# Cardiac Output Monitoring Using Indicator-Dilution Techniques: Basics, Limits, and Perspectives

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The ability to monitor cardiac output is one of the important cornerstones of hemodynamic assessment for managing critically ill patients at increased risk for developing cardiac complications, and in particular in patients with preexisting cardiovascular comorbidities. For >30 years, single-bolus thermodilution measurement through a pulmonary artery catheter for assessment of cardiac output has been widely accepted as the "clinical standard" for advanced hemodynamic monitoring. In this article, we review this clinical standard, along with current alternatives also based on the indicator-dilution technique, such as the transcardiopulmonary thermodilution and lithium dilution techniques. In this review, not only the underlying technical principles and the unique features but also the limitations of each application of indicator dilution are outlined. (Anesth Analg 2010;110:799–811)

"It is astonishing that no one has arrived at the following obvious method by which the amount of blood ejected by the ventricle of the heart with each systole may be determined directly . . ."—Adolf Fick, 1870[1]

With this introduction, Adolf Fick described, in the proceedings of the Würzburg Physikalische Medizinische Gesellschaft, July 9, 1870, how to compute an animal's cardiac output (CO) from arterial and venous blood oxygen measurements. Fick's original principle was later adapted in the development of Stewart's indicator-dilution method in 1897[2] and Fegler's thermodilution method in 1954[3] for measuring CO. The introduction of the pulmonary artery (PA) catheter (PAC) in 1970[4] and its subsequent use in performing thermodilution measurements in humans[5] translated the ability to measure CO from the experimental physiology laboratory to multiple clinical settings.

The ability to monitor cardiac performance is crucial not only in managing patients in the setting of an intensive care unit but also in the perioperative management of patients with increased risk for developing cardiac complications. These patients include those with coronary artery disease or associated risk factors,[6] and those undergoing high-risk procedures such as major thoracic or vascular surgery.[7] Of the 27 million surgical procedures performed annually in the United States, 8 million occur in patients with increased coronary artery disease risk; each year, 50,000 perioperative myocardial infarctions and 1 million cardiac complications occur.[8] In critically ill patients, optimizing CO is considered an integral part of therapeutic approaches aiming to improve oxygen delivery because this variable is substantially determined by CO.

Measuring CO by thermodilution using a PAC has most frequently been used in the clinical setting and has been regarded as the de facto reference method. PACs and the more recently introduced alternative methods provide CO and other hemodynamic measurements not obtainable by clinical examination.[9–11] Having such information can alter therapeutic decisions both in the perioperative setting and in intensive care. Nevertheless, current users of PACs rely on an underlying assumption that these changes in management lead to improved patient outcomes.[12] In the absence of definitive studies, various professional groups have developed guidelines for PAC use.[13,14] Similar to the pulse oximeter, the PAC attained widespread use despite its lack of proven benefit.[15,16] Its nearly 40-year history made it the de facto standard for cardiac monitoring for the past decades, but this role has recently been increasingly challenged because large trials questioned a positive effect of the PAC use on outcome in critically ill patients, and because alternative methods claiming less invasiveness have become available.

Unlike pulse oximeters, PACs have associated morbidities that limit their routine use.[17–19] This article reviews the classic PAC-based method, along with the alternative methods also based on indicator-dilution technique, i.e., the transcardiopulmonary thermodilution (TCPTD) and the lithium indicator-dilution techniques. For each method, the underlying technical principles and the unique features and limitations are outlined.

## INTERMITTENT BOLUS PA THERMODILUTION

In the intermittent bolus PA thermodilution (IB-PATD) method for measuring CO, an injectate of known volume and temperature is injected into the right atrium via the proximal port of the PAC. The theory behind IB-PATD, and all other indicator-dilution techniques, is developed below; its specific advantages and limitations follow from an understanding of this theory.

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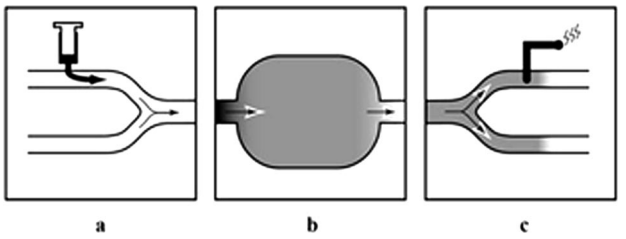


**Figure 1.** Three principle phases of indicator dilution: (a) an indicator is brought into the circulation (injection), (b) the indicator mixes with the bloodstream (mixing and dilution), and (c) the concentration of the indicator is determined downstream (detection).

## Technical Description: Indicator-Dilution Principles

Indicator-dilution methods rely on inert, soluble indicator substances that are introduced into the circulation. Figure 1 illustrates the conceptual stages of an indicator-dilution experiment: (a) a known amount of indicator is injected into the circulation; (b) the circulation carries the injectate through the heart where it is mixed and diluted; and (c) a detector positioned downstream measures and records the concentration of indicator over time.

### *The Stewart Method and the Hamilton Modification*

In 1897, Stewart[2] described experiments in which he injected a bolus of a sodium chloride solution into the central venous circulation of anesthetized dogs and rabbits and then collected blood samples containing diluted sodium chloride from a catheterized femoral artery. An electric transducer on the contralateral femoral artery heralded the arrival of diluted injectate. To derive the CO, Stewart used the following computation: let $V_0$ (mL) denote the initial injectate's volume and $C_0$ ($mg \cdot mL^{-1}$) its concentration. The circulation dilutes the injectate to a presumed uniform concentration $C_1$ occupying a volume $V_1$, where $V_1 = V_0 (C_0/C_1)$. The heart expels the diluted indicator over an interval $t$ (seconds). Because the vascular resistances of the major arterial conduits are negligible, $t$ is also duration over which the collection catheter encounters diluted indicator. The blood flow, i.e., the CO $F$ ($mL \cdot s^{-1}$) is the blood volume transferred per unit time or

