The Validity of Central Venous to Arterial Carbon Dioxide Difference to Predict Adequate Fluid Management during Living Donor Liver Transplantation. A prospective observational study.

CURRENT STATUS: ACCEPTED

Mohamed Elayashy
Cairo University Kasr Alainy Faculty of Medicine

Hisham Hosny
Kasr Al-Ainy faculty of medicine, Cairo University

hishamhosny@kasralainy.edu.eg

Corresponding Author
ORCID: https://orcid.org/0000-0001-6797-6989

Amr Hussein
Cairo University Kasr Alainy Faculty of Medicine

Ahmed Abdelaal Ahmed Mahmoud
Beni Suef University Faculty of Medicine

Ahmed Mukhtar
Cairo University Kasr Alainy Faculty of Medicine

Amira ELKhateeb
Cairo University Kasr Alainy Faculty of Medicine

Mohamed Wagih
Cairo University Kasr Alainy Faculty of Medicine

Fawzia AboulFetouh
Cairo University Kasr Alainy Faculty of Medicine

Amr Abdelaal
Ain Shams University Faculty of Medicine

Hany Said
Ain Shams University Faculty of Medicine
Abstract
Background: to assess the validity of Central and Pulmonary CO2 gaps to predict and guide fluid management during liver transplantation. Methods: Intraoperative fluid management was guided by pulse pressure variations (PPV). PPV of ≥15% triggered fluid resuscitation with 250 ml albumin 5% boluses to restore PPV to <15%. Simultaneous blood sampling from central venous and pulmonary artery catheters (PAC) were collected to calculate central and pulmonary CO2 gap. Patients were considered Fluid Responsive (FRS) if fluid boluses restored PPV to <15% and Fluid non-Responsive (FnRS) if not. CO and lactate and their correlation to CO2 gaps were also recorded. Results: The discriminative ability of Central and Pulmonary CO2 gaps between the two statuses (FRS and FnRS) was poor. AUC of ROC were 0.698 and 0.570 respectively. The Central CO2 gap was significantly higher in FRS than FnRS (P=0.016), with no difference in Pulmonary CO2 gap between both statuses. Conclusion: Central and the Pulmonary CO2 gaps cannot be used alone as valid tools to predict fluid responsiveness and guide fluid management during liver transplantation. CO2 gaps do not correlate well with the changes in PPV or CO Trial registration: Clinicaltrials.gov NCT03123172. Registered on 31-march-2017

Background
End-stage liver disease (ESLD) patients undergoing orthotopic liver transplantation can be prone to severe hemodynamic and metabolic changes. In the dissection phase; bleeding and hypovolemia are frequent [1], while in the an-hepatic period venous return may decrease resulting in a reduction in left ventricular preload[2] while after de-clamping and starting the neo-hepatic phase, the reperfusion injury and metabolic derangement can be severe enough to cause serious consequences[3]. Adequate tissue perfusion is an essential component of oxygenation during high-risk surgery and may improve the outcome[4, 5]. Proper monitoring of fluid resuscitation has been shown to reduce organ failure and hospital stay[6, 7]. The early warning signals of tissue hypoxia, such as lactate, central venous to arterial CO2 gradient and central venous oxygen saturation (ScvO2)[8], are essential indicators of the changes in the O2 delivery/consumption (DO2/VO2) relationship during high-risk surgery [8–10].
The difference between PCO2 in mixed venous blood (PvCO2) and PCO2 in arterial blood (PaCO2) is defined as the mixed venous-to-arterial CO2 tension gap [Pulm (P-a) CO2] and is affected by cardiac output and global CO2 production, as well as the complex relationship between PCO2 and CO2 content[11]. Normally, Pulm(P-a) CO2 does not exceed 6 mmHg. Elevated [Pulm(P-a) CO2] gradient has been observed in all types of circulatory failure (cardiogenic, obstructive, hypovolemic and distributive shock)[12].

