Methods and considerations concerning cardiac output measurement in pregnant women: recommendations of the International Working Group on Maternal Hemodynamics

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Introduction

Pregnancy is a unique condition which greatly alters a women's physiology. In order to successfully meet the demands of a growing fetus, profound hemodynamic changes occur. Early in pregnancy peripheral vascular resistance (PVR) drops, inducing a substantial increase in cardiac output (CO).[1-7] CO is the amount of blood the heart pumps into the arterial system (liters/minute). It is the product of stroke volume (SV) and heart rate (HR). SV is determined by the driving force filling the ventricles (preload), the contraction strength of the ventricle and resistance against which the heart has to pump (afterload). Blood pressure (BP) is a product of CO and PVR (BP = CO x PVR), linking these 3 hemodynamic parameters into one equation.

During the course of pregnancy (placental and fetal growth, delivery) and possible pregnancy complications (preeclampsia, intra-uterine growth restriction, hypertension, sepsis, postpartum hemorrhage, thrombosis), large fluctuations in these hemodynamic parameters occur.[1, 8-21] Consequently, the interest in measuring these parameters during pregnancy has been growing.

CO can be measured with several very different techniques. Most of them were primarily developed for use in critical care settings and non-pregnant populations. Many of them have been imported into obstetrics, however often without proper validation in pregnant women. Each technique has distinctive implications, benefits and limitations. It is of great importance to know these characteristics in order to select the most appropriate technique for the specific occasion.

For example, if one wants to study hemodynamic adaptation to pregnancy in order to predict or manage hypertensive problems, intermittent but accurate measurements are appropriate. If one wants to compare findings between individuals, indexing for body composition can be important. On the other hand if one would like to monitor the hemodynamic condition during acute events, continuous operator independent trend monitoring can be more useful.

Important considerations are the degree of invasiveness, the degree of operator dependency, the availability, costs, whether intermittent measurements or continuous measurements are possible, the accuracy and precision in reflecting absolute values or trends and validation in pregnancy.

The use of different techniques has sometimes resulted in conflicting findings, thus limiting the possibilities of comparing studies.

This position statement aims at describing the characteristics of the different methods and standardizing the detection of CO and PVR in clinical practice and research studies on maternal hemodynamics.

Physiology in pregnancy

Cardiac output

As stated above, already in the first trimester of pregnancy a rapid increase in CO occurs which continues throughout the second trimester.[1, 22, 23] There is a debate in literature concerning the changes in CO during the third trimester: some studies found a decline,[7, 24-26] whereas others observed no change[2, 5, 6, 27] or an increase towards term.[28, 29] These differences have been attributed to variations in methodology and/or population characteristics.[24, 30]

HR and SV and thus CO are very sensitive to changes in position and are highly variable among women.[6] Doppler studies in the third trimester in normal pregnant subjects comparing measurements in lateral and supine positions, have shown no differences in cardiac output near term.[31, 32] However, cardiovascular magnetic resonance (CMR) in pregnancy showed significant increment of left ventricle ejection fraction, SV and CO in left lateral position in third trimester pregnant subjects.[33, 34] Therefore, it is highly recommended that CO-related assessments are performed in a left lateral position as early as from 20 weeks gestation. Multiple studies investigating CO during delivery using a modified pulse pressure method after arterial and central venous catheterization and CW ultrasound suggested that SV and CO increase during labor and immediately postpartum due to pain, maternal bearing-down efforts and the increase in venous return by autotransfusion from the contracted uterus and the sudden release of inferior vena cava obstruction, which was readily accepted as common knowledge for several decades.[35-41] Recent prospective studies using continuous measurement methods suggest a different perspective with similar baseline hemodynamic parameters during the course of labor (stage 1, 2 and postpartum) and substantial hemodynamic stress during contractions, without an increase in CO directly postpartum.[42, 43]

Blood Pressure

Mean arterial pressure (MAP) reduces by approximately 10% by the end of the second trimester. After this period, MAP starts to increase towards term.[1] BP detection during pregnancy should be standardized to be taken in a seated or semi-recumbent position with the arm at the level of the heart and the feet supported or on the ground.[44-46] When BP measurement is performed in association with the evaluation of CO for the calculation of PVR, BP should be taken as closely as possible to the CO assessment and in the same position as during CO assessment, to provide a reliable calculation of PVR from highly variable parameters in time.

BP can be obtained invasively from appropriately levelled arterial catheters or non-invasively using either a sphygmomanometer or automated oscillometric devices which are validated for use in pregnancy, all with an appropriate sized arm cuff.[44, 45, 47, 48] Recent developments in technologies have provided new insight into the role of peripheral (typically brachial) and central (= aortic) BP, and the associated aortic stiffness.[49] The role of aortic stiffness and central aortic BP in pregnancy remains to be fully determined.[50-54]

Peripheral Vascular Resistance

The afterload represents the mechanical opposition to the movement of blood out of the left ventricle and can be divided into: a steady component (PVR) and a pulsatile component.[55] PVR is primarily due to the cross-sectional diameter of the resistance vasculature. During pregnancy the increased CO associated to the decline in MAP results in a decline in calculated PVR. The steady component of the afterload (i.e. PVR) decreases with pregnancy.[1, 5, 56-58] The pulsatile component represents the load faced by the heart due to the response of the arterial tree to oscillations in pressure and flow.[55]

The global arterial compliance increases with pregnancy, with most of the increase occurring early during gestation and remaining elevated thereafter. Reduced smooth muscle tone appears to be the likely mechanism responsible for increased vascular distensibility.

The increase in the global arterial compliance appears to be one of the body's adaptive mechanisms to accommodate greater intravascular volume without increasing mean arterial pressure. Moreover, the increased arterial compliance counterbalances the effects of reduced PVR and helps maintain the efficiency of left ventricle-to-arterial system mechanical energy transfer. Another aspect to underline is that increased compliance also balances the effect of reduced PVR on aortic diastolic pressure decay, thus preserving perfusion pressure to the coronary arteries and other vital organs.[55]

The reduced PVR (steady component) allows to maintain MAP within the normal range at the time of greatly increased CO.[26] Therefore, concomitant changes in arterial pulsatile load during normal pregnancy, especially arterial compliance, are such that the potentially deleterious effects of PVR reduction are mitigated.[55]

Methods of Cardiac Output measurements

Invasive methods

Pulmonary artery catheterization.

A pulmonary artery catheter (PAC) is advanced via a brachial, subclavian or jugular vein, through the right atrium and ventricle into the pulmonary artery. The catheter has several lumens, injection and sampling ports and a thermistor and balloon at the tip, permitting various pressure (central venous pressure, pulmonary artery pressure and pulmonary capillary wedged pressure) and output measurements (illustrative video available via Kelly et al.).[59]

The direct Fick method calculates CO by dividing the oxygen consumption (measured with a spirometer) by the difference in arterial and mixed venous oxygen content (sampled from the PAC). This method is rarely used in clinical practice.

