Analysis of Cerebral Blood Flow Autoregulation in Neonates

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Abstract—**The dynamic response of cerebral autoregulation to spontaneous changes in arterial blood pressure (ABP) is described by the relationship between cerebral blood flow velocity (CBFV) and resistance-area product (RAP). CBFV was measured with Doppler ultrasound in the middle cerebral artery and ABP with an intra-arterial catheter in 66 neonates. Spontaneous changes in mean ABP were automatically detected and the maximum derivative was used to synchronize the coherent averaging of corresponding CBFV and RAP transients. These were classified into two groups corresponding to intact (group A) or impaired (group B) autoregulation. The cross correlation between RAP and CBFV indicates a significant relationship with a time delay of 5 s for group A. The frequency response of RAP was estimated by the cross spectra with CBFV. Groups A and B present a similar amplitude spectra but the phase spectra of group A lags that of group B. The impulse responses of the two groups are also markedly different and were used to simulate the velocity response to a 5% step change in ABP. Impulse responses were also obtained for four different levels of pCO_2 showing that hypercapnia leads to an impulse response similar to that of group B (impaired autoregulation). This method can be used to extend the usual dichotomic classification adopted in clinical studies of autoregulation.**

NOMENCLATURE

ABP	Arterial blood pressure.
CBF	Cerebral blood flow.
CBFV	Cerebral blood flow velocity.
CrCP	Critical closing pressure.
$C_{rv}(f)$	Cross-spectrum between RAP and CBFV.
CVR	Cerebrovascular resistance.
$C_{vv}(f)$	Power spectrum of CBFV.
$G(f)$	Frequency response of transfer function between RAP and CBFV.
$g_{\bar{v}}$	Impulse response of $G(f)$.
MABP	Mean arterial blood pressure.
MCA	Middle cerebral artery.
$\bar{P}$	Mean value of ABP for one cardiac cycle
RAP	Resistance-area product.
$\bar{V}$	Mean value of CBFV for one cardiac cycle.

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I. INTRODUCTION

AUTOREGULATION of cerebral blood flow (CBF) can be described as a feedback mechanism which attempts to minimize disturbances in CBF due to changes in other physiological variables, most notably in mean arterial blood pressure (MABP) [19]. This mechanism is usually described by an "autoregulation curve" in which a plateau of CBF indicates that this variable is maintained relatively constant over a certain range of MABP [29]. In adults the range of MABP in which autoregulation operates has been estimated to be from 60 to 170 mmHg [19], [29]. In neonates there is evidence that this range is much narrower although precise limits have not been established [31], [39]. Moreover, a number of studies have shown that cerebral autoregulation is not fully developed in premature newborns and that failure of autoregulation may play a role in the pathogenesis of intraventricular hemorrhage [17], [21], [22]. In infants and adults autoregulation can be impaired in a number of clinical situations including head injury [6], [8], [33], stroke [29], convulsions [23], hypotension [3], hypothermia [7], [35], or carotid endarterectomy [18] with attendant complications such as intracranial hypertension, hyperperfusion, and orthostatic syncope [6], [18], [20], [29].

Understanding of the precise mechanisms responsible for cerebral autoregulation has met with difficulties resulting from lack of appropriate measuring tools in humans [19] and a great anatomical and physiological variability in animals [29], [30]. Above all, it is not clear whether autoregulation operates through a neurogenic, myogenic, or endocrine mechanism, or a combination of these [29]. A systems approach to the phenomenon of cerebral autoregulation might allow a greater understanding of the mechanisms involved while leading to improvements in clinical management. Unfortunately, most studies of autoregulation in humans have used a "static" approach in which autoregulation is characterized by the steady-state autoregulation curve [6], [17], [29], [31], [39]. A relatively recent study by Aaslid *et al.* [1] has shown that it is possible to obtain indications of the dynamics of autoregulation in human volunteers using a transcranial Doppler to measure cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA). These investigators have produced a negative step change in MABP which led to an instantaneous reduction in CBFV which then returned to baseline value in approximately 5 s. Time constants of this order of magnitude, which were also observed in animal studies [15], [34], indicate limitations in the attempt of Giller [16] to

characterize autoregulation in the frequency domain because this author used sampling rates of 30 s or more. Although aimed at explaining the effects of oxygen on the cerebral circulation of the rat, the mathematical model developed by Ursino *et al.* [37]–[38] stands out as a milestone in the systems analysis of cerebral autoregulation.

Using continuous recordings of CBFV of relatively long duration, from the MCA of premature and term newborns, we have been able to characterize the presence/absence of autoregulation by signal analysis of spontaneous transients in beat-to-beat changes in MABP [27]. The present study has extended this approach by testing the hypothesis that it should be possible to characterize the dynamics of cerebral autoregulation by its feedback loop gain. This possibility was investigated by estimation of the frequency and time domain relationship between changes in cerebrovascular resistance and CBF provoked by spontaneous changes in MABP.

II. Experimental Methods

A. Patients and Measurements

A cohort of consecutive admissions to the NICU at the Rosie Maternity Hospital, Cambridge, UK, was recruited. The study involved only newborns who were admitted to the NICU before 12 hours of age to receive respiratory care and did not present lethal malformations, intracranial pathology, or birth asphyxia. This corresponded to 59 premature newborns and seven term infants (median gestational age 30 weeks, range 24–40 weeks). Informed consent was obtained from one or both parents. The study had prior approval from the Cambridge District Ethical Committee.

Cerebral blood flow velocity (CBFV) was measured using a system previously described [14]. A small 1-cm diameter 4-MHz continuous wave Doppler ultrasound probe (with a total acoustic power output of <5 mW and I (spta) < 50 mWcm^{-2}) was securely fixed to the skin overlying the middle cerebral artery. The Doppler signal was processed using the microcomputer based system of Schlindwein *et al.* [32]. This system performs an FFT every 6.25 ms and calculates the peak and intensity weighted mean of the Doppler frequency spectrum. An analogue signal representing the peak velocity envelope was stored on a multichannel digital instrumentation recorder (DIR, PC-108M Sony, Japan).