$$F = V_1/t = \frac{C_0 V_0}{C_1 t}. \quad (1)$$

Note that the CO relates inversely to the diluted indicator concentration $C_1$ and its transit duration $t$. Decreased values of $C_1$ reflect increased volumes of diluted indicator transferred per unit time; decreased values of $t$ reflect faster movement of a given blood volume. Stewart's computations excluded his own recognition that the indicator concentration at the collection catheter initially increased and subsequently decreased in a nonstepwise manner over the collection interval as illustrated in Figure 2.[2] In 1928, Hamilton et al.[20] promoted the concept of an explicit time-concentration curve $c(t)$ that captured these transition phenomena (Fig. 2). A number of physical phenomena explain this curve: in particular the fact that in the human circulation, blood flow is laminar; particles travel faster in the axial stream than at the periphery; some paths through the circulation are shorter than others; and dilution of indicator commences upon injection and continues to occur downstream.[21] The Stewart-Hamilton equation substitutes, in place of the uniform concentration $C_1$, the time-averaged concentration of diluted indicator traversing the detector.[22] The resulting CO $F$ is

$$F = \frac{C_0 V_0}{\int_t c(t)dt}. \quad (2)$$

Similar to the original Stewart equation, the CO is inversely related to the average diluted indicator concentration and the total time of indicator passage. This can be simplified in the equation: CO = amount of indicator injected/area of dilution curve. This technique, using indocyanine green as indicator, was the conventional indicator-dilution method used to measure CO in critically ill patients until the 1970s.[5,23]

### *The Thermodilution Method*

The thermodilution method adapts the indicator-dilution principle to injectates that cause changes in blood temperature detected downstream.[5] Classically, iced saline 0.9% or dextrose 5% is injected.[5,24] Adapting Stewart's first-order analysis to this situation, let $T_0$ (°C), $\sigma_0$ (Joules $kg^{-1} \cdot °C^{-1}$), and $\rho_0$ (unity) denote, respectively, the temperature, specific heat, and specific gravity of the injectate; let $T_B$, $\sigma_B$, and $\rho_B$ denote the corresponding properties of the circulating whole blood. The injectate occupies a volume $V_0$ (mL), thus carrying an amount of negative heat (cold indicator) $V_0\ \sigma_0\ \rho_0\ (T_B - T_0)$ relative to blood temperature. Once introduced into the circulation, the injectate mixes with a volume $V_1$ of blood and cools it to a temperature $T_1$. If thermal energy is conserved, $V_0\ \sigma_0\ \rho_0\ (T_B - T_0) = V_1\ \sigma_B\ \rho_B\ (T_B - T_1)$. The cooled blood traverses a thermistor in a major vessel branch

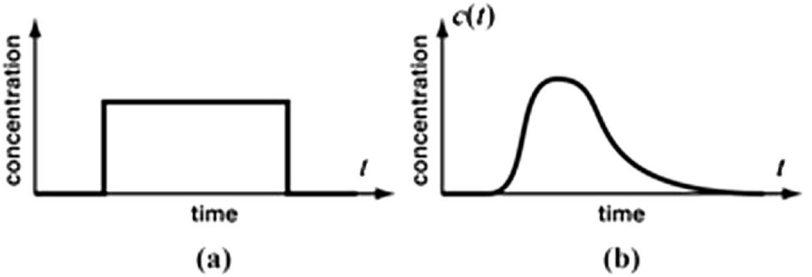


**Figure 2.** Time-concentration curves. Stewart formulation (a), which excludes the observation that the indicator concentration at the collection site initially increases and subsequently decreases in a nonstepwise manner over the collection interval. This observation is considered in the Hamilton formulation (b), illustrating the concept of an explicit time-concentration curve.

downstream over a duration $t$ (seconds). The CO $F$ ($mL \cdot s^{-1}$) is computed in a manner analogous to Eq. (1):

$$F = \frac{V_1}{t} = \frac{V_0}{t}\frac{\sigma_0\rho_0(T_B - T_0)}{\sigma_B\rho_B(T_B - T_1)}, \quad (3)$$

which asserts that the CO is inversely proportional to the temperature depression $T_B - T_1$ of cooled blood and the duration of its passage $t$ (i.e., area under the curve). In reality, the nonuniform velocities of circulating particles and the continuous dilution of injectate result in a temperature depression $\Delta T_B(t) \cong T_B - T_1(t)$ at the thermistor site that initially increases, then gradually decreases. The thermodilution curve $\Delta T_B(t)$ is essentially the time-concentration curve of Figure 2b. Modification of the constant temperature change $T_B - T_1$ in Eq. (3) with the time-averaged temperature change yields the thermodilution equation

$$F = \frac{V_1}{t} = \frac{V_0(T_B - T_0)K_1}{\int_t \Delta T_B dt}, \quad (4)$$

where the density or heat capacity factor $K_1 = \frac{\sigma_0\rho_0}{\sigma_B\rho_B}$ (= 1.08 for 5% dextrose). The CO is inversely proportional to the mean blood temperature depression and the duration of transit of cooled blood (i.e., area under the curve).

## Sources of Measurement Error and Variability

IB-PATD requires the injection of a known quantity of cold indicator through the proximal lumen of the PAC into the right atrium. The indicator mixes with the surrounding circulation in the right ventricle (RV) and enters the PA where it produces a thermodilution curve detected by a thermistor located near the catheter tip. Equation (4) is then used to compute the CO. In numerous investigations, IB-PATD has been compared with other techniques, such as the Fick-Principle, dye dilution, or aortic flow measurements with ultrasonic or electromagnetic flowprobes.[25–27] Comparisons are performed not only using correlations and regression analysis but also, in terms of bias, summarizing the lack of agreement (the bias is estimated by the mean difference and the SD of the differences between both measurements), limits of agreement (95% confidence limits of all the individual bias measurements), and precision (i.e., when looking at the mean values of each compared pair of measurements).[28,29] Although seemingly deterministic, these steps produce measurements whose accuracy and reproducibility are limited by multiple, exogenous factors: physical factors regarding injectate and injection, physiologic factors from the monitored patient, and numerical factors used to estimate the denominator of Eq. (4).[30,31]

### *Loss of Indicator Before Injection*

Suppose that the actual amount of cold indicator entering the circulation was less than the "assumed quantity." The area underneath the thermodilution curve, and therefore the mean blood temperature depression, would consequently be reduced. Equation (4) would therefore overestimate the true CO. For example, a thermodilution experiment that assumed an injectate volume of 10 mL would overestimate CO by approximately 11%, if in fact only 9 mL of injectate was used. In practice, the accurate filling of syringes by visual sighting does not present significant difficulties.[31] The occult warming of cold indicator before injection, however, is more difficult to avoid and can also produce indicator losses leading to overestimates in CO. Incompletely chilled "iced" injectate can produce such errors; in the 0°C to 4°C range, each 1°C increase in temperature contributes an approximate 3% error to the computed CO.[31] Furthermore, the catheter itself contains saline at an undetermined temperature in its dead space (see discussion below), which is injected first. The use of a room-temperature (RT) injectate eliminates conductive losses from the transfer of cold indicator before injection and avoids the inconveniences associated with the proper preparation of an iced injectate; however, it also commits the experiment to a smaller initial thermal bolus signal, which increases the effect of subsequent losses during and after injection (see discussion below).[31]

