

Comparison of the USCOM Ultrasound Cardiac Output Monitor with Pulmonary Artery Catheter Thermodilution in Patients Undergoing Liver Transplantation

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The aim of the study was to compare the standard technique of cardiac output determination by pulmonary artery catheter thermodilution (PAC-TD) with a noninvasive ultrasound Doppler monitor (USCOM Pty., Ltd., Coffs Harbour, Australia) in surgery for liver transplantation. We wished to determine if the degree of accuracy would allow the ultrasound cardiac output monitor (USCOM) to be used as an alternative monitor in a clinical setting in which wide fluctuations in cardiac output could be expected. This was a prospective method comparison study, with 71 paired measurements obtained in 12 patients undergoing liver transplantation in a university teaching hospital. Bland-Altman analysis of the 2 techniques showed a bias of 0.39 L/minute, with the USCOM cardiac output lower compared with that of PAC-TD. The bias was small and did not vary with the magnitude of the cardiac output. The 95% limits of agreement were -1.47 and 2.25 L/minute. There was good repeatability for USCOM measurements, with a repeatability coefficient of 0.43 for USCOM versus 0.77 for PAC-TD. We conclude that USCOM is acceptable for the clinical determination of noninvasive cardiac output, particularly in situations in which tracking changes over time is more important than knowing the precise value. However, the utility of USCOM is limited by its inability to measure pulmonary artery pressure. *Liver Transpl* 14:1038-1043, 2008. © 2008 AASLD.

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During liver transplantation, large hemodynamic swings can be expected from blood loss, from clamping of the inferior vena cava, and after reperfusion. The measurement of cardiac output (CO) in these patients is useful for guiding clinical therapy, including fluid administration and use of vasopressors. Pulmonary artery catheter thermodilution (PAC-TD) has been the standard method of CO measurement in liver transplantation. Recently, attention has turned to other measurement techniques. One such method, which is noninvasive, is the ultrasound cardiac out-

put monitor (USCOM) from USCOM Pty., Ltd. (Coffs Harbour, Australia), which was introduced into clinical practice in 2001. The USCOM monitor has been studied in surgical intensive care patients, Doppler-derived CO being compared with that determined by PAC-TD. Good agreement was found between the 2 techniques, but there was an increased difference at higher COs.¹ This study was therefore planned to compare USCOM and PAC-TD in patients undergoing liver transplantation, during which a large range of COs could be expected. To our knowledge, there has been no prior study published that compares these 2 CO measurement methods in liver transplantation.

Abbreviations: CI, confidence interval; CO, cardiac output; CO_{Thermo}, cardiac output measured with the thermodilution method via a pulmonary artery catheter; CO_{USCOM}, cardiac output measured with the ultrasound cardiac output monitor; CSA, cross-sectional area; PAC, pulmonary artery catheter; PAC-TD, pulmonary artery catheter thermodilution; USCOM, ultrasound cardiac output monitor.

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PATIENTS AND METHODS

The study was approved by our hospital institutional review board. Written informed consent was obtained prior to surgery from patients undergoing liver transplantation. Exclusion criteria were any contraindication to pulmonary artery catheter (PAC) insertion or encephalopathy (because of difficulty in obtaining consent). Venovenous bypass was not used in any patient. The anesthesia technique was standardized, with intravenous induction using propofol or thiopentone followed by maintenance with an oxygen/air/isoflurane mix and fentanyl infusion. Atracurium was used for muscle relaxation. A trilumen central line was inserted into the superior vena cava via the external jugular vein for drug infusions. All patients then had two 8.5-Fr percutaneous introducer sheaths (Arrow SI 09880, Arrow International, Inc., Reading PA) inserted into the internal jugular vein, and a PAC (7.5-Fr, 4-lumen, 110-cm Arrow AH-05000-H) was placed through one of the vascular sheaths, the other being reserved for large volume transfusions. Simultaneous paired CO measurements (module M1012A, Hewlett-Packard Co., Boeblingen, Germany) were made, with PAC-TD and USCOM, at the following points during surgery: at baseline (before hepatectomy), during hepatectomy with the portal vein clamped, during the anhepatic phase with the inferior vena cava cross-clamped, and 1 hour after liver graft revascularization. Care was taken not to measure CO during periods when there were transient changes from surgical manipulation, such as retraction of the liver or inferior vena cava during hepatectomy. Further paired measurements were performed on transfer to the intensive care unit and just before removal of the PAC while the patients were still on mechanical ventilation.

