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Assessment of cardiac output during liver transplantation: a never ending-story?

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"Cirrhotic cardiomyopathy" is usually characterized by a hyperdynamic state with high cardiac output (CO), low systemic vascular resistances and arterial blood pressure, and impaired cardiac response under conditions of stress.[1-3]

During liver transplantation (LTx) abrupt hemodynamic changes, due to massive blood loss, circulating volume fluctuations, and vascular clamping/unclamping occur.[4] Besides, the heart may have reduced responsiveness to stress, as its adrenergic compensatory mechanism to sudden hemodynamic changes could be severely impaired.[4, 5] In addition, end-stage liver diseases are frequently complicated by autonomic neuropathy, associated with vascular hyporesponsiveness to surgical manipulations, changes in blood volume, and vasopressors.[5]

In patients undergoing LTx, surgical insults may affect the subtle equilibrium between cardiac and vascular function observed in this complex "sepsis-like" clinical condition. Hence, there is the need for advanced hemodynamic monitoring that could allow the detection of sudden hemodynamic changes, enabling timely corrective therapy to be initiated. Unfortunately, there is no agreement at present on what hemodynamic system should be used during LTx.[6-8] The intermittent thermodilution (TDi) technique, obtained through the pulmonary artery catheter (PAC), is still widely considered as the standard method of reference for CO monitoring.[9] However, as the PAC has been criticized for its invasiveness and potential complications, interest in alternative and less invasive monitoring systems has surged in recent years for CO estimation.

There are now many different hemodynamic monitoring systems available.[9] Feltracco *et al*. have extensively described the advantages and the most frequent drawbacks of different hemodynamic devices used during LTx.[6] Although acclaimed in various clinical scenarios,[9] intraoperative transesophageal echocardiography (TEE) cannot be considered an ideal monitoring system during LTx. Indeed, it is operator dependent and does not provide CO on a beat-by-beat basis. Also, echocardiography instruments and expertise are not readily available everywhere.[6, 9]

Among the devices for real-time, continuous, operator-independent and less-invasive CO assessment, the uncalibrated pulse contour methods (PCMs) have not shown acceptable agreement with the reference TDi method in this setting.[6, 10] The abnormalities of the arterial pressure waveform, and the rapidity with which the vascular tone and compliance change in patients undergoing LTx are the main hypotheses advanced to explain the poor performance of PCMs.[6]

Continuous pulmonary thermodilution CO (CCO), obtained through a modified PAC, offers a continuous measure of the trend in CO but presents a long response time (3-8 minutes)

Comment on p. 1178.

of providing CO, limiting the usefulness of this system for assessing rapid hemodynamic changes in unstable LTx patients.[6, 9]

The transpulmonary thermodilution (TPTD) technique has gained popularity in recent years because: 1) its CO values correlate well with those measured using TDi; 2) it allows CO to be assessed less invasively, using a central venous (to allow calibration) and an arterial catheter; 3) it can also estimate CO on a continuous basis from the arterial pressure waveform; 4) it can be recalibrated (to improve accuracy) when changes in vascular tone and compliance may have occurred; 5) it provides additional hemodynamic variables of loading conditions, fluid responsiveness, and ventricular function. As such, more complete hemodynamic assessment could be carried out with TPTD in critically ill patients.[6, 9, 11]

In this issue of Minerva Anestesiologica, Vilchez-Monge *et al*. compared three different devices (TDi, Vigilance II, and $PICCO_2$) for cardiac index (CI) measurements during LTx.[12] The aim of this study was to investigate whether CI measurements with the TPTD ($PICCO_2$) and CCO (Vigilance II) methods agree sufficiently with those performed with TDi to be considered interchangeable during LTx. The TDi technique was considered the reference method. The authors prospectively enrolled 72 patients undergoing LTx. The only exclusion criteria was a second liver transplantation due to primary graft failure. In order to evaluate the reliability of the three monitoring techniques to track changes in CI, the measurements were performed at eight time points and subsequently grouped into three major phases of surgery (hepatic dissection phase, anhepatic phase, and after graft implantation).