Arterial blood pressure (ABP) was measured continuously via either an umbilical or peripheral arterial catheter using a P23 Spectromed transducer connected to an S&W Quadriscope monitor. The system used had a flat frequency response to at least 10 Hz [12]. Prior to each study the blood pressure calibration signal for each monitor was recorded on digital tape. Simultaneous recordings of CBFV and ABP were obtained for at least five minutes. Recordings were performed at 6, 12, and 24 hours following admission and on subsequent days if the infant had a functioning arterial catheter.

Recorded signals were low-pass filtered at 30 Hz and converted to digital format at a rate of 200 samples/s on a Dell 486DX2 computer. Narrow spikes in the CBFV signal were detected and removed by linear interpolation. Both CBFV and ABP signals were low-pass filtered with an 8th-order Butterworth zero-phase filter with cutoff frequency of 20 Hz. The filtered ABP signal was used to estimate the R-R interval and to mark the beginning and end of each cardiac cycle. A total of 209 records were available for analysis.

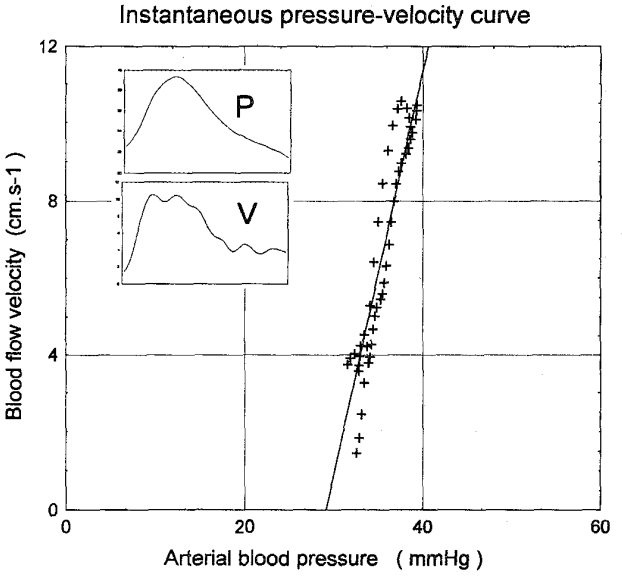

Fig. 1. Instantaneous pressure-velocity curve for one cardiac cycle of a premature neonate born at 26 weeks gestational age. Inset: original pressure and velocity waveforms.

B. Pressure-Velocity Relationships

The instantaneous relationship between ABP and CBFV has been modeled previously [25]–[26]. Fig. 1 shows a representative pressure velocity relationship during one cardiac cycle of a newborn with gestational age 26 weeks and birthweight 1170 g. A linear model corresponding to ABP $= a + b \cdot$ CBFV, was used to estimate the slope and the pressure-axis intercept of the relationship for each cardiac cycle. Although arterial compliance improves model performance [25], we have shown that more robust estimations of a and b are obtained by restricting the model to only two parameters [26]. The pressure-axis intercept (a) has been interpreted as an estimation of the critical closing pressure (CrCP) of the cerebral circulation [10], [25], [26]. The slope (b), reflects the cerebral vascular resistance. However, since CBF is given by the product between CBFV and cross sectional area, it is appropriate to express the slope of the ABP-CBFV relationship by a resistance-area product (RAP) as suggested by Evans *et al.* [13]. In addition to the parameters CrCP and RAP, mean values of ABP and CBFV $(\bar{P}, \bar{V})$ were obtained for each cardiac cycle of each recording.

C. Coherent Averages

The resulting beat-to-beat sequences of $\bar{P}$, $\bar{V}$, CrCP, and RAP were interpolated with a sliding spline and resampled with an interval of 0.2 s to produce signals with an uniform time axis. The four sequences were low-pass filtered with the