Pulse Pressure Variation (PPV) is derived from the analysis of the arterial pulse waveform and is currently integrated in many monitors and is used as a valid tool to predict fluid responsiveness and to guide fluid management during liver transplantation.[13]

To the best of our knowledge, no previous study assessed the ability of the Central CO2 gap or Pulmonary CO2 gap to predict fluid responsiveness and to guide optimization of fluid status during liver transplantation.

Our study aimed to assess the ability of the Central and Pulmonary CO2 gaps to guide adequate fluid management during liver transplantation. We hypothesize that CO2 gaps can be a complementary tool to PPV to guide adequate fluid management.

Methods

This prospective observational study was approved by the Research Ethics Committee of Kasr Al-Ainy faculty of medicine, Cairo University (N-21-2017) and written informed consents was obtained from all study participants. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03123172).

The study was designed to include 20 adult (>18 years) ASA III to IV physical status patients with an end-stage liver disease (ESLD) scheduled for orthotopic liver transplantation. Patients were excluded if they were less than 18 years old or suffering from chronic respiratory disease. Induction of anesthesia was performed using propofol, fentanyl, and atracurium and maintained with sevoflurane adjusted to achieve an expired minimal alveolar concentration (MAC) between 1–2% in a mixture of air/oxygen, fentanyl infusion (1–2 μg/kg/h), and atracurium infusion (0.5 mg/kg/h). Patients were mechanically ventilated (Dräger Primus®, Germany) with a 6–8 ml/kg tidal volume and respiratory
rate adjusted to maintain the ETCO2 between 4-4.6 kPa and positive end expiratory pressure (PEEP) of 5 cmH2O. Patients monitoring included five-lead ECG, pulse oximetry, invasive arterial blood pressure, core temperature, ETCO2, hourly UOP, and central venous pressure (CVP). A 7-Fr triple lumen CV catheter (Arrow International Inc, Reading, PA, USA) and an 8.5Fr pulmonary artery catheter sheath were placed in the right internal jugular vein and a pulmonary artery catheter (OPTIQ SVO2/CCO; Abbott Laboratories, North Chicago, IL, USA) was positioning guided by chamber pressures and confirmed with fluoroscopy. All patients received 6ml/kg crystalloids as maintenance intraoperative fluid. Pulse pressure variations (PPV) [Philips Intellivue MP50 monitor (Philips Medical Systems, BG Eindhoven, The Netherlands)] used to guide intraoperative fluid management. If pulse pressure variation (PPV) was more than 15%, the patient was considered as a fluid responder and received a 250-ml boluses of 5% albumin to maintain ≤15% PPV Arterial, central venous and pulmonary artery blood samples were collected and analyzed (ABL 300, Radiometer Copenhagen, Denmark). We calculated the central venous to arterial CO2 gap [C(v-a) CO2] and the pulmonary mixed venous to arterial CO2 gap [Pulm(P-a) CO2] at two time periods, 30 minutes after the start of the pre-anhepatic dissection phase and 30 minutes after the reperfusion of the transplanted graft. No data was recorded during the an-hepatic phase or during partial or complete obstruction of the IVC by either clamping or surgical manipulation. A transfusion trigger of 7 g/dL guided the need for blood transfusion while. Fresh frozen plasma and platelets were transfused if the INR reached > 1.5 and the count was <50,000/μl respectively guided by thromboelastography and according to the severity of bleeding.

Patient characteristics; age, weight, MELD Score, child score and associated HCC were recorded. Intraoperatively central CO2 and pulmonary CO2 gaps were recorded apart from during the anhepatic phase and IVC obstruction as described earlier. Cardiac output (CO), lactate, central venous oxygen saturation (ScvO2) and PPV were all recorded throughout the procedures.

Primarily, the current study aimed to investigate the ability of CO2 gaps to predict fluid responsiveness appreciated by PPV. Area Under the Curve (AUC) for Receiver Operating Characteristic (ROC) was used to calculate the discriminative ability of both CO2 gaps to distinguish between FRS
and FnRS with calculation of a cutoff value for either CO2 gaps should it be existing.

