Full methods

Ethical approval was obtained from the local research ethics committee; all subjects gave written, informed consent. All procedures were in accordance with the Declaration of Helsinki.

Patients were eligible provided they had been established on hemodialysis for at least a month, were over 18 years of age and were able to give consent. The protocol was for each patient to undergo the following physiological monitoring for 9-12 consecutive sessions:

- Continuous blood pressure (volume-clamp method, Finometer PRO® or Finometer MIDI®, Finometer Medical Supplies)

- Continuous cerebral tissue oxygenation (NIRS, INVOS® system, Covidien)

- 30 minute oscillometry, ie automated upper arm cuff blood pressure (Colin BX-100, Colin Corporation)

- Continuous relative blood volume and venous saturations (Crit-Line, Fresenius)

- Continuous dialysis machine parameter monitoring including access pressures, ultrafiltration rate/volume, blood flow and dialysate flow (Nexadia® software, BBraun).

- Real-time recording of type, onset and offset of symptoms, with a patient-friendly computer interface and response pad (Cedrus RB-844 handset, Superlab v5 software)

A single computer was used as a time reference to ensure all data streams were tightly

synchronised. Dialysis nurses made medical records as per standard practice on a purpose-designed flow sheet: data gathered included nursing interventions (e.g. saline infusion, bed tipping, slowing down ultrafiltration rate) and any concerns about the patient. Clinical staff and patients were blinded to all data except relative blood volume and oscillometry, so this could not influence symptom reporting or intervention.

Both oscillometry cuff and volume-clamp cuff were placed on the non-access arm. The INVOS® adhesive sensor was placed on one side of the forehead, after cleaning of the skin. If the case of previous anterior circulation stroke, the non-affected hemisphere was chosen. All patients underwent clinical examination for carotid stenosis at baseline, and if positively identified, the opposite hemisphere was used.

Accepting the limitations of any arbitrary threshold, we chose a relative drop of 15% of the baseline value as the cutoff for potential cerebral ischemia based on previous literature. There is no consensus on the cerebral saturations cutoff value that should be considered abnormal. Healthy baseline values in the general population range from 60 to 80%. Thresholds for cerebral ischaemia have included absolute cerebral saturations ranging from 40 to 60%, absolute drops from baseline ranging from 15 to 25%, and relative drops from baseline ranging from 20 to 30% [1, 2]. However, some have suggested that an absolute drop of 10% should be the point for intervention, given that there appeared to be definite harm once a 15% drop occurs [1]. In our dialysis population, although baseline was still normally distributed, it was markedly shifted to the left: the 5th and 95th percentiles for cerebral saturations were 35% and 67% respectively, with mean 52%. An absolute drop of 10% is likely to have different significance for a population with a mean baseline rSO2 of 70% and a population

with a mean baseline of 52%, representing a 14% and a 27% relative change in oxygenation respectively. Therefore, we chose a relative drop of 15% of the baseline value as the cutoff for potential cerebral ischaemia.

At baseline and at 12 months from study entry, all patients underwent cognitive function testing consisting of the 100 point modified mini-mental state test (3MS) and the Trails Test B (TTB), and screening for depression using the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a validated screening tool for depression, which may affect performance on the 3MS and TTB. All patients were assessed by the same individual, and strictly in accordance with published protocols. This included capping the TTB at 5 minutes if the patient had been unable to complete the task by this time. At baseline, all patients were assessed on the dialysis unit, within the first two hours of treatment; at 12 months, a small number of individuals had had transplants, and they were assessed either on the dialysis unit or outpatients, a similar environment. We chose to assess during dialysis based on patient feedback that any extension of time already spent in hospital would be unacceptable; this is a protocol that has been applied by other groups[3].

Dialysis protocol

This was a real-world study and we did not alter usual treatment procedures. Eight individuals underwent hemodialfiltration and the remainder hemodialysis, all with Dialog+ Hemodialysis Systems, (BBraun). For hemodialysis we used high flux BBraun Diacap polysulfone dialysers, either the PS18 High (membrane area 1.8 m^2, K_{UF} 55 ml/hr/mmHg, K_0A 911 ml/min) or PS20 High (membrane area 2.0 m^2, K_{UF} 58 ml/hr/mmHg, K_0A 1005 ml/min) depending on clearance requirements. For

hemodialfiltration we used the Fresenius polysulfone FX100 dialyser (membrane area 2.2 m^2, K_{UF} 73 ml/hr/mmHg, K_0A 1351 ml/min).