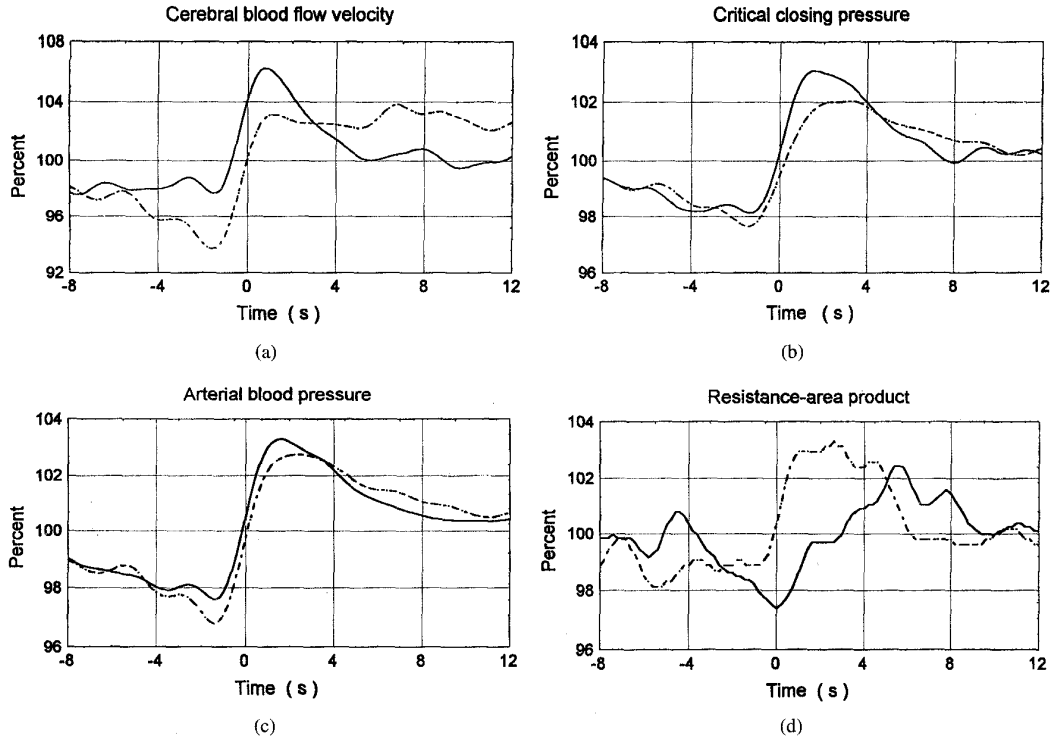

Fig. 2. Coherent averages of (a) CBFV, (b) CrCP, (c) ABP, and (d) RAP for records classified as showing an intact (continuous line) or impaired (dashed line) cerebral autoregulation. All coherent averages are represented in percent of their mean value.

same Butterworth filter but using a cutoff frequency of 0.5 Hz. Peaks in the $\bar{P}(n)$ sequence were automatically detected and the position of their maximum derivative was marked for the largest 30 peaks in each recording subject to the conditions that their relative amplitude (peak to foot) was equal or greater than 2% of the baseline value and that they were at least 6 s apart. The position of the maximum derivative of each $\bar{P}(n)$ peak was used as the point of synchronism for coherent averaging. Signals were only accepted into the average if $\bar{V}(n)$ and $\bar{P}(n)$ had a correlation coefficient $r >$ 0.2 for the 4-s interval centered on the point of synchronism. To test whether the results of averaging could be due to artifact, averages were also obtained using random aligment between the pressure peaks and the $\bar{V}(n)$ signal using the same number of waveforms. Coherent averages were also obtained for CrCP(n) and RAP(n) using the same point of synchronism.

D. Classification of Recordings

Two distinct methods were used to classify each individual record with respect to the presence or absence of autoregulation [27]. In the first method, mean values of CBFV and MABP were calculated every 8 s of the five-minute recording. For recordings with MABP changes >5 mmHg, a linear regression of CBFV on MABP was performed using MABP as the independent variable. Recordings were classified as showing the absence of autoregulation (group B) if the regression had a significant slope greater than 1.5%/mmHg [27]. Otherwise the recording was classified as showing the presence of autoregulation (group A).

The second classification of individual records was based on the morphology of the CBFV coherent average corresponding to a peak in $\bar{P}(n)$. The total population of records was randomly split into two groups and the coherent average of each group was computed. Using the correlation coefficient between the $\bar{V}(n)$ average of each record and the group coherent average (for the period of 10 s following the foot of the $\bar{P}(n)$ transient), individual records were reallocated to the group corresponding to the highest correlation. A new coherent average was computed for the two groups and the process was repeated until there were no more transitions between the two groups. The morphology of the final averages give a clear indication of which group reflects an intact regulation and which correspond to an impaired one [27].

Representative coherent averages for groups A and B were recalculated using only records for which both the linear and the clustering classification agreed (Fig. 2).

E. Identification of the Autoregulation Loop Gain

Fig. 2 indicates that CrCP(n) has a similar morphology in both groups (A and B) of records but that RAP(n) shows a delayed increase in group A records. This temporal pattern can explain the early return to baseline in $\bar{V}(n)$ which seems to characterize an active autoregulation. This observation is in agreement with the accepted view that autoregulation takes place through adjustments in cerebral vascular resistance [29]. Nevertheless, it is important to note that the $\bar{P}(n)$

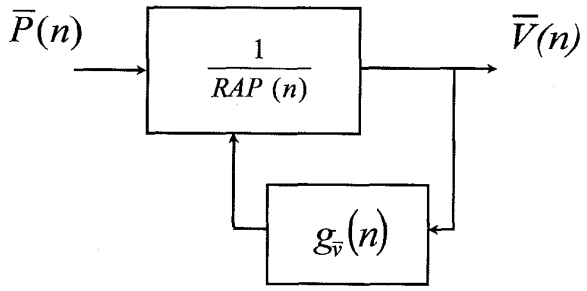

Fig. 3. Block diagram of cerebral autoregulation model assuming adjustments in resistance-area product (RAP) through a feedback loop from cerebral blood flow ($\bar{V}(n)$) with an impulse response gain $g_{\bar{v}}(n)$. $\bar{P}(n)$ is the beat-to-beat sequence of mean arterial blood pressure.

transient is accompanied by a similar transient in CrCP(n). The significance of the relationship between RAP(n) and $\bar{V}(n)$ for each group of records considered was characterized by their cross-correlation function [4] computed in the time domain using 25.6 s of data (128 samples). The 95% confidence interval of the cross-correlation function was calculated as $1.96\sqrt{5/N}$ where $N = 128$ and 5 is the reduction in degrees of freedom produced by low-pass filtering [4].