### *Loss of Indicator During Injection*

Some of the injected cold indicator does not immediately enter the central circulation. The catheter lumen occupies a small dead space (ranging from 0.7 to 1 mL, depending on the type of catheter) that retains the trailing injectate volume. More significant losses arise from the dissipation of cold indicator through intravascular portions of the catheter, which have been prewarmed by the surrounding blood. For a 10-mL bolus of iced injectate, this indicator loss is approximately 9% to 17% that, unaccounted for, leads to a >20% overestimate of CO, as described by Kim and Lin.[32] Several physical variables influence the extent of indicator loss through the catheter: (a) the intraluminal surface area; (b) the intraluminal dead space volume; (c) the injectate volume; (d) the temperature gradient between blood and injectate; and (e) the injection rate.[31,33,34] Conductive losses through the catheter wall can be circumvented by using an additional thermistor that measures the temperature of injectate as it enters the bloodstream.[5,32,33] Practical considerations in catheter construction, however, favor the alternative of measuring the temperature of the injectate immediately before entering the catheter and actually calculating the temperature of the injectate entering the bloodstream.[24] This can be accomplished by multiplying the result of Eq. (4) by a corrective, catheter-specific computation constant $K_2$. $K_2$ is precomputed in vitro for various combinations of injectate temperature and volume and is provided in the information booklet that accompanies each catheter.[24] Experience shows that $K_2$ does not vary appreciably with typically encountered injection rates, blood temperatures, or intravascular catheter lengths. $K_2$ typically incorporates a multiplier that converts milliliters per second to liters per minute. For practical considerations, it is recommended to discard the first measurement, which is done in a row, because it is most prone to incorrect results.

### *Loss of Indicator After Injection*

Cold indicator continues to escape from the circulation during its intravascular transit. Conductive rewarming of indicator by surrounding tissue is more pronounced in

low-flow states or when the indicator travels longer distances en route to the arterial thermistor[35]; a classic example is the distance traveled by the indicator with TCPTD compared with the IB-PATD. These losses can lead to falsely increased COs. Overestimates of CO can also occur with mass diversion of cold indicator from its normal itinerary through the right heart, which can occur with a right-to-left intracardiac shunt, venovenous extracorporeal lung assist,[36] or certain instances of tricuspid regurgitation (TR) (see discussion below).

#### Variation of Injectate Temperature and Volume

Several investigators have examined whether room temperature (RT) injectates can be used to obtain accurate and reliable CO measurements.[35,37–39] Less indicator is lost at various stages of the thermodilution process because of the smaller temperature gradients involved. However, the initial thermal signal is smaller than with iced injectate, thus magnifying the percent effect of lost indicator on the computed result. Although several studies demonstrated the practical equivalence of using 10-mL RT and 10-mL iced injectates over a wide range of COs,[37–39] there were also reports of significant differences between measurements with iced injectate versus RT, in particular in low- and in high-flow states.[40] The highest reproducibility of CO measurements in critically ill patients was demonstrated with 10-mL iced injectate,[41] which also reflects common clinical practice.

#### Recirculation and Detainment of Indicator

Underestimates of CO can occur when processes other than a low-flow state increases the denominator of Eq. (4). For example, in IB-PATD, a left-to-right intracardiac shunt allows cold indicator to recirculate and be detected multiple times.[42] Underestimates can also occur when decreases in blood velocity at the arterial thermistor do not reflect proportionate decreases in ventricular output. For example, suppose a patient undergoing a right thoracotomy in the left decubitus position has a PAC threaded into a branch of the right PA. When the right lung is collapsed during one-lung ventilation, blood flow to the thermistor decreases markedly secondary to hypoxic pulmonary vasoconstriction. However, the thermistor does not detect continued (and possibly increased) blood flow through the left PA. The thermodilution curve is inappropriately prolonged, and therefore the CO is underestimated.[43]

#### Tricuspid Regurgitation

PA thermodilution CO measurements are generally considered unreliable in the presence of significant TR.[44] However, the data conflict on the direction and magnitude of measurement error.[45–49] One case report demonstrates both overestimates and underestimates of CO during a single patient's hospital course,[50] suggesting that the hemodynamic context of TR influences its effect on thermodilution computations. Explanations for both directions of error begin with the reverse flow of indicator that occurs with each RV contraction.[51] The regurgitated indicator takes longer to reach the PA thermistor. Overestimates of CO occur to the extent that this indicator fails to be detected. The increased transit time of the regurgitant indicator increases its dissipation to surrounding tissues, and some indicator may arrive too late, after the thermodilution curve has been truncated (see discussion below). Underestimates of CO, however, can occur when the regurgitant indicator produces a thermodilution curve that is abnormally flat and prolonged, such that the area underneath is increased.[47,48] Some of the indicator delay can reflect real decreases in CO secondary to TR; however, the CO can be underestimated when cold indicator is preferentially regurgitated before complete admixture in the RV. It has also been suggested that in TR, the computed area underneath the curve can be artifactually increased by algorithms used to truncate and extrapolate the acquired waveforms.[47] One study suggests that TR produces overestimates of thermodilution COs in low-flow states and underestimates in high-flow states.[51] How the severity of TR affects the measurements is unresolved and requires further investigation.[47,51]

#### Fluctuations in Baseline Temperature

Equation (4) assumes that the baseline arterial temperature $T_B$ is constant, and that temperature changes $\Delta T_B(t)$ at the arterial thermistor can be wholly attributed to injected cold indicator. Exogenous disturbances in arterial temperature, which occur, for example, during cooling or rewarming,[52] after cardiopulmonary bypass,[53] or with concurrent IV infusions,[54] can therefore alter the computed CO. There are also endogenous fluctuations in PA temperature that result from cardiac and respiratory oscillations.[31] Although modest under normal circumstances, these fluctuations can increase during respiratory distress or other agonal breathing patterns. To acquire a value of $T_B$ for computational purposes, the CO computer averages the baseline PA temperature for a short interval before injection; the patient's respiratory pattern should be stable and regular during this premeasurement period.[31]