Blood flow (Qb), dialysate flow (Qd), acid concentrate, and the filter itself were individualised according to patient characteristics and monthly bloods, including kT/V. Qd was 500-800 ml/min in all cases. Qb for tunneled lines was usually 250-300 ml/min, and for arteriovenous fistulae 250-400 ml/min depending on fistula characteristics and clearance requirements. The acid concentrates in use (BBraun) could provide a dialysate sodium 135-140 mmol/L, potassium 2-4 mmol/L, ionised calcium 1.25-1.75 mmol/L, magnesium 0.5-1.0 mmol/L, acetate 2-3 mmol/L, chloride 100-116 mmol/L, and glucose 1 g/L. Bicarbonate was provided with the BBraun Sol-cart B cartridge, which produced a dialysate bicarbonate of 32-36 mmol/L. Ultrafiltration volume was determined based on the difference between pre-dialysis weight and target dry weight, which was determined at the beginning of the month on clinical grounds.

The temperature of the dialysate was generally matched to the temperature of the patient except for those with a history of repeated IDH, in which case it would be set to approximately 0.5^{o}C lower than body temperature. If IDH persisted despite this, patients were switched to hemodialfiltration. Therefore patients had been optimized as per unit protocol prior to inclusion in the study.

Selection of blood pressure index for analyses

In order to determine whether changes in downstream cerebral oxygenation were better explained by changes in MAP or changes in SBP, we compared univariate multilevel models predicting nadir in cerebral oxygenation during hemodialysis where

the explanatory variable was either maximum drop in MAP or SBP during the session. We compared goodness of fit using the log likelihood ratio test statistic assessed against a Chi square distribution.

Volume clamp data collection and pre-processing

Continuous blood pressure monitoring was achieved using Finometer devices, which detect blood pressure using volume clamp technology [85]. The patient wears a finger cuff that incorporates an inflatable bladder in combination with an infra-red plethysmograph. The point of maximum arterial unloading is determined, i.e. when cuff pressure equals intra-arterial pressure so that transmural pressure across the arterial walls is zero. The arterial diameter at this cuff pressure is estimated from the absorption of infra-red light. The artery is then ”clamped” at this diameter by varying the cuff pressure so as to dynamically unload the finger arterial walls: the cuff pressure is therefore an indirect measure of intra- arterial pressure. There are regular automatic recalibrations of arterial size to compensate for changes in smooth muscle tone and haematocrit. A transforming function is applied to the finger arterial pressure waveform to estimate the brachial arterial pressure waveform, and a height sensor corrects for position of the finger relative to the heart.

The Finometer devices have been extensively validated against intra-arterial measurements in several populations[4-10] . They have also been used by a number of groups to monitor continuous blood pressure in the dialysis population, in whom readings correlate reasonably well with blood pressures measured by non-invasive oscillometric techniques [11-13].

The agreement between volume-clamp and oscillometric patients in our study population was also examined, excluding cases where there were technical difficulties

with measurement. Oscillometry cuff and Finometer cuff were placed on the non-access arm. Each oscillometry measurement was compared to the median value of 10 beats of volume-clamp data before arm cuff inflation. Data was discarded if it did not meet the standards of a signal quality index (SQI) based on waveform quality (see below). Bland-Altman plots were constructed for both SBP and MAP (see figures S1 and S2). Modified standard deviations were calculated to account for repeated measures within patients, using ANOVA as recommended by Bland and Altman[14]. The result are consistent with the agreement seen between intra-arterial and oscillometric measurements[15-18].

The beat-to-beat blood pressure data was processed by removal of extreme outliers (3 standard deviations from mean or more) and low pass filtering (Hamming-window based with cutoff 0.083 Hz) to attenuate high frequency noise. Data was downsampled to a frequency of 0.0167 Hz. Data was discarded if it did not meet the standards of an SQI based on waveform quality (see below). Baseline blood pressure was defined as the median value from a window beginning 2 minutes after recording start (to allow time for the Finometer to calibrate) and ending at the point of bleedout, i.e. when the patient's blood enters the dialysis circuit and treatment commences.

Volume-clamp SQI

The finometer waveform (data recorded at 200Hz) was then divided into 30 second windows, with a sliding interval of 5 seconds. Physiocal calibrations were detected by searching for a square wave signal. The interval between Physiocal calibrations depends on the quality and stability of the PPG signal, and each calibration takes approximately 2 seconds. If more than 7.5 seconds in a given window consisted of calibrations, an SQI of 0 (poor) was assigned. The remaining windows underwent

removal of outliers (+/- 3 standard deviations from the mean amplitude for each window): if there was more than 0.5 seconds of outlying values, an SQI of 0 was assigned. A peak detector was then applied using a maximum/minimum threshold technique, with an initialisation period of 1.5 seconds to detect a sample peak and trough: subsequent peaks were discounted if they did not reach 40% of the preceding peak-trough amplitude. The waveform quality of remaining windows was assessed with a correlation method: the minimum acceptable average correlation coefficient was set at 0.8.