We define the effective perfusion pressure, $\Delta\bar{P}(n)$ by

$$\Delta\bar{P}(n) = \bar{P}(n) - \mathrm{CrCP}(n) \tag{1}$$

and, consequently

$$\bar{V}(n) = \frac{\Delta\bar{P}(n)}{\mathrm{RAP}(n)}. \tag{2}$$

A simple model to represent changes in RAP(n) resulting from disturbances in $\Delta\bar{P}(n)$ is depicted in Fig. 3. We assume that changes in $\bar{V}(n)$ will lead to changes in RAP(n) through a feedback loop gain that is both a function of time and $\bar{V}(n)$. This does not imply that autoregulation is elicited purely by changes in flow but possibly by flow related variables such as tissue pCO_2 or pH for example. Rigorously speaking the relationship between RAP(n) and $\bar{V}(n)$ cannot be assumed to be described by a linear system. However, as we are dealing with relatively small perturbations (Fig. 2), we use the linear approach as a first approximation to compute the gain function in the frequency domain [4]

$$G(f) = \frac{C_{rv}(f)}{C_{vv}(f)} \tag{3}$$

where $C_{rv}(f)$ is the cross spectrum of RAP(n) and $\bar{V}(n)$, and $C_{vv}(f)$ is the power spectrum of $\bar{V}(n)$ [4]. To estimate $C_{rv}(f)$ and $C_{vv}(f)$ for groups A and B, the respective waveforms (Fig. 2) were extended to 256 samples, the mean values were subtracted, and a Tukey window (20% cosine taper) was applied before computing the spectra with the FFT. A low-pass cosine filter was applied to $G(f)$ in the frequency domain with a cutoff frequency of 0.25 Hz.

The dc-loop gain for the model in Fig. 3 should be given by the ratio Δ RAP$(n \to \infty)/\Delta\bar{V}(n \to \infty)$ for a step change in $\Delta\bar{P}(n)$. However, the pressure transient [Fig. 2(c)] is not a perfect step and we have estimated the dc gain as the ratio between RAP(n) and $\bar{V}(n)$ using as reference points the foot of the $\bar{P}(n)$ transient [$t = -1$ s in Fig. 2(c)] and the values at $t = 8$ s. A sensitivity analysis was performed to test the influence of different dc gains on the final results.

Finally, the impulse response $g_{\bar{V}}(n)$ is given by the inverse transform, that is

$$g_{\bar{V}}(n) = \frac{1}{N}\sum_{k=0}^{N-1} G'(k)\cdot\exp\left[j\frac{2\pi kn}{N}\right] \qquad n = 0.1, 2, \cdots, N-1 \tag{4}$$

where $N = 256$ samples and k is the harmonic index number. $G'(k)$ is the discrete frequency version of $G(f)$ after low-pass filtering.

Since pCO_2 is known to influence the autoregulatory response [1], [16], [26], coherent averages were also obtained for four distinct intervals of pCO_2 (irrespective of autoregulatory status) by selecting records with pCO_2 within the following intervals: 1) < 5 kPa, 2) 5.00–5.99 kPa, 3) 6.00–6.99 kPa, and 4) $\geq$ 7.00 kPa. Each of these averages of $\bar{V}_i(n)$ and RAP$_i(n)$, $i = 1, 2, 3, 4$ were subject to the analysis described above yielding gain impulse responses for each pCO_2 interval.

F. Simulation of Step Responses to Pressure Changes

The estimated gain impulse responses $g_{\bar{V}}(n)$ were used to simulate CBFV responses to a 5% step change in $\Delta\bar{P}(n)$ starting at $t = 4$ s. Using the estimated impulse responses, values of RAP(n) can be predicted by the discrete convolution

$$\mathrm{RAP}(n) = \sum_{i=0}^{N-1} g_{\bar{V}}(n-1)\cdot\bar{V}(i) \qquad n = 1, 2, \cdots, N-1. \tag{5}$$

An iterative procedure was adopted for obtaining successive values of $\bar{V}(n)$ with (2) and RAP(n) with (5). Separate velocity responses to the step change in pressure were calculated for group A and B using the respective impulse responses.

III. Results

Of the 209 records initially available, 154 could be classified by the coherent average method, but only 70 of these had MABP changes >5 mmHg to allow classification by the linear regression method. Agreement between the two methods ($\kappa = 0.262$, $p = 0.015$) was obtained for 23 records corresponding to group A (intact autoregulation) and 21 records for group B (impaired autoregulation). These two groups of neonates were significantly different in relation to their gestational age ($p = 0.002$) and pCO_2 ($p = 0.007$). For gestational age the mean $\pm$ sd for groups A and B were, respectively, 30.8 $\pm$ 3.6 and 28.1 $\pm$ 1.7 weeks and for pCO_2 4.8 $\pm$ 0.71 and 5.5 $\pm$ 0.89 kPa.

The coherent averages presented in Fig. 2 were obtained from 101 individual transients from group A and 156 transients from group B. As described previously [27], ABP has a similar pattern in both groups, but there is a marked difference in the CBFV average which returns to baseline values much earlier for the case of an intact autoregulation (group A). The corresponding coherent averages for CrCP and RAP have not been shown before. Again, the time course of CrCP is

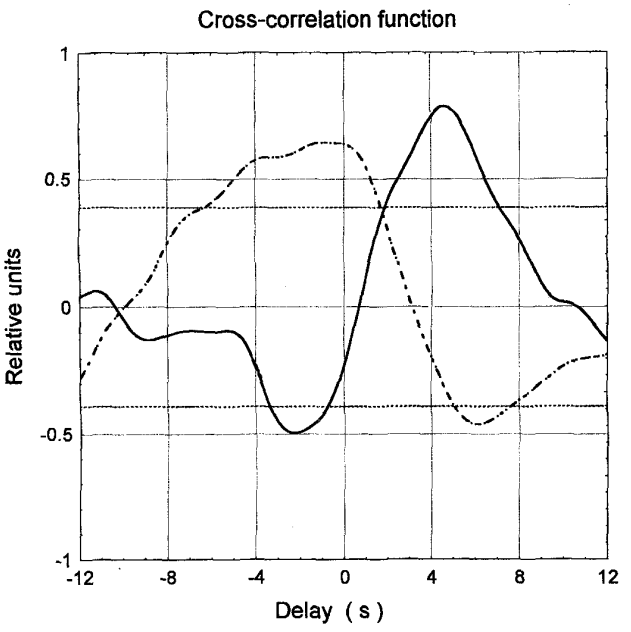

Fig. 4. Cross-correlation function of CBFV and RAP for records classified as showing an intact (continuous line) or impaired (dashed line) cerebral autoregulation. The horizontal dotted lines mark the 95% confidence limits.

fairly similar for the two groups but RAP for group A has a delayed rise following the CBFV and ABP peaks. This delayed increase in RAP is clearly reflected by the cross-correlation function between $\bar{V}(n)$ and RAP(n) depicted in Fig. 4. For group A there is a very significant peak with a time delay of approximately 5 s, while for group B the peak value is obtained for delays around $\tau = 0$.

