Noninvasive Doppler Determination of Cardiac Output in Man
Clinical Validation

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SUMMARY A noninvasive technique for assessing cardiac output (CO) was evaluated by comparing it with thermodilution determinations in patients in the intensive care unit. The new method uses pulsed ultrasound to measure aortic diameter and continuous-wave Doppler ultrasound to obtain aortic blood velocity. An initial study evaluating just the velocity measurement showed that changes of the Doppler index of output (DI) correlated well with those of thermodilution cardiac output (TDCO). Linear regression analysis yielded ΔDI = 0.87 ΔTDCO + 0.14 (r = 0.83, n = 95). Using a university research instrument these measurements were possible in 54 of 60 patients (90%). A second study using a prototype commercial device incorporated the diameter measurement. Ultrasonic cardiac output (UCO), calculated as the time integral of velocity multiplied by the aortic area, was compared to TDCO. The data, obtained from 45 of 53 patients (85%), are described by the linear regression UCO = 0.95TDCO + 0.38 (r = 0.94, n = 110) over a range of 2–11 l/min. Patients with aortic stenosis, aortic insufficiency or a prosthetic valve have been excluded from the second study due to conditions likely to violate the assumptions upon which the calculation of absolute cardiac output is based. These results indicate that accurate CO can be measured by noninvasive ultrasound in most patients. The technique may be useful for extended CO monitoring in acute care patients and for CO assessment in many other types of patients undergoing diagnostic studies and therapeutic interventions.

THE CLINICAL IMPORTANCE of cardiac output (CO) is well recognized in the clinical management of patients with acute myocardial infarction. Forrester and colleagues demonstrated that the clinical status of patients with acute myocardial infarction is related to their CO and that after myocardial infarction, prognosis worsens as CO declines. Almost half of the patients with acute myocardial infarction have a subnormal CO at the time of presentation, and 25% of infarctions are not recognizable by standard clinical criteria. Current criteria for the clinical evaluation of circulation in myocardial infarction are often time-consuming, subjective and prone to error. Clinicians are urged to rely on monitoring of heart rate and rhythm, measurement of systemic and arterial pressure by cuff, obtaining chest roentgenograms to detect heart failure, careful and repeated auscultation of lung fields for pulmonary congestion and edema, measurement of urine flow, examination of the skin and mucous membranes for evidence of the adequacy of perfusion, and arterial sampling of PO2, PCO2, and pH when hypoxemia or metabolic acidosis is suspected. Physicians are often reluctant to use invasive CO determinations, except in selected patients, because they cause discomfort and may result in complications. Given the importance of CO assessment, a noninvasive, easily
repeated CO measurement technique that could be widely and quickly applied in the intensive care unit, the outpatient setting, and clinical research laboratories would be useful.

We report the results of two studies designed to test a technique that is based on the measurement of ascending aortic blood velocity and cross-sectional area (CSA). Several investigators have suggested that blood velocity may be measured in the aorta using ultrasound. Initial attempts focused on directing an ultrasonic beam from the suprasternal notch toward the aortic arch. Later it was found that high-quality velocity signals could be obtained from the ascending aorta and with the transducer placed in the suprasternal notch. The present report describes a totally noninvasive CO technique, the results of which are compared with thermodilution CO (TDCO).

Methods

The noninvasive determination of CO is computed from the product of Doppler-derived stroke volume (SV) and heart rate (HR). SV is estimated using ultrasound to measure the volume of blood moving through the ascending aorta during systole. SV is calculated as

\[ SV = \int v(t) \, \text{csa}(t) \, dt, \]

where \( v = \) the spatial average blood velocity in the aorta during systole, \( ET = \) ejection time and \( \text{CSA} = \) the cross-sectional area of the lumen. The ascending aortic blood velocity and ejection time are determined by Doppler transcutaneously from the suprasternal notch and the CSA is calculated from the aortic diameter measured by pulse echo from the parasternal border.

Validity of Doppler CO may be established by proving each of the underlying assumptions or by empirically testing the Doppler estimate of CO against a clinical standard. Although in this report the latter approach is taken, a discussion of the assumptions involved in the measurement concept is presented to clarify the conditions for which the assumptions may not be appropriate.

Basic Considerations

Inherent in this approach are the assumptions that the size of the aorta indicates the size of the flow channel and that total forward flow during systole equals net SV. The former cannot be expected to hold in the presence of significant aortic valve stenosis and the latter will not be true when there is regurgitant flow across the valve. Although the technique may be useful even when there is aortic valve disease, quantitation of CO will probably not be possible. For the purposes of this study, patients with documented stenosis, insufficiency or a prosthetic aortic valve, which may alter the flow channel, have been excluded.