CO can also be measured by thermodilution based the law of conservation of energy. A bolus solution of known volume (5-10mL) and temperature (either ice-cooled or at room temperature) is injected as an indicator through a proximal port of the PAC and mixes with blood thereby cooling it. CO is deducted from curves of temperature difference over time between the injection site and the tip of the PAC using the modified Stewart-Hamilton equation. Intermittent CO values are obtained by averaging 3 to 5 thermodilution curves.

Some manufacturers (Table 1.) incorporated an electric heating filament into the PAC permitting continuous CO trend measurements of every 30-60 seconds after initial and regular subsequent calibration with the intermittent bolus technique. The obtained values do not reflect the instantaneous CO but an average over the last 5 to 15 minutes.

The technique is highly invasive with substantial procedure related risks and limited to ICU settings. Catheter insertion, performing measurements and interpreting the thermodilution curves can be technically challenging and requires specific expertise and training. Despite being considered the reference method for CO measurements, it is good to realize that even in optimal conditions the accuracy and precision of the method reflecting the “true actual CO” remains around 10-20% due to inherent technical limitations. It means that PAC, even as a reference

technique, can only reliably demonstrate changes in CO of at least 15-30%, being on average 0.75-1,5 L/min for a mean CO of 5 L/min in adults.[60, 61]

While popular in intensive care settings and obstetric critical care for hemodynamic monitoring and treatment guidance until the beginning of the 21st century, controversy about its risk/benefits ratio and the development of less invasive techniques make that PAC nowadays, especially in obstetrics, has mostly been abandoned, thereby depriving us of a generally accepted reference method to compare alternatives. Recommendation: PAC should only be used on strict clinical indication in critically ill pregnant women in either an intensive care setting of obstetrical critical care unit.

Less or minimally invasive methods

Pulse contour and pulse power analysis and pressure recording analytical method (PRAM)

Pulse contour and pulse power analysis are less invasive methods to measure CO, both in essence based on the relation between arterial pressure and SV. By analyzing the peripheral arterial pressure waveform, taking several assumptions on aortic compliance, impedance and wave reflection into account, CO can be estimated in a continuous, real time and operator independent manner. The arterial waveform is obtained by an intra-arterial line. The methods require initial calibration to account for the assumptions on aortic compliance, impedance and peripheral resistance and regular subsequent recalibration, especially after major hemodynamic changes.

The PiCCO® system (Figure 1) and Volume View/EV1000® systems (pulse contour; Table 1) use transpulmonary thermodilution similar to thermodilution with PAC. They require a central venous line and femoral or axillary arterial line with thermistor tip, and are only slightly less invasive as compared to PAC, limiting their use to ICU settings. In addition to CO and central venous and intra-arterial pressure, global end diastolic volume (as a measure of preload) and extravascular lung water (as a measure of pulmonary edema) can be obtained.

LiDCOplus® system (pulse power; Table 1) dilutes small boluses of lithium chloride as indicator for calibration. Lithium can be administrated via a peripheral intravenous access and measured by a disposable sensor coupled to a peripheral arterial line. Being far less invasive, it can therefore be considered in obstetric high care settings. Lithium is contraindicated in the first trimester of pregnancy, being associated with an increased risk of Ebstein anomaly.[62] However, a recent European registry-based study suggests the prevalence of Ebstein anomaly to be associated with maternal mental health problems generally rather than lithium specifically.[63] The amounts of lithium used to calibrate LiDCOplus® are very low, certainly as compared to standard therapeutic doses in pregnant women with bipolar disorders, however, lithium freely crosses the placenta.[64] Two recent meta-analyses addressed the long term neurodevelopment outcomes in offspring with in utero exposure to lithium.[65, 66] While preclinical data in animals suggested a potential adverse effect, clinical data in humans, although limited to 97 children, seem reassuring.[67] The manufacturer does not advice against the use of LiDCOplus® in pregnant woman or during breast feeding, except in the first trimester.

The same three manufacturers also developed systems requiring only a peripheral arterial line without prior calibration (Table 1). The assumptions for the algorithms are based on patient characteristics and experience obtained with their calibrated alternatives. Some of them permit calibration by an external source such as ultrasound. The pressure recording analytical method (PRAM) also derives CO continuously from a peripheral arterial waveform without need for prior calibration using a different algorithm (Table 1).

LiDCOplus® has been validated in 18 postpartum severe preeclamptic women against PAC and showed good agreement with a low bias and percentage error within 30%.[68] It has also been used in the second and third trimester of pregnancy.[69, 70] It can serve as an alternative minimally invasive reference method in pregnant (after the first trimester of pregnancy) and postpartum women. It is mostly suited for short term real time continuous CO trend monitoring.

Most other systems (LidCOrapid®, FloTrac®, PiCCO®, ProAQT®, MostCare^{up}®) have been used, but not been validated in pregnant women.[71-76] Given the unique effects of pregnancy on arterial wall composition and function, it is questionable whether these techniques can be reliably used without prior calibration or validation, especially in rapidly changing hemodynamic conditions.

Although substantially less invasive compared to PAC, the abovementioned techniques require insertion of arterial lines and performing dilution procedures to calibrate the devices, which in turn requires specific medical skill, training and learning curves.

Recommendation: We recommend prior validation of these techniques in pregnancy before further use in clinical or research setting. LiDCOplus® can be used for short term real time continuous CO trend monitoring after the first trimester of pregnancy, taking the concerns on peripheral arterial cannulation and lithium use into account.

Transesophageal Doppler monitor (TDM)

With Transesophageal Doppler monitoring a 6mm Doppler probe is inserted either nasally or orally into the lower esophagus. It is then oriented and aligned to optimally measure blood flow using either continuous or pulsed wave Doppler in the thoracic aorta (Table 1). Continuous real-time CO can be calculated by an algorithm assuming a correctly estimated fixed aortic cross sectional area, fixed blood flow distribution in the aorta and provided good probe alignment and limited probe movements. While most commonly used with sedation, the device is also tolerated in awake individuals as the procedure and discomfort is similar to the insertion of a nasogastric tube, notwithstanding the increased risk of aspiration in pregnant women. To obtain the necessary waveforms, experience with an intra-esophageal probe is required.

TDM has been validated against PAC in 17 women with severe preeclampsia. While absolute values of cardiac output were consistently underestimated by 36%, in women above 40 years of age the accuracy increased.[77, 78]

Recommendation: TDM could potentially be of value for trend monitoring but needs further validation in pregnant women, especially in younger women.