Fig. 5 shows that the amplitude spectra of the transfer function between RAP and CBFV is slightly greater for group A in relation to group B. However, there is a distinct difference in the phase spectra of $G(f)$ [(3)] with the phase for group A records lagging behing those for group B for all frequencies up to 0.16 Hz. The corresponding impulse responses [(4)] are also markedly different [Fig. 5(b)]. While the impulse response for group B peaks at $t = 0$ and then becomes negative, the corresponding response for group A rises from $t = 0$ to reach a peak at approximately $t = 5$ s. The simulated velocity response to a step change in pressure, based on these impulse responses [(2) and (5)] show that CBFV is also an approximate step function for group B. For the group A situation however, the velocity response shows a tendency to return to the original value. In Fig. 5 the dc gain for group A is approximately ten times that of group B, corresponding to 3.9 10^{-2} mmHg·s^2·cm^{-2} and 3.7 10^{-3} mmHg·s^2·cm^{-2}, respectively. Varying this ratio from 1 to 20 had only a slight effect on the DC level of the impulse responses [Fig. 5(b)] but did not affect their morphology. Since the dc gain determines the area of the impulse response, changes in the dc gain ratio between the two groups will affect the simulated step responses represented in Fig. 5(d). Nevertheless, for a dc gain ratio of 1.0, a marked difference could still be observed between the two responses but in this case the velocity response for group A tends to settle at about half the plateau value attained by group B.

The effect of averaging records from neonates with pCO_2 levels within specified intervals is best described by the corresponding impulse responses represented in Fig. 6. As the pCO_2 interval limits are increased, the impulse response peak shifts to the right and it begins to be attenuated for the interval 6.00–6.99 kPa [Fig. 6(c)]. For the last interval however (Fig. 6(d), $pCO_2 \geq 7$ kPa) the impulse response pattern becomes very similar to the one observed for group B (impaired autoregulation) as shown in Fig. 5(b). The number of records contributing to the coherent averages for estimation of these impulse responses were 110 ($pCO_2 < 5$ kPa), 105 (5.00–5.99 kPa), 57 (6.00–6.99 kPa), and 11 ($pCO_2 \geq 7$ kPa).

IV. Discussion

Coherent averages of CBFV transients produced by spontaneous changes in MABP constitute a promising new approach to characterize cerebral autoregulation, without having to disturb the patient to induce larger changes in MABP [27]. Whether this method can be applied to other patient populations remains to be established. In the present study this approach was adopted to derive representative waveforms of velocity, blood pressure, critical closing pressure, and resistance-area product for two distinct groups of records corresponding to situations suggesting the presence or absence of autoregulation (groups A and B, respectively).

The possibility that the findings reported in this study are the result of signal processing artefacts can be ruled out for several reasons. The coherent averages in Fig. 2 can be reproduced in different sub-groups of patients and, in a few cases, identified in individual records without the need for averaging. In addition, the patterns observed in Fig. 2 are destroyed when the coherent averages are computed with random alignment between the maximum derivative of the MABP transient and the other signals. Other parameters and signal processing choices that could affect the results of Figs. 4–6 were exhaustively tested. One example is the choice of cutoff frequency for low-pass filtering the frequency response $G(f)$ [(3)] before obtaining the impulse response by inverse transform [(4)]. Although we have chosen to display the results in Figs. 5 and 6 corresponding to a cutoff frequency of 0.25 Hz, similar patterns are obtained for cutoff frequencies up to 0.4 Hz. Above this point the frequency response exhibits some high amplitude components which are produced by small values in the denominator of (3) and which appear in the impulse response as oscillations. Spectral smoothing of the cross-spectra in (3) reduce this effect somewhat but does not change the impulse response patterns shown in Figs. 5 and 6. One effect of using cutoff frequencies above 0.25 Hz though is an increase in the oscillations observed in Fig. 5(d) for the velocity response to a step change in MABP for group A.

The classification of autoregulation using the coherent average method jointly with the linear regression or "static" approach led to two groups of newborns which also differ significantly on their gestational age and pCO_2 levels. Prematurity is known to predispose to a loss of autoregulation [17],