#### Cyclic Changes in CO

Spontaneous or mechanical ventilation affects the actual CO; the stroke output can vary by as much as 50% at various phases of the respiratory cycle,[55,56] a phenomenon that is more prominent for right ventricular (RV) stroke volume than for left ventricular (LV) stroke volume.[57] Successive thermodilution CO measurements are therefore most reproducible when performed at the same point in the respiratory cycle.[31,56] This reproducibility is further improved by averaging multiple (typically 3) consecutive measurements.[31,58] However, the reproducibility of even synchronized measurements can be impaired by subtle irregularities in respiratory mechanics.[55,59] To further complicate matters, variations between successive measurements may reflect not only respiratory variation but actual changes in CO.[59] Strictly speaking, synchronized measurements may not accurately reflect the underlying cardiac performance; the CO of interest is the average of all instantaneous COs over the entire respiratory cycle. The averaging of multiple measurements at different phases of the respiratory cycle has therefore been proposed.[55] It is unclear how many

asynchronous measurements are needed for sufficient accuracy and reproducibility, but it seems that 3, although clinically mostly performed, is insufficient.[56,59,60]

#### *Truncation and Extrapolation of Thermodilution Curves*

Practical considerations require that the thermodilution curve be truncated when further acquisition no longer contributes appreciably to the final result. If the downslope of the curve was a simple exponential (as it is with chemical indicators[21]), the remaining portion could be extrapolated mathematically. Unfortunately, thermodilution curves obtained in practice are further distorted by multiple exogenous phenomena, including the recirculation of "lost" indicator from the catheter and surrounding tissues,[31] the aforementioned fluctuations in arterial temperature, and abnormally turbulent flow patterns such as TR. Because the cumulative effects of these influences conform to no easily recognizable pattern, further complicated by the fact that only very small net changes in temperature are measured, the current practice is to use numerical algorithms for estimating area underneath the thermodilution curve, which vary among manufacturers and types of monitors. For example, many monitors simply measure the area under the curve until a certain time, in most cases when the curve returns to 50% of the peak and then add an empirically derived percent of the initial curve to "calculate" the total area and hence CO.[32]

### Advantages and Limitations

Nearly 4 decades of clinical experience have given the IB-PATD the status of being the standard method for advanced hemodynamic monitoring, and in particular for CO determination. Measurements can be obtained quickly and are clinically feasible, compared with other techniques such as the Fick method. Furthermore, successive measurements can be obtained rapidly without significant interference from recirculated indicator.[24] Thermodilution measurements correlate well with the earlier methods.[31] However, it is important to stress that IB-PATD measures right heart output, i.e., pulmonary blood flow, and not systemic CO, which of course is essentially equal in normal patients, but not so in the presence of right-to-left and left-to-right cardiac or great vessel shunts. The PAC also provides other hemodynamic measures (e.g., PA pressures and mixed venous oxygen saturation) and facilitates other functions, such as blood sampling that can aid cardiovascular management.[12] The disadvantages of IB-PATD include its finite precision, various associated complications, and inherent limits on the frequency and number of measurements. Intrinsic limits on the reproducibility of measurements require a measured change of approximately 22% (or 13% for triplicate measurements) for the difference to be statistically significant, as demonstrated by Stetz et al. in 1982.[60] It is remarkable that since 1982 no continuative data regarding these findings have been published. Complications associated with placement and continuing residence of a PAC (some of them catastrophic, such as rupture of a pulmonary vessel, or serious embolism) are well documented.[12] Successive measurements, although rapid, are not continuous.

## CONTINUOUS PA THERMODILUTION CO

### Technical Description

Following the same principles described above, continuous PA thermodilution (CPATD) CO measurements also involve a PAC and rely on thermodilution principles. Instead of applying cool saline in a bolus fashion, blood flowing through the superior vena cava is heated intermittently by an electric filament attached to the PAC approximately 15 to 25 cm before its tip. Two systems currently available use different algorithms. The Vigilance II system (Edwards Lifesciences, Irvine, CA) activates a flat heating filament for 1 to 4 seconds in a pseudorandom sequence. The resulting series of heat signals from the thermistor on the tip of the PAC are analyzed stochastically to determine a single thermodilution curve.[61] The Q2plus system (Hospira, Lake Forest, IL) applies 20-second heat pulses to a coiled filament in a repetitive on-off cycle every 40 seconds.[62] The response from each pulse is analyzed as a separate thermodilution curve. A proprietary averaging algorithm is applied to reduce the influence of thermal noise. The monitoring system repeats the individual measurements in preset intervals automatically and displays the current CO and the trends.

### Sources of Measurement Error and Variability

CPATD CO measurements have been shown to correlate well with IB-PATD CO measurements under a wide range of CO in patients[62–68] (Table 1) and in animal models.[69,70]

**Table 1. Comparisons of Continuous Pulmonary Artery Thermodilution Versus Intermittent Bolus Pulmonary Artery Thermodilution Cardiac Output**

| | Study variables | | | | Measures of agreement | | |
|---|---|---|---|---|---|---|---|
| Investigators (y) | Population | Ages | *N* | *n* | *r* | Bias | Precision |
| Yeldermann 1990[61] | Intensive care unit | ni | 54 | 222 | 0.94 | 0.3% | 11.5% |
| Boldt et al. 1994[131] | Intensive care unit | ni | 35 | 404 | ni | 0.03 L · min$^{-1}$ | 0.52 L · min$^{-1}$ |
| Haller et al. 1995[76] | Intensive care unit | 24–79 | 14 | 163 | 0.91 | 0.35 L · min$^{-1}$ | 1.01 L · min$^{-1}$ |
| Böttiger et al. 1995[75] | Liver transplant | 48 ± 11 | 20 | 192 | 0.89 | 0.240 L · min$^{-1}$ | 1.79 L · min$^{-1}$ |
| Burchell et al. 1997[132] | Intensive care unit | ni | 21 | 202 | | 0.49 L · min$^{-1}$ | 1.01 L · min$^{-1}$ |
| Mihm et al. 1998[62] | Intensive care unit | ni | 47 | 372 | 0.92 | 0.12 L · min$^{-1}$ | 0.84 L · min$^{-1}$ |
| Medin et al. 1998[63] | Intensive care unit | 17–77 | 20 | 306 | 0.87 | ni | ni |
| Zöllner et al. 1999[67] | Cardiac surgery | 29–86 | 20 | 240 | 0.89 | 0.52 L · min$^{-1}$ | 1.29 L · min$^{-1}$ |
| Schmid et al. 1999[66] | Intensive care unit | 15–81 | 56 | 167 | 0.85 | 0.052 L · min$^{-}$ | 0.9 L · min$^{-1}$ |
| Singh et al. 2002[68] | Cardiac surgery | 57.1 ± 11.6 | 20 | 400 | 0.78 | −0.095 L · min$^{-1}$ | 0.729 L · min$^{-1}$ |

*N* = number of individuals; *n* = number of measurements; Precision = SD of differences, if not otherwise noted; ni = not indicated.