PAC Technique

The standard thermodilution technique was used, with 10 mL of saline injectate at room temperature (approximately 22°C). All measurements were performed by an investigator (B.-H.Y.) or one other attending anesthetist who was blinded to the USCOM readings. Usual precautions were taken, such as rapid injection within 2-3 seconds, not running any rapid IV fluid infusion into the vein during measurement, and not warming the injectate syringe in the hand. Washout curves were examined and accepted if the baseline was stable, upstroke was smooth, and exponential decay was present. For each technique, three consecutive measures, taken at random with respect to the ventilatory cycle, were averaged. Although CO may vary with the respiratory cycle, the effect would apply to both methods of measurement.

USCOM Technology

USCOM uses continuous-wave Doppler to determine CO by a nonimaging transducer placed at the left parasternal position to measure transpulmonary blood flow or at the suprasternal notch to measure transaortic blood flow. The flow profile is presented as a time-

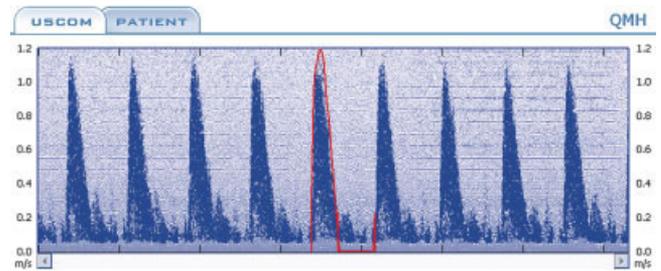


Figure 1. Doppler wave profile with the velocity-time integral from the ultrasound cardiac output monitor (USCOM). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

velocity spectral display showing variations of the blood flow velocity with time (Fig. 1). Once the optimal flow profile is obtained, the trace is frozen on the screen. CO is then automatically calculated as the product of the heart rate and stroke volume. The stroke volume is the product of the velocity-time integral and the cross-sectional area (CSA) of the chosen valve. The CSA of the aortic valve is determined by the application of the height-indexed Nidorf regression equation.^{1,2} The pulmonary valve area is calculated by a separate regression equation derived from the Nidorf equation: pulmonary valve annular diameter = $0.011 \times \text{height (cm)} + 0.273 \text{ cm}$.^{1,2}

USCOM Technique

Concurrently with PAC-TD, CO was independently determined with the USCOM monitor by a second study investigator using the suprasternal window to obtain the aortic flow profile. Three replicate measures were taken, as was done for PAC-TD. The pulmonary arterial flow profile was not used for this study. Measurements were not made during times when there was electrical signal noise from diathermy. USCOM measurements were performed by study investigators (L.-S.G.W. and L.-S.L.) who had undertaken a training course and performed supervised CO measurements on more than 30 patients. A study of operators with no prior ultrasonographic experience showed that reliable measurements could be obtained with USCOM following supervised measurement on at least 20 patients.³

Statistical Methods

As this population of patients with cirrhosis is known to have high COs, a mean CO of 8 L/minute with a standard deviation of 2 L/minute was assumed for power calculation. To detect a difference between the methods of 10% or less at a desired power of 0.8, 68 pairs of measurements were required at the 0.05 significance level. CO was measured at 6 different times in each patient, so 72 paired measurements were obtained from 12 patients. As repeated measurements were made over time in each patient, some correlation of data points at different times for the same patient may occur. However, tests for agreement between the 2 meth-