In addition, it has proved helpful to make additional assumptions that simplify the measurements. A rigorous, assumption-free treatment of the SV relationship given above would allow for dynamic changes in velocity \((v(t))\) and CSA \((\text{csa}(t))\). This would require continuous computation of the product of velocity and area or, in other words, an integration.

\[ SV = \int v(t) \, \text{csa}(t) \, dt, \]

over systole. If the changes in \( \text{csa}(t) \) during systole are small, we can treat it as a constant and replace \( \text{csa}(t) \) with the average CSA and restate the equation as

\[ SV = \text{CSA} \int v(t) \, dt, \]

where \( \int v(t) \, dt = \) the systolic velocity integral.

CO is a function of pressure and studies in man indicate that it may change \( \pm 3\% \) to \( \pm 12\% \) over the cardiac cycle. The maximum error in CO due to an assumption of a nonchanging CSA, measured at random during the cardiac cycle, would be \( 3\% - 12\% \), the worst case resulting from a diameter measurement made at end-diastole. The range of published CSA (t) changes is likely due predominantly to factors such as age and mean arterial pressure. We used a constant CSA assumption in this study. Furthermore, we extended this assumption by using a single CSA value for each patient, regardless of the changes in patient condition occurring over the period of observation.

The CSA of the aorta is assumed to be of circular geometry and is computed from the aortic diameter (D) as

\[ \text{CSA} = \frac{\pi D^2}{4}, \]

Diameter is taken to be that indicated by A-mode pulse echo. If the ultrasonic beam interrogating the aorta either does not pass through the center of the lumen, or if it passes through the center but at a non-normal angle, errors in the diameter estimate could occur; but an angle of inclination, or angle due to off-center measurement, of as little as \( 15^\circ \) \((\pm 7\% \) in CSA) could cause a decrease in reflection by a factor greater than 100. It is therefore unlikely that significant errors of this type occur.

Aortic blood velocity is measured by means of the Doppler effect, using the relationship

\[ f_\Delta = \frac{2v f_v \cos \theta}{c}, \]

where \( f_\Delta = \) Doppler shift frequency, \( f_v = \) transmitted frequency, \( v = \) velocity of erythrocytes, \( c = \) velocity of sound in blood and \( \theta = \) angle between the ultrasound beam and the blood flow vector. The transmitted frequency is \( 2.5 \text{ MHz} \pm 0.001\% \), and the velocity of sound in blood is assumed to be \( 1570 \text{ cm/sec} \). The angle between the ultrasound beam and the blood flow vector is shallow (fig. 1), and is assumed to be 0°, so that \( \cos \theta = 1 \). Two aspects of the cosine function should be noted: The value changes slowly for small angles (e.g., \( \cos 20^\circ = 0.94 \)), and a non-zero angle will always cause the velocity to be underestimated.
Velocity in equation 1 must be the instantaneous velocity averaged over the whole cross section of the aorta. Based on the fluid dynamics of pulsatile flow near the entrance to a pipe,\textsuperscript{18} we assume the velocity to be constant at all points in a cross section of the lumen. Experimental data from dogs indicate a very thin boundary layer in the ascending aorta with a velocity profile that is flat or moderately skewed.\textsuperscript{19-22} Data from the ascending aorta of the horse, however, indicate a strikingly flat profile.\textsuperscript{23} There are only a few examples of data from man,\textsuperscript{19} but the flow conditions and anatomy in the ascending aorta in man suggest that a flat profile is a reasonable assumption. Deviations from a flat velocity profile will cause an overestimate of flow because the instrumentation measures the highest velocity.

We further assume that the Doppler transducer can be aimed such that the highest detected blood velocity toward the transducer in the suprasternal notch is in the ascending aorta. That is, one can access aortic flow such that the ultrasound beam does not intersect a higher velocity flow than the aorta and that the product $v \cos \theta$ will be higher for the signal from the aorta than for the other blood and tissues moving in the sound beam. The two most likely confounding signals are from the pulmonary artery (PA) and from the innominate artery (IA). The angle between the ultrasound beam and the PA is not as shallow as that for the aorta, so the detected velocities in the PA will be lower than those in the aorta.\textsuperscript{11} Blood velocity in the IA can exceed the blood velocity in the aorta, but aortic velocity can be differentiated from inominate velocity in that the characteristic of inominate velocity is such that the duration of systolic flow is longer and the acceleration of flow is not as rapid in the IA. We have not found inominate flow to be accessible with our continuous-wave Doppler (CWD) in very many people, presumably because the CWD transducer was designed to be insensitive to velocities near to the transducer (fig. 1).