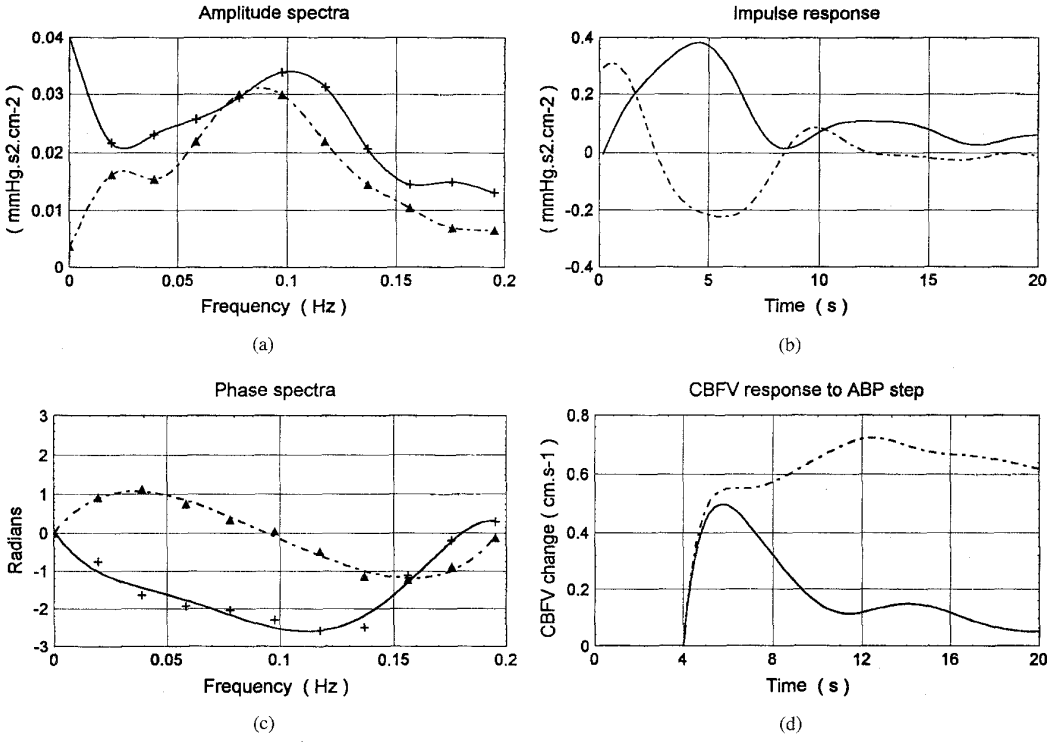

Fig. 5. Frequency and time domain relationship between RAP and CBFV for records classified as showing an intact (continuous line) or impaired (dashed line) cerebral autoregulation: (a), (c) Amplitude and phase of frequency response [(3)], (b) Impulse response [(4)], and (d) simulated velocity response to a 5% step change in ABP (see text).

[21], [22], [27], [39] and hypercapnia abolishes autoregulation [19], [29]. Although it could be argued that the absence of autoregulation for group B is simply caused by elevated values of pCO_2, a closer look indicates that this is not the case. First of all, group B has only three records corresponding to $pCO_2 \geq 6.0$ kPa. As shown in Fig. 6, for $pCO_2 < 6.0$ kPa, the impulse responses for RAP are similar to the ones observed for group A, i.e., suggestive of an intact autoregulation. Secondly, impulse responses for groups A and B [Fig. 5(b)] indicate a much stronger effect, which is attributed to the loss of autoregulation, than those resulting from graded levels of pCO_2 (Fig. 6) showing that the differences between group A and B records cannot be attributed exclusively to pCO_2.

Despite the accepted view that the autoregulatory response to changes in MABP takes place through adjustments in cerebrovascular resistance (CVR), very limited information is available about the time course of this phenomenon. Our results confirm the relatively fast time response of this mechanism as observed by other investigators [1], [2], [15], [24], [34]. In addition, using the cross-correlation function, we have shown a time dependent, significant association between CBFV and RAP with distinct patterns for the two groups of records considered (Fig. 4). Corresponding differences are also observed in the frequency response, impulse response, and CBFV response to a simulated step change in MABP [Fig. 5(d)]. As a whole these results present a coherent description of the dynamic response of cerebral autoregulation to small transient changes in MABP. Nevertheless, these initial results have to be kept in perspective because of the assumptions involved. Above all we have assumed that changes in MABP do not affect the RAP directly. This possibility cannot be ruled out by our study and it is supported, at least partially, by the myogenic theory of autoregulation [29]. The main reason for ignoring direct effects of MABP on RAP at this stage though is the fact that $\bar{P}(n)$ is very similar for groups A and B [Fig. 2(c)] while both CBFV and RAP are very distinct [Fig. 2(a) and (d)]. On the other hand, Fig. 2(d) shows that RAP for group B is increasing in phase with MABP and CBFV. One possible explanation for this finding would be an elastic increase in the MCA cross-sectional area resulting from the pressure rise. Although the population coherent average for group A [Fig. 2(d)] does not show a similar in-phase change, in some patients of this group we have observed a distinct dual peak pattern of RAP in which the delayed increase observed in Fig. 2(d) is preceded by a smaller peak synchronous with the rise in MABP. In addition, the RAP waveform for group A also suggests that there is a delayed fall in RAP, from -4 to zero s, which might be the result of a reduction in $\bar{P}(n)$ preceding the steep rise in Fig. 2(c). If this is true, this delayed fall in RAP would be concealing the in-phase, direct effect of MABP on RAP thus increasing the importance of future work to separate the effects of MABP and CBFV on RAP.

We have previously shown that CrCP of the neonatal cerebral circulation have a mean $\pm$ sd of 23.9 ± 11.6 mmHg, with a very strong correlation with MABP [28]. The waveforms

