Association of blood pressure and symptoms with end organ ischaemia during haemodialysis

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OBJECTIVES

Intra-dialytic hypotension (IDH) is a common problem: from the patient's perspective, it is associated with disabling symptoms and prevents achievement of dry weight; from the nursing perspective, it increases workload. However, proving that IDH is associated with hard outcomes has been problematic. Only one definition of IDH has been linked independently with an increased mortality, namely an intra-dialytic systolic nadir below 90mmHg, and this in a retrospective review of datasets with limited blood pressure and symptom data(1). This is likely a surrogate for the most extreme hypotension. Difficulty in defining a threshold for harm arises from several factors: patient heterogeneity; reliance on non-invasive blood pressure (intermittent with large measurement error); unjustified extrapolations of haemodynamic data from one or two treatments; and, returning to physiological principles, the fact that blood pressure is only a surrogate for downstream tissue perfusion pressure and oxygen delivery.

We have taken a complementary, physiological approach to the problem, and continuously monitored blood pressure, real-time symptoms and cerebral near-infrared-spectroscopy (NIRS) in a large number of haemodialysis sessions. Cerebral NIRS is a validated measure of regional cerebral tissue oxygenation (rSO2), and has been shown to correlate with ischaemic impairment of other organs (2,3). Our objective was to assess the relationship between blood pressure, symptoms, and downstream organ ischaemia in order to identify: 1) which if any blood pressure threshold best predicts tissue ischaemia during dialysis on the population level; and 2) whether symptoms or other covariates improved this prediction.

METHODS

Physiological data was prospectively gathered from 635 haemodialysis sessions in 59 patients; each patient was monitored on consecutive sessions for a month. Data gathered included: continuous blood pressure (Finometer® PRO, Finapres Medical Systems); continuous cerebral oxygenation (NIRS, INVOS™, Covidien); type, onset and offset of symptoms, electronically recorded in real time with a patient-friendly computer interface. Staff and patients were blinded to finometer readings so this could not influence symptom reporting or intervention. Cerebral ischaemia was defined as a drop of 15% of baseline value based on existing literature(3).

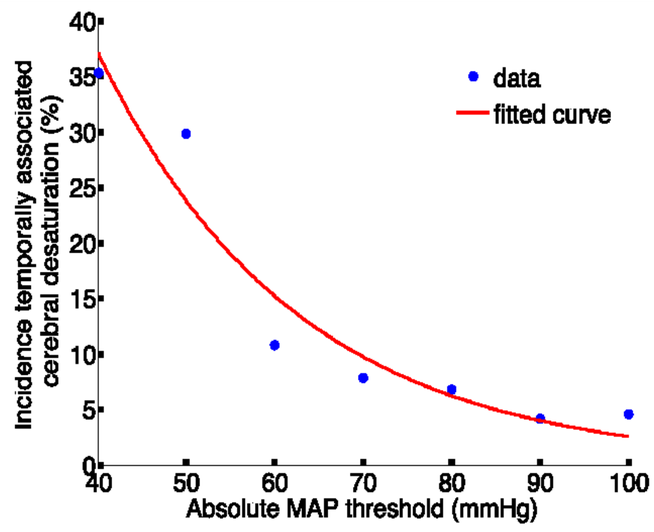
For the first analysis, we identified the overall incidence of new symptoms, ischaemia or interventions within 20 minutes of a sustained drop in mean arterial pressure (MAP, according to predefined absolute and relative thresholds). Specificity, sensitivity and positive predictive value (PPV) of MAP thresholds for predicting ischaemia were calculated.

For the second analysis, a multi-level zero-hurdle poisson GLM was used to model the AUC below the ischaemia threshold (ischaemia AUC (min*%)) for each session. This is a two part model: the zero part, the binary outcome of whether the ischaemia threshold is achieved or not, uses logistic regression; the count part, the depth and duration of the ischaemia once the threshold is crossed, uses a truncated poisson model. The AUCs below different MAP thresholds were calculated for each session, and tested in turn as univariate covariates (+/- adjustment for baseline MAP) in both parts, to find the index which provided most information. Goodness of fit was compared with the log likelihood ratio, tested against a chi square distribution. We then tested whether symptom data made a significant, independent improvement to the model over blood pressure alone. Finally several plausible covariates were tested, including age, dialysis vintage, diabetes vintage, relative blood volume (RBV), ultrafiltration (UF) volume and vascular disease.

RESULTS

23.5% of sessions had at least one episode of cerebral ischaemia, though variable in duration and severity. There was a weak linear relationship between relative thresholds of MAP and incidence of temporally related ischaemia (3% increase per 10mmHg drop from baseline, $p<0.001$). For absolute MAP thresholds, the relationship was better described by a negative exponential, with a sharp increase in cerebral desaturation below MAP 60mmHg (doubling in incidence for every 20mmHg drop p 0.001), see figure 1. The sensitivity and specificity of different absolute and relative thresholds of MAP for new onset cerebral ischaemia is depicted in figure 2. Cramp was associated with neither tissue ischaemia nor absolute blood pressure, but the presence of non-cramp symptoms substantially improved PPV, at the expense of sensitivity (not shown).