Precise measurement of SV according to equation 2 would require measurement of the CSA and velocity at the same site. To insure this condition would require that the transducers were mechanically instrumented for position. Instead, we have made the assumption that the aortic velocity will be highest at the level of the narrowest aortic diameter; hence, we aim the Doppler transducer for the highest aortic systolic velocity integral and the pulse-echo transducer for the narrowest aortic diameter.

**Instrumentation Approach**

Two methods are available for making Doppler velocity measurements: CWD or pulsed Doppler (PD). CWD receives signals from any moving target in the entire length of the ultrasound beam, whereas PD allows localization of signals with respect to distance along the beam. The maximum velocity that PD can discriminate is reduced for deeper measurements.\textsuperscript{24} Typical peak aortic velocities are 60–120 cm/sec, but may be much higher, even in normal persons.\textsuperscript{20, 25-27} We used CWD for aortic velocity determinations. With CWD, only two-dimensional aiming is required because there is no need for the operator to set range, and the ability to detect high velocities at deep ranges is preserved. A consequence of this choice is that the instrumentation must identify the aortic velocity (i.e., the highest Doppler frequency) from among the other velocities detected along the beam.

In the first study, an instrument developed in our laboratory was used for the comparison of the integral of Doppler velocity over systole (systolic velocity integral) to stroke volume. The transducer consists of a handle incorporating two semicircular piezoelectric crystals mounted side by side, one for transmitting the ultrasound and one for receiving the echoes. The mobile portion of the instrument yields tape recordings of the Doppler signals. A phase-locked, loop-based peak frequency follower is used as on-line feedback to the operator to aid in aiming the transducer.\textsuperscript{28} The recordings are processed off-line using spectral frequency analysis (Reticon 5603), and the results are used to determine the highest frequency present during each analysis interval (6.7 msec). The highest frequency was defined as the highest frequency with an amplitude 12 db below the maximum amplitude of the Doppler spectrum. Electronic determination of systolic velocity integral is initiated by an R-wave trigger from the ECG and terminated by a timed interval set by the operator to include all of systole, as judged by the velocity and systolic velocity integral traces. The spectral information is presented in gray-scale hard copy along with the highest frequency trace, ECG and systolic velocity integral. A sample off-line record is presented in figure 2. Each record analyzed was six to 10 beats long so as to include beats from throughout the respiratory cycle.

The second study used the prototype of a new, commercially available instrument (UltraCOM, Lawrence Medical Systems, Inc.) designed expressly to measure CO. Although using a completely different electronic implementation, this device is based on the same assumptions as described above. In addition to measur-
ing velocity and calculating systolic velocity integral, provision is made for assessing aortic diameter using A-mode pulse echo techniques with a freeze-frame display. On-line output of HR, SV, stroke index, CO, cardiac index, and identifying patient data is provided on the CRT and in hard copy on command by the operator. In addition to the Doppler audio, the beat-by-beat systolic velocity integral is displayed on the CRT continuously to assist the operator in aiming the transducer. All variables are averaged over 12 consecutive beats.

Measurement Technique

Velocity

Doppler measurements have been made in the same manner with both instruments. The transducer is placed in the suprasternal notch, with adequate coupling fluid, and positioned so as to aim the beam toward the expected location of the aortic root. A slow search of the region is made while listening to the audio output of the Doppler shift frequencies. The optimal aim is taken to be that which yields the highest systolic velocity integral concomitant with a perception of rapid onset and cessation of flow, and minimal diastolic flow. This is judged by the audio sound, which has characteristic higher frequencies for the aorta, and by the on-line readout of velocity or systolic velocity integral. The time necessary to obtain the first velocity measurement is about 5 minutes; subsequent determinations can be accomplished much more quickly—generally in less than 1 minute.