NIRS data collection and pre-processing

Cerebral NIRS (Covidien, INVOS device) was used as a continuous, non-invasive measure of cerebral tissue oxygenation during HD, providing a measure of the adequacy of major organ perfusion down- stream from blood pressure. Cerebral NIRS relies on the fact that infra-red light can penetrate the skull: changes in haemoglobin oxygen saturation in the frontal cortex are estimated from the absorption of different wavelengths of near-infra-red light by oxygenated and deoxygenated haemoglobin [19]. The INVOS device uses two wavelengths of light at 730 and 810 nm, either side of the isosbestic point (the wavelength absorbed equally well by oxygenated and deoxygenated haemoglobin). In addition, it uses two photodiode detectors at a distance of 3 and 4 cm, a technique called spatially resolved spectroscopy. The light reaching the proximal detector has taken a shallower course through the more superficial tissues such as the scalp and skull, whilst the signal at the distal detector has passed through both superficial and deep tissues: by subtracting the proximal from the distal signal, the oxygen saturation from cortical tissues can be isolated. It is estimated that approximately 85% of the final output is derived from the frontal

cortex. Cerebral NIRS has been shown to correlate well with more invasive or operator dependent measures of cerebral perfusion, including transcranial Doppler and functional MRI [20, 21]. Moreover desaturation detected by NIRS is associated with hard outcomes, as discussed in the introduction of the main manuscript.

The INVOS adhesive sensor was placed on one side of the forehead, after cleaning of the skin. If the case of previous anterior circulation stroke, the non-affected hemisphere was chosen. All patients underwent clinical examination for carotid stenosis at baseline, and if positively identified, the opposite hemisphere was used.

Data was processed with removal of extreme outliers (4 standard deviations from mean or more) and application of a low pass filter (Hamming-window based with cutoff 0.083Hz) to attenuate noise. Data was downsampled to a frequency of 0.0167Hz. Baseline cerebral saturations were taken as the median of good quality data spanning the first 2-6 minutes of recording.

Analysis 1: Overview of association between MAP thresholds and adverse events

We first aimed to get an overview of the frequency of blood pressure drops, and temporally associated adverse events. The aim of this analysis was to get an overview of the frequency of blood pressure drops, and temporally associated adverse events. We identified sustained drops in MAP below predefined thresholds, and screened for temporally related symptoms, interventions or new onset cerebral desaturation. The thresholds were either absolute (e.g. 90mmHg, 80mmHg, 70mmHg, 60mmHg, 50mmHg, 40mmHg) or relative to baseline (e.g. -10mmHg, -15mmHg, -20mmHg, -25mmHg, -30mmHg, -40mmHg), and had to be sustained for a minimum of 2 minutes. Recovery was defined as the sustained return of MAP to above the threshold, again for a minimum of 2 minutes. New onset ischaemia was defined as a sustained (2

minutes minimum) drop in cerebral saturations below the 15% threshold within a window of -10 to +20 mins around the MAP change. In rare cases where the oxygenation had already dropped 15% or more from baseline before the start of this window, temporally related ischaemia was defined as a further 5% drop, e.g. from 20 to 25%. Symptoms were deemed to be temporally associated if they occurred within +/-20 minutes of change in MAP.

These windows are generous and include a short anticipatory period for several reasons: the thresholds for both hypotension and ischaemia are arbitrary; the timing of some interventions could not be confirmed electronically from dialysis parameters (eg Trendelenberg), so were dependent on documentation by clinical staff; a reduction in tissue oxygenation may only occur after a sustained period of hypotension due to compensatory mechanisms; finally, symptoms may precede as well as follow a decompensation due to attempts to maintain homeostasis eg tachycardia, diversion of blood from the splanchnic circulation. For comparison, data segments of the same length (30 minutes) where the MAP did not fall below the given threshold were used as controls. The control segments were taken from sessions where the MAP remained above the threshold throughout, or from sessions before the first drop occurred.