TABLE 1. Repeatability of Cardiac Outputs by Thermodilution and USCOM

Cardiac Output	Thermodilution	USCOM
Number of paired measures	71	71
Number of replicates for each measure	3	3
Mean \pm SD (L/minute)	7.32 \pm 2.25	6.92 \pm 2.11
Range (L/minute)	2.14-13.00	2.83-12.33
Repeatability coefficient	0.77	0.43

Abbreviations: SD, standard deviation; USCOM, ultrasound cardiac output monitor.

TABLE 2. Agreement of Cardiac Outputs by Thermodilution and USCOM

Indices of Agreement and Correlation	Thermodilution Versus USCOM (n = 71)
Correlation coefficient	0.896
Mean difference or bias (SD): thermodilution - USCOM	0.39 L/minute (0.95)
Limits of agreement	-1.47, 2.25
95% CI for the lower limit of agreement	-1.82, -1.12
95% CI for the upper limit of agreement	1.90, 2.60
Rank correlation of the difference and mean	0.1678 ($P = 0.1618$)

Abbreviations: CI, confidence interval; SD, standard deviation; USCOM, ultrasound cardiac output monitor.

ods at each time point would be valid, provided that the data points were independent. Analysis of variance with blocks was performed to confirm this. The Bland-Altman statistical method was used to study agreement between the 2 methods of measurement.^{4,5} A plot of the difference between paired measurements against the mean (with 95% limits of agreement indicated) was constructed. On this plot, the mean difference between measurement techniques is the bias, an estimate of how closely the 2 methods agree. The paired t test was used to detect any significant difference between the USCOM and PAC-TD measurements. Replicate measurements are important in method comparison studies, as poor repeatability for each method limits the amount of agreement possible.⁵ Three replicate measures were taken at each time point, and the repeatability coefficient was calculated to evaluate the variability of repeated measurements for each of the 2 devices. An important assumption in the limits of agreement method is that the mean difference (bias) does not vary across the range of measurement.⁵ The rank correlation coefficient was used to detect any relationship between the bias and magnitude of the CO. The statistical software used was the SAS System for Windows, release 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Fourteen patients were enrolled, and 71 paired measurements were obtained in 12 patients, 10 male and 2 female. The age ranged from 16 to 71 years, with a mean (standard deviation) of 46.3 (12.1) years. Indications for liver transplantation were hepatitis B cirrhosis (9 patients, including 6 with hepatocellular carcinoma), hepatitis C cirrhosis (2 patients, both with hepatocel-

lular carcinoma), and Caroli's disease (1 patient). Nine patients received live-donor right lobe grafts, and 2 received cadaveric whole grafts. All CO measurements were made in the supine position. The aortic flow profile was easily obtained through the suprasternal window in all 12 patients. Measurements had to be abandoned in 2 patients: one had the transplant procedure cancelled because of disseminated malignancy, and there was failure of the CO module in the other.

The CO data and repeatability coefficient are shown in Table 1, whereas the bias and limits of agreement are shown in Table 2. The scatter plot of the cardiac output by thermodilution (CO_{Thermo}) against the paired USCOM measure [cardiac output by USCOM (CO_{USCOM})] is shown in Fig. 2. Of the 71 data points, 10 were at CO less than 5 L/minute (by both methods of measurement), and 32 were greater than 7 L/minute; that is, a total of 42 data points (more than half) were outside the usual CO range of 5 to 7 L/minute. Furthermore, in patients with high CO, 21 data points were at CO greater than 8 L/minute, and 8 were greater than 10 L/minute. The majority of points lie above the line of unity. As we were more interested in agreement (and not correlation) between the 2 methods, a better way to visualize the data is to use the Bland-Altman plot, which is shown in Fig. 3. This shows that as the CO increased, the difference between the 2 methods did not. The mean of the differences ($CO_{\text{Thermo}} - CO_{\text{USCOM}}$), the bias, was 0.39 (standard deviation: 0.95). The lower and upper limits of agreement, which define the range within which 95% of differences would lie, was -1.47 [95% confidence interval: -1.81 to -1.12] and 2.25 L/minute (95% confidence interval: 1.9 to 2.6), respectively. The paired t test showed a tendency for the USCOM measurements to be lower than the thermodilu-