Secondarily, a comparison between central and pulmonary CO2 gaps in both fluid states (FRS and FnRS), the correlation of the CO2 gaps to the hemodynamic and metabolic parameters (PPV, CO and lactate), the correlation between hemodynamic and metabolic parameters (CO and lactate) and fluid responsiveness (FRS and FnRS) were also studied.

Sample size calculation:
The sample size was calculated after obtaining preliminary data of seven fluid non-responding status data points, which revealed a mean (SD) of the central CO2 gap to be 3.8 (1.7). Assuming a mean difference of 30% between responding and non-responding and by using G power software (version 3.1.3, Heinrich-Heine-Universität, Düsseldorf Germany) with a power of 0.8 and 0.05 alpha error sample size was calculated to be 20 patients.

Statistical analysis:
Central and pulmonary CO2 gaps, cardiac output and lactate level are presented as mean (SD). Mann-Whitney test was performed for comparison of cardiac output and the Central and the Pulmonary CO2 gaps. The Receiver Operating Characteristic (ROC) curves were constructed, and the area under the curve (AUC) calculated to compare the performance of the central CO2 gap and the pulmonary CO2 gap in predicting fluid responsiveness. MedCalc version 12.1.4.0 (MedCalc Software bvba, Mariakerke, Belgium) generated values with the highest sensitivity and specificity (Youden index). Comparison of the AUC of the ROC curves used a Hanley-McNeil test. Correlations between either central CO2 gap and pulmonary CO2 gap and each of CO, lactate and PPV were done using Pearson moment correlation equation. A P value of less than 0.05 was considered statistically significant. All but ROC curves statistical calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program.

Results
Twenty patients (16 males and 4 females) were enrolled in the study. Their mean (SD) age was 53.1 (7.6) years, mean (SD) weight 79.2 (11.5) kg, and mean (SD) height 170.1 (7.2) cm. Thirteen patients had ESLD following hepatitis C, two patients had a hepatocellular carcinoma (HCC), and five
patients had combined hepatitis C and HCC. Median (range) of MELD score was 17 (13-29). Fourteen patients had a child-class C, and six patients had a child-class B and fifteen patients presented with ascites. There were 67 data points recorded (20 FRS points and 47 FnRS points).

Mean values of central CO2 gap, pulmonary CO2 gap, lactate, ScvO2, and CO are presented in Table 1. Central CO2 gap was significantly higher in fluid-responder compared to the fluid non-responders (P=0.016). Lactate level, ScvO2, pulmonary CO2 and CO were comparable between both FRS and FnRS.

A correlation was found between the central CO2 gap and PPV (r=0.291, P=0.017) (Figure 1) and between the pulmonary CO2 gap and the PPV (r=0.367 and P=0.002) (Figure 2).

The ROC for the central CO2 gap and pulmonary CO2 gap to predict fluid responsiveness was 0.698 and 0.570 respectively. From ROC curve, the optimal cutoff value 3.6 was determined for the central CO2 gap to predict fluid responsiveness with sensitivity 83% and specificity 55%. (Figure 3)

There was no correlation between central CO2 gap and CO (r=0.168, P=0.17) or between pulmonary CO2 gap and CO (r=0.22) with P=0.076. Also, there was no correlation between either central or pulmonary CO2 gap and the lactate level(r) = 0.071 and 0.202 respectively.

Discussion
The target of the current study was to answer three questions; first, are the central and the pulmonary CO2 gaps valid indicators of fluid responsiveness in liver transplant patients? And is there a difference between the central and the pulmonary CO2 gaps in this setting? Second, do central and pulmonary CO2 gaps correlate with other hemodynamic and metabolic parameters such as CO, PPV and lactate? Third, are there any differences between fluid responding and fluid non-responding states in the hemodynamic and metabolic parameters?

