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Abstract The coherence method (COH) has been widely used to study the concordance between continuously measured signals intervening in the assessment of cerebral autoregulation in neonates. Several research groups applied this method to mean arterial blood pressure (MABP) combined with cerebral signals such as the intravascular oxygenation (HbD), the cerebral tissue oxygenation (TOI), and the regional oxygen saturation (rSO_2) acquired by near-infrared spectroscopy (NIRS). All groups contributed in a particular way to the fine-tuning of the application of COH with the Welsh averaged periodogram (WAP) method. We made a comparative study of all published results coupled to an optimization of the use of the WAP method within COH. We also proposed a preprocessing algorithm to remove signal artefacts, and defined a new critical score value (*CSV*) for COH to discriminate infants with impaired autoregulation from those without.

1 Introduction

Tsuji et al. (2000) were the first to use continuously NIRS-measured signals to study over non successive 30min epochs impaired cerebral autoregulation in neonates. They looked at the concordance between HbD and MABP -reflecting impaired autoregulation- by means of the COH method combined with the WAP method. If COH >0.5 the infant was considered to have a bad autoregulation. Morren et al. (2001) introduced the use of an overlapping sliding window approach dividing prior to analysis the long duration signal in smaller 30min epochs. They also attempted to maximize the *SNR* of the WAP method. Finally

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Soul et al. (2007) introduced the use of the *CSV* defined by Taylor et al. (1998) applied to the case of impaired autoregulation.

In this study, we looked at the influences -on COH- of the signal sample frequency, the parameters intervening in the WAP method, and the frequency band of interest. Furthermore we developed a new method to fix the *CSV*, based on the calibration of the mean COH score on the mean absolute-valued correlation coefficient (COR) score, which allows us to use the value 0.5 as threshold above which a patient is said to have an impaired autoregulation. Finally we developed a preprocessing algorithm to remove signal artefacts in the time domain which is based on the removal of outlying data and isolated noise peaks.

2 Datasets

All mathematics were developed for and applied on preterm infants from the University Hospital Zurich (Switzerland), the University Medical Centre Utrecht (The Netherlands), and the University Hospital Leuven (Belgium). SaO_2 was measured continuously by pulse oxymetry, and MABP by an indwelling arterial catheter. Transcranial NIRS signals HbD (measured by the Critikon Cerebral Oxygenation Monitor 2001), rSO_2 (INVOS4100, Somanetics), and TOI (NIRO300, Hamamatsu) were measured for non-invasive monitoring of cerebral oxygenation. All signals were measured simultaneously in the first days of life, and recorded at the frequency of 0.333Hz (periodicity=3s).

3 Methods

The first constraints concern the signal sample frequency and the frequency band of interest. Urlesberger et al. (1998) and later von Siebenthal et al. (1999) showed the NIRS-measured signals could have a cyclic duration as little as 10s. Because of the use of the fast Fourier transform (FFT), the *Nyquist theorem of digital sampling* imposes the sampling frequency to be at least twice the smallest signal intrinsic frequency, i.e. at least 0.2Hz. von Siebenthal et al. also showed that MABP was fluctuating with a periodicity of 60 to 150s. MABP being the most influential signal of all considered, we studied impaired autoregulation in the periodicity band 25s-300s (Soul et al.).

The continuously recorded signals were beforehand divided in epochs of a shorter duration, allowing us to have a continuous assessment of impaired autoregulation (Morren et al.). For this reason we called them calculation epochs (*C-epochs*), of duration *TC* (min). The WAP method computes an averaged frequency spectrum of the signal on each of these C-epochs. The average is performed on the basis of *N* smaller overlapping epochs in which each C-epoch is divided. We called these smaller epochs *H-epochs* as they apply a highpass (time-

domain) filtering on the signals. The duration of a H-epoch (*TH*, min) should be at least one cycle of the signal periodicity. To ensure the last H-epoch contained in a C-epoch is not cropped (which would mean that the signal is again highpass filtered), we could demonstrate:

$$N = \frac{TC - THOver}{TH - THOver} \qquad (1)$$

where TH_{Over} (min) is the overlap width between two successive H-epochs. As it was not sure we included in each H-window an integer number of signal cycles, we applied on each H-epoch a *Hanning window* to avoid the leakage phenomenon when using the FFT. Notice that no Hanning windowing was applied to the C-epochs, as it generated an artefact in the low frequencies of the COH spectrum. Carter et al. (1973) showed the H-epochs should be half-overlapped in the case of the application of Hanning windowing. At the other side, we found out that the higher the value of *N* (the higher the *SNR*), the lower the amplitude of COH. Thus by choosing a different *N*, we obtained different COH values. Eq. 1 became:

$$TC = \frac{TH(N+1)}{2} \qquad (2)$$

The duration of the C-epochs in which the full-length signals are originally divided may thus ideally not be chosen. We otherwise found out that the ratio *TH/TC* should be in the range of 0.5 or smaller, otherwise it is no worth to apply the WAP method as the H-epoch duration tends to the C-epoch one.

In 1998, Taylor et al. already found out that the amplitude of COH was influenced by the parameters intervening in the WAP method. To discriminate patients presenting a concordance between the two investigated signals from those presenting no concordance, they set up a new *CSV* definition computed from *TC*, *TH*, and a *F*-hypothesis test. However this definition did not take into account the influence of TH_{Over} intervening in Eq. 1. Therefore we proposed a new methodology: adapt *N* until the mean COH -on all infants from the same medical centre- equals the mean absolute-valued (for comparability with COH) COR, the *CSV* of COR being per definition 0.5. Making *N* variable changes only the *SNR* of the frequency spectrum, and do not affect the signals. The sole free parameter in Eq. 2 is *TH*, in so far it fulfils some conditions. We chose *TH* equal to 5min accordingly to the work of Soul et al. Please find in Table 1 the summary of the parameter values used by all working groups, to which we added the ones of Wong et al. (2008).

Finally, we also develop a preprocessing stage to remove measurement artefacts induced by medical interferences and by the conversion between analog and digital data. Each artefact point in a signal was simultaneously deleted in all other signals, as Soul et al. did for artefacts lasting more than 1.5s. The steps of the algorithm we developed are:

1. Remove artefact-like repetitive points included in the recordings.
2. Keep the signals in normal physiological ranges, particularly SaO_2 in the range 80-100%.

3. Divide the signals in non overlapping 10min epochs from each of which we only kept the portions belonging to interval [*median-IQR*, *median+IQR*].
4. As this is not enough to detect some extra peak artefacts of longer duration contained in MABP and SaO_2 (the two most influential signals), centre and absolute-value MABP (and afterwards SaO_2) (result 1), and at the other side differentiate, square, and reduce it (result 2) with the aim to emphasize the signal extremes. Result 1 gives an average peak amplitude, and result 2 acts as a ponderation coefficient with value close to 1 at peak abscises. Finally multiply together the obtained signals, which points out which signal points may be deleted.

4 Results

There are about 55% repetitive points for the INVOS, 45% for the Critikon, and 15% for the NIRO spectrometers. They were all removed prior to application of preprocessing steps 2 to 4 which deletes themselves about 60% of the data. Steps 2 to 4 are very effective: values of COH and COR are significantly higher than without preprocessing. Fig. 1 illustrates an example of preprocessed data. The optimized values of *TC* (*N*) for the Zurich, Leuven, and Utrecht data are 10min (3), 12.5min (4), and 15min (5). The *CSV* computation of Taylor et al. generates high values (around 0.7) in the case of NIRS-measured signals, only affordable with a low *N*, i.e. a low *SNR*.

5 Discussion

The repetitive points in the data prior to analysis may be due to the conversion from analog to digital data, to the spectrometer resolution, and some of them simply to the sometimes constant nature of the signals. We determined the possible repetitive character of a data point following two ways: with and without rounding the data of all centres to keep only two decimals after zero prior to point removal, but there was no difference between these two approaches in the percentage of points removed. The preprocessing has otherwise a bad influence on the frequency content of the signals. We should complementary set up an *intelligent interpolation* for artefacts lasting more than 1.5s otherwise we break the signal periodicities. The preprocessing makes finally the recording much shorter in duration, with the risk to render it impossible to analyse by means of a sliding-window approach.

