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Oesophageal Doppler guided optimisation of cardiac output does not increase visceral microvascular blood flow in healthy volunteers

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Abstract

Background

Oesophageal Doppler Monitoring (ODM) is used clinically to optimise cardiac output (CO) and guide fluid therapy. Despite limited experimental evidence, it is assumed that increasing CO increases visceral microvascular blood flow (MBF). We used contrast-enhanced ultrasound (CEUS) to assess if ODM-guided optimisation of CO altered MBF.

Methods

Sixteen healthy male volunteers (62±3.4 years) were studied. Baseline measurements of CO were recorded via ODM. Hepatic and renal MBF were assessed via CEUS. Saline 0.9% was administered to optimise CO according to a standard protocol and repeat CEUS performed. Time-intensity curves were constructed, allowing organ perfusion calculation via time to 5% perfusion (TT5). MBF was assessed via organ perfusion rise time (5-95%) (RT).

Results

CO increased (4535 ± 241 ml/min vs 5442 ± 329ml/min, p<0.0001) following fluid administration, while time to renal (22.48 ± 1.19secs. vs. 20.79 ±1.31secs; p=0.03), but not hepatic (28.13 ± 4.48s. vs 26.83 ±1.53secs; p=0.15) perfusion decreased. Time to renal perfusion was related to CO (renal: r=-0.43, p=0.01). Hepatic nor renal

RT altered following fluid administration (renal: 9.03 ± 0.86 vs. 8.93 ± 0.85secs p=0.86; hepatic: 27.86 ± 1.6 vs. 30.71 ± 2.19secs, p=0.13). No relationship was observed between changes in CO and MBF in either organ (renal: r=-0.17, p=0.54; hepatic: r=-0.07, p=0.80).

Conclusions

ODM optimised CO reduces time to renal perfusion but does not alter renal or hepatic MBF. A lack of relationship between microvascular visceral perfusion and CO following ODM-guided optimisation may explain the absence of improved clinical outcome with ODM monitoring.

Trial Registration

The study was registered at clinicaltrials.gov (reference number NCT02167178).

Keywords

Contrast-enhanced Ultrasound, CEUS, oesophageal Doppler, healthy volunteers, cardiac output.

Background

The ability to measure cardiovascular performance is integral to anesthetic and critical care practice. Traditional clinical monitoring modalities such as blood pressure (BP), heart rate (HR), and central venous pressure fail to provide a continuous, accurate assessment of microvascular haemodynamic performance or identify instances of tissue hypoperfusion [1, 2] with uncorrected tissue hypoperfusion increasing surgical morbidity and mortality [3].

Alternative monitoring techniques provide estimates of stroke volume (SV) in an attempt to guide fluid and vasoactive drug therapy and optimise tissue perfusion. Traditional measurement of SV involved insertion of a pulmonary artery flotation catheter (PAFC) and measurement via thermodilution techniques. PAFC use has declined over the past decade, primarily due to concerns about the complications of insertion and an absence of studies demonstrating clinical benefit [4, 5]. Consequently, less invasive techniques for measuring SV have been developed. Thermodilution, however, remains the gold standard for the assessment of SV against which new monitors are compared [6].

The oesophageal Doppler monitor (ODM) is one such less invasive monitoring device. ODM has been validated against PAFC thermodilution techniques in a number of patient populations [7]. ODM has allowed a number of algorithms to be

developed to guide intravenous (IV) fluid administration [8-11]. It is recommended for intra-operative use by the National Institute for Health and Care Excellence (NICE) and has been advocated for use in awake patients [12].

SV and cardiac output (CO) are intrinsically linked, with CO the product of SV and HR. Whilst ODM permits reproducible estimates of CO, it is unclear what benefits are brought to the patient by its use. Despite studies initially suggesting a reduction in morbidity and mortality with ODM guided perioperative fluid therapy [13, 14], recent randomised controlled trials and meta-analysis' have questioned these conclusions [15, 16]. CO monitoring provides more information than pressure-related measures, but it is limited to the assessment of changes in whole-body haemodynamics. The complexity of regulatory mechanisms that have been observed to impact upon blood flow through the abdominal organs would suggest that no simple relationship can exist between CO and visceral perfusion. This challenges the notion that clinical benefit will directly result from maximisation of CO. Therefore, assessment of visceral microvascular blood flow (MBF) (e.g. in the gastrointestinal mucosa during and after abdominal surgery) may provide more relevant end points for guiding fluid therapy to reduce perioperative visceral hypoperfusion.

Contrast enhanced ultrasound (CEUS) is an imaging modality that can provide near-real time imaging of perfusion within viscera at a capillary level. CEUS has been validated for accurately measuring visceral blood flow against a number of proven technologies. Numerous *in-vitro* and *in vivo* studies, have validated the accuracy of

CEUS in assessing microvascular blood flow, demonstrating close correlation with thermodilution [17], mechanically controlled flow [18] and end organ microvascular perfusion [19], [20] .