Non-invasive methods

Cardiovascular magnetic resonance imaging

CO can be calculated with CMR using either cine-CMR or phase contrast imaging technique without need for ionizing radiation or contrast agents. Cine-CMR produces high resolution images discerning the myocardium from the blood pool allowing detailed 3D measurements of cardiac dimensions during systole and diastole. It permits accurate and reproducible calculation of the SV without the necessity to rely on geometric assumptions. The phase contrast imaging permits flow analysis in a similar way as Doppler ultrasound, by relating measured phase shifts produced by moving blood in a vessel to velocity. When measured at the aortic root along with its diameter, LV output can be calculated. CMR data are usually acquired over multiple cardiac cycles with the subject holding its breath. CMR provides highly accurate information on cardiac functioning but only during the examination and cannot be used for continuous monitoring. In non-pregnant individuals, CMR is considered the reference method for non-invasive assessment of CO.[79, 80] It is often the method of choice in complex structural heart disease. Operator dependency is less than for echocardiography, but CMR still requires specific expertise in obtaining high quality images and interpretation of the images. Thereby, a specific MRI device and set-up is needed. Subjects must lie still in a narrow tunnel during the image acquisition, which can be experienced as claustrophobic, especially in late pregnancy. The subject must be free of devices that might affect or react with the magnetic field, limiting the possibilities of simultaneous comparison of CO with other techniques. The availability and also costs make that it is not suitable for routine or bedside use.

CMR is considered safe in the second and third trimester of pregnancy. While caution is advised in the first trimester, clinical data of occasional use seem to indicate that it is equally safe.[81] CMR has been evaluated next to TTE in 34 pregnant women in which CMR was proven to have

a higher reproducibility and smaller intra- and inter-observer variability.[82] As with other methods it is essential not to forget to position pregnant women in a left lateral position as early as from 20 weeks gestation as CMR studies have clearly showed the effect of caval compression by the pregnant uterus on the CO.[33, 34] A retrospective study by Romagano et al. showed CMR findings can alter the clinical management in pregnant women with complex cardiac disease or suspected aortic pathology in addition to the findings by TTE.[83] CMR seems to be an accurate and precise method to assess maternal hemodynamics and is especially helpful in women with complex cardiac anatomy of suspected cardiac pathology.

Recommendation: CMR could be considered as a reference method for CO assessment in pregnancy. However costs, availability and specific set-up limit its use for CO measurements in clinical and research settings.

Transthoracic echocardiography

Echocardiography and Doppler ultrasound have been widely used for the detection of CO during pregnancy,[3-8, 11-15, 24-30, 32, 56, 84-86] demonstrating to be reliable against the invasive techniques.[3, 87, 88] The general availability of the technique, low cost, portability and true noninvasiveness, make TTE an ideal method for rapid hemodynamic assessment in pregnancy.

M-mode echocardiography

Measurement of CO with this method is based on the calculation of left ventricular diastolic and systolic volumes from M-mode measurements. Left ventricular end-diastolic and end-systolic diameters (D) are detected in the parasternal long axis view during M-mode tracing (Figure 2).[89] Left ventricular volumes (V) are calculated according to the Teichholz formula from end-diastolic and end-systolic diameters $V = 7D^3 / (2{,}4 + D)$.[90] SV is calculated as the difference between end-diastolic and end-systolic volumes. CO is calculated as the product of SV and HR derived from electrocardiographic

monitoring. Ejection fraction (EF) also can be calculated as the fractional reduction of the volumes (Supplementary video available on request).

The Teichholz formula may potentially underestimate left ventricular volumes, particularly in patients with an extremely elliptic shaped left ventricle, with minor to major hemiaxis ratio < 0,33.[91, 92] Because of the assumptions of the shape of the LV, which may change differentially across pregnancy in different mothers, this method has several limitations in the correct estimation of SV and CO.[93]

Doppler studies

The Doppler method estimates the area under the curve of the aortic flow velocity waveform while two dimensional echocardiography determines the area of the aortic valve. The diameter of the left ventricular outflow tract (LVOT) during systole is measured in the 2D parasternal long axis view; the aortic cross sectional area (CSA) is calculated from this diameter and is multiplied by the time-velocity integral of aortic flow (Figure 3). The SV is therefore obtained and CO can be calculated. This method has been validated against thermodilution in 3 studies including altogether 34 severally ill pregnant women.[3, 87, 88]

LVOT CSA is determined from the maximum systolic diameter measured at the level of the valve annulus and averaged over three to five cardiac cycles.[94] This can be done using M-mode or 2-D echocardiography although CO calculated by the latter method correlates most closely with invasive measurements.[4]

The time-velocity integral of aortic flow can be measured with continuous wave Doppler (CW) or pulsed wave Doppler (PW). CW method is not incorrect, but in this case the velocity profile reflects the highest velocity of the moving blood cells; the measurement with CW is related to the cross sectional area (CSA) of the aorta more than to the annulus of the aortic valve. This will influence the calculation of SV and CO, which will result in higher values than those detected with PW.[94] This is a general problem and a limitation when comparing SV, CO, and PVR from different studies performed with different methods (CW or PW). Most studies in pregnancy have measured flow across the aortic valve either recording velocities from the suprasternal

notch using CW Doppler[5, 8, 25, 95] or from the apical five-chamber view using PW Doppler,[3, 21, 87, 88] one study reports on both methods.[28] Also the coefficient of variation (6,7%) is lower as compared to Teichholz or Simpson method.[96]

An advantage of the Doppler method is clearly its assessment of 'hemodynamics', as it captures the blood velocity profile quite accurately. However, it is important to note that this method will not provide any information on the volumes of the heart in the filling state, nor following contraction.

2D and 3D echocardiography

LV volumes can be measured using 2D or 3D echocardiography. The detection of LV end-diastolic and end-systolic volumes allows for the calculation of SV and, therefore CO. Volume calculations derived from linear measurements for the calculation of SV, in fact, may be inaccurate, since they rely on the assumption of a fixed geometric LV shape. Therefore, the Teichholz and Quinones methods are no longer recommended for clinical use, as outlined in a previous paragraph.[95, 97]

The most commonly used method for 2D echocardiographic volume calculations is the biplane method of disks summation (modified Simpson's rule), which is the recommended 2D echocardiographic method in any patient population (Figure 4).[97] This method requires experienced echocardiographers in order to obtain reliable volume measurements and is much more operator-dependent than the Doppler technique. Besides, in pregnancy it can be more difficult to obtain an acceptable acoustic window due to body composition changes. Several studies have used 3D echocardiographic for the detection of left ventricular volumes in healthy subjects with a wide variability from study to study probably due to differences in populations, echocardiographic equipment, and analysis software, as well as variability in measurement techniques.[97]

Despite ultrasound experience in most obstetric and fetal maternal medicine specialists, TTE requires specific echocardiographic expertise which can be obtained by training from cardiologists or certified echocardiographers.