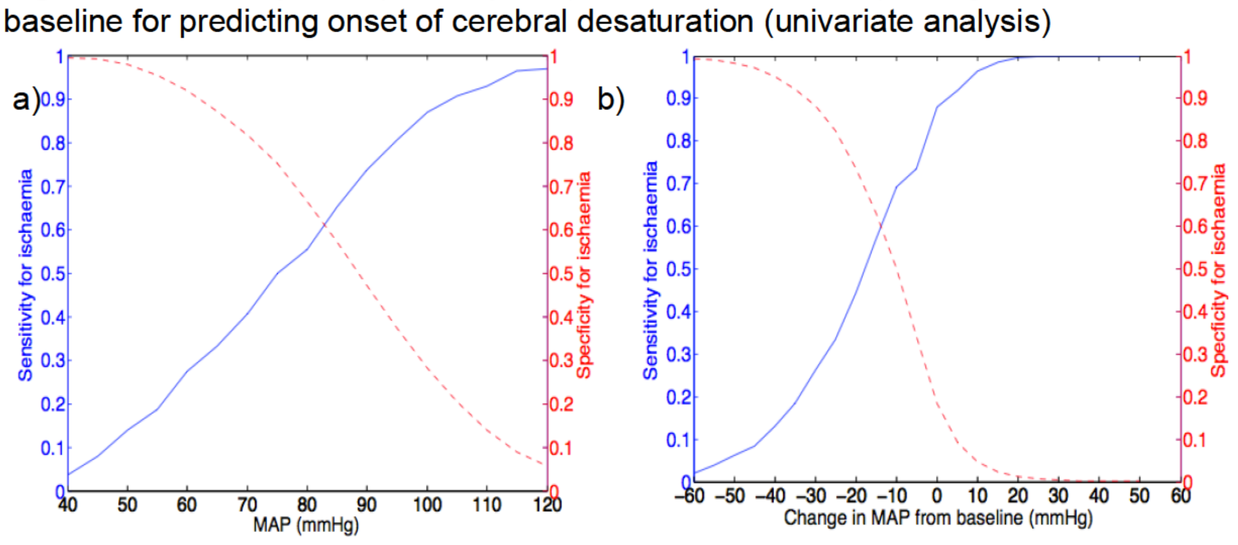
Figure 1: Incidence of new cerebral ischaemia within 20 minutes of crossing absolute MAP threshold



Count model covariates (predicting total cerebral ischaemia in %*min once threshold crossed)		Coefficients (incidence rate ratio)	95% confidence intervals	p value
ΔMAP <60 mmHg AUC (mmHg*min)	Baseline MAP<80mmHg	1.01	1.00-1.01	0.050
	Baseline MAP 80-100mmHg	1.02	1.01-1.03	< 0.001
	Baseline MAP >100mmHg	1.03	1.01-1.05	< 0.001
Zero hurdle model covariates (predicting if ischaemia threshold is reached or not)		**Coefficients (odds ratio)**	**95% confidence intervals**	**p value**
MAP <60 mmHg AUC (mmHg*min)	Baseline MAP<80mmHg	1.04	0.98-1.09	0.167
	Baseline MAP 80-100mmHg	1.05	0.98-1.13	0.167
	Baseline MAP >100mmHg	1.37	1.02-1.72	0.017
UF volume (normalised to dry weight, ml/kg)		1.05	1.02-1.08	0.002
Non-cramp symptoms (present)		2.50	1.30-4.82	0.006
Diabetes vintage (years)		1.05	1.01-1.08	0.008
Relative blood volume (%)		0.98	0.94-1.01	0.167

On multivariate analysis, AUC below MAP 40 mmHg resulted in the best fit, followed by AUC below absolute MAP 60 mmHg: these indices were highly correlated and produced essentially identical models (population mean baseline MAP 98 mmHg). The MAP <60 mmHg model is shown in the table above. The non-blood pressure terms were significant only for the zero part of the model. RBV, though not in itself significant, substantially improved the model fit. MAP provided significantly better models of ischaemia than systolic blood pressure.

Figure 2: Sensitivity and specificity of a) absolute MAP and b) change in MAP from baseline for predicting onset of cerebral desaturation (univariate analysis)



CONCLUSIONS

At the population level, blood pressure thresholds alone have a poor trade off between sensitivity and specificity for predicting downstream tissue ischaemia during haemodialysis. Extreme drops in blood pressure (e.g. MAP <60 mmHg or a 40 mmHg drop from baseline), especially when accompanied by non-cramp symptoms, have a reasonable PPV. However, the majority of ischaemic episodes are asymptomatic and occur at higher pressures. Other factors which provide predictive information independent of blood pressure and symptoms include diabetes vintage (autonomic function) and UF volume (cardiovascular challenge). Personalised models taking into account individual cerebral autoregulation thresholds may allow the identification of clinically useful, patient-specific MAP targets, and this is the subject of our next paper.

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