CEUS utilises echogenic microspheres that return a characteristic echo pattern. During CEUS, intravenous administration of a bolus of the contrast agent permits construction of time-acoustic intensity (AI) curves. From these curves the time from bolus to 5% of peak AI (TT5) for each organ, pre- and post-fluid administration and rise time (RT), defined as the time taken to rise from 5-95% of the peak AI (Figure 1), may be calculated. This technique has previously been validated as a method of tracking changes in MBF of the intra-abdominal viscera [21, 22].

We hypothesised that administration of intravenous (IV) fluid to achieve ODM-guided CO optimisation would reliably track visceral perfusion in both liver and kidney of a healthy individual.

Methods

The University of Nottingham Medical School Research Ethics Committee (A12012012) granted ethical approval for the study. The study was registered at clinicaltrials.gov (reference number NCT02167178) and conformed to the Declaration of Helsinki. Sixteen healthy male participants aged between 18 and 80 years were recruited using a standard demographically targeted postal invite. Participants attended for a pre-study health screening appointment and written informed consent was obtained. Participants were excluded if they presented with: BMI <20 or >30 $kg \cdot m^{-2}$, recent acute coronary syndrome, use of β-blockers, cerebrovascular disease, metabolic disease, known malignancy, clotting dysfunction, previous oesophageal surgery or oesophageal varices, history of epistaxis or known sensitivity to SonoVue™. For subject demographics see Table 1.

Subject preparation

Subjects attended the University of Nottingham; Clinical, Metabolic and Molecular Physiology laboratories fasted for 12 hours of food and fluids. A medically qualified doctor was present throughout the study and subjects were continuously monitored with pulse oximetry (SpO_2), electrocardiogram (ECG) and non-invasive blood pressure recording (NIBP). A 20G intravenous cannula was sited in the right ante-brachial vein and an 18G in the left. Venous blood was drawn for measurement of haemoglobin concentration (Hb) and haematocrit (Hct). A trans-oesophageal Doppler probe (Deltex Medical, Chichester, UK) was inserted into the oesophagus via the nostril, following local anesthesia to the naso-pharynx with 10% lidocaine

spray and 2% lidocaine gel (ClinMed Ltd, High Wycombe, United Kingdom). The probe was connected to a CardioQ Oesophageal Doppler Monitor (ODM) (Deltex Medical) and probe position was corrected to achieve an optimal Doppler flow signal. ODM placement was well tolerated by all subjects.

Contrast agent

SonoVue™ (Bracco SpA, Milan, Italy), an established contrast agent for quantitative CEUS [23] was used, with preparation as per the manufacturer's instruction [24]. In brief, 25mg of lyophilised powder was reconstituted with 5ml of 0.9% sodium chloride solution (NaCl) in an SF_6 atmosphere.

Ultrasound settings

A Philips iU22 ultrasound machine (Philips Healthcare, Reigate, UK) with a C5-1 MHz curvilinear probe (Philips Healthcare) was used for all examinations, using dual contrast/tissue side-by-side mode. Cine recordings were made at 9Hz with a contrast resolution of C40, a working mechanical index (MI) of 0.04, a maximum depth of 16cm and focus at 8-14cm. Gain was optimised for each subject.

Experimental protocol

Patients were placed in a semi-recumbent position. The ultrasound probe was positioned to allow concurrent imaging of the liver and right kidney with probe

position manipulated to optimise visualised liver and renal parenchyma. Following optimisation the probe position was marked with ink to facilitate repeat visceral imaging.

Once the probe was positioned and marked baseline recordings of SpO_2, ECG, mean arterial blood pressure (MAP), HR and SV were made. CEUS was then performed by administering a rapid bolus of 0.5ml of SonoVue™ via the 20G cannula, immediately followed by a rapid flush of 5ml of 0.9% NaCl. At the same time, a continuous, real-time low MI ultrasound recording of the liver and kidney commenced, and continued for 2 minutes. After each 2 minute cycle, a 5 minute pause was observed, to allow elimination of microbubbles. During which time SpO_2, MAP, SV and HR were again measured. This sequence was repeated three times.

Subjects were then given a 250ml bolus of 0.9% NaCl solution as rapidly as possible via the 18G cannula with a 50ml syringe and 3-way tap used to facilitate rapid infusion of an accurate fluid volume. On completion of this bolus, SV, HR, NIBP and SpO_2 were recorded. Repeat fluid boluses were administered and observations made until the SV no longer increased by >10%, at which point the SV was deemed optimal [11]. Median fluid administration to optimise SV was 1000ml (IQR 1000-1000ml, range 1000-2000ml). Immediately after optimisation of SV a further set of CEUS recordings and cardiovascular observations were performed, using the protocol outlined above. A further blood sample was then taken for measurements of

hemoglobin (Hb) and hematocrit (Hct). Patients were monitored for 30 minutes following completion of the study protocol (Figure 2).