CPATD CO measurements were also compared with electromagnetometry and ultrasound using aortic flowprobes, representing most closely a "gold standard" for continuous determination of CO, in cardiac surgery patients, as well as in the presence of an LV assist device, allowing predetermination of aortic blood flow.[71–73] Those data showed that the accuracy and precision of the Abbott Opti-Q, the predecessor of the Hospira Q2plus, versus the Edwards Vigilance CPATD CO measurements were comparable with IB-PATD. In addition, TR affected CPATD CO measurements less adversely than IB-PATD CO measurements, as shown in a pig model.[74] Although CPATD and IB-PATD rely on the same principle of thermodilution, extreme temperature variations can cause poor correlation between them. In patients recovering from hypothermia after cardiopulmonary bypass[75] or liver transplantation,[65] IB-PATD CO exceeded CPATD CO significantly until resolution of hypothermia. Indeed, IB-PATD CO may be less sensitive to thermal noise because the magnitude of the temperature change induced by the single cold saline bolus is much greater than the small heat signals induced with CPATD CO.

### Advantages and Limitations

CPATD CO monitors eliminate the need for intermittent fluid boluses and the associated operator time, reduce contamination risk, and provide a continuous trend of CO.[63] However, during periods of hemodynamic instability, the clinical usefulness of CPATD CO monitors can be decisively limited by a time delay, which is caused by averaging procedures used to reduce noise artifacts. Haller et al.[76] reduced the CO of patients with an LV assist device abruptly by 1 $L \cdot min^{-1}$ and measured the CO using the Vigilance system (Edwards, Irvine, CA). A 50% response was noted at 9 minutes; the full response was not obtained until 12 minutes. In an animal model, Siegel et al.[77] used the Vigilance system (Edwards, Revision 4.4) in the stat-mode, which is designed to reduce the time delay. After manipulating the CO by rapid IV fluid administration, the CPATD CO lagged behind the ultrasonic flowprobe measurement by approximately 12 minutes for an 80% response. In an in vitro system, the times required to detect a change in CO by the CPATD CO catheters were 2.9 vs 3.3 minutes for a 20% response and 4.7 vs 11.2 minutes for an 80% response,[78] markedly restricting their suitability for the assessment of rapid hemodynamic changes.

## TRANSCARDIOPULMONARY THERMODILUTION

TCPTD and transpulmonary dye dilution use the same principles as IB-PATD to measure CO, but avoids PA catheterization and its attendant risks.[79,80] Transcardiopulmonary refers to the passage of thermal indicator through the pulmonary circulation and the left heart before detection. Historically, TCPTD is actually the older technique. The literature also describes TCPTD as transpulmonary and arterial thermodilution.

### Technical Description

#### *Cardiac Output*

TCPTD CO measurements begin with the injection of cold indicator into the superior vena cava via a central venous catheter.[79] The cold indicator mixes with the ambient circulation as it travels through the right heart, pulmonary circulation, left heart, and aorta. A thermistor in the aorta (or a major branch thereof) records the surrounding blood temperature and generates a thermodilution curve qualitatively similar to the IB-PATD curve. Figure 3 contrasts the timing and magnitude of the temperature curves as measured by a thermistor in the PA or the femoral/iliac artery. The thermodilution equation (Eq. (4)) is used to calculate the CO. TCPTD does not involve the use of a PAC. Standard central venous access is sufficient for the initial injectate, making the technique considerably less invasive compared with the IB-PATD. However, central arterial access is needed to obtain the resultant thermodilution curves. Measurements in adults typically utilize a thermistor-tipped femoral artery catheter; however, use of the axillary or brachial artery is also feasible.[81] The currently available system using TCPTD is the PiCCO monitor (Pulsion Medical Systems, Munich, Germany).[81–87] It performs a monoexponential extrapolation on the TCPTD curve before using it to calculate the CO. Note that the PiCCO system combines TCPTD with pulse contour analysis, a technique enabling continuous real-time assessment of LV CO.[87,88] In addition to CO, several other clinical variables can be readily measured in patients who are already catheterized for TCPTD, i.e., the global end-diastolic volume (GEDV) as volumetric measure of cardiac preload, and the extravascular lung water (EVLW), a measure of pulmonary edema.[89–92] The derivation of these variables uses the concept of an indicator bolus's mean transit time and the exponential decay time between injection and detection sites, as illustrated in Figures 4 and 5. Furthermore, description of these variables is beyond the scope of this review.

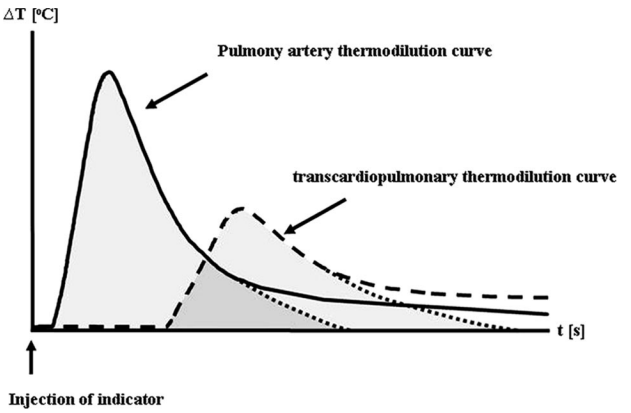


**Figure 3.** Comparison of thermodilution curves after injection of cold saline into the superior vena cava. The peak temperature change arrives earlier when measured in the pulmonary artery (a) than if measured in the femoral artery (b). Thereafter, both curves soon reapproximate baseline. For reasons leading to a delayed reapproximation, see Sources of Measurement Error and Variability on page 803.