The main finding of this study was that the Bland-Altman analysis corrected for repeated measures showed poor agreement between TDi and CCO, with a percentage error (PE) of 64%. Conversely, a lower PE (45%) between TDi and TPTD was found. The polar plot analysis showed unsatisfactory performance of CCO and TPTD to track TDi-CI changes (95% radial limits of agreement of 40° and 41° for CCO and TPTD, respectively).

Two key messages result from the study performed by Vilchez-Monge *et al*. Firstly, this research shows poor agreement between CCO and TDi during LTx. This may not come as a surprise, as it has become actually clear that the CCO technique cannot replace TDi due to its long-time response of providing CO.[6, 9] Indeed, such an issue represents the major limitation of this method, as it may weakly reflect the abrupt hemodynamic changes faced by patients undergoing LTx.[6] Secondarily, in contrast to previously published literature,[11, 13] this study demonstrates that there is "too questionable clinical agreement" between TPTD and TDi.

Della Rocca *et al*. were the first to assess the value of TPTD against TDi in patients undergoing LTx.[11, 13] The authors found good agreement between the two techniques with a presumable PE <30% during anhepatic phase (data not shown in the original papers). Conversely, Vilchez-Monge *et al*. showed poor agreement between TPTD and TDi, with a PE of 52% during anhepatic phase. Also, the PE was 39% after graft implantation and 45% for all data analysis.

It is difficult to explain the apparent divergence existing between similar studies that have been conducted in comparable clinical settings. However, some practical considerations may be of help when interpreting discrepant findings on CO measurements.

A) In the majority of cases, in research field, a new CO monitoring device is tested against the reference method (*i.e*., TDi) according to rigorous exclusion criteria, such as collecting data during hemodynamic instability and in the presence of cardiac arrhythmias. Indeed, these conditions may affect the reliability of the device being studied.[9] Vilchez-Monge *et al*. and Della Rocca *et al*. compared TPTD against TDi in a population of unselected patients during hemodynamic instability. They could not have done otherwise, as cardiovascular fluctuations represent a common scenario in patients undergoing LTx. That is what really happens in clinical practice. Unfortunately, there is still a big gap between clinical research studies evaluating these systems and clinical practice.[14] Other pathophysiological conditions may have played a role in determining such a divergence. For instance, although the tricuspid valve regurgitation (TVR) may not affect CO measurements obtained with TPTD,

it is considered an exclusion criteria whenever using TDi for CO estimation.[15] Unfortunately, information on patients with or without TVR was not stated in these papers. All the abovementioned issues represent potential biases that might have affected the reproducibility of the results coming from these studies.

B) A further point is that Vilchez-Monge *et al.* used a new version of TPDT (*i.e.*, $PICCO_2$) and CCO (*i.e.*, Vigilance II), while Della Rocca *et al.* performed the CO estimations using the first generation of PICCO and Vigilance.[11, 13] Although first and second generation devices are based on the same physical assumption (*i.e.*, the Stewart-Hamilton equation), having used different systems could also explain, in part, the disagreement between these studies. Actually, different monitor models, catheters, and generation devices may contribute to determine biases and errors in CO measurements in some circumstances. Indeed, Yang *et al.*, using an *in vitro* continuous flow test rig, compared three different models of thermodilution CO monitor with two models of PAC.[16] The actual flow rate through the test rig was measured by an ultrasonic transit flow-probe. The authors demonstrated that the precision error of thermodilution CO is dependent on, and significantly worsened by the selection of catheter and monitor model.[16] In light of these recent data, and after considering the limitations of a "continuous" flow test rig *versus* a "pulsating" one, re-evaluation of the current acceptance criteria of a PE <30% would be very welcome!