Image processing

Ultrasound video files were analysed using QLAB™ software (Philips Healthcare). Regions-of-interest (ROI) were defined within liver and kidney images to allow computation of the mean pixel intensity within each ROI for each frame of the ultrasound loop (Figure 3). The ROI was chosen to ensure as large an area as possible was available for analysis, whilst avoiding tissue close to the capsule of each organ to minimise the effect of the subtle movement of these organs seen with respiration. Large hilar blood vessels were excluded from the ROI to achieve preferential assessment of microvascular haemodynamics.

Image analysis

For each bolus injection, ROI AI was calculated for liver and kidney from each frame (i.e. at 9Hz) and subsequently standardised to that organs maximum intensity. Standardised AI traces were smoothed and low-pass filtered by calculation of a 3 second moving average. The resultant time–intensity trace was used to measure RT (time from 5-95% of peak AI) and TT5 (time from bolus to 5% of peak AI) for each organ pre- and post-fluid administration. Results were averaged across the 3 cycles recorded at each time-point.

Cardiovascular parameter analysis

Data for SV, MAP, HR, Hb, Hct and SpO_2 were recorded as described above and data stored on an Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA). Mean values for each of these variables before and after SV optimisation were recorded.

Statistics

Sample size calculations required n=16 (for α=0.05, β=0.85), to detect a 30% change in hepatic microvascular blood flow, results we have been able to achieve for previous work looking at similar physiological systems. Statistical analysis was performed using GraphPad Prism™ v6.0 (La Jolla, CA. USA). Distribution of data was tested using Kolmogorov-Smirnov tests, with normal data expressed as mean ± standard error of the mean (SEM) and non-normal data as median ± interquartile range. Independent *t*-tests were applied to normal data and Mann-Whitney tests to non-normal data. Categorical values were compared using Fisher's test. $p<0.05$ was considered significant.

Results

CO and SpO_2 increased significantly following fluid administration (4535±241 vs. 5442 ± 329 $ml \cdot min^{-1}$, *P*<0.0001; 96.9±0.4 vs. 97.8±0.3%, *p<0.*01, respectively), whilst Hb and Hct decreased (149±2.5 vs. 138.5±2.8 $g \cdot l^{-1}$, p<0.01; 0.441±0.01 vs. 0.412±0.01, *p*<0.01, respectively). MAP and HR remained unchanged following fluid administration (105.3±2.4 vs. 106.3±2.8 mmHg, p=0.31; 61.8±1.8 vs. 62.1±1.9 bpm, p=0.54, respectively).

Despite increases in CO and decreases in Hct following fluid administration, MBF was not altered by fluid administration in either the hepatic (RT: 27.86±1.6 vs. 30.71±2.19 secs, p=0.13) or renal (RT: 9.03±0.86 vs. 8.93±0.85 secs, p=0.86) circulation (Figure 4). Likewise no relationship was observed between CO and MBF in either the kidney (r=-0.17, p=0.54) or liver (r=-0.07, p=0.8) (Figure 5).

Time to renal perfusion decreased following fluid administration (TT5: 22.48±1.19 vs. 20.79±1.31 secs, p= 0.03), whilst time to hepatic perfusion was unaltered (TT5: 28.13±4.48 vs. 26.83±1.53 secs, p=0.15.). Similarly time to renal, but not hepatic perfusion, was correlated with CO (renal: r=-0.43, p=0.01; hepatic: r=-0.21, p=0.26) (Figure 5).

There was no significant relationship observed between change in cardiac output (Δ CO) and change in renal rise time (Δ renal RT), (r=-0.17 and p=0.27). A significant

correlation was observed between Δ CO and change in renal TT5 (Δ TT5), (r=-0.50, p=0.05; Figure 6).

In the hepatic circulation, Δ CO did not correlate with change in hepatic rise time (Δ hepatic RT), (r=0.07, p=0.40); nor with change in hepatic TT5 (Δ hepatic TT5), (r=0.09, p=0.36).

Discussion

In this study we use the novel technologies of CEUS and ODM to explore the relationship between CO and MBF. As expected fluid administration reliably increased CO, reduced time to renal perfusion and reduced haematocrit. Despite these changes in macrocirculatory variables, CO showed no significant correlation with measures of MBF in either renal or hepatic circulations.

The relationship between venous filling and SV is relatively simple, and is described by the Frank-Starling law; essentially, higher filling pressures lead to greater preload, and hence more forceful contraction of myocardial fibers, resulting in a greater SV and thus CO [25] (other afterload mediated effects remaining constant over the short period of this study).

The relationship between MBF and fluid administration is more complex, with multiple factors affecting perfusion of the liver and kidney. Strong autoregulatory mechanisms exist within the kidney to maintain a constant blood flow across a range of blood pressures and volaemic conditions [26]. In this healthy volunteer study these mechanisms are likely to have remained intact.