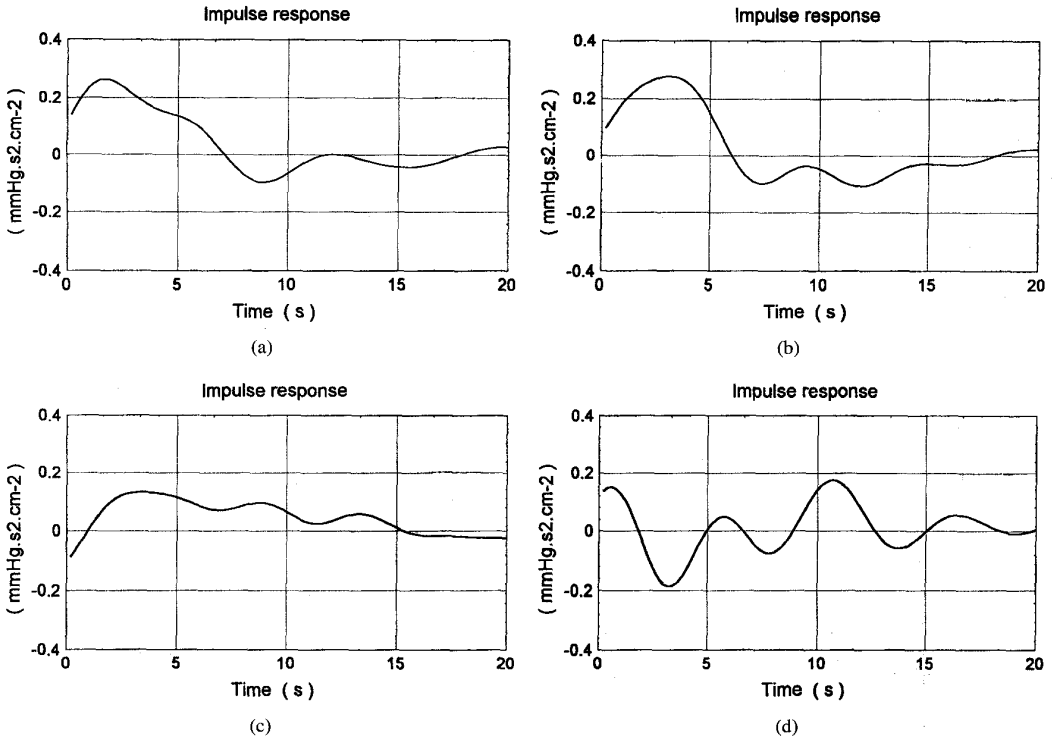

Fig. 6. Impulse responses of RAP to CBFV at four different intervals of pCO_2: (a) $pCO_2 < 5$ kPa, (b) 5.00–5.99 kPa, (c) 6.00–6.99 kPa, and (d) $pCO_2 \geq 7$ kPa.

depicted in Fig. 2(b) show that coherent averages of CrCP also have the same temporal and relative amplitude changes as MABP with similar pattern for both groups of neonates. This finding does not support the contention of Dewey *et al.* [10] that CrCP plays a major role in autoregulation. As we have discussed previously [28], further work is necessary, possibly involving an animal model, to shed light on the origin and haemodynamic significance of this back pressure. Although the CrCP waveforms shown in Fig. 2(b) have not influenced the present analytic study, they are a reminder that estimations of RAP or CVR will be in error unless CrCP is taken into account.

Previous attempts to estimate the time course of CVR following step changes in MABP have ignored the pressure-axis intercept (CrCP) [1], [34]. In addition, both groups of authors have estimated CVR as the ratio MABP/CBF (or CBFV). This means that no allowance has been made for the time-delayed responses which we have observed and that the resulting values of CVR are linearly dependent on MABP and CBF^{-1}. This is crucially different from our method since the CrCP and RAP estimates represented in Fig. 2 are independent of MABP and CBFV. This is so because we extract the RAP and CrCP values from instantaneous pressure-velocity curves as indicated in Fig. 1. In these curves, the corresponding values of $\bar{V}(n)$ and $\bar{P}(n)$ are the center of gravity around which the curve can turn. In other words, for each pair $\{\bar{V}(n), \bar{P}(n)\}$, there is an infinite number of CrCP, RAP combinations. Despite this critical difference, the patterns of CVR obtained by Aaslid *et al.* [1] and Symon *et al.* [34] show some resemblance to the time course of our estimates of RAP. In both cases a delayed peak in CVR is observed approximately 5 s after the pressure step.

The utilization of linear analysis to describe the intrinsically nonlinear system sketched in Fig. 3 is not adequate but, given the small relative amplitudes of the signals involved (Fig. 2) it seems an acceptable option to give an initial description of the dynamic relationship between CBFV and RAP. Increases in the amplitude of the MABP changes are likely to jeopardize this approach. Some evidence in this direction is provided by the recent work of Newell *et al.* [24] showing a much slower return of CBFV to baseline (~20 s) when large negative steps in MABP (~20 mmHg) are produced with deflating leg cuffs. This result might indicate a nonlinear mechanism with amplitude dependent time constants.

The large variability of the CBFV signal associated to individual MABP transients precludes the more classical approach of characterizing the significance of the CBFV-RAP relationship in the frequency domain by means of the coherence function [4]. As an alternative, the significance of this association was established with the cross-correlation function (Fig. 4) showing a statistically significant relationship between CBFV and RAP with a time delay of approximately 5 s for group A records and a broader peak around $\tau = 0$ for records classified as showing absence of autoregulation (group B). The significant time delay for group A explains the corresponding characteristics of the phase spectra of the frequency response [Fig. 5(c)] and the position of the first peak of the impulse response [Fig. 5(b)]. The meaning of the significant cross-

correlations for negative time delays for both groups A and B is not clear. The best explanation seems to be the shape of the MABP transient. Instead of a perfect step, the MABP coherent average is more like an ac pulse with the fast rising phase being preceded by a negative going change. This negative excursion is likely to produce CBFV changes and, when the maximum derivative pressure change takes place, CBFV and RAP are still responding to the preceding stimulus. This hypothesis can explain the shape of both cross-correlation functions in Fig. 4 as well as the RAP pattern for group A [Fig. 2(d)].