For the first question, there were two main findings; (1) central CO2 gap was significantly higher in FRS than in FnRS during the pre- and post anhepatic phase of liver transplantation surgery, however the ability of the central CO2 gap to predict fluid responsiveness was weak (AUC=0.698) and the
cutoff gap value to predict fluid responsiveness was 3.6 mmHg. On the other hand, the pulmonary CO2 gap was comparable between FRS and FnRS. (2) Both central and pulmonary CO2 gaps were comparable (4.65 ±2.996 versus 4.31±3.34 respectively, P= 0.405) and both showed significant correlation (r=0.444, P value=0.0001). Possibly this contradiction between the two findings is the result of the presence of intrapulmonary shunt[14] in our patients characterized by cirrhosis and the high-risk present of hepato-pulmonary syndrome[15]. The similarity in hemodynamic pathophysiology between our patients and septic shock patients explains the agreement between our results and the previous findings of the use of CO2 gap in cases of septic shock, both gaps cannot be used alone as valid indicators of fluid responsiveness despite the central CO2 gap in our patients being higher in fluid responder, but the diagnostic validity of which remained weak. Based on our findings, veno-arterial CO2 gap cannot be relied upon as a tool to predict fluid responsiveness in these patients with complex hemodynamic and pathophysiological changes. Additionally, both CO2 gaps (central and pulmonary) are approximate and the central CO2 gap can replace the pulmonary[16–22]

Answering the second question, both CO2 gaps were only correlated with PPV but not with cardiac output or lactate level. PPV is a validated monitor for prediction of fluid responsiveness in major abdominal surgeries[13] however, the correlation of the CO2 gaps with PPV, despite being significant, was weak. this supports our finding that the CO2 gaps cannot be used alone as a valid predictors of fluid responsiveness in liver transplant patients.

Lactate level reflects both tissue anaerobic metabolism and the ability of the liver to metabolize it, with both conditions present in liver transplant patients during different phases of the transplant procedure (hepatic dissection, an-hepatic and neo-hepatic phases). Lactate level is a validated parameter to monitor adequate fluid resuscitation and the absent correlation between lactate and the CO2 gap in our patients supports the disputed validity of CO2 gaps as sole monitor of fluid responsiveness. Mekontso et al [23] confirmed the correlation between CO2 gap and lactate level during hypoxic metabolic states with decreased oxygen consumption. Mekontso et al. used the ratio, rather than the absolute value, of CO2 gap to arterio-venous oxygen difference to relate to lactate
levels.

for a constant total CO2 production (VCO2), changes in cardiac output result in large changes in pulmonary CO2 gap at low cardiac output values, whereas changes in cardiac output will not result in significant changes in pulmonary CO2 gap at the high values of cardiac output [22, 24] This relation supports our finding of the absence of correlation between CO2 gaps and the CO in our patients known to have a high CO as part of the pathophysiology of liver cirrhosis.

Moving forward to the third question, FRS and FnRS patients were comparable regarding their lactate level, pulmonary CO2 gap and CO. These findings support the verdict not to rely only on CO2 gaps alone as valid indicators of fluid responsiveness.

In our study, both central and pulmonary CO2 gaps correlated with PPV. Cuschieri et al. [25] and Van Beest PA et al [26] showed strong agreement between central and pulmonary CO2 gaps in their studies of critically ill patients and on septic patients. In the current study, there was no correlation between central and pulmonary CO2 gaps with cardiac output. Many studies [12, 25, 27] stated an increased central CO2 gap in low cardiac output states due to venous flow stasis which decreased with increased cardiac output. Cuschieri et al [25] showed the correlation between the central CO2 gap and the pulmonary CO2 gap with cardiac index. Troskot et al [12] concluded in their study of patients with severe sepsis and septic shock that the central CO2 gradient could predict fatal outcomes in non-ventilated patients only. Also, Mallat et al.[11] in their study on 80 patients with sepsis, measured the central CO2 gap and cardiac index using PICCO technology at time 0 (start of the study) and at time 6 (6 hours after resuscitation) and found a correlation between CO2 gap and CI at T0 (r = -0.69, P<0.0001) and at T6 (r = -0.54 P<0.0001). Also, the changes in CI between T0 and T6 were also correlated with changes in CO2 gap (r= -0.62, P<0.0001)