The autoregulatory ability of the liver is less robust; with the main determinants of hepatic perfusion being sympathetic nervous system activity, circulating catecholamines, and the interaction between the arterial and portal venous circulations (the hepatic arterial buffer response) [27]. In hypovolaemia, large volumes of blood may be mobilised from the splanchnic circulation to preserve perfusion of the brain, heart and musculature [28]. Hypovolaemia reduces splanchnic perfusion, portal venous flow and hence hepatic blood flow and these effects persist for some time after restoration of euvolaemic [29].

These complex interactions challenge simplistic assumptions that SV and CO are key determinants of MBF. As microvascular perfusion is vital for normal organ function and tissue healing, including for example, at anastomoses, this lack of response to SV optimisation with intravenous fluid may help to explain why recent publications and meta-analyses have failed to show a consistent reduction in morbidity or mortality when ODM-guided fluid management protocols have been used in the perioperative period [15, 16].

There are a number of limitations to this present study. Firstly, the use of healthy subjects may limit the applicability of the findings to the perioperative and critical care patient. Also in an attempt to somewhat mirror a clinical population subjects were taken from a predominantly older male age range, which may limit the conclusions of this study to a wider clinical group. Subjects were hypovolaemic after a 12-hour fast, as evidenced by the increase in SV with intravenous administration of c. 1L of IV crystalloid, and this reflects modern surgical practice [30]. However, the impact of anaesthesia has not been addressed in this study. Additionally, as ODM measurement of cardiac output varies with change in subject position, it was decided that subjects should studied in a semi-recumbent position to aid subject comfort. This position corresponds to the recommended positioning for patients on the intensive care unit. Importantly participant position was not altered between CEUS measurements, in order to reduce any error due to change in subject or probe positioning. However, findings may therefore not be relevant in a population in a fully recumbent position.

The absolute values of CO measured in this study by ODM are in several instances around 3L per minute. This is lower than would be expected for a healthy male population and may relate to position and relatively increased age of the study volunteers. In addition, although ODM measurements were taken by clinicians, experienced and skilled in the use of ODM monitoring, there are undoubted limitations to the use of ODM to acquire exact discrete measures of cardiac output. Furthermore, ODM calculates the volume of blood transiting the descending aorta and employs a number of assumptions to calculate cardiac output from this, while by necessity excluding perfusion of head and upper limbs. Although these factors may

have resulted in lower than expected numerical values for CO the ability of the ODM to accurately determine changes in cardiac output is preserved.

Efforts were made to ensure consistency of tissue imaged throughout. Despite this, absolute probe fixation is not possible and small movements, such as with respiration, induce movement artifact to CEUS measures [31]. To overcome this problem, we employed a validated time-based surrogate for tissue perfusion, the RT, which is more robust to small variations in the imaged tissue [22]. This technique does provide a less comprehensive assessment of microvascular status than techniques that generate volumetric data [21, 31], such as microbubble destruction-replenishment [18], but is ultimately more reliable in this cohort of subjects.

A sample size calculation was determined for the primary hypothesis of a 30% change in hepatic microvascular blood flow following fluid optimisation. Despite ODM assessed fluid optimisation we found no significant change in hepatic microvascular blood flow. Of note, the study was not powered to expose a relationship between the change in CO and change in MVBF before and after fluid optimization and thus may have been underpowered for detect such a relationship. It is important however to note, that there was also no suggestion of a clear relationship between CO and RT (r=-0.07 (hepatic), r=-0.17 (renal)).

Conclusion

This study describes a bolus method for comparison of ODM-derived CO and CEUS-derived measures of renal and hepatic perfusion in the healthy, awake subject. Our data suggest that ODM guided fluid administration reliably increases CO and time to

renal perfusion, but that such changes do not increase MBF within hepatic or renal parenchyma. This challenges the assumption that optimisation of CO improves abdominal visceral perfusion. The inability of ODM-guided fluid management to increase renal and hepatic MBF may be a factor in the lack of improved clinical outcome with ODM monitoring.

List of Abbreviations

CO – Cardiac Output

ODM – Oesophageal Doppler Monitoring

MBF - Microvascular blood flow

RT - Rise time (5-95%)

SV – Stroke Volume

TT5% - Time to 5%

Competing Interests

The other authors declare that they have no competing interests.