Recommendation: TTE has been mentioned as the new reference standard for measuring CO in pregnancy. However, it remains a specialized technique in which obstetricians and/or obstetric anesthesiologists are only rarely trained. We therefore recommend more obstetricians with interest in maternal critical care should be trained in the technique to enhance the availability of TTE for hemodynamic monitoring in clinical care.

Alternative Doppler technique

Lately a new method has been introduced in pregnancy for the detection of SV and CO, the UltraSonic Cardiac Output Monitor (USCOM 1A®).[9, 10, 98-108] This is a non-invasive Doppler method to determine hemodynamic values by placing a non-imaging continuous-wave Doppler transducer on the suprasternal notch to determine ascending transaortic blood flow (Figure 5). After manually adding a woman's BP, body mass and height into the system, USCOM 1A® is able to calculate the following cardiovascular parameters: CO, HR, PVR, inotropy index (INO) and time flow correct (TFC). This method is based on an algorithm, which takes into account the patient's height, to provide the outflow tract diameter. A limitation of this assumption is that it does not take into consideration a possible modification of aortic diameter and compliance during pregnancy. On the other hand it is easy to use and much less operator-dependent compared to echocardiography. A individual training session before using USCOM 1A® is advised, including up to 50 test cases prior to the use for research of clinical purposes.[106]

To date, the validation of this method during pregnancy was performed against 2-D and 3-D TTE in respectively 98 and 92 women and showed good reproducibility, but variable accuracy and precision depending on which trimester and which USCOM waveform tracing technique was used.[102, 106]

Recommendation: Despite the necessity for further validation, USCOM 1A® with its user friendly profile is promising and can provide important information about the maternal hemodynamic condition in clinical settings and at the outpatient clinic.

Inert gas rebreathing technique

Using the technique, an O_2 enriched mixture containing of two inert gases, one blood soluble (N_2O) and one insoluble (SF_6), are administered through a closed breathing assembly. Relative levels over a few respirations are measured by a gas analyzer in the mouthpiece, from which the Innocor® monitor calculates CO relying on Fick's principle (Figure 6). The method is based on the assumption that the rate of disappearance of the blood soluble gas from the alveolar space is proportional to the pulmonary blood flow being CO. The insoluble gas helps to ascertain the long volume from which the soluble gas disappears. The technique can be used in rest and during exercise and is operator independent.[109, 110] It is good to mention the inert gas rebreathing technique only represents the ventilated part of the lungs, so in subjects with increased alveolar dead space assumptions on CO may not hold. Also, in subjects with pulmonary edema such as in severe preeclampsia, there is no steady respiratory state and the assumptions may not apply. The technique has been validated in adults with heart failure against PAC using thermodilution and direct Fick method.[109] While used in several studies in pregnant women, the method has not been validated in pregnancy.[17, 110-112]

Recommendation: Further evaluation of the inert gas rebreathing technique during pregnancy, including the feasibility of the method for instance during labor, is needed prior to implementation in clinical care.

Impedance cardiography and bioreactance

The technique uses electrodes to transmit a very low amplitude high frequency current through the thorax and detect impedance changes (bioimpedance) or phase shifts (bioreactance) induced by changes in blood flow throughout the cardiac cycle. Interferences from other sources (e.g. respiration, movement, other devices) are filtered out. From these changes SV and CO can be derived. Some techniques also rely on impedance changes measured more peripherally. Several devices exist, each relying on specific algorithms with distinctive features and filters to remove

distortions intended at improving accuracy and signal stability. As such, by using 4-6 cutaneous electrodes on the thorax, CO can be measured in a continuous, easy, relatively cheap and operator independent way with high repeatability (E.g. Figure 7).[113] Some devices reflect the actual instantaneous CO and can be used to assess rapid changes, others reflect mean CO over the last minute.

Given its accessibility and ease of use which makes it operator independent, impedance cardiography (ICG) became very attractive for CO measurements in both pregnant and non-pregnant populations.[96, 114-117] Nevertheless, most validation studies in both non-pregnant and pregnant women, using any of the available devices, have not been able to show sufficient accuracy and precision as compared to reference methods like PAC or TTE in reflecting absolute CO values.[10, 96, 105, 106, 117-121] As such, all these devices (Table 1) are at the moment probably not suited in reflecting "true CO" values. Nevertheless these techniques might be very convenient to monitor trends and relative changes over a shorter period of time as e.g. during labor, caesarean section or for monitoring therapy in acute conditions.

Recommendation: Before further use in pregnancy for trend monitoring we would recommend validation of bioimpedance and bioreactance devices for this purpose against established reference methods, which is under way for several devices.

Non-invasive pulse contour analysis

Similar to the minimally invasive counterparts, these devices rely on the on the relation between arterial pressure and SV and derive CO from the peripheral arterial waveform. The arterial wave form is obtained by several sometimes innovative methods varying from oscillometric BP cuffs to high tech volume clampfinger clips at various sites (brachial artery, finger, ankle). Multiple non-invasive pulse contour analysis devices have been developed over the last years (Table 1), all easy to use and operator independent (E.g. Figure 8). Nevertheless, validation studies both outside and during pregnancy often show inappropriate accuracy for absolute measurements.

Recommendation: While potentially interesting for short term trend monitoring, the same concerns and limitations apply as for their minimally invasive analogues and prior validation during pregnancy for this purpose remains essential before implementation in clinical or research setting.[122, 123]

Comparing methods of CO measurement

When comparing techniques for CO determination both accuracy (potential of the technique in reflecting the "true CO"), as well as other factors like ease of use, degree of invasiveness, costs and operator dependency are to be taken into account. Ideally, the accuracy and precision (how often the same value is obtained if measurements are repeated) of a method are compared to a reference method. Usually an investigated technique is considered appropriate if accuracy and precision are at least equivalent to the reference method. However, one could still consider the acceptance of a technique with inferior accuracy and precision if the additional benefits outweigh this inferiority for its specific intended use.

It is important to realise that CO, being the product of HR and SV, is highly variable in time. Therefore comparative measurements are best performed simultaneously at the exact same time. Also, all reference methods have inherent errors which can be calculated by assessing the coefficient of variation (calculated as the standard deviation / mean). As the traditional reference method, PAC with thermodilution, is not justifiable for comparative studies in pregnant woman anymore, LidCOplus®, CMR and TTE (using Doppler method) are probably the best alternatives, all with their inherent limitations.

