhat surprising that the clinical validation of the GEDV as a preload index has been largely based on measuring changes in the GEDV and CO/SV in response to volume loading in volume-responsive patients. In this scenario, GEDV and CO may show a close correlation just on the basis of their mathematical derivation.[14, 21, 22] Additional evaluation of the GEDV should include the demonstration of (1) an increase in GEDV without an increase in CO, for example by volume loading in nonvolume responsive patients

[ii] The volumetric hemodynamic indices illustrated in this review are available in the PiCCO2™ monitor, manufactured by Pulsion Medical Systems AG, Munich, Germany.

and (2) an increase in CO with a concomitant decrease in GEDV, for example during the infusion of an inotropic agent. These experiments have not been performed in a prospective, controlled fashion.

The virtual nature of the GEDV

The normal values of GEDV are reported as 680–800 mls/m^2, a range several times larger than the actual volume of the right and left heart at the end of diastole. This discrepancy has been addressed by pointing out that the GEDV is a volume that is divided over the number of beats that occurred during the time of the analysis (MT*t* and DS*t*) of the thermodilution curve, a duration that may be as long as 20 to 30 seconds.[iii] Although this explanation is sound, the concept remains puzzling because of two reasons. This is an index of preload that should be superior to traditional parameters such as the CVP; however, in contrast to CVP, which has unquestionable physiological basis,[1] the GEDV cannot be defined anatomically. (2) The GEDV is a fundamental piece of the calculation of the EVLW. If the GEDV is a "virtual volume," so must be the EVLW.

The indirect derivation of the ITBV

The computation of the EVLW by single-indicator TTT uses a value of ITBV that is not measured in real time but rather is derived from a clinical study (see above).[13] From a methodological standpoint, there is uncertainty when using as a fundamental component of the EVLW a variable that is actually not measured. Also, given the multiple concerns expressed in this review regarding the derivation and significance of the GEDV, the need to use the GEDV to calculate the ITBV is unfortunate. Consistent with these observations, a number of studies that have attempted to validate the results of Sakka *et al.*[13] have failed to reproduce a high level of correlation.[23]

In addition, such a close and highly reproducible correlation between GEDV and ITBV remains perplexing from a physiological standpoint. While a certain degree of correlation between the blood volume in the heart and the blood volume in the cardiopulmonary circulation is sensible, it is hard to imagine that these two volumes would change with nearly perfect and predictable reproducibility.

Nature of the EVLW

From the above discussion, we have demonstrated that there are multiple levels of uncertainty regarding the actual nature of the EVLW, an index that clinicians would like to think of as a quantitative measure of pulmonary edema. First, single-indicator TTT does not measure EVLW (see above). Second, a number of factors other than the degree of pulmonary edema are known to affect the measurement of EVLW (see above).[8, 24] Third, there is an inherent incongruity between measuring EVLW by loss of a thermal indicator and the need for conservation of mass for the measurement of CO.[6] Accordingly, the higher the sensitivity of the method for EVLW calculation, the larger the error in CO, which, of course, is itself a fundamental component of the EVLW calculation.

Conclusion

TTT provides novel and potentially valuable volumetric hemodynamic indices. However, despite the already widespread use of this technology in clinical practice, concerns regarding the derivation and the physiological significance of the GEDV and the EVLW still exist. Further mathematical modeling and rigorous physiologic validation are still required.

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Corresponding author: L. M. Bigatello, Anesthesiology Service, VA Boston Healthcare System, Harvard Medical School, Boston, MA, USA. E-mail: luca.bigatello@va.gov