For formal sensitivity and specificity calculation, the median MAP from a window of +/-5 minutes around the time cerebral saturations fell below the 15% threshold was taken as the blood pressure at which ischaemia occurred. The MAPs at which ischaemia occurred were binned into 5 mmHg categories. The cumulative occurrence of cerebral ischaemia at or below each 5 mmHg threshold, and above each threshold, was calculated.

Analysis 2: Lower limits of cerebral autoregulation

The lower limit of cerebral autoregulation is often considered a surrogate for "safe" blood pressure, and was explored as a complementary method of assessing the relationship between blood pressure and cerebral ischaemia. First we established whether patients had autoregulation or not. There is good evidence that the cerebral autoregulation curve is best modelled with a third degree polynomial with positive first coefficient[22-24]. In comparison, in the absence of autoregulation, regional blood flow and cerebral saturations vary linearly with blood pressure. First the MAP data was grouped into 5 mmHg bins (sliding every 1 mmHg) and the mean and 95% confidence intervals of the corresponding cerebral saturation values were found for each bin. For each patient, we assessed whether the relationship between MAP and cerebral saturations was best modelled with an appropriate polynomial or an appropriate (i.e. positive gradient) straight line: goodness of fit was compared using the F test statistic (based on residual sum of squares for each model) against an F distribution. If the polynomial provided a statistically significant better fit, upper and lower autoregulation limits were estimated by drawing a horizontal straight line from the peak of the positive inflection and the nadir of the negative inflection respectively, and identifying where they intersected the ascending and descending limbs of the polynomial (Figure 3S). This is the so-called curve fitting method, and is well documented[25, 26].

As a illustration, Figure 4S shows the data from a 79 year old man with renovascular disease who was confirmed to have intact autoregulation, with clear upper and lower limits. Figure 5S shows an example of absent autoregulation: this was a frail 79 year old lady with membranous nephropathy and end stage emphysema, who demonstrated a clear linear relationship between blood pressure and cerebral saturations. The patient died during the month of monitoring: the error bars are larger than usual due to

the smaller amount of data available. Figure 6S shows the data from a fit 39 year old man with glomerulonephritis who underwent transplantation shortly after completion of his month of monitoring: although the blood pressure range was insufficient to allow identification of the lower limit, he clearly has intact autoregulation, with stable cerebral saturations over MAPs ranging from 80 to 130, ie cerebral oxygenation is independent of blood pressure. In fact this segment likely represents the slightly downsloping middle section of the third degree polynomial which describes the autoregulation curve (see figure 3S for comparison), and indeed a third degree polynomial with positive first coefficient was a better fit than a linear model with positive gradient.

Analysis 3: Relationship between intra-dialytic physiology and change in physiological function

For each session, the area under the curve (AUC) below the cutoff of a relative 15% drop in cerebral saturations was calculated, known hereafter as the ischemia AUC (min*%). The average session ischemia AUC over the month of monitoring was calculated for each patient as an estimation of typical exposure to cerebral ischaemia. In addition, the AUC in mm Hg*min below different MAP thresholds, relative and absolute, were calculated for each session (absolute thresholds were MAP <70 mm Hg and <60 mm Hg, and relative thresholds MAP drop >10 mm Hg, >20 mm Hg, and >30 mm Hg).

Linear models were then constructed to predict the change in TTB and 3MS scores between baseline and 12 month follow up. The changes in TTB and 3MS were expressed as a ratio of baseline and follow up scores. Patients who had undergone transplantation during this period were excluded. Covariates tested included

hypotension exposure, ischemia exposure, age, level of education, cerebrovascular disease, diabetes vintage, hemodialysis vintage, and PHQ. Variables were transformed to ensure a linear relationship between predictors and outcome, and checks were performed on the residuals to confirm that models were valid. As there were more deaths and transplants than expected, and the number of patients was relatively small, the robustness of all results was tested with the boot strapping (resampling with replacement) and jack knifing (resampling without replacement). This method also allows for some control of type 1 errors resulting from the multiple comparisons. Cook's distance, jack knifing and visual assessment of residuals were used to identify influential outliers.

The relationship between change in TTB and exposure to intra-dialytic ischaemia was not linear, with proportionally greater effect size as exposure increased. To obtain a linear relationship, typical exposure was transformed with the power of 0.2. The final equation was:

$$\delta TTB = -5.4 + 13.1 * Ischemia\_AUC^{0.2}$$

where δ TTB= percentage change in TTB over 12 months (positive change marks a deterioration), Ischemia_AUC= estimated typical intra-dialytic cerebral ischemia in %min.