### Sources of Measurement Error and Variability

CO values obtained with TCPTD can be considered adequate to the extent that they compare favorably with IB-PATD measurements, if evaluated with widely accepted criteria.[28,29] TCPTD is vulnerable to the same sources of measurement error and variability as IB-PATD because the 2 methods are based on the same physical principles.

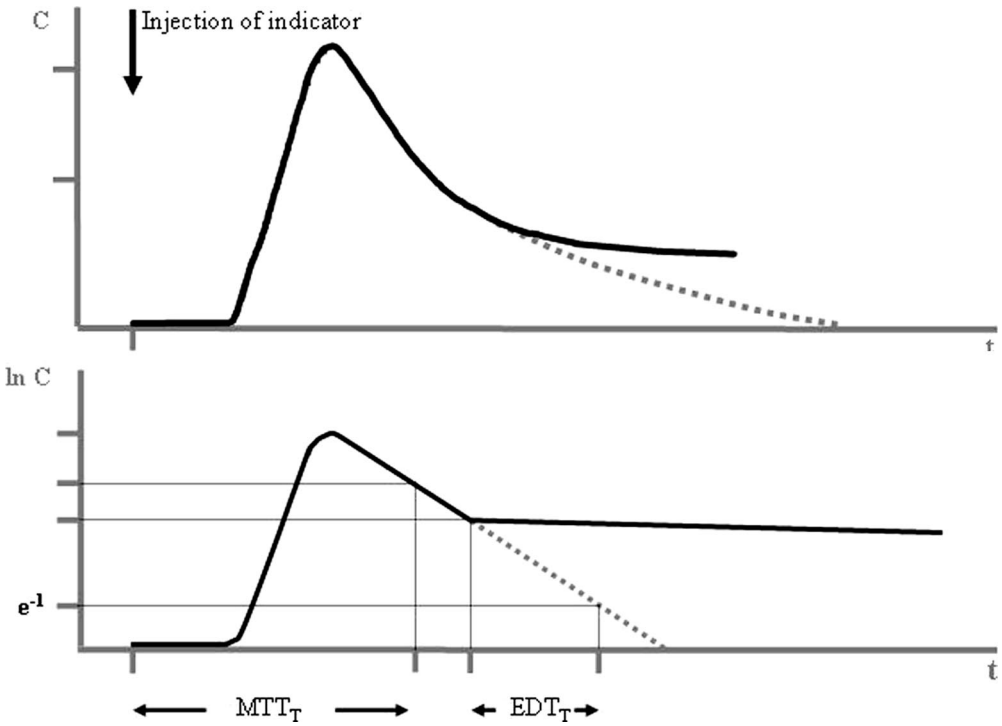


**Figure 4.** The upper curve represents the classic thermodilution curve, showing the concentration of an indicator over time at the site of detection. By extrapolation of the curve (dashed line), potential recirculation phenomena are excluded. Logarithmic illustration (lower curve) allows defining the mean transit time ($MTT_T$) and the exponential decay time ($EDT_T$) of the indicator.

Nevertheless, CO measurements from TCPTD can differ quantitatively from PATD measurements. One reason is that TCPTD measures the net LV CO, whereas PATD measures RV CO. As cold injectate traverses the central circulation, it causes a transient decrease of the heart rate that affects the RV CO and, to a lesser extent, the LV CO[93]; several investigators postulate this mechanism as the primary reason why TCPTD CO values are slightly higher than those obtained by IB-PATD in their studies.[85] Respiratory variations in CO secondary to spontaneous or positive-pressure ventilation also seem to affect the right side more than the left.[94] However, the differential effect of cyclic changes in intrathoracic pressure on actual TCPTD and IB-PATD measurements is attenuated because thermodilution curves are typically acquired over several cardiac cycles. The aforementioned applies particularly to the IB-PATD, whereas TCPTD measurements are less prone to these cyclic influences. This is because 1 TCPTD measurement typically comprises several cardiorespiratory cycles because of the longer distance from injection site to the thermistor. Quantitative differences in indicator loss and recirculation are the other frequently cited explanations for differences in TCPTD and IB-PATD measurements.[79,82,85,88] Such losses may be attributed in part to the larger distances between the injection and the sampling sites.[35,88,95] The passage of indicator through the lungs in TCPTD was thought to be a potential source of increased indicator loss,[96] but this speculation has failed to manifest in studies comparing TCPTD and IB-PATD in subjects with acute lung injury.[82,85,88] Considering all mechanisms of indicator loss taken together, Bock et al.[88] estimated that 96% to 97% of the indicator that reaches the PA is recovered in the aorta. Complicating the story of indicator loss, however, are the coexisting phenomena of indicator detainment and recirculation. For example, cold indicator that translocates into the pulmonary extravascular space in states of pulmonary edema eventually returns back into the intravascular space.[88] This indicator, although preserved, arrives late, causing an abnormal prolongation of the TCPTD curve that, taken alone, causes TCPTD to underestimate IB-PATD CO values. Algorithms that extrapolate the early, relatively noiseless portions of thermodilution curves are designed to eliminate such recirculation phenomena; however, the frequently used monoexponential extrapolation procedure (and its derived, simplified variants) retains recirculated indicator to a greater extent in TCPTD than in IB-PATD.[89] The effects of indicator loss and indicator recirculation tend to cancel one another; which mechanism is of greater quantitative significance remains unclear.[89] Table 2 summarizes the results of several studies that compared TCPTD and IB-PATD COs in various critically ill patient populations. In each of these studies, the subjects underwent both PA and large arterial cannulation, so that a single bolus of cold injectate could yield both an IB-PATD and, seconds later, a TCPTD curve. Multiple such paired measurements were then analyzed by computing the correlation coefficient of a standard linear regression, as well as the statistical measures of agreement (bias and precision). Taken together, these studies demonstrate an overall agreement between TCPTD and IB-PATD CO measurements for a variety of clinical settings; most investigators report correlation coefficients >0.9 and biases <10%. Where reported, the coefficients of variation of these techniques are comparable and modest.[80,84,87] Studies that

compare TCPTD and the Fick method also demonstrate close agreement.[83,97]