The main assumption of this work, reflected by the block diagram Fig. 3 is that failure of cerebral autoregulation corresponds to a depression of the feedback loop gain. Although the estimated dc loop gains confirm this hypothesis, for frequencies greater than zero there is only a slight difference between the amplitude spectra of the two groups of newborns. To some extent this result might reflect an inherent limitation of the coherent average method. The $\bar{P}(n)$ averages shown in Fig. 2(c) are not perfect step functions and, due to the extension to 256 points before the FFT, it is fair to say that the amplitude spectra is not reliable for frequencies below the second harmonic (0.04 Hz). On the other hand, the phase spectra show unequivocal differences between the two groups of records [Fig. 5(c)]. The phase lag observed for group A is coherent with the delayed increase in RAP [Fig. 2(d)] which is also reflected by the impulse response of Fig. 5(b). The difference between the two phase spectra also explains the differences between the two impulse responses. However, the impulse response for group B is somewhat puzzling because it implies an immediate reaction to changes in CBFV for neonates with an impaired autoregulation. The morphology of this impulse response is clearly due to the change in RAP in phase with MABP and CBFV which, as we hypothesized, might be produced by a direct effect of MABP rather than by changes in CBFV. What is important though is that despite this possible artefact and the small difference between the amplitude spectra, the CBFV responses for simulated step changes in MABP show the expected behavior for the two groups considered. Futhermore, the plateau for group B and the tendency of the group A response to return to baseline are maintained even when the difference between the dc loop gains [Fig. 5(a)] is artificially eliminated by making the dc gain for group A equal to that of group B. What the step responses demonstrate then is that the phase differences, or alternatively, the shape of the impulse responses, are sufficient to explain the immediate return of CBFV to baseline for group A and the plateau for group B as observed in Fig. 2(a). It should be emphasized though that this is a transient response only and it is not possible to extrapolate these results to predict responses beyond the time frame of the coherent average technique which is limited to approximately the first 20 s after the MABP transient.

The finding that the dynamic response of cerebral autoregulation is characterized by phase differences is supported by three recently published studies. Birch *et al.* [5] and Diehl *et al.* [11] have induced periodic changes in MABP by repeated squatting/standing and controlled respiration, respectively, and recorded CBFV's which were also cycling with the same frequency as MABP. In healthy individuals CBFV led MABP by a mean phase angle of 0.80 rad's at 0.05 Hz [5] and 0.75 to 1.52 rad's at 0.1 Hz [11]. Moreover, these phase differences were significantly reduced in individuals/situations suggesting an abnormal autoregulation. In the third study, Tiecks *et al.* [36] induced changes in the cerebral autoregulation of patients undergoing surgery and compared the linear regression method with the dynamic response produced by deflating a thigh pressure cuff. These authors observed that the most sensitive indicator of autoregulation impairment was the *latency* of the dynamic response rather than its amplitude. These three sets of results [5], [11], [36] can be explained by the phase spectra and impulse responses shown in our Fig. 5. Accepting that for small perturbations the linear systems assumption is valid, steady-state sinusoidal changes of MABP will result in CBFV and RAP waveforms which are also oscillating sinusoidally at the same frequency. With an intact autoregulation, RAP will lag CBFV [Fig. 5(c)] but, due to the relationship represented by (2), CBFV will lead MABP. This can be demonstrated by substituting the variables in (2) by a constant plus sine terms. Conversely, when autoregulation is defective, the disappearance of the phase differences between RAP and CBFV [Fig. 2(c)] result in a reduction of the phase differences between CBFV and MABP as observed by Birch *et al.* [5] and Diehl *et al.* [11]. As for the results of Tiecks *et al.* [36], they possibly reflect a gradation of the two extremes represented in Fig. 5(c) whereby reductions in phase difference for group A result in a slower return of CBFV to baseline following a step change in MABP.

Previous dynamic studies of autoregulation have shown a depressed response during hypercapnia [1], [34] and Birch *et al.* [5] reported a reduction in the phase difference between CBFV and MABP with increasing levels of pCO_2. Czosnyka *et al.* [9] have modeled the effect of hypercapnia on autoregulation by assuming a shift of the upper limit of autoregulation with the disappearance of the classical flow/velocity plateau. This loss of autoregulation is reflected in the impulse responses represented in Fig. 6(d). The importance of these results is two fold. First, they have been obtained from a much larger number of records than the dichotomic results of Fig. 5, they involve additional patients and, above all, are independent of any classification of autoregulation. Despite these differences, impulse responses similar to the intact and absent autoregulation can be observed for groups of records corresponding to normocapnia and hypercapnia, respectively. Second, the observation that increasing levels of pCO_2 lead to changes in the amplitude and shape of the impulse response of RAP to changes in CBFV suggests that the methods we present here might be of use to express the status of autoregulation as a continuum rather than the usual dichotomic classification. In this regard, Tiecks *et al.* [36] have recently demonstrated an excellent agreement between the dynamic and static (i.e., linear regression) methods for the graded classification of autoregulation in adults.

In addition to clinical applications, the possibility that cerebral autoregulation might be controlled by a mechanism which is more sensitively reflected by the phase spectrum rather than by amplitude changes has implications for research

on the physiology of autoregulation. It is not clear whether the flow/velocity responses to changes in MABP, pCO_2, or O_2 demand are controlled by a single or multiple mechanisms, or whether these mechanisms involve neurogenic, myogenic or endocrine actuators [29]. To these uncertainties one should add the time span of the response. Similarly to the control of arterial blood pressure, there might be different mechanisms involved in the dynamic (short term) versus the static (long term) responses. As an example the control of the dc loop gain could be myogenic/endocrine while the dynamic responses for frequencies above 0.05 Hz could be neurogenic. Limiting this discussion to the case of dynamic responses, the time constants that we and others reported [1], [5], [11], [24], [34] favor the endocrine theory. On the other hand, a phase dominated control system could be consistent with either the neurogenic or endocrine hypotheses but is less likely to originate from a myogenic mechanism.

V. Conclusion

We have shown that beat-to-beat estimations of RAP coupled to coherent averaging of CBFV, synchronized by MABP transients, can lead to a description of autoregulation dynamics which is sensitive to changes in autoregulatory performance as reflected by impairment and the effects of pCO_2. Further work is required to validate this approach in other populations but the agreement obtained with studies performed in adults [1], [5], [11], [36] and animals [34] suggest that the results described here may not be restricted to neonates.

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