Author contributions

TPH – Analysis and acquisition of data, drafting/revising article, final approval of submitted article

DJR – Data analysis, drafting/revising article, final approval of submitted article

WKM – Concept and design of study, data acquisition and analysis, drafting/revising article, final approval of submitted article

AB – Concept and design of study, data acquisition and analysis, revising article, final approval of submitted article

BEP – Concept and design of study, data acquisition and analysis, revising article, final approval of submitted article

JNL – Concept and design of study, data analysis, revising article, final approval of submitted article

JPW – Concept and design of study, data analysis, revising article, final approval of submitted article

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Tables

Table 1. Subject demographic data

	Mean	Standard Deviation
Age (years)	62	±13.6
Height (m)	1.76	±0.06
Weight (kg)	83.8	±10.3
BMI (kg/m^2)	27.1	±2.4

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Legends for Figures

Figure 1. Example time-intensity curve for the liver. Dotted lines show 5 and 95% of the maximum values. In this example, the 5% value is 0.037 arbitrary units (AU), occurring at 18.41 seconds (TT5). The 95% value is 0.699 AU, occurring at 32.83 seconds, resulting in a rise time of 14.42 seconds.

Figure 2. Outline of study protocol. SV, Stroke Volume; CEUS, Contrast Enhanced Ultrasound; Hb, Haemoglobin; Hct, Haematocrit; SpO_2, Oxygen saturation; NIBP, Non-invasive blood pressure; ECG, Electrocardiogram.

Figure 3. Example of region of interest quantification in QLAB™ software. Top - regions of interest defined on the contrast-enhanced image of the liver (red) and kidney (yellow), Bottom - graph of acoustic intensity against time, as output from QLAB™ for liver (red) and kidney (yellow).

Figure 4. Normalised Cardiac output, renal rise-time and hepatic rise-time before and after fluid optimisation, **** *significant difference, pre- vs. post-fluid administration, p<0.0001.*

Figure 5. Rise time (RT, sec) within the hepatic (A) and renal (B) microcirculations plotted against cardiac output (hepatic r= -0.07, p=0.8; renal r= -0.17, p=0.54). Time

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to 5% perfusion (TT5, sec) within the hepatic (C) and renal (D) microcirculations plotted against cardiac output (hepatic r=-0.21, p=0.26; renal r=-0.43, p=0.01).

Figure 6. Change in rise time (Δ RT, sec) within the hepatic (A) and renal (B) microcirculation plotted against change in cardiac output (Δ CO, l/min). Change in Time to 5% perfusion (Δ TT5, sec) within the hepatic (C) and renal (D) microcirculations plotted against change in cardiac output (ΔCO, l/min)

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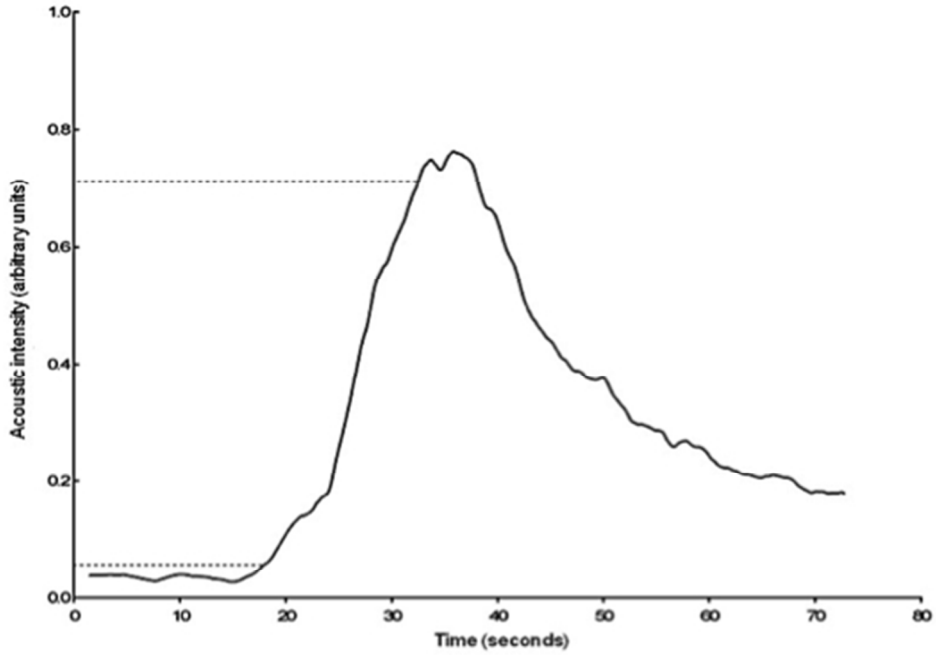

Figure 1. Example time-intensity curve for the liver. Dotted lines show 5 and 95% of the maximum values. In this example, the 5% value is 0.037 arbitrary units (AU), occurring at 18.41 seconds (TT5). The 95% value is 0.699 AU, occurring at 32.83 seconds, resulting in a rise time of 14.42 seconds.