## Advantages and Limitations

TCPTD inherits the same advantages that IB-PATD possesses over the earlier Fick and chemical indicator-dilution methods. Furthermore, TCPTD, while producing CO measurements compatible with the earlier accepted methods, avoids the risks of pulmonary embolism, PA rupture, and other complications of PA catheterization.[12] Thus, from a morbidity standpoint, TCPTD is less invasive than IB-PATD, making it also suitable for use in pediatric patients, where frequently, because of the patient's size, the use of a PAC is not feasible.[97–100] Although TCPTD requires percutaneous arterial access in addition to central venous access, many critically ill patients who require CO monitoring already have arterial catheters in place.[81,85,86] In any event, the arterial cannulation that is required for TCPTD seems to be safe and no relevant drawbacks for the usually used femoral insertion site have been demonstrated thus far.[101–105] Moreover, in some patients, in particular under high doses of catecholamines, pressure measurement in the femoral artery was described as being advantageous compared with measurement in the radial artery.[101,106] However, the possibility of an increased risk of infection with femoral arterial access needs to be considered and implies diligent nursing care. In patients with severe peripheral vascular disease, cannulation of a femoral artery can be contraindicated because of the risk of thromboembolism. Furthermore, detailed analysis of TCPTD curves with the detection of double peaks in these curves allows detecting right-to-left shunting.[107] Another advantage conferred by TCPTD is the unique ability to monitor a patient's GEDV and EVLW.[108] Multiple investigators have demonstrated the superiority of GEDV over left- or right-sided filling pressures as an estimate of cardiac preload.[91,92,109,110] This observation is clinically relevant because inadequate intravascular volume resuscitation often results from excessive concerns about iatrogenic pulmonary edema triggered by increased filling pressures. The EVLW, however, provides a measure of pulmonary edema that provides information not necessarily obtainable from serial chest roentgenograms or trends in filling pressures.[100,111–113] Compared with a reliance on these traditional observations, the use of fluid-management protocols based on EVLW can hasten the resolution of pulmonary edema, shorten the time to tracheal extubation, and decrease the duration of stay in the intensive care unit in patients requiring mechanical ventilation for respiratory failure.[92,111,114] Because TCPTD does not involve PA catheterization, it cannot monitor trends in PA pressures, PA occlusion pressure, or mixed venous oxygen saturation. However, there is strong evidence that filling pressures

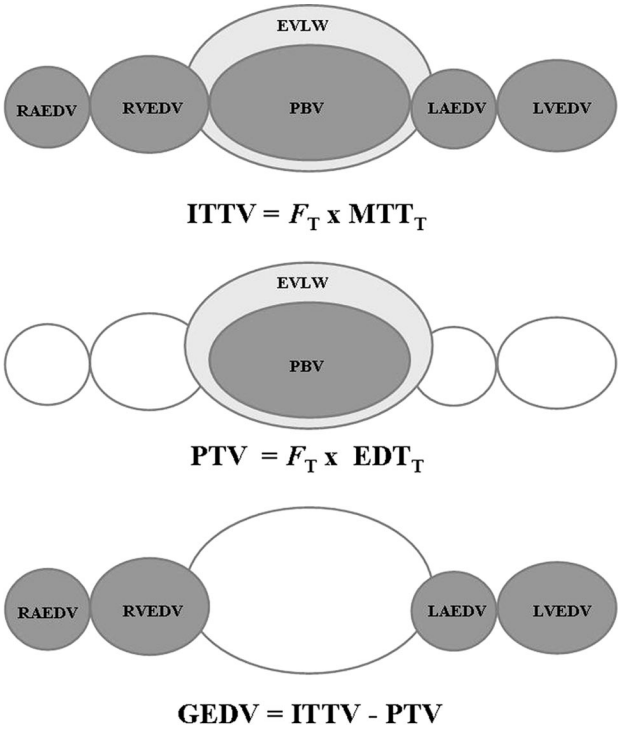


**Figure 5.** Assessment of global end-diastolic volume (GEDV) by transcardiopulmonary thermodilution. Upper row: The intrathoracic thermal volume (ITTV) is the complete volume of distribution of the thermal indicator, including the right atrium end-diastolic volume (RAEDV), the right ventricle (RVEDV), the left atrium (LAEDV), the left ventricle (LVEDV), the pulmonary blood volume (PBV), and the extravascular lung water (EVLW). It is calculated by multiplying cardiac output (FT) with the mean transit time ($MTT_T$) of the indicator. Middle row: The pulmonary thermal volume (PTV) represents the largest mixing chamber in this system and includes the PBV and the EVLW and is assessed by multiplying FT with the exponential decay time ($EDT_T$) of the thermal indicator. Bottom row: The GEDV, including the volumes of the right and the left heart, now is calculated by substracting PTV from ITTV.

**Table 2. Comparisons of Transcardiopulmonary Thermodilution Versus Pulmonary Artery Thermodilution Cardiac Output**

| | Study variables | | | | Measures of agreement | | |
|---|---|---|---|---|---|---|---|
| Investigators (y) | Patient population | Ages | *N* | *n* | *r* | Bias | Precision |
| Della Rocca et al. 2002[128] | Liver transplant | 24–66 | 62 | 186 | 0.93 | +1.9% | 11% |
| Friesecke et al. 2009[129] | Severe heart failure | ni | 29 | 325 | ni | 10.3% | 27.3% |
| Goedje et al. 1999[87] | Cardiac surgery | 41–81 | 24 | 216 | 0.93 | +4.9% | 11% |
| Holm et al. 2001[85] | Burns | 19–78 | 23 | 109 | 0.97 | +8.0% | 7.3% |
| Kuntscher 2002[86] | Burns | 21–61 | 14 | 113 | 0.81 | ni | ni |
| McLuckie et al. 1996[84] | Pediatrics | 1–8 | 10 | 60 | ni | +4.3% | 4.8% |
| Segal 2002[81] | Intensive care unit | 27–79 | 20 | 190 | 0.91 | +4.1% | 10% |
| von Spiegel et al. 1996[80] | Cardiology | 0.5–25 | 21 | 48 | 0.97 | −4.7% | 12% |
| Wiesenack et al. 2001[130] | Cardiac surgery | 43–73 | 18 | 36 | 0.96 | +7.4% | 7.6% |
| Zöllner et al. 1999[67] | ARDS | 19–75 | 18 | 160 | 0.91 | −0.33% | 12% |

*N* = number of patients; *n* = number of measurements; Precision = SD of differences, if not otherwise noted; ni = not indicated.