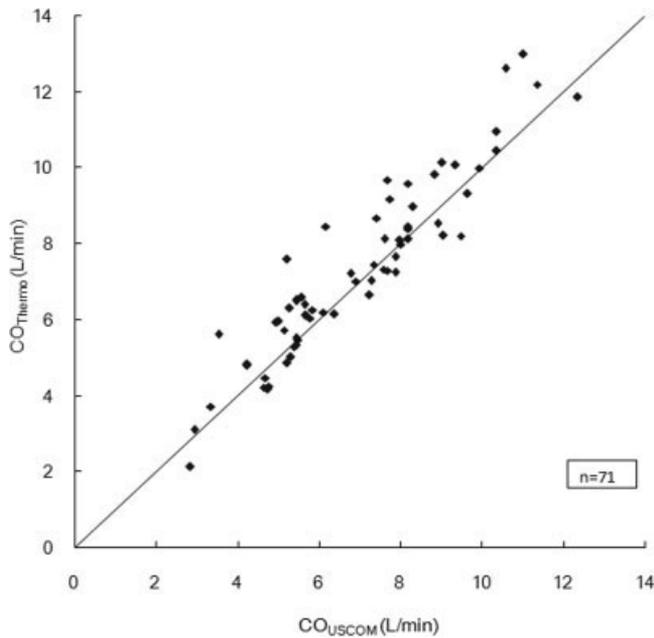


Figure 2. Comparison of cardiac outputs measured by thermodilution (CO_{Thermo}) and the ultrasound cardiac output monitor (CO_{USCOM}). The line of equality is superimposed for reference.

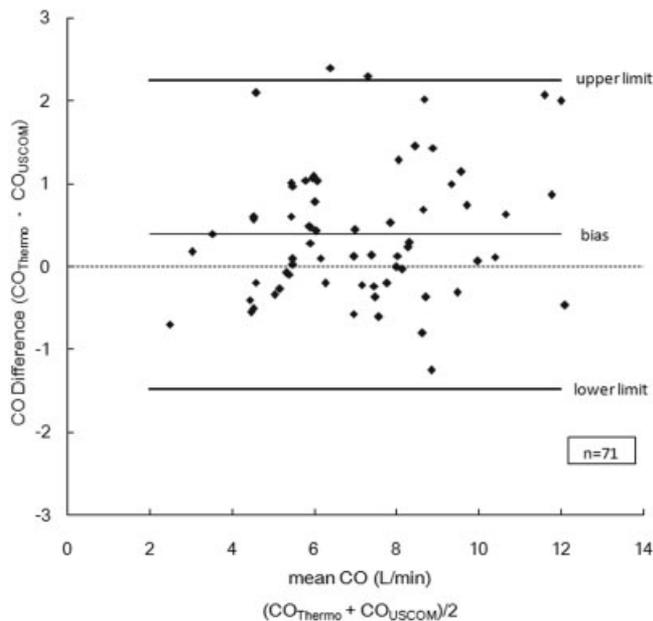


Figure 3. Bland-Altman plot: cardiac output (CO) difference [CO measured by thermodilution (CO_{Thermo}) – CO measured by the ultrasound cardiac output monitor (CO_{USCOM})] versus the mean CO with 95% limits of agreement.

tion measurements ($P = 0.0328$). With analysis of variance with blocks, there were no significant differences in the CO measurements ($P = 0.1962$) by each method at the 6 different time points, and this confirmed that the tests of agreement at each time point were valid. The rank correlation coefficient showed that there was no correlation between the bias and magni-

tude of the CO (rank correlation coefficient = 0.1678, $P = 0.1618$). The repeatability coefficient of USCOM for CO measurement was 0.43, whereas that for thermodilution was 0.77. This coefficient, which is derived from the within-subject standard deviation, defines the CO range within which one can expect 95% of repeat measurements to fall. Therefore, USCOM has greater reproducibility with repeated measurements. There were no adverse events detected with the use of either device.