Several statistical approaches to validate new methods of CO measurement have been used in the past. Bland and Altman introduced a method in 1986 where bias (mean difference) and limits of agreements (1.96 * SD around the bias, wherein 95% of all points fall) are depicted in a simple plot.[124]

For absolute CO measurements, Critchley and Critchley[125] suggested that in all comparisons between techniques, mean CO, bias, limits of agreement and percentage error (limits of agreement divided/mean CO; PE) should be reported. The accuracy and precision of an investigated technique is traditionally considered sufficient if bias is low and PE is within +-30 %. However, this is based on the precision of PAC thermodilution technique and ideally the

calculated precision of the used reference method in the study should be taken into account instead of the generally accepted precision of thermodilution.[125]

To compare ability of CO monitoring devices, differences in CO are best plotted in a four quadrant or polar plot. Concordance rate, angular bias and radial limits of agreement can be calculated and added along with an exclusion zone for small differences in both graphs. The four quadrant plot is a visually more intuitive method to show trending ability, the polar plot is statistically a little more advanced but more difficult to interpret.[126, 127]

For more in-depth information on the statistical approach of comparing methods, we recommend several recent reviews by Odor et al., Hapfelmeier et al., Cecconi et al., Saugel et al. and Critchley et al..[60, 61, 126-128]

Interpreting Cardiac Output measurements in pregnancy: when and how to index or normalize?

The scientific basis and accuracy of CO measurement aside, the issue of how to interpret CO in pregnancy remains a contentious topic.

Normal CO at rest ranges between 4-8 L/min in healthy non-pregnant women, but can rise up to more than 15-20 L/min during exercise.[129-134] It shows that CO is a highly variable parameter which can easily be raised or lowered by modifying SV and/or HR. This flexibility permits the cardiovascular system to both meet varying tissue oxygen requirements and maintain cardiovascular homeostasis in a wide range of conditions, but requires a complex interplay with other cardiovascular parameters like vascular resistance, compliance, redistribution properties etc..

This variability is also influenced by body size, basal metabolic rate, degree of fitness, advancing age and gestational age. These factors have a significant impact on maternal tissue metabolic oxygen demands with advancing gestation in pregnancy, and by definition, impact on the interpretation of measured CO data in pregnancy. For example, a CO of 6 L/min is considered physiologically normal in a 35yr old woman weighing 60kg at 24 weeks' gestation, but may be considered hypodynamic in a 25yr old who reaches a weight of 90kg at 41 weeks' gestation.

Determining normality within this variability can thus become challenging. Researchers and clinicians have divided approaches to overcome this issue. Some prefer to use the raw, absolute data despite its variability, considering that this actual value is the most accurate. Others opt to index the absolute values in an attempt to correct for the abovementioned factors, still acknowledging that none of the indexing tools can fully compensate for the whole complexity of the variation and the inherent limitations of the indexing tool itself which could introduce an additional error in the value.

Indexing can be done for actual maternal BSA (body surface area), pre-pregnancy BSA or using pregnancy CO ranges:

Indexing by maternal BSA at each visit

The relationship between body mass and metabolic rate is negatively allometric, resulting in metabolic rate (and by definition oxygen demand) being more closely related to BSA than BMI.[135] Neither BSA nor BMI changes accurately reflect changes in pregnancy due to the uterus, amniotic fluid and fetus and maternal body composition of fat and muscle so any use of BSA or BMI must take into account the inherent assumptions involved in this calculation. Even correction of CO for BSA has a known limitation – inaccuracy at extremes of body weight and height, where this indexing is likely to be unreliable whether pregnant or not. A limitation specific to pregnancy is the assumption that metabolic activity in pregnancy is the same as the non-pregnant state. Available data indicates that the basal metabolic rate in pregnancy is some 1.5-times higher than the non-pregnant state, suggesting that indexing for BSA is systematically under-correcting for the potential increase in pregnancy metabolic and oxygen demands.[136]

Indexing by pre-pregnancy BSA

This allows all measurements to start from the same 'point' but does not take into account for change in weight and significant increase in metabolic demands with advancing pregnancy.

Normalizing using pregnancy CO reference ranges

Gestational age and preferable device specific reference ranges for hemodynamic parameters in normal pregnancy constructed from women of differing ages and weights would permit the interpretation of measured CO as a fraction of expected CO.[137] Individual values can then be converted to gestation specific z-scores, multiples of the median (MoMs) or percentiles to allow comparison. Although this represents the most accurate way to index CO measurements in pregnancy, the availability of such constructed reference ranges is currently limited.

Despite all controversy, it is probably much more important to consider when and how to index rather than whether or not to index. There are certainly situations in which indexing can offer a

different perspective and, thus, be of additional value in interpreting the raw absolute data. It very much depends on the indication why cardiac output was determined.

When comparing single measurements between individuals or assessing one's cardiovascular status based on a single measurement (e.g. to predict her risk of preeclampsia or degree of shock), indexing can offer a distinctive perspective that helps interpreting the absolute data.

When comparing evolution in CO over a longer (e.g. CV adaptation in the course of pregnancy) or shorter (e.g. effects of treatment, CO during course of labor or acute illnesses) period of time, the differences between trajectories or absolute values are of importance and the individual becomes their own control. The additional value for indexing is then far less prominent.

Overall recommendations for clinical use

- At present, there is no ideal method for CO measurement in pregnancy. All methods have particular strengths and limitations. Which method is best selected, strongly depends on the indication why CO needs to be assessed.
- PAC should only be used on strict clinical indication in critically ill pregnant women, which is extremely rare.
- CMR provides accurate CO values in pregnancy and could be considered as a reference technique for comparison, if available and simultaneous measurements are possible.
- TTE using Doppler technique is more readily available and can be considered as an alternative reference technique for CO determination in pregnancy.
- Taking the necessity for an arterial line and concerns of lithium use in pregnancy into account, pulse pressure analysis using lithium calibration with the LiDCOplus® system can be used for accurate CO determination and trend analysis.
- Other techniques like non-imaging continuous-wave Doppler, impedance cardiography, inert gas rebreathing techniques and non-calibrated pulse contour analysis can be promising, but need prior validation in pregnancy for absolute values and/or trend monitoring.
- Different techniques measure in different ways relying on different assumptions and should not be used interchangeably.
- When individual measurements of CO over longer periods in time (e.g. each trimester) are indicated, CMR, TTE (Doppler) or inert gas rebreathing technique is the preferred method.
- When continuous monitoring of CO over a shorter period of time is indicated (e.g. during labor, or to monitor short-term treatment), pulse pressure/contour analysis or impedance cardiography is most applicable.
- When rapid and instantaneous evaluation of CO is indicated, TTE or USCOM 1A® could be the method of first choice.