In our study, the central CO2 gap did not correlate with cardiac output presumably due to the hyperdynamic state of the hepatic patient which preserves systemic blood flow even in states of
tissue hypo-perfusion. Mecher et al. [28] studied 37 septic patients divided into two groups according to the central CO2 gap; high gap group >6 mmHg and normal gap group <6 mmHg. They found normal gap group to have a high cardiac index (3±0.2) despite circulatory failure. In this group; the gap did not change after fluid resuscitation (pre-fluid gap 4±0 vs. post fluid 4±1 mmHg) with an increase in cardiac index. While in the other group cardiac index was lower (2.3±0.2) and gap decreased after resuscitation.

In our results, there was no correlation between either central CO2 gap or pulmonary CO2 gap and the lactate level. This was consistent with the study of Vallee et al. [29] in which 50 patients with septic shock, hyperlactatemia > 2 mmol/L and ScvO2> 70% were enrolled. Patients were divided into two groups according to central CO2 gap with cut off value of 6 mmHg, low gap (<6mmHg), and high gap (>6mmHg). Patients’ resuscitation resulted in significantly larger clearance of lactate in low gap group than high gap group. There was also no correlation between CvCO2 gap and lactate level at time of inclusion T0 (r = 0.17, P = 0.22.) and poor correlation at six hours T6 (r = 0.37, P = 0.003) and twelve hours T12 (r = 0.36, P = 0.008).

In agreement with our results, Monnet et al. [30] found that volume expansion in all patients increased cardiac index and there was correlation between pulmonary CO2 gap and cardiac index at baseline (r = -0.36, p = 0.0002) but not between pulmonary CO2 gap and lactate at baseline (p = 0.58). Also, Mecher et al. [28] showed no significant decrease in Pulmonary CO2 gap and lactate after fluid resuscitation in all patients with severe sepsis and systemic hypo-perfusion involved in the study.

fCO2 gap was found to be complementary tool for early resuscitation of patients with circulatory failure. [31] In the present study, despite the presence of significant difference in the central CO2 gap between fluid responding and non-responding states, the validity of CO2 gap is poor which makes its use to guide fluid resuscitation in liver transplant recipient is questionable. The present study had several limitations. First, This is a single center experience. Second, we avoided periods of marked hemodynamic instability caused by manipulation of the liver and downward retraction of the inferior
vena cava which may intermittently obstruct venous return and causing hemodynamically significant changes in preload. Such changes in the preload are typically transient and may not reflect the actual volume status of the patient. Finally, we did not compare the CO2 gaps recorded during the pre-anhepatic phase to the CO2 gaps recorded during the neo-hepatic phase as the two periods represent different hemodynamic and pathophysiologic situations with the presence of a cirrhotic liver in the former and a potentially healthy graft in the latter. A future study can check this aspect.

Conclusion
Both central CO2 gap and pulmonary CO2 gaps could not be used to predict fluid responsiveness or to guide adequate fluid management during living related liver transplantation. Both CO2 gaps could be used interchangeably, and both did not correlate well with changes in cardiac output or lactate level. These results suggest that CO2 gap may not be a good hemodynamic endpoint of resuscitation of patients undergoing living related liver transplant.

Declarations
Ethical approval and consent to participate: study has been approved by Kasr Al-Ainy faculty of medicine ethics committee, Cairo University. (N-21-2017). written informed consents was obtained from all study participants

Trial registration: Clinicaltrials.gov Identifier: NCT03123172. Registered on 31-march-2017

All authors read and approved the manuscript

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare no competing interests. HH is an associate editor in BMC anaesthesiology

Funding: No external funding received

Authors contribution:
HH: collected data and revised the manuscript

ME: collected data and wrote the initial manuscript and performed analysis.