Cross-sectional Area

CSA is calculated automatically using an assumption of cylindrical shape and constant dimensions throughout the cardiac cycle. Aortic diameter measurements use a separate pulse echo transducer positioned near the sternum in the third or fourth intercostal space. Using the A-mode display, aim is established by scanning through the ventricles to the posterior left ventricular (LV) wall, mitral valve and then to the aortic valve. A careful scan is made of the aortic root. The image selected for measurement is that which shows the narrowest aortic diameter in the region immediately above the sinuses. This view is frozen on the display screen and cursors are positioned over the interior edges of the wall echoes (fig. 3). On command, the machine enters the indicated diameter and calculates the area. The diameter measurement is normally repeated two or three times, with consistency expected within 1 mm, to assure an adequate determination. Typically, this process may take 10 minutes. Repeated CO measurements do not require new diameter estimates, only velocity determinations.

Figure 2. Sample output from off-line processing with the university research instrument. In gray-scale spectral output, the highest velocities are indicated by the position of the black segments overlaid on the spectral display. SVI = systolic velocity integral.

Figure 3. Representative pulsed echocardiographic A-mode tracing showing the near and far walls of the aorta. Cursor placement, shown here by the vertical lines, indicates the luminal diameter. Since the axial resolution of the instrument (2 mm) is less than half the width of the anterior aortic wall complex, the most accurate estimate of the luminal dimension is a trailing edge to leading edge measurement. This will cause a systematic underestimation of aortic diameter equal to the axial resolution of the instrument. This probably compensates for a boundary layer thickness of approximately the same dimension.
Potential Experimental Errors

**Ultrasonic Cardiac Output**

Although in each of the studies presented here the instruments were operated by only a few persons, our experience in teaching the technique indicates the most common operator-induced errors are overestimation of aortic diameter due to measurement at the level of the sinus of Valsalva or aortic valve, and underestimation of aortic velocity because the aiming of the transducer has not been optimized to yield a minimum Doppler angle. Typically, both errors are a result of not taking enough time for the procedure.

**Thermomilution Cardiac Output**

Several ways in which error can be introduced into thermomilution measurements have been recognized and analyzed.\(^29\,30\) The accuracy of TDCO can be affected by accurate knowledge of the blood and injectate temperature, volume of injectate, improper positioning of the thermistor, injection technique and loss of indicator to the environment. Based on such considerations, it is to be expected that TDCO measurements will include some error, but with careful technique, since any of the above errors are small,\(^29\) such error will not be large (less than 10%). For the purposes of this comparison study, therefore, TDCO has been considered correct as measured.

Protocols

**Doppler Index–Cardiac Output Proportionality**

Proportionality between systemic velocity integral and SV was studied in 54 intensive care unit patients in whom flow-directed thermomilution pulmonary artery catheters were placed for clinical indications. After obtaining informed consent from the patients, Doppler signals were recorded during thermomilution measurements. Each observation of a patient state usually consisted of repeated thermomilution measurements 1 minute apart depending on the clinical circumstances. The Doppler transducer was generally removed and replaced between each measurement. Corresponding measurements of systemic velocity integral and HR were done off line on records obtained between the time of injection and the display of the results of the thermomilution calculation, or a section of the recording as close to this time as possible. The systemic velocity integral was multiplied by HR to yield the Doppler index (DI) of CO. The measurements of TDCO and DI were each averaged to obtain single TDCO and DI measurements for each patient state. In a subset of 31 patients, multiple observations were obtained, usually on different days. To combine data from all patients, each with a different aortic area, proportional changes in DI were computed by dividing the individual DI measurements from a patient by the average of all DI measurements from that patient. Changes of TDCO were computed in a similar manner for each patient.

**A-mode and M-mode Aortic Diameter Measurements**

The A-mode section of the commercial instrument was evaluated by comparison with a standard M-mode device. The two instruments actually use slightly different estimates of acoustic velocity in tissue, such that the A-mode values should be 2% higher than the M-mode determinations. Measurements were made in 15 patients undergoing routine ultrasound studies for clinical indications. All data were collected by an experienced echocardiographic technician. With both instruments, the measurement was made from the trailing edge of the anterior aortic wall to the leading edge of the posterior aortic wall at the level of the aortic valve. A-mode measurements were taken randomly during diastole and M-mode measurements at end-diastole.

**Comparison of Ultrasound and TDCO**

The TDCO was the standard of comparison for the ultrasonic cardiac output (UCO). In our hospital, this is the only practical standard of comparison in the clinical environment. The data were collected from 53 patients who underwent 110 successful observations of CO in the intensive care unit. Patients were selected if they had a thermomilution catheter placed for clinical indications. Standard indications are cardiac surgery patients requiring valve replacement, cardiac surgery patients with coronary artery disease who have ejection fractions less than 40%, myocardial infarction patients with clinical evidence of failure who are unresponsive to initial therapy or show clinical evidence of low CO, patients with respiratory failure, and patients with heart disease undergoing noncardiac surgery with elevated risk of complications.