- When CO is assessed in a supine pregnant woman, she should be turned to a left lateral position of at least 15 ° as from 20 weeks of gestation.
- Inherent limitations in the precision of most reference techniques mean that only changes of at least 20% can be reliably be considered as valid.
- BP should be taken in the seated or semi-recumbent position with the arm at the level of the heart and the feet supported or on the ground.
- When BP is taken for the calculation of PVR, it should be taken at the end of the examination in the same position as during the method used to determine CO.
- Depending on the indication for CO determination, indexing can be of additional value in interpreting absolute CO values.
- In case of indexing of the hemodynamic parameters, this is ideally performed from - where available - device specific, established reference ranges from normal pregnancies that take into account maternal age, height, weight and gestational age.
- Comparison of techniques should be performed using mean values bias, limits of agreement and percentage error for absolute values and four quadrant plot or polar plot for trend monitoring.

Recommendations for future research

- Non-invasive methods for measurement of CO should be validated in both healthy and complicated pregnancies.
- Hemodynamic adaptations should be studied in pregnancy complications such as preeclampsia.
- The effects of therapies on hemodynamic values in hypertensive and critically ill pregnant women should be investigated.
- The hemodynamic responses to and the value of functional hemodynamic testing during pregnancy should be studied.

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Figure legends:

Figure 1. Overview on PiCCO® technology. After thermodilution calibration by bolus injection through a central venous catheter (CVC), the PiCCO® catheter located in a peripheral artery continuously sends the arterial waveform to the output monitor and several hemodynamic parameters, including cardiac output, are calculated.

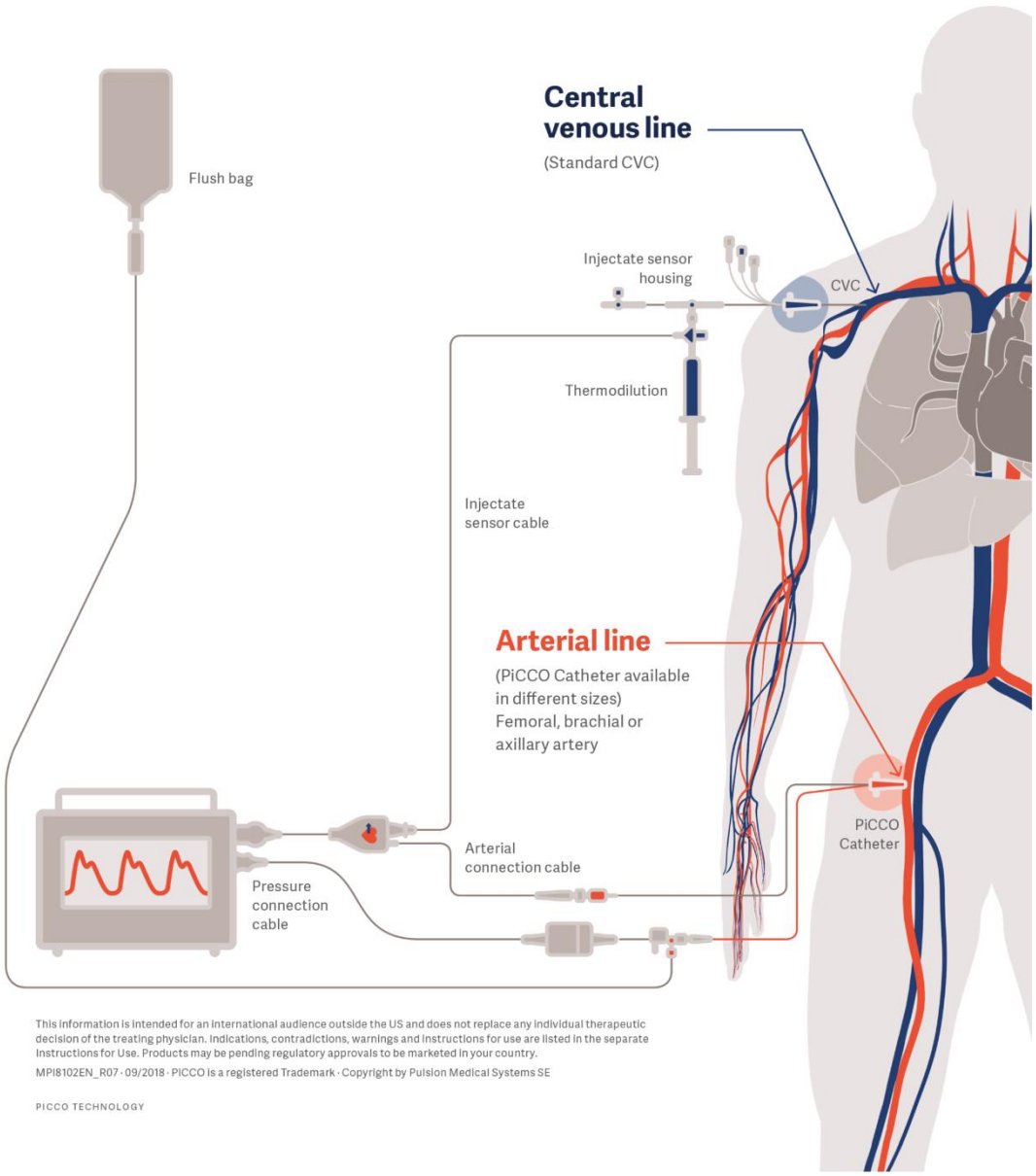

Figure 2. Transthoracic echocardiography using M-mode tracing to measure end diastolic diameter (EDD) and end systolic diameter (ESD) of the left ventricle in the parasternal long axis view. Left ventricular volumes are calculated according to the Teichholz formula from EDD and ESD and stroke volume (SV) is calculated as the difference between end-diastolic and end-systolic volumes. Cardiac output is calculated as the product of SV and heart rate derived from electrocardiographic monitoring.