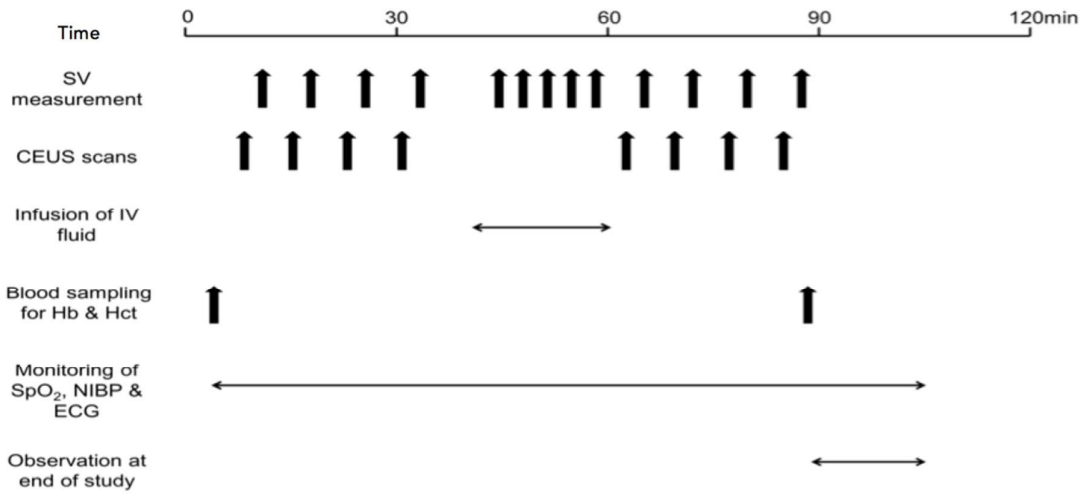

Figure 2

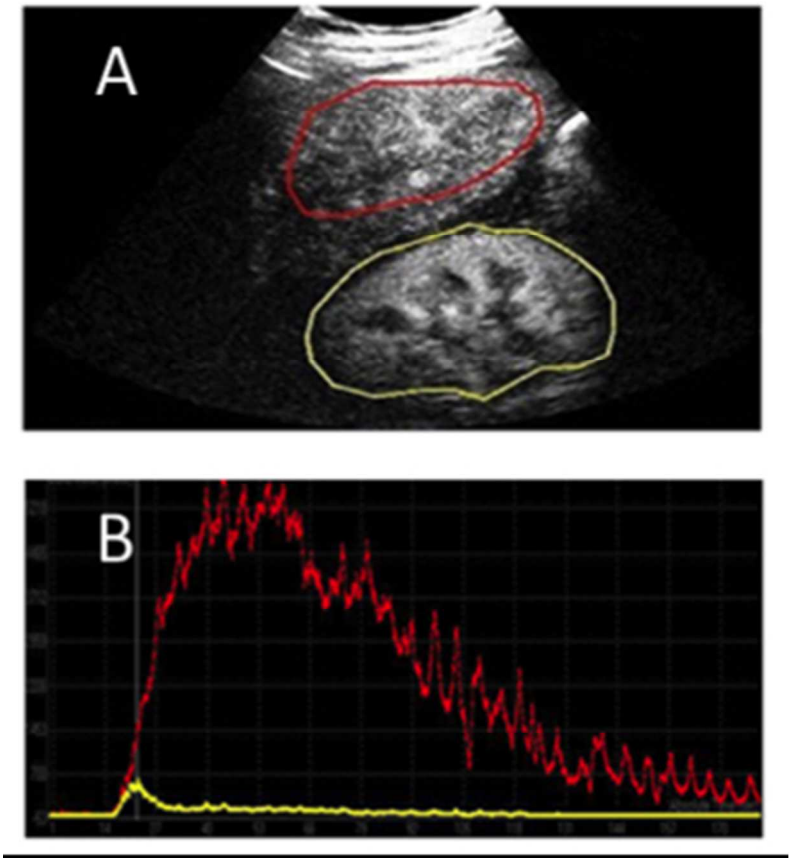

Figure 3. Example of region of interest quantification in QLAB™ software. Top - regions of interest defined on the contrast-enhanced image of the liver (red) and kidney (yellow), Bottom - graph of acoustic intensity against time, as output from QLAB™ for liver (red) and kidney (yellow).