C) Another remark concerns the statistical approach followed in these papers. The study performed by Vilchez-Monge *et al.* is based on current statistical methods for validating CO monitoring systems.[17-19] As a matter of fact, many years have passed since the publication of the first results about the reliability of the TPTD method during LTx.[11, 13] As such, any attempt at comparing potential divergences between recent and old studies on concordance analysis would be inappropriate, as well as not applicable. Of note, there is a growing interest regarding new statistical methodologies to demonstrate whether or not a monitor can measure and track CO. The statistical methods have made significant steps forward over the last four decades (Figure 1), but a consensus to define the gold standard

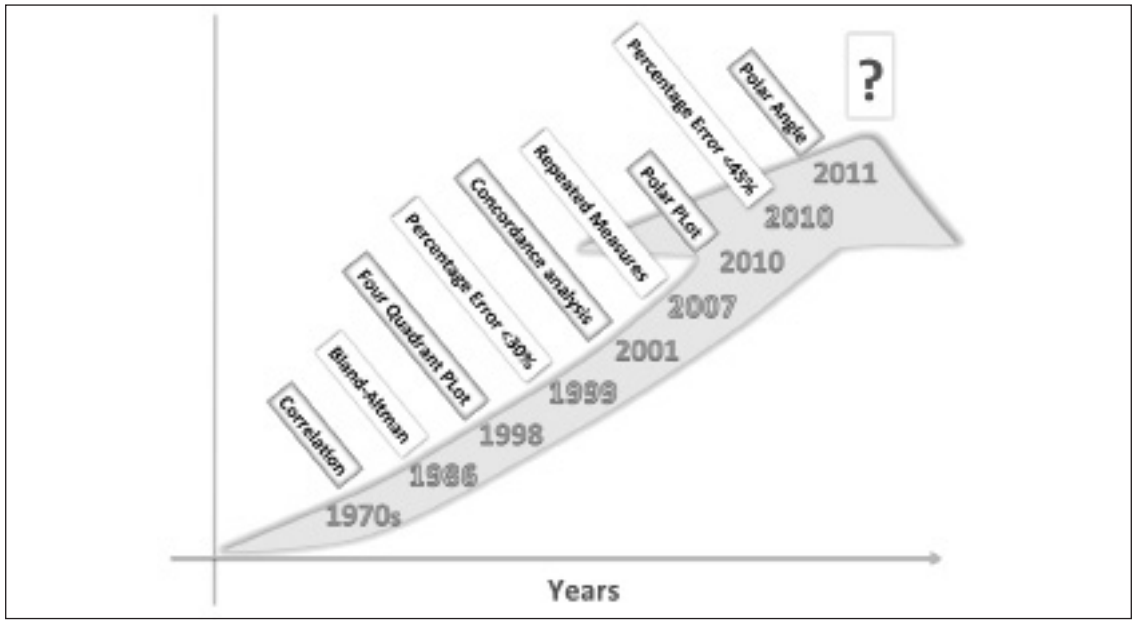

Figure 1.—The statistical approaches considered "historical milestones", over the last four decades, for assessing agreement and concordance between two methods of cardiac output measurement. Bland JM and Altman DG (Lancet 1986), Critchley LAH and Critchley JAJH (J Clin Monitor 1999), Perrino AC *et al.* (Anesthesiology 1998), Jansen JR *et al.* (Br J Anaesth 2001), Myles PS *et al.,* Cui J (Br J Anaesth 2007), Peyton PJ *et al.,* Chong SW (Anesthesiology 2010), Critchley LA *et al.* (Anesth Analg 2010), Critchley LA *et al.* (J Cardiothorac Vasc Anesth 2011).

approach in the clinical setting seems to be always one step behind.

D) Finally, at present there is no agreement in literature on what system should be used to monitor hemodynamic changes during LTx. The CCO technique is not considered the gold standard method for CO monitoring in LTx, but a recent Italian survey revealed that it is the most widely used device in this setting (88% of the Italian centres use CCO).[20] As mentioned above, TPDT may have some advantages over CCO during LTx, because during instability it would be preferable to have beat-by-beat continuous CO measurement rather than a built-in delay like the semi-continuous CO provided with the modified PAC. On the other hand, the PAC has a key advantage over TPDT in that it provides simultaneous recording of pulmonary artery pressures, cardiac filling pressures, and mixed venous oxygen saturation.[6, 9]

In conclusion, there is no "one size fits all" type of technique, and it is clear that it is not the monitoring itself that can improve outcomes but the changes in therapy guided by the data obtained. Large multicenter randomized controlled trials are warranted to prove the reliability of different monitoring techniques to track CO changes and improve outcomes in patients undergoing LTx.

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