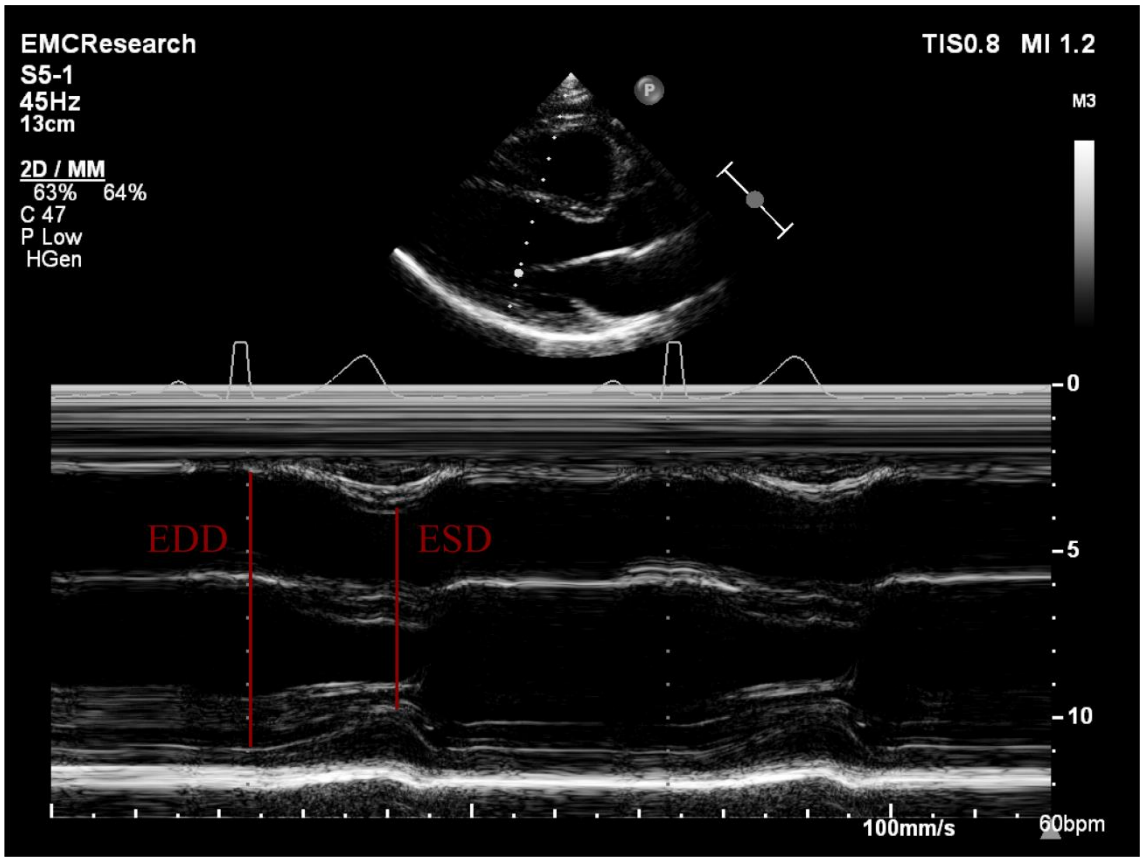

Figure 3. Transthoracic echocardiography using the Doppler method for calculation of left ventricular cardiac output. In the parasternal long axis view, the diameter of the left ventricle outflow tract (LVOT) during systole is measured, which then is used to determine LVOT cross sectional area (CSA). By pulsed wave Doppler the LVOT velocity time integral (VTI) is measured. Multiplying the LVOT CSA by LVOT VTI provides the stroke volume (SV) of the left ventricle and by multiplying SV times heart rate (HR) provides the left ventricular cardiac output (CO).

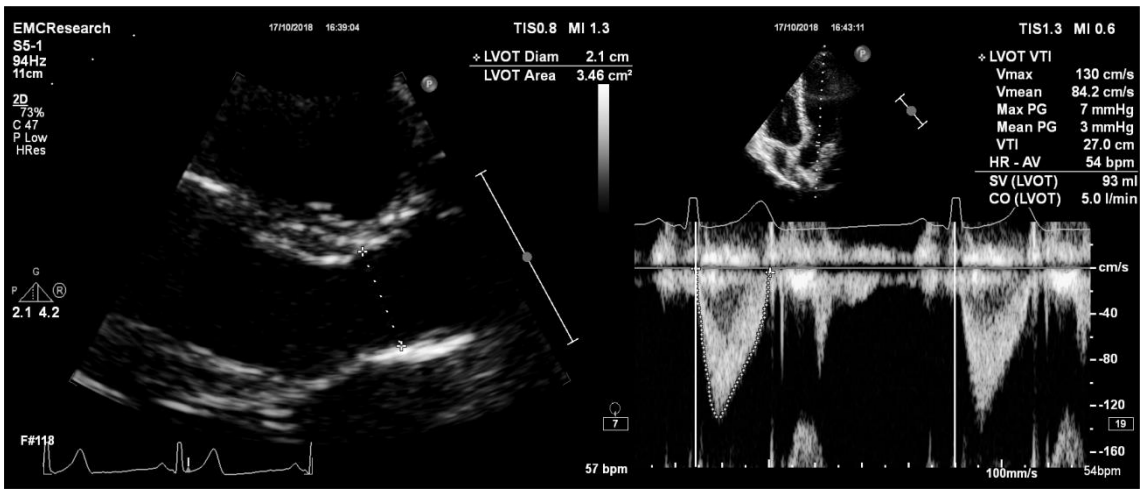

Figure 4. Transthoracic echocardiography from the apical four chamber view. By using the biplane method of disks summation (modified Simpson's rule) left ventricular end-diastolic and end-systolic volumes are calculated, which allows for the calculation of stroke volume and therefore cardiac output.

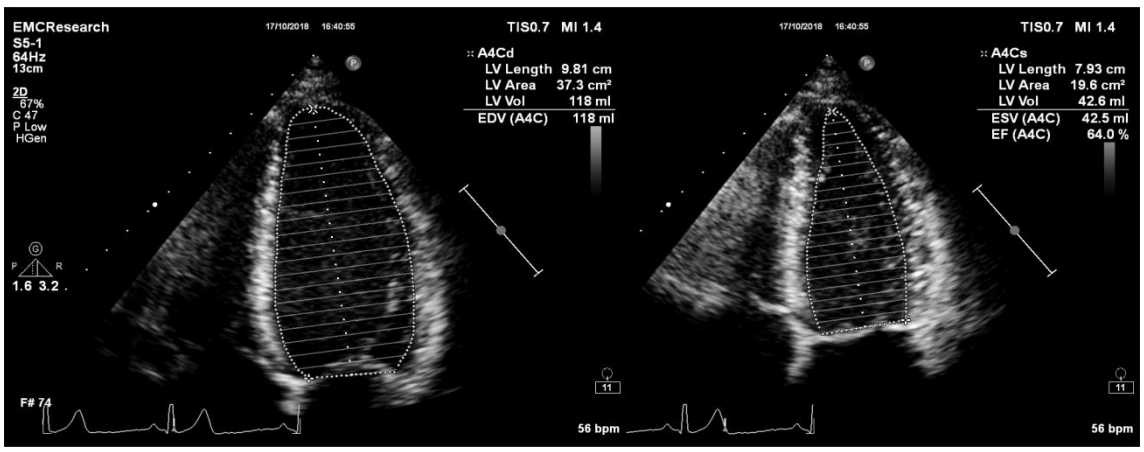

Figure 5. With the USCOM 1A® device a non-imaging continuous wave Doppler transducer is placed on the suprasternal notch to determine ascending transaortic blood flow. After manually adding the blood pressure, body mass and height of the subject, USCOM 1A® is able to calculate various cardiovascular parameters, including cardiac output. The method is based on an algorithm to provide the left ventricular outflow tract diameter of the subject.

Figure 6. Inert gas rebreathing technique: an O2 enriched mixture containing two inert gases (blood soluble N2O and insoluble SF6) is administered through a closed breathing assembly. Relative levels over a few respirations are measured by a gas analyzer in the mouthpiece, from which the Innocor® device as shown on the right side of the image, calculates cardiac output relying on Fick's principle.