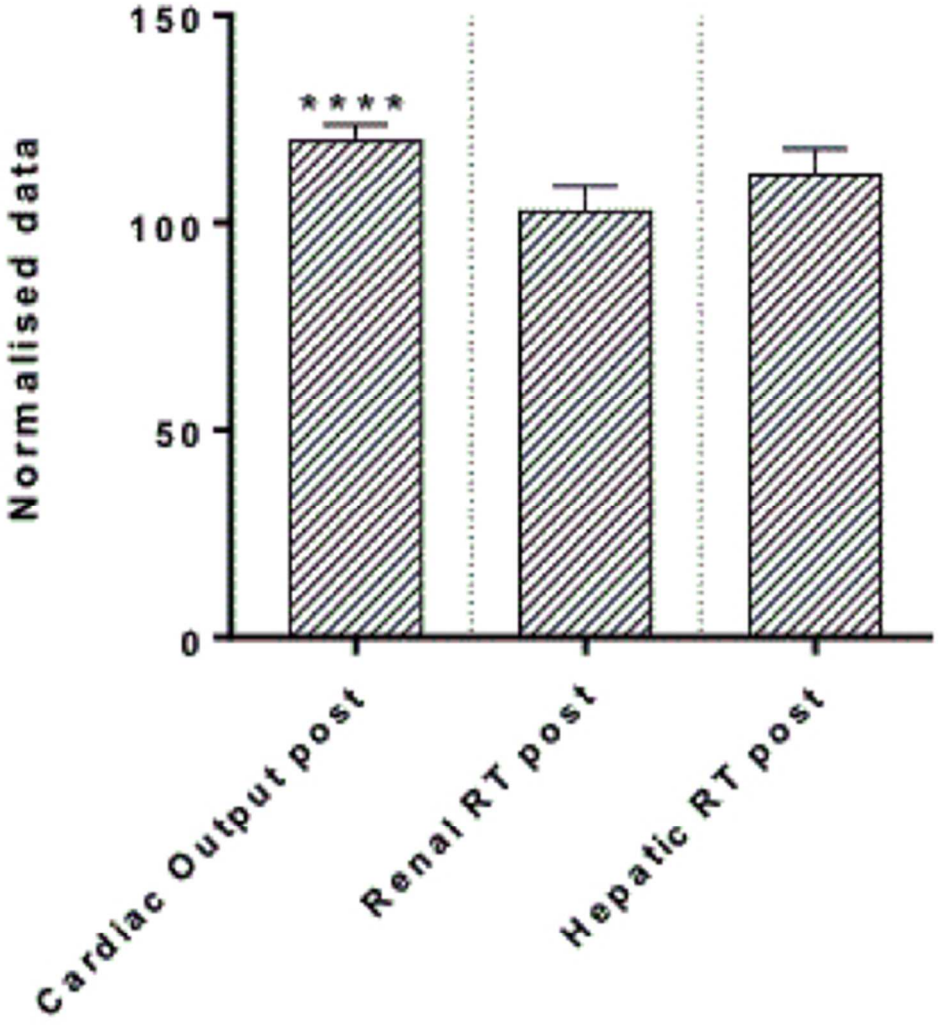

Figure 4. Normalised Cardiac output, renal rise-time and hepatic rise-time before and after fluid optimisation, **** significant difference, pre- vs. post-fluid administration, $p<0.0001$.