All available patients with thermomilution catheters in place were entered into the study except those with known aortic stenosis, aortic insufficiency or a prosthetic aortic valve. Aortic stenosis and prosthetic valves may lead to altered hemodynamics in the aortic root such that the effective flow channel is not equal to the aortic diameter. Aortic insufficiency will cause the systolic flow to exceed net SV.

The measurement of TDCO is well standardized in this facility and routinely performed by nursing personnel. In this study, TDCO was measured by the hospital staff as required clinically, using their standard protocol. Ten-milliliter syringes of 5% dextrose in water solution are prepared and stored in an iced bath under refrigeration. Typically, four readings are taken and the first is disregarded. The TDCO value is taken as the mean of the subsequent three if agreement is within 10%. Outliers are discarded and other measurements taken at the discretion of the nurse. We believe that this system works well, but did not attempt to audit the actual performance.

CO tends to be relatively stable after surgery after patients have returned to normal CO levels but are still unconscious. Immediately after surgery, marked, transient changes are often seen. Short-term variations are common when the patient is awake. To minimize the effects of such variations on our comparisons, we make ultrasonic and thermomilution measurements as nearly simultaneous as possible. In practice, this
meant that, if circumstances permitted, Doppler measurements were made on the 12 beats immediately preceding each injection of the thermal indicator. If this were not possible, measurements made as much as 10 minutes apart were allowed if the patient's condition had been stable for the previous 2 hours as exhibited by other vital signs. The Doppler and the thermodilution measurements were each averaged to form a paired observation. Factors preventing complete simultaneity include limited physical access to the patient and artifacts in the Doppler signal due to movement or talking by the patient during the TDCO measurements.

Analysis of the data has, for each study, been by simple linear regression. The mean, standard deviation, and coefficient of variation were also used in some cases.

Results

Doppler Index–Cardiac Output Proportionality

In the first study, aortic velocity measurements were recorded in 54 of 60 patients (90%). In 31 patients, observations were made for more than one patient state, where the observation for each patient state is defined as the average of the DI and CO measurements made over a short period of time, generally less than 5 minutes. A scatter plot of the change in DI (ΔDI) vs the changes in CO (ΔCO), calculated as previously described, is shown in figure 4. Linear regression analysis yields: ΔDI = 0.87 ΔCO + 0.14 (r = 0.83, n = 95, SEE = 0.11). This variability is the result of variation in both the thermodilution and ultrasound measurements. A coefficient of variation was calculated for each group of repeated estimates from each patient state. The coefficients of variation were then pooled to yield a pooled coefficient of variation of repeated TDCO estimates of 8.5% and Doppler estimates of 9.4%.

A-mode and M-mode Aortic Diameter Measurements

The range of M-mode aortic root diameters was 26–36 mm; the average (mean ± SD) was 30.4 ± 2.9 mm (fig. 5). Paired aortic root measurements showed differences of 0.2 ± 0.6 mm, or 0.8 ± 2.3% (n = 15). The maximum difference between any paired measurements was 1.3 mm.

Comparison of Ultrasound and TDCO

In the second study, 110 successful observations of UCO were obtained in 45 of 53 patients (85%). A maximum of 12 observations was made in any one patient. There were eight patients for whom complete measurements could not be obtained (fig. 6). Every patient with a functioning thermodilution catheter and no aortic valve disease was attempted, if the technician was available, during the 3-month period of the study. The average age of the patients was 59.5 ± 13.7 years (range 24–92 years).

A plot of all 110 observations is shown in figure 7. Both the line of identity and the least-squares regression line are indicated. The equation for the regression line is: UCO = 0.95TDCO + 0.38 (r = 0.94, n = 110, SEE = 0.58 l/min).

The average ascending aortic diameter in this study was 29.8 ± 3.1 mm (range 24–38 mm).