Figure 7. Impedance cardiography uses 4-6 cutaneous electrodes on the thorax to transmit a very low amplitude high frequency current and to measure impedance changes by changes of blood flow throughout the cardiac cycle. From these changes stroke volume can be derived. On the left side an example of impedance signals and abnormalities is shown, on the right side the PhysioFlow® device is shown in use during exercise testing. ECG=electrocardiogram. d(HD-Z)/dt=derivative impedance signal divided by derivative over time.

Figure 8. With peripheral pulse contour analysis the arterial waveform is obtained either by oscillometric blood pressure cuffs or, as shown here by the ClearSight® device, by photo-plethysmographic volume recordings. Since the device is limited to 8 hours of continuous monitoring on one finger, two cuffs on two fingers are used to guarantee uninterrupted monitoring.

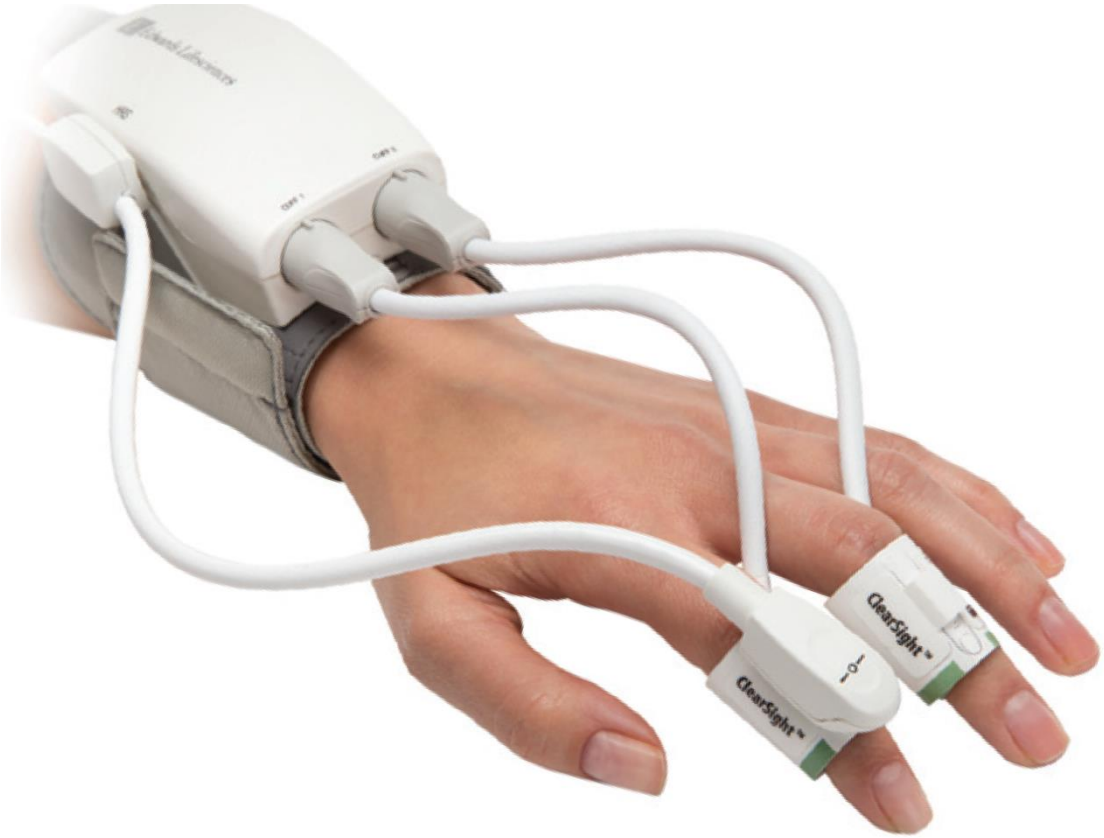

Table 1: Overview on methods for cardiac output monitoring.

Invasiveness	**Technique**	**Device (Manufacturer)** *if applicable*
Invasive		
	Pulmonary artery catheterization with intermittent thermodilution	
	Pulmonary artery catheterization with thermodilution and continuous CO measurements	Swan Ganz continuous cardiac output catheters (Edwards Lifesciences Corporation) TDQ™ and OptiQ® continuous cardiac output catheter (ICU Medical Inc.)
Less or minimally invasive		
	Peripheral pulse contour analysis with transpulmonary thermodilution calibration	Volume View/EV1000® (Edwards Lifesciences Corporation) PiCCO® (PULSION medical systems SE)
	Peripheral pulse power analysis with lithium calibration	LiDCOplus® (LiDCO)
	Peripheral pulse contour analysis without calibration	ProAQT® (PULSION medical systems SE) FloTrac/Vigileo® (Edwards Lifesciences Corporation) CardioFlo™ (ICU Medical Inc.)
	Peripheral pulse power analysis without calibration	LiDCOrapid® (LiDCO)
	Peripheral pressure recording analytical method without calibration	MostCare^{up}® (Vytech)
	Transesophageal continuous-wave Doppler monitor	CardioQ-ODM® (Deltex Medical Ltd.)
	Transesophageal M-mode and pulsed-wave Doppler monitor	HemoSonic 100® (Arrow International)
Non-invasive		
	Cardiovascular magnetic resonance imaging	
	Transthoracic echocardiography	
	Non-imaging continuous-wave Doppler	USCOM 1A® (Uscom Limited)
	Inert gas rebreathing	Innocor® (Innovision)

	Bioimpedance	PhysioFlow® (Manatec Biomedical) BioZ® (CardioDynamics) Niccomo/Cardioscreen 2000/Cardioscreen 1000 (Medis) AcqKnowledge® (BIOPAC systems Inc.) NCCOM® (Bomed Medical) ICG (Philips Medical Systems) NICOMON (Laresen and Toubro Ltd.) CSM3000 (Cheers Sails Medical)
	Whole body bioimpedance	NICaS® (NI*medical*)
	Bioreactance	Cheetah NICOM® (Cheetah Medical Inc.) AESCULON™ (Osypka Cardiotronic)
	Non-invasive pulse contour analysis	Vicorder® (SMT medical GmbH&Co. KG) Mobil-O-Graph® (I.E.M. GmbH) SphygmoCor® (AtCor Medical Holdings Limited) ClearSight® (Edwards Lifesciences Corporation) CNAP® (CNSystems Medizintechnik GmbH) Finometer PRO® (Finapres Medical Systems B.V.) Portapres® (Finapres Medical Systems B.V.)
	Non-invasive pulse power analysis with continuous non-invasive blood pressure	LiDCOrapid® with CNAP™ (LiDCO)