95% boot strap confidence intervals for the coefficient were 1.2 to 24.9, p=0.030

Figures

Figure 1S Bland-Altman plot for the agreement between oscillometric and Finometer measurements of SBP. The x axis shows the mean value of each measurement pair, ie 0.5*(oscillometric + Finometer measurement). The y axis shows the oscillometric value – Finometer value for each measurement pair. The red line indicates the mean bias, and the blue lines the 95% limits of agreement.

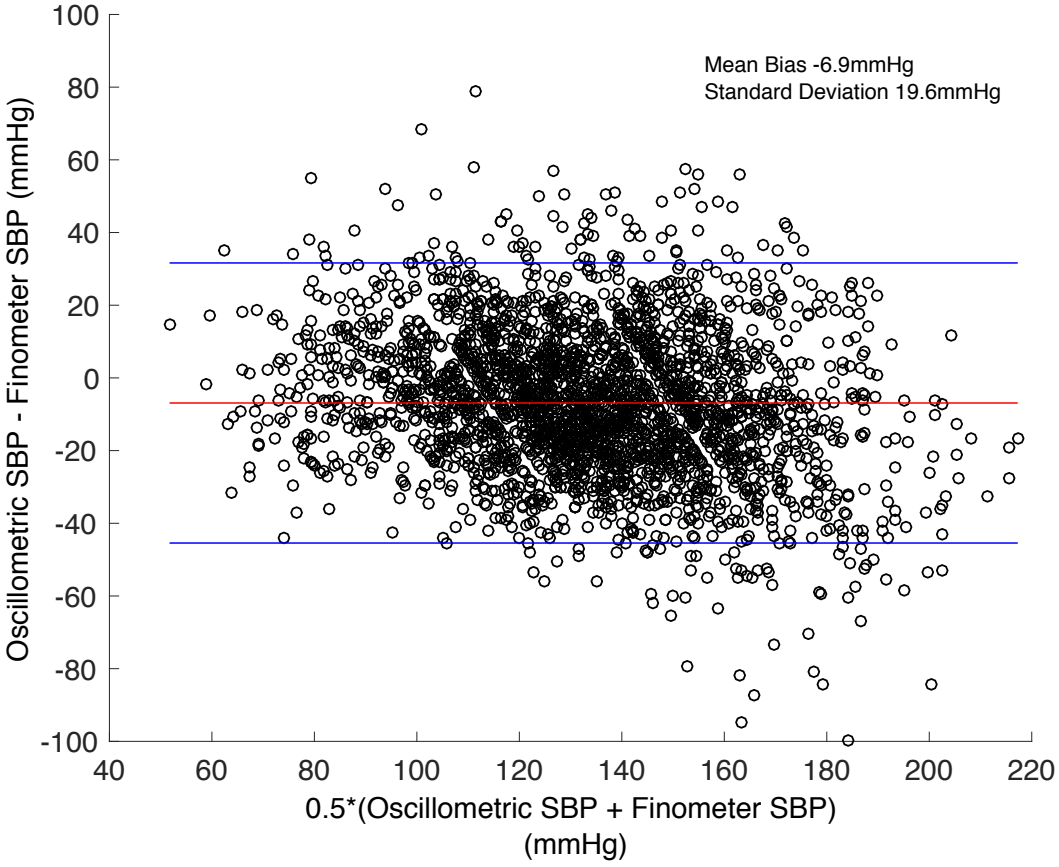


Figure 2S Figure 1S Bland-Altman plot for the agreement between oscillometric and Finometer measurements of SBP. The x axis shows the mean value of each measurement pair, ie 0.5*(oscillometric + Finometer measurement). The y axis shows the oscillometric value – Finometer value for each measurement pair. The red line indicates the mean bias, and the blue lines the 95% limits of agreement.