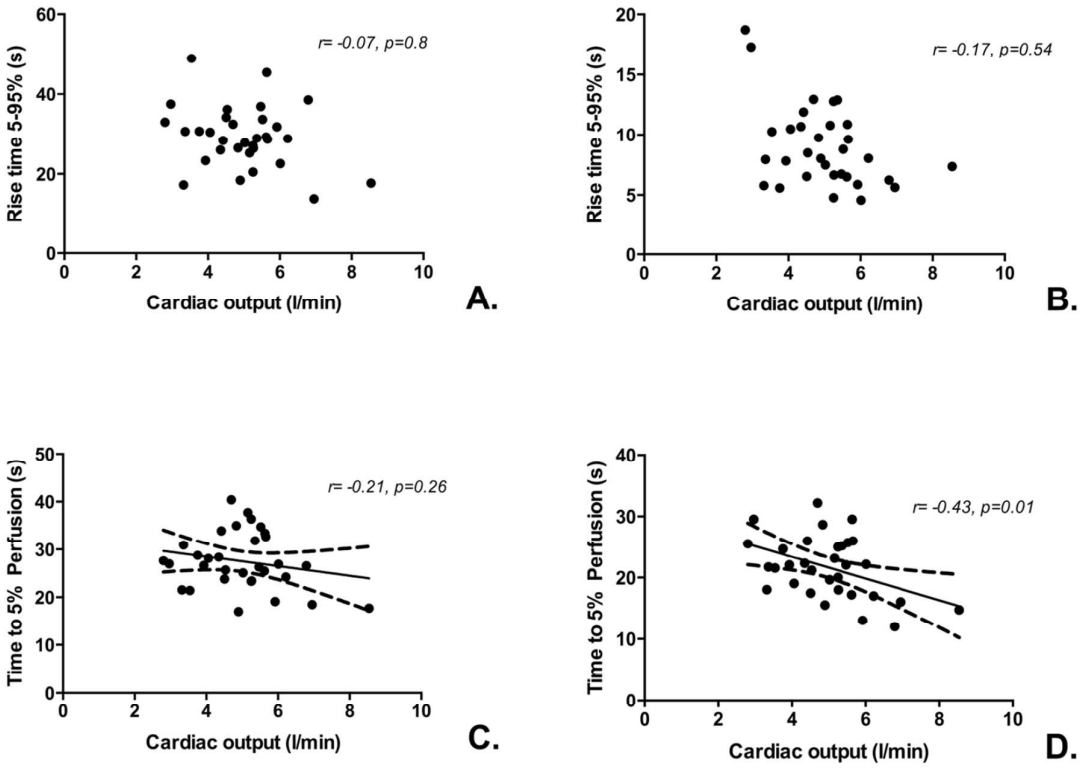

Figure 5

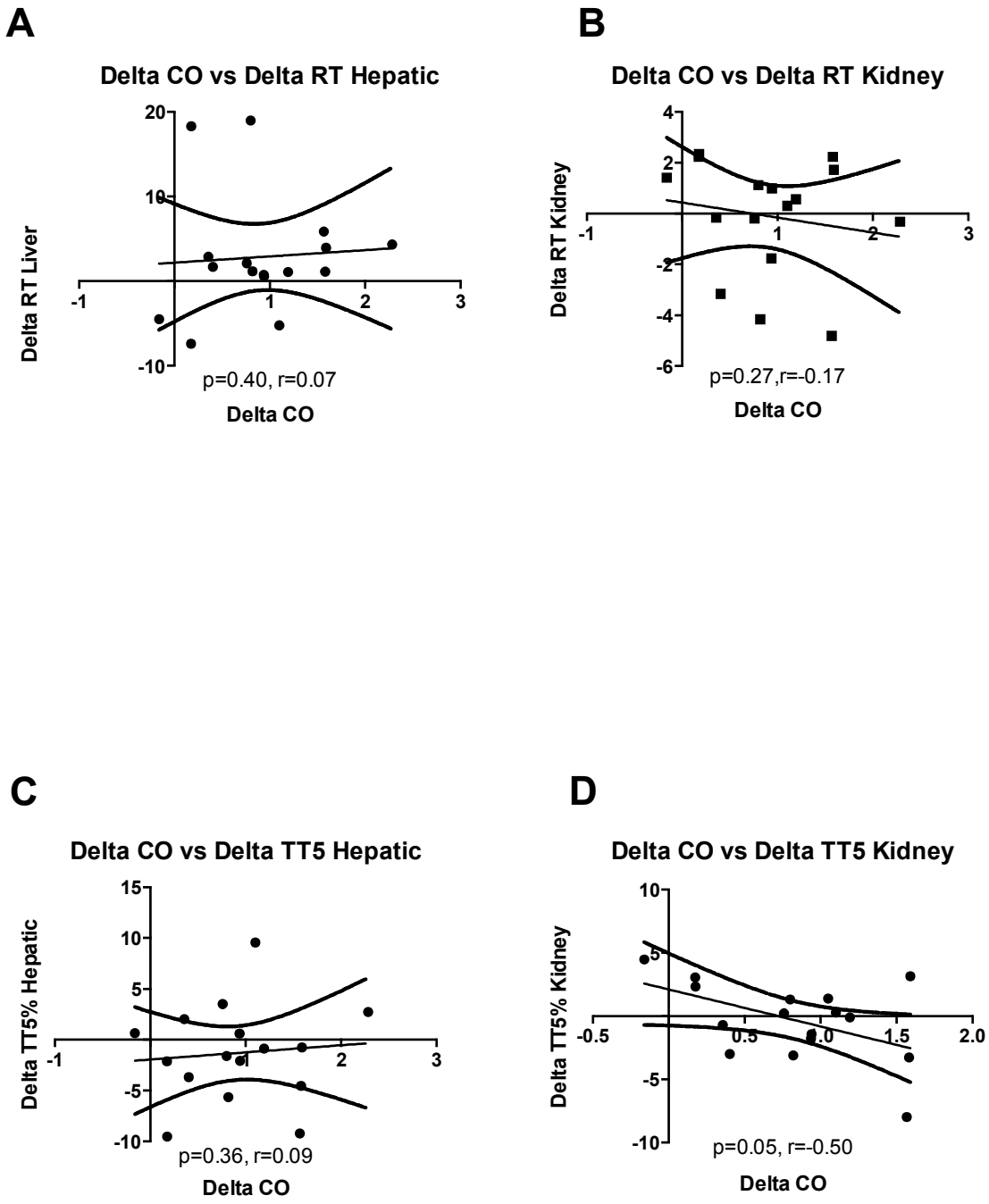
A
Delta CO vs Delta RT Hepatic
Delta RT Liver
Delta CO
p=0.40, r=0.07
B
Delta CO vs Delta RT Kidney
Delta RT Kidney
Delta CO
p=0.27,r=-0.17
C
Delta CO vs Delta TT5 Hepatic
Delta TT5% Hepatic
Delta CO
p=0.36, r=0.09
D
Delta CO vs Delta TT5 Kidney
Delta TT5% Kidney
Delta CO
p=0.05, r=-0.50

Figure 6