AH: collected data and wrote the initial manuscript and performed analysis

AM: revised manuscript and data analysis

AM: study design and revised the manuscript and data analysis

FA: study design and revised the manuscript

AA: patient recruitment and revised the manuscript

HS: patient recruitment and revised the manuscript

MA: patient recruitment and revised the manuscript

AE: revised the manuscript and data analysis and replied to reviewers' comments

MW: revised the manuscript and data analysis and replied to reviewers' comments

Acknowledgements: N/A

List Of Abbreviations

ASA: American society of anesthesiologists

AUC: Area Under the Curve

C(v-a) CO2: central CO2 gap

CO: Cardiac output

CO2: carbon dioxide
CVP: central venous pressure

DO2/VO2: O2 delivery/consumption

ECG: electrocardiogram

ESLD: End-stage liver disease

ETCO2: end tidal CO2

FnRS: fluid non-responsive status

FRS: fluid responsive status

HCC: hepatocellular carcinoma

MAC: minimal alveolar concentration

PAC: pulmonary artery catheter

PaCO2: arterial carbon dioxide pressure

PCO2: partial carbon dioxide pressure

PEEP: positive end expiratory pressure

PPV: Pulse pressure variations

Pulm (P-a) CO2: mixed venous-to-arterial CO2 tension gap

PvCO2: mixed venous carbon dioxide pressure

ROC: Receiver Operating Characteristic
ScvO2: central venous oxygen saturation

UOP: urine output

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Table 1
Table 1: Comparison between fluid responding status (FRS) and Fluid non-Responding Status (FnRS).
Values presented as Mean (SD).

|                         | Fluid Responding Status (N= 20) | Fluid non-Responding Status (N=47) | P value |
|-------------------------|---------------------------------|------------------------------------|---------|
| C(v-a) CO2gap           | 5.5(2.6)                        | 4.3(3.2) *                        | 0.016   |
| Pulm(P-a) CO2 gap       | 5.16(4.24)                      | 3.96(2.89)                        | 0.18    |
| Lactate                 | 3.9(1.6)                        | 3.5(2.3)                          | 0.18    |
| CO                      | 6.7(2.6)                        | 8.8(3.4)                          | 0.06    |
| Scvo2                   | 80.3(12.1)                      | 82.5(11.9)                        | 0.32    |

*P value = 0.016 with significant difference between two groups. Mann Whitney test. N= Number of
data points, C(v-a) CO2; central venous to arterial carbon dioxide tension difference, Pulm(P-a) CO2; mixed venous to arterial carbon dioxide tension difference, CO; cardiac output, Scvo2; central venous oxygen saturation.

Figures

Figure 1
Correlation between PPV and C(v-a) CO2 gap. C(v-a) CO2; Central venous to arterial carbon dioxide tension difference, PPV; pulse pressure variation.

Figure 2
Correlation between PPV and Pulm(pv-a) CO2 gap. Pulm(p-a) CO2; mixed venous to arterial carbon dioxide tension difference, PPV; pulse pressure variation

Figure 3
ROC curve of C(v-a) CO2 gap and Pulm(pv-a) CO2 gap. C(v-a) CO2; central venous to arterial carbon dioxide tension difference, Pulm(p-a) CO2; mixed venous to arterial carbon dioxide tension difference

Figure 4
Correlation between CO and C(v-a) CO2 gap. C(v-a) CO2; central venous to arterial carbon dioxide tension difference.

Figure 5
Correlation between CO and Pulm(p-a) CO2 gap. Pulm(p-a) CO2; Mixed venous to arterial carbon dioxide tension difference.

Figure 6
Correlation between Lactate and C(v-a) CO2 gap. C(v-a) CO2; central venous to arterial carbon dioxide tension difference.
Figure 7

Correlation between Lactate and Pulm(pv-a) CO2 gap. Pulm(p-a) CO2; Mixed venous to arterial carbon dioxide tension difference.