For one patient, the thermodilution measurements were open to doubt. Before any ultrasonic measurements, the TDCO values exhibited a sudden drop from the 3 l/min range to about 2 l/min. This shift was unexplained and uncorrelated with other clinical signs or measurements, including pulmonary artery oxygen saturation. In fact, attempts were made to obtain more reasonable TDCO values. The five data points obtained from that patient are indicated by special symbols in figure 7. If these points are deleted, regression analysis of those remaining yields: UCO = 0.98TDCO + 0.17 (r = 0.96, SEE = 0.44, n = 105). The close approximation of the regression lines to the
line of identity suggests that it will be possible to use UCO determinations directly, without any correction factors. For this approach, the appropriate error characterization is not the linear regression see; rather, it is a measure of scatter about the line of identity. This is equivalent to the differences of paired UCO and TDCO values. The mean (± sd) of the differences is 0.12 ± 0.58 l/min for all 110 points, and 0.05 ± 0.43 l/min for the 105 points. Alternatively, these differences can be expressed as a percentage of the TDCO values at each point. For this approach, the differences are 2.89 ± 13.1% for 110 points and 0.21 ± 8.6% for 105 points. Using the second of these as an error estimate, we can expect with 95% confidence that an average UCO determination will be within 17% (2 standard deviations) of the average TDCO.

Discussion

The results of these two clinical validation studies indicate that measurements of CO using an UCO monitor are possible in a high fraction of intensive care unit patients (85% of an unselected population). Excellent correlation with TDCO was achieved ($r = 0.94$), with the line of regression falling close to the line of identity. No major systematic errors were observed over the range of CO of 2–11 l/min. Differences between UCO and TDCO appear random, with a standard deviation of 8.6%.

The process of making ultrasound measurements offers little opportunity for operator bias, even in cases where TDCO is known. In the first study, there was no chance for bias because no quantitative output was provided on line. In the second study, peculiarities of the clinical situation did open some possibility for bias. Many patients were first approached with the instrument immediately after surgery. To take advantage of the TDCO measurements during that early phase, it was often desirable to postpone the diameter determination to a later, more convenient time. In these cases, a temporary default diameter of 30 mm was entered. Thus, the subsequent diameter measurement could have been biased by knowledge of how the ultrasonic and thermodilution values compared. To evaluate the contribution of such bias, we have performed separate analyses on the data from patients for whom diameter was determined before any velocity. When diameter measurements were postponed, the data showed a relationship described by: $UCO = 0.85 TDCO + 0.97$ ($r = 0.90$, see = 0.68, n = 63) or, deleting the five suspect points, $UCO = 0.91 TDCO + 0.51$ ($r = 0.95$, see = 0.50, n = 58). When the diameter was measured prior to CO measurements, the situation with no possibility for bias, the data exhibited an equally good correlation: $UCO = 1.07 TDCO - 0.25$ ($r = 0.98$, see = 0.32, n = 47). Thus, no effect of bias is apparent, for the portion of the data immune from such bias shows correlation and error characteristics superior to the portion that is potentially biased. The unbiased data are presumably better correlated because most were collected later in the study when skill with the instrument had improved and when we made still greater effort to assure simultaneity of measurements. Accordingly, all our data have been combined to reflect the total experience with the technique (fig. 7).

Different personnel conducted the ultrasonic measurements in the two studies. For the first study, an engineer with no ultrasound or patient measurement experience, other than practicing with the instrument on normal subjects, made the Doppler velocity determinations. He also carried out the off-line processing. In the second study, a premed student made the measurements. He had several months of experience, part-

**Figure 6.** Successful measurements were achieved in 85% of patients attempted in the second study. The three Doppler failures were due to subcutaneous air, very tight skin above the sternum because of suturing, and a spine abnormality that prevented a fully supine position. The five diameter failures were due to insufficient time as a result of clinical exigencies in two cases and to the lack of acoustic access in three (subcutaneous air in one case, a possible pneumonia-induced lung expansion in one and no apparent reason in one).

**Figure 7.** All ultrasonic and thermodilution cardiac output (UCO and TDCO) data obtained from the 45 patients successfully measured in the second study. The line of identity (dashed) and the least-squares regression line (solid) are shown. The regression line is described by: $UCO = 0.95 TDCO + 0.38$ ($r = 0.94$, see = 0.58, n = 110). See text for explanation of special symbols and other regression and error estimates.
time, with the university research instrument making Doppler measurements before beginning this series. He had no experience with pulse echo techniques, but did receive instruction and assistance from a trained echocardiographic technician during the early phases of this study.