DISCUSSION

There have been relatively few studies comparing the USCOM device to PAC-TD. The accuracy of the USCOM device has been validated in post-cardiac surgery patients in the intensive care unit. One study,¹ using the transpulmonary window with 1 to 3 sets of readings taken for each patient, found better agreement of the methods within the physiological range of CO , and the authors felt that further studies were needed in low and high CO states. Another study⁶ compared USCOM with PAC-TD at a single postoperative time point. Although there was difficulty in obtaining a good Doppler profile in some patients, particularly with the aortic window, excellent agreement between the 2 methods was demonstrated. The authors stated the need to investigate the stability of the correlation and agreement over time as well as the suitability in patients with high and low CO states. A third study⁷ in patients who had undergone coronary revascularization also found good correlation between the 2 methods. In addition, flows identical to those from PAC-TD were found when the USCOM probe was directly applied to the pulmonary artery in 6 patients. The authors commented that the USCOM device may be of special value in the hands of anesthesiologists in the operating room during the perioperative period, when hemodynamic management may be critical. We believe that our present study addresses issues raised in these previous studies, in that our patients were studied over time during intraoperative and postoperative periods, with readings taken at 6 different time points. Furthermore, liver transplantation patients have high CO states to begin with, which drop to low values on clamping of the inferior vena cava (range of 2.14 to 13 L/minute in our patients, in contrast to about 5 L/minute in the cardiac surgery patients). These changes are particularly marked if venovenous bypass is not used, which is the practice in our center (we do not use the piggyback technique for liver graft implantation). Knowing the CO in such dynamic situations (together with derived parameters such as systemic vascular resistance) is useful in helping us select appropriate vasoactive drugs to maintain the circulation, especially during inferior vena cava cross-clamp. These patients are thus the ideal population in which to study this novel measurement method at extremes of CO .

Since the introduction of the PAC by Swan and Ganz⁸ in 1970, measurement of CO by PAC-TD has become a de facto gold standard against which new methods are compared. This practice obscures the fact that CO by

thermodilution is an indirect measure derived with the Stewart-Hamilton equation. Recent interest in alternative cardiac-output measurement techniques has been prompted by questions raised regarding many aspects of PAC usage: the validity and correct interpretation of the physiological parameters measured, correct clinical response, and whether outcome is improved or worsened.⁹ These concerns have resulted in decreased usage of the PAC, as documented in a recent review on practice in the United States.¹⁰ Many factors may significantly affect PAC-TD measurement, including the accuracy of the injectate volume and temperature and the phase of the respiratory cycle during injection.^{11,12} CO measurement by thermodilution is validated, but intrinsic variability necessitates multiple measurements per determination; even with 3 measurements per determination, a minimum change of 12%-15% is required to suggest clinical significance.¹³ In addition, there are risks related to central venous cannulation in patients with coagulopathy, making a noninvasive cardiovascular monitor an attractive option in liver transplantation patients. A noninvasive device that allows repeated hemodynamic measurements would also be very useful for monitoring patients with cirrhotic cardiomyopathy. A recent study¹⁴ compared transthoracic pulsed-wave Doppler echocardiography with PAC-TD in post-liver transplantation patients. Good agreement was found for CO but not for filling parameters, and bias was negligible at CO < 6 L/minute. The transthoracic approach, however, cannot be used during the intraoperative period. Another study in patients undergoing liver transplantation without venovenous bypass¹⁵ compared intermittent and continuous CO measurement with arterial pulse wave analysis (PiCCO system, Pulsion Medical Systems, Munich, Germany) and PAC-TD. Bias was small (0.15 L/minute) with 95% limits of agreement within 2 L/minute in both intermittent and continuous measurements.