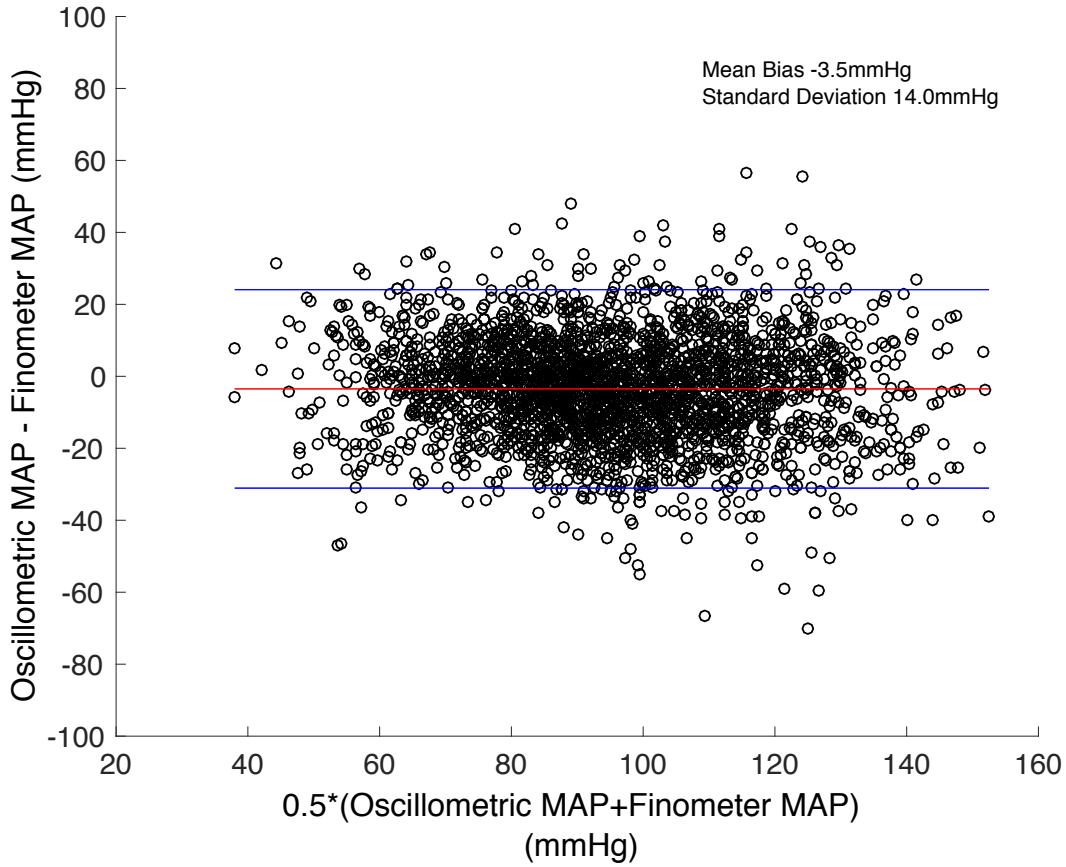


Figure 3S Curve fitting method of determining limits of cerebral autoregulation

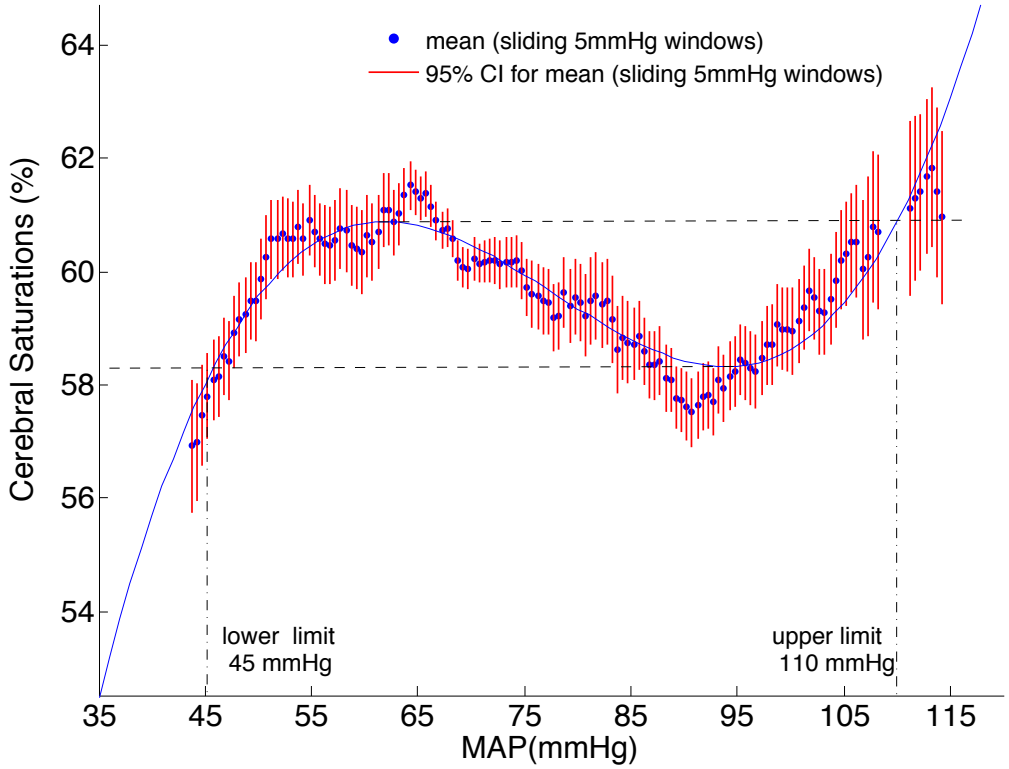


Figure 4S. A patient with intact cerebral autoregulation: the relationship between blood pressure and cerebral saturations is described by a third degree polynomial with positive coefficient (superimposed blue line). It can be seen that cerebral saturations are successfully held steady between MAPs of approximately 70 and 110 mm Hg.