The nature and sequence of these studies reflect the course of development of the technique, beginning with a university research instrument, followed by a prototype commercial instrument, and then the present production model. Initial efforts were devoted to instrumentation and animal experiments. Patient studies with the university device have necessarily focused on DI-CO proportionality. Both the data reported here and comparison with radionuclide measurements during supine exercise indicate direct proportionality. In the latter study, in nine subjects, we used the difference of diastolic and systolic gated scintigraphy counts as an estimate of SV during supine bicycle exercise. Patients with healthy ventricles showed little change of SV while those with poor ventricles typically decreased SV in response to modest levels of exercise. For all cases, however, the ultrasonic and radionuclide SV estimates tracked closely, with a difference (mean ± SD) of −6% ± 10% (unpublished data). With the availability of the commercial instrument, which offers both Doppler and diameter measuring capabilities, we have undertaken quantitative CO measurements. All of our results to date are reported here.

The present clinical application study extends work by several other groups using continuous wave ultrasound. Light et al. evaluated the value of aortic arch velocity measurements using Doppler ultrasound originating in the suprasternal notch. He reported good tracking of Doppler velocity integral with SV. Using pulsed rather than CWD techniques, several groups have indicated that CO may be measured noninvasively. Hoekenga et al. report a 0.87 correlation with Fick determinations in adults. Similar results are presented by Bommer et al. using thermodilution for comparison. Elkayam et al. report that ultrasonic SV tracks SV by thermodilution linearly with a correlation coefficient of 0.91. Applying the technique to children, two groups have reported excellent agreement with established methods. Berman et al. studying neonates and children found a correlation value of 0.96 with Fick outputs of 403–3260 ml/min. Against indicator-dilution techniques, Hoenecke et al. found an r value of 0.95 in a study of children ages 3 months to 12 years. These studies all confirm that there is close agreement between noninvasive CO derived from CWD or PD techniques and values obtained with the commonly used techniques of invasive measurement.

Reproducibility of Doppler flow measurements has been addressed by Gardin et al., Voyles et al., and Gisvold and Brubakk. Gardin et al. found little interobserver variability in estimates of cardiac velocity integral, time and peak value. Voyles et al. had 200 serial measurements done in 10 normal subjects by two observers. Using a one-way analysis of variance, they found pooled coefficients of variation of 9% and 10% for their two observers with no statistically significant difference between observers. Gisvold and Brubakk made 10 repeated measurements in five subjects and found that the mean coefficient of variation of any measured variable was 6–11%. These results agree well with the 9.4% pooled coefficient of variation found in this study.

In the context of these previous investigations, the excellent results of our studies indicate that a quantitative noninvasive method for measuring CO is available. Several aspects of our experience further emphasize the clinical applicability of the technique. In the present form, the instrument provides a compact, mobile unit capable of measuring both aortic blood velocity and aortic diameter. The validation testing has been carried out in a group of unselected intensive care unit patients, with all the realities which make the intensive care unit a difficult place for consistent measurements. Although the errors in UCO are not large, it is anticipated that they may be still smaller for repeated determinations in a single patient. If so, the method will offer enhanced capability for detecting and quantifying changes of CO.

Our experience suggests that satisfactory results can be obtained by inexperienced personnel. Though both velocity and diameter measurements require some training, the method is more practical, and learning is facilitated by consultation with an ultrasound technician. We believe that it is best to train one person well, who can then train others.

Measurement time varies, of course, but we allow 10–15 minutes for the initial diameter assessment. This provides for unhurried examination of the anatomy and repeated diameter determinations. The first velocity measurement may take as long as 5 minutes, but subsequent measurements are typically very rapid and easy. For all patients, we measured diameter once and then assumed it to be constant. Although this has worked well, repeated measurements might be in order if large blood pressure changes are observed.

For critical care patients, the ultrasonic determination of CO is likely to be a supplement to, rather than a replacement for invasive methods, for the need for pressure data often requires placement of a catheter. It may be used for screening of potential candidates for invasive monitoring or for monitoring before and after the period when a catheter is in place. The technique is well suited for assessing CO responses to therapeutic interventions in all circumstances. The effects of vasodilator drugs or varying pacemaker modes may be evaluated in the outpatient setting, for example. Noninvasive CO may, in addition, be useful for early detection of the cardiotoxic effects of drugs used in the treatment of cancer. The hemodynamic responses to various hypertensive states can also be assessed. The method has also been successfully used to monitor CO responses to submaximal bicycle exercise.

Although we excluded from this study patients with known aortic valve disease, the Doppler technique may be useful in the assessment of the severity of such
disease. In the case of aortic insufficiency, the Doppler method should correctly indicate the forward flow during systole. This amount, less the net CO assessed by thermodilution, should indicate the magnitude of the regurgitant flow. For aortic stenosis, the high velocity through the valve orifice can be assessed by CWD.\(^{40}\) It has been recently demonstrated that peak systolic velocities can be related to peak pressure gradients across the valve.\(^{40}\) Alternatively, the Doppler velocity integral divided into the actual SV as measured by an invasive method, may yield a useful value for the orifice area.