In the current study, it is important to note that we are comparing 2 indirect measures of CO; neither is a direct measurement, and the true value is not known. The statistical issues therefore are (1) the degree of agreement between the 2 measures and (2) the reproducibility (or repeatability) of the measurement. We are not dealing with calibration, where a new technique is compared with a direct measurement that can give us a true value. The positive bias of 0.39 L/minute indicates that CO_{USCOM} is lower than CO_{Thermo}. However, the bias is small and of similar magnitude to those found in earlier USCOM studies, which ranged from 0.1 to 0.23 L/minute.^{1,6,7} One possible cause for the discrepancy is difficulty in selecting and capturing the best flow profile for CO calculation, an issue that has been addressed by software upgrades that incorporate automatic flow profile selection. Errors may also result from assumptions made in estimating CSA of the aortic valve from algorithms. The 95% limits of agreement of -1.47 to 2.25 L/minute are within an acceptable range and similar to other studies,^{1,6,7} in which the range was -1.43 to 3.5 L/minute. Thus, the accuracy of USCOM in liver transplantation is comparable to that in post-

operative cardiac surgery patients. It has good repeatability and satisfactory limits of agreement in comparison with PAC-TD and would be useful in tracking changes across a wide range of CO values. In many clinical circumstances, knowing the ballpark CO values and the trend in response to therapy is more important than the precise measurements.

In liver transplantation, during the perireperfusion phase, many microbubbles pass through the heart. These microbubbles act to enhance blood ultrasound reflection, resulting in a brighter signal and easier tracing of the flow profile. The phase shift and velocity and hence quantitative measured values remain unchanged, and the effect would probably be negligible (R. Phillips, personal communication, 2007). Other monitoring, such as transesophageal echocardiography, may be in use in the patient simultaneously. The probes will not interfere with each other, as transesophageal echocardiography is directed at the descending thoracic aorta behind the esophagus, whereas USCOM is directed at the aortic valve transcutaneously, which is quite some distance away in adults. The aortic flow will be in opposite directions, with USCOM flow having positive velocity toward the transducer and descending thoracic aorta flow having negative velocity away from the transducer.

Limitations of this study include the fact that we are comparing left heart output (derived from aortic flow) with right heart indices (from PAC-TD), which may not be valid in tricuspid regurgitation. In our study, only 1 patient had trivial tricuspid regurgitation on full echocardiography assessment. This would have no material impact on our results. The USCOM device does not provide any information on volume status or pulmonary artery pressures. Measurement of filling pressures was not a subject of this study. Regardless of the type of CO device used, all our patients will still have a central venous catheter inserted for drug infusion and central venous pressure measurement. However, knowledge of pulmonary artery pressures remains an important indication for the PAC in liver transplantation, as pulmonary hypertension has a major impact on outcome in these patients.

The USCOM device is attractive in many ways. Being noninvasive, it is safe; the skill required to use it can be quickly acquired, and it is relatively inexpensive. It can be useful in clinical situations in which CO needs to be quickly measured and the response to therapeutic interventions needs to be tracked. We have shown that, even at CO values beyond the normal range, agreement with traditional PAC-TD measurements is maintained. Other parameters such as systemic vascular resistance can be derived with input of blood pressure data. However, the utility of the USCOM device is limited by its inability to measure pulmonary artery pressures. Whether USCOM data alone are sufficient for cardiovascular management in liver transplantation will need to be determined by individual clinicians in their own practice. We believe that our study will contribute to proper assessment of alternative monitors to the PAC in patients undergoing liver transplantation.

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