**Table 3. Comparisons of Lithium-Indicator Dilution Versus Intermittent Bolus Pulmonary Artery Thermodilution Cardiac Output**

| | Study variables | | | | Measures of agreement | | |
|---|---|---|---|---|---|---|---|
| Investigators (y) | Patient population | Ages | *N* | *n* | *r* | Bias | Precision |
| Linton et al. 1993[116] | Cardiac surgery | 38–73 | 9 | 22 | 0.89 | 0.3 L · min$^{-1}$ | 0.5 L · min$^{-1}$ |
| Linton et al. 2000[a120] | Pediatrics | 0–9 | 19 | 48 | 0.9 | −0.17 L · min$^{-1}$ | 0.39 L · min$^{-1}$ |
| Garcia-Rodriguez et al. 2002[124] | Intensive care unit | 42–80 | 24 | 216 | 0.9 | −0.53 L · min$^{-1}$ | 0.63 L · min$^{-1}$ |
| Costa et al. 2008[122] | Liver transplant | 37–68 | 23 | 150 | 0.88 | 0.11 L · min$^{-1}$ | 1.94 L · min$^{-1}$[b] |

*N = number of patients; n* = number of measurements; Precision = SD of differences, if not otherwise noted.
[a] Comparison with transcardiopulmonary thermodilution.
[b] 2 SD.

are not suited to reflect preload, for which the central venous pressure or PA occlusion pressure are unfortunately mostly used.[18] Furthermore, although with limitations, mixed venous oxygen saturation can be approximated by central venous oxygen saturation.[115] Thus, the TCPTD technique may represent a useful alternative to IB-PATD as a tool for monitoring cardiac performance in those patients in whom specific knowledge on PA pressures is not required.

## TRANSCARDIOPULMONARY LITHIUM DILUTION

### Technical Description

#### *Cardiac Output*

Measurement of CO by lithium dilution is based on the same principles as the aforementioned thermodilution techniques. Using lithium as indicator was first described in 1993.[110] The indicator, isotonic lithium chloride (150 mM), is injected as a bolus (0.002–0.004 mmol · kg$^{-1}$) either via a central or a peripheral venous route. It mixes with the venous blood as it travels through the right heart, pulmonary circulation, left heart, and the aorta. In the only commercially available monitor, the LidCO-Plus (LidCO, Cambridge, England), the concentration-time curve of the indicator is, in contrast to the thermodilution methods, routinely generated not in a central arterial vessel but in a peripheral artery by the use of an ion-selective electrode. This electrode, which is integrated in a flow-through cell, is attached as a disposable to the arterial line manometer system. By the use of a battery-powered peristaltic pump, arterial blood is drawn through the sensor with a constant rate of 4 mL · min$^{-1}$. The electrode contains a membrane that is selectively permeable to lithium. After applying a correction factor for the plasma sodium concentration, which determines the baseline voltage across the membrane, the voltage is related by the Nernst equation to the plasma lithium concentration. The voltage is amplified and then digitalized for online analysis. The plasma flow is then derived from the dilution curve by dividing the injected dose of lithium chloride by the area, which would have been inscribed by the curve, if there had not been recirculation of the indicator. Effects of recirculation are minimized by cutting off and extrapolating the indicator-dilution curve after the concentration had decreased by 50% of its peak. For the calculation of CO, plasma flow needs to be converted to blood flow (division by 1-PVC [packed cell volume]), assessed on the basis of hemoglobin concentration/33, because lithium is distributed only in the plasma fraction of blood.[116] Note that the LidCO-Plus system combines the transcardiopulmonary lithium dilution also with pulse contour analysis so that a continuous and real-time assessment of LV CO is possible.[117]

### Sources of Measurement Error and Variability

CO by lithium indicator dilution was compared with measurement of blood flow in the ascending aorta assessed with an electromagnetic flowprobe in 10 pigs.[118] CO was altered by using dobutamine, propranolol, and increasing the sevoflurane concentration. The measured CO ranged from 0 to 3 L · min$^{-1}$, with a bias compared with this experimental gold standard of overall 0.11 L · min$^{-1}$ and a precision of 0.04 L · min$^{-1}$, respectively. Those data were confirmed by several studies in animals and humans (Table 3), in which lithium indicator dilution was compared with IB-PATD and TCPTD.[119–122,124]

### Advantages and Limitations

Using the commonly based principles of indicator dilution, lithium indicator dilution is an accurate method for measurement of CO in the critically ill. It does not need PA catheterization, thus avoiding the risks associated with the PAC. In most studies that investigated lithium indicator dilution for measurement of CO, application of lithium was done via a central venous access. However, 2 studies demonstrated that application of lithium via a peripheral venous access yields results comparable with the central venous application,[121,123] which was confirmed, and when compared with IB-PATD.[124] Thus, lithium indicator dilution allows accurate measurement in patients with only arterial and peripheral venous access. The measurement of EVLW by lithium indicator dilution was also described by Maddison et al.,[125] with encouraging results in an animal experiment, compared with postmortem gravimetry. However, just recently, those data could not be confirmed in a clinical study.[126]

The use of this technique is limited in patients receiving lithium therapy; the background blood concentration would lead to an overestimation of CO. According to the manufacturer, the number of measurements over a short period of time is limited because of a potential accumulation of lithium. However, the precise number is not given by the manufacturer. According to the manufacturer, patients who are <40 kg in weight and patients in the first trimester of pregnancy are contraindicated. A drift of the electrode in the presence of certain muscle relaxant infusions has been discussed, with the consequence of inaccurate measurements.[117,127]

## CONCLUSION

Accurate assessment of the hemodynamic status is desirable in the treatment of critically ill patients with hemodynamic instability or in perioperative patients at increased risk for cardiac complications. Measurement of CO is 1 cornerstone of this hemodynamic assessment. The widely used PAC is very versatile, providing both measurement of CO by thermodilution as well as PA pressures and mixed venous $Sao_2$. However, the risks associated with placement and chronic instrumentation have prompted development of potentially less-invasive methods, also based on the principle of indicator dilution, i.e., TCPTD and lithium indicator dilution. Both techniques allow accurate measurement of CO without the need of PA catheterization. TCPTD yields useful additional information also based on the principle of indicator dilution, pertaining to GEDV as a measure of preload, and EVLW quantifying pulmonary edema. However, monitoring of CO alone represents only a single aspect of hemodynamic assessment. Therefore, choices for a specific approach to monitoring cardiac performance should always reflect the necessity for information that might alter patient management (e.g., PA pressures for PAC-based techniques or measurement of preload volumes and EVLW for the TCPTD).

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