The Doppler technique can yield more information about the character of LV ejection than SV and CO. Since the time course of aortic velocity is inherently measured, it is possible to determine additional features of ejection, such as peak velocity, ejection time, acceleration, deceleration and, in conjunction with an ECG, pre-ejection time. Physiologic and clinical studies have suggested diagnostic utility for some of these.\(^{26,40-45}\) Combinations of Doppler-derived variables with blood pressure can provide additional measurements, such as stroke work and peripheral vascular resistance. As this technique permits assessment of CO on a beat-by-beat basis, it may prove to be useful as investigators develop a better understanding of cardiac transients.

References


38. Honecke HR, Goldberg SJ, Carnahan Y, Sahn DJ, Allen HD, Valdez-Cruz LM: Controlled quantitative assessment of pulmonary and aortic flow by range gated pulsed Doppler in children with...
Treatment of Chronic Orthostatic Hypotension with Ergotamine

ARAM V. CHOBANIAN, M.D., CHARLES P. TIFFT, M.D., DAVID P. FAXON, M.D., MARK A. CREAGER, M.D., AND HOWARD SACKEL, M.D.

SUMMARY  The acute and chronic effects of ergotamine were examined in four patients with chronic orthostatic hypotension. Chronic oral administration of ergotamine tartrate produced significant increases in standing blood pressure and marked clinical improvement, without appreciable recumbent hypertension. The blood pressure increases were not associated with significant changes in plasma norepinephrine or plasma renin activity. No major toxicity was observed at doses of 2–6 mg/day over treatment periods of 3–18 months.

Hemodynamic studies on the effects of i.v. ergotamine tartrate (0.25–0.50 mg) revealed that the ergotamine-induced increase in blood pressure in the supine position was associated with an increase in total peripheral resistance (from 1616 ± 165 to 2574 ± 583 U) without a change in cardiac output. During 45–60° upright tilt, ergotamine increased both total peripheral resistance (1801 ± 296 to 3262 ± 1107 U) and cardiac output (2.42 ± 0.46 to 3.34 ± 0.54 l/min). Forearm plethysmographic studies revealed decreased forearm blood flow and venous volume and increased vascular resistance with ergotamine.

The orthostatic hypotensives had more platelet α-receptors (390 ± 31 receptors/cell) than the control subjects (234 ± 17 receptors/cell). The increased receptor level was associated with abnormally low circulating levels of norepinephrine and increased pressor responsiveness to infused norepinephrine in three of the four patients. Chronic ergotamine therapy appeared to reduce platelet α-receptor number to normal.

The results indicate that ergotamine is of value in certain patients with chronic orthostatic hypotension and that blood pressure effects are related to vasoconstriction in both arterial and venous beds.

THE MANAGEMENT of chronic orthostatic hypotension is a difficult clinical problem. Many approaches have been advocated, including mechanical supports to minimize peripheral pooling of blood, mineralocorticoid drugs, sympathomimetic agents either alone or in combination with a monoamine oxidase inhibitor, β blockers, indomethacin, vasopressin, metoclopropamide or atrial pacing.1-7 These treatments generally have been only partially effective, and at times, they have induced significant side effects.

Recent reports indicate that parenteral administration of dihydroergotamine may increase standing blood pressures and decrease postural hypotension in patients with chronic orthostatic hypotension. However, the results of chronic oral treatment with the drug have been equivocal,8,9 perhaps because of low bioavailability.8,10

Hemodynamic studies indicate that the blood pressure–enhancing effect of dihydroergotamine in orthostatic hypotension is associated with increases in total peripheral resistance.8,9 Changes in cardiac output have been variable. An increase in cardiopulmonary blood volume has been observed and has suggested that dihydroergotamine may have a vasoconstrictive action.8

The current study was performed to examine the clinical efficacy of ergotamine tartrate in selected refractory patients with orthostatic hypotension. The mechanism of action of ergotamine on blood pressure was also studied by investigating the effects of the drug on systemic hemodynamics, including peripheral resistance and capacitance vessels.
Noninvasive Doppler determination of cardiac output in man. Clinical validation.
L L Huntsman, D K Stewart, S R Barnes, S B Franklin, J S Colocousis and E A Hessel

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