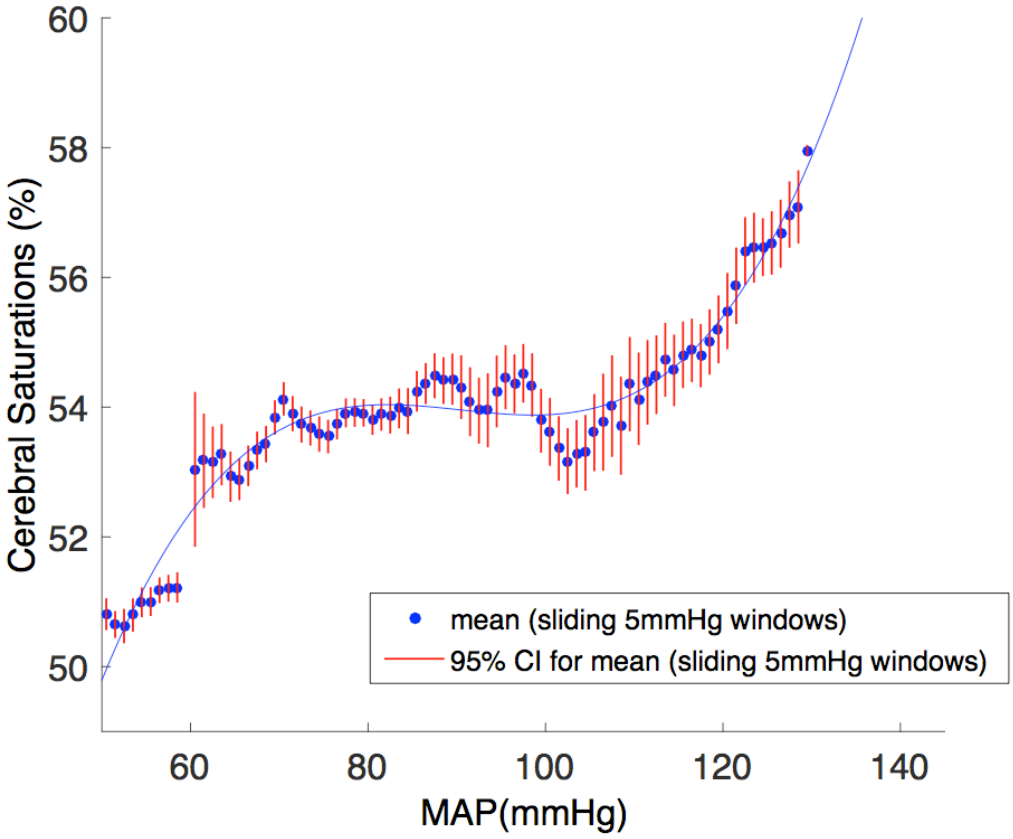


Figure 5S. A patient with absent cerebral autoregulation demonstrating a clear linear relationship between blood pressure and cerebral saturations (line of best fit superimposed in blue)