Concerning the WAP method, the FFT assumes the signals to be periodic, what we experimentally didn't observe that clearly in opposition to von Siebenthal et al. and Urlesberger et al. The decrease in the coherence amplitude with increasing *N*

should thus actually not occur, because from one H-epoch to the other, the extremes in the frequency spectrum of COH should occur at the same frequencies.

Finally, working with a *CSV* of COH equal to 0.5 suggests a relation between two signals based on 50% shared variance, which can be defended. But this *CSV* should be ideally determined empirically from the patient clinical characteristics and outcomes, or statistically on the way Taylor et al. did it. With the *CSV* fixation we proposed, the amplitude of COH is in the range of COR which allows comparability of these two complementary methods. The *CSV* definition of Taylor et al. generates high values in the case of detection of impaired cerebral autoregulation, but could be used maybe in other applications (e.g. for cardiologic data).

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Table 1 The following table is a summary of all parameters intervening in the Welsh averaged periodogram method applied by Tsuji et al. (2000), Morren et al. (2001), Soul et al. (2007), Wong et al. (2008), and the optimization we made of these parameters.

	Tsuji et al.	Morren et al.	Soul et al.	Wong et al.	Optimization
f_s	2Hz (0.2Hz)	6Hz (0.2Hz)	2Hz (0.4Hz)	1Hz	≥0.2Hz
f_{cut}	0.01Hz	0.01Hz	0.04Hz	0.02Hz	$0.0067 \leq f_{cut} \leq 0.1$Hz
TH	-	12min	5min	10min	$2.5\text{min} \leq TH \leq TC/2$
TH_{Over}	-	11min55s	2.5min	7.5min	*TH*/2
N	-	217	3	5	≥3, calibr. of COH on |COR|
TC	30	30	10	20	$TH(N+1)/2$
TH/TC	-	0.4	0.5	0.5	$2/(N+1), \leq 0.5$
TC_{Over}	-	10	0	0	*TC*/2
CSV	0.5	0.5	0.77	0.5	0.5

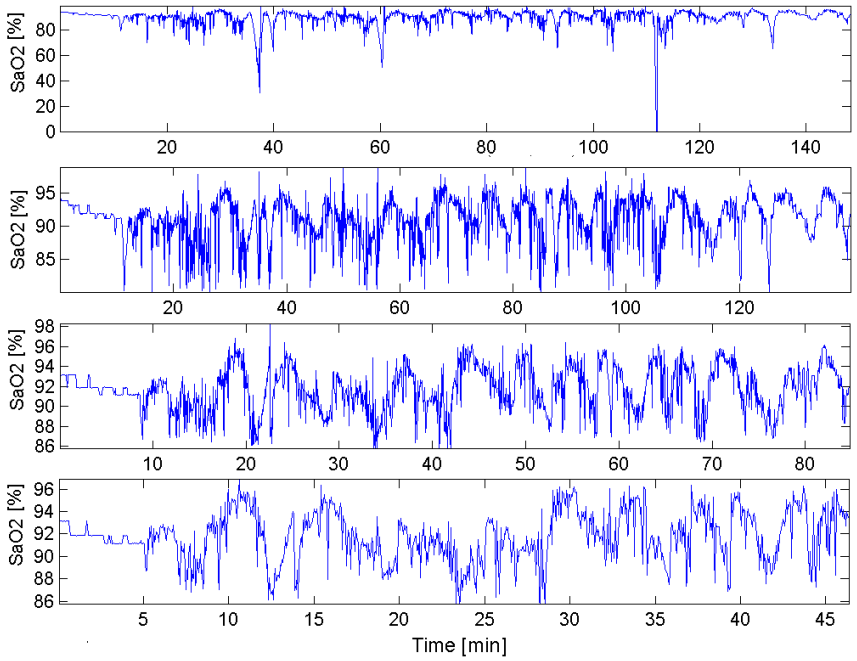


Fig. 1 Illustration of the preprocessing algorithm applied to SaO_2, MABP, and HbD/rSO_2/TOI. Most of artefacts due to medical interferences and patient handling were removed. Repeating points probably due to conversion between analog and digital data were also removed. Unless its efficiency, the preprocessing makes the signals very short and breaks partly their frequency content.