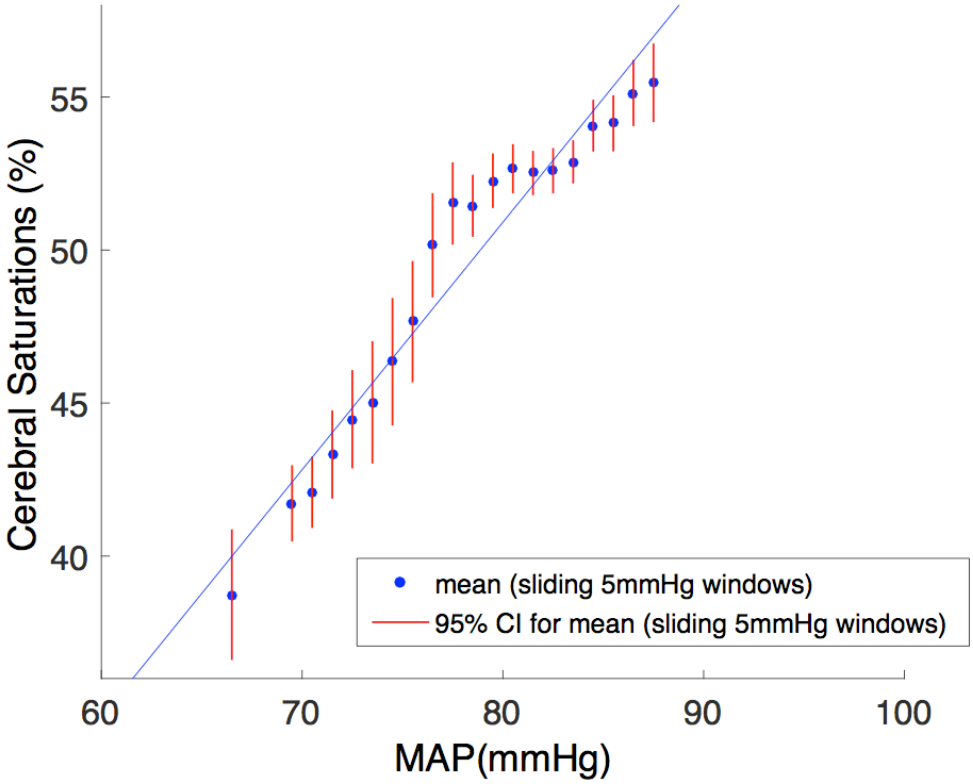
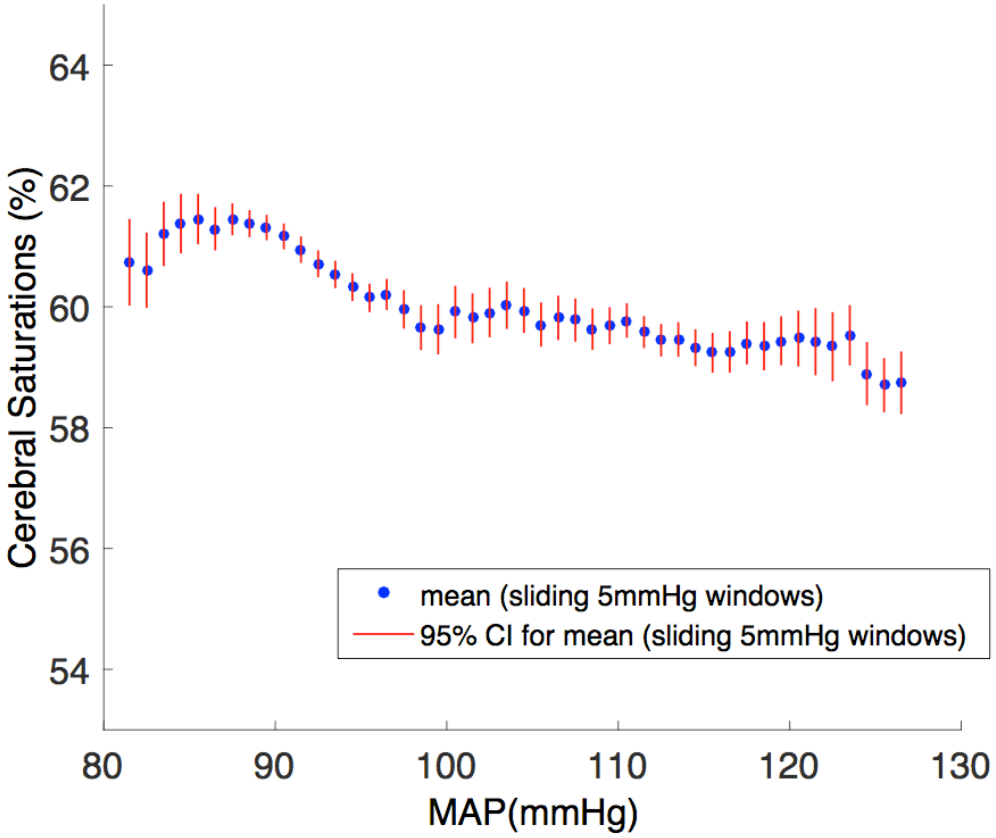


Figure 6S. A patient with intact cerebral autoregulation demonstrating steady cerebral saturations over a wide range of MAP from 80 to 130 mm Hg. However it is not possible to ascertain where the lower limit of autoregulation lies with any certainty as the MAP did not fall below 80 mm Hg in the 12 monitored sessions.



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