

MONITORING THE BRAIN-STEM STATE THROUGH THE ASSESSMENT OF THE BARORECEPTOR-HEART RATE REFLEX IN CRITICALLY BRAIN-INJURED PATIENTS

P. Castiglioni¹, F. Conci², G. Parati³, M. Di Rienzo¹

¹Centro di Bioingegneria, Fondazione D. Gnocchi ONLUS, Milan, Italy

²Department of Anesthesiology, Niguarda Hospital, Milan, Italy

³Istituto Auxologico Italiano, Università Statale Milano-Bicocca, Milan, Italy

Abstract- Aim of this study was to evaluate whether the analysis of cardiovascular dynamics and the assessment of the baroreceptor-heart rate reflex can be used to derive information on the functionality of the cardiomotor brain-stem centers and whether this information may facilitate the diagnosis of brain death. We estimated during impending brain death in 11 comatose patients hospitalized in ICU 1) spontaneous variability of systolic and diastolic blood pressure (SBP and DBP) and pulse interval (PI, the reciprocal of heart-rate) by spectral analysis; and 2) spontaneous baroreflex sensitivity (BRS) and baroreflex effectiveness index (BEI) by the sequence technique. Brain death was associated with significant spectral changes, including a generalized reduction in PI spectra and a decrease of the 0.1 Hz power in SBP and DBP spectra. BRS and BEI, close to normal values just before brain death, dropped to 0 after the brain death event. These changes –likely to reflect the cessation of activity of the cardiovascular brainstem centers- suggest that techniques for blood pressure and heart rate spectral analysis and for the dynamic estimation of spontaneous baroreflex control of the heart can be used for monitoring the brain-stem state in ICU and may complement the traditional assessment of brain-stem death.

Keywords - Baroreflex sensitivity, heart rate variability, blood pressure variability, brainstem, spectral analysis

baroreceptor-heart rate reflex, the afferences of which are interconnected with the efferent limbs in various areas of the brain stem) has never been considered among the criteria for determining brain death.

Aim of this study is to evaluate whether the analysis of cardiovascular dynamics and the assessment of the baroreceptor-HR reflex can be used to derive information on the functionality of the cardiomotor brain-stem centers, and, in particular, whether this information may potentially complement the diagnosis of brain death.

To address this issue, as a preliminary step we evaluated baroreflex control of the heart, blood pressure and heart rate variabilities, in a group of comatose patients before and after brain-stem death. The baroreflex control of the heart was investigated by using recent techniques based on the evaluation of spontaneous changes in BP and HR beat-to-beat variability [3,4]. These techniques do not require any specific stimulation of the patient, and allowed us to obtain an almost continuous quantification of the baroreflex function without introducing any disturbance to the patients, nor interfering with their clinical care.

II. METHODOLOGY

I. INTRODUCTION

Monitoring the brain-stem state in comatose patients with severe brain damages is a critical task, and requires perceptive and experienced physicians for reliable testing. In particular, this evaluation is of fundamental importance in the determination of brain death, which is defined as the *"irreversible cessation of all functions of the entire brain, including the brain stem"* [1]. The diagnosis of the brain-stem death is currently performed by checking the irreversible loss of specific brain-stem reflexes, like pupillary light, corneal, oculocephalic, oculovestibular, oropharyngeal and cough reflexes. Major alterations in cardiovascular dynamics can be also expected from the impairment of the cardiovascular centres located in the brain stem, and actually differences in heart-rate (HR) and arterial blood pressure (BP) variability, and in the baroreflex function have been observed in brain dead patients, when compared to vegetative patients or healthy controls [2]. However, no information is available on the decay of the functionality of cardiovascular centres, from the impending brain death to the complete inactivity of the brain stem. For this reason, the assessment of a permanent loss of cardiovascular regulation (and in particular of the

Eleven subjects of age between 21 and 66 yr. hospitalised in the Neurological Intensive Care Unit were enrolled in the study. At the time of admission no patient had a medical history of neurological and cardiovascular disorders. All patients were in a coma grade 3-4, according to the Glasgow coma scale. They received standard therapy to maintain physiological homeostasis, and were mechanically ventilated. Intra-arterial BP was measured by a catheter inserted into the radial artery, and recorded continuously from the time of admission up to the establishment of brain death and during the following observation period of 6 hours required by law. Brain death was identified by verification of apnoea at $p\text{CO}_2 > 60$ mmHg, absence of brain-stem reflexes for a legal observation period of 6 hours, with no hypothermia or drug-induced depression, and recordings of isoelectric EEG for periods of 30 minutes every two hours during the observation period. Twelve-hour BP recordings, each including about 6 hours before and 6 hours after brain death, were considered. Systolic and diastolic blood pressures (SBP and DBP) were identified on a beat-to-beat basis and the cardiac rhythm was derived from the BP wave by computing PI, i.e., the time interval between consecutive systolic peaks. Two segments of data, one before and one after brain death, (hereafter defined

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"before-BD" and "after-BD" respectively) were identified for the subsequent analyses. On average, the before-BD and after-BD segments lasted 3 and 4 hours respectively. The after-BD segment started 1 hour after the onset of brain death.

Blood pressure and heart rate variability. SBP, DBP and PI series were split into short-term data-records, each lasting 512 s, and the FFT spectrum was estimated in each record. Then, the spectra falling in the before-BD and after-BD segments were averaged to obtain a single spectrum for each condition. Spectra were integrated over three frequency bands: at very-low frequencies, VLF (from 0.003 to 0.06 Hz); at low frequencies, LF (from 0.06 to 0.12 Hz); and at high frequencies HF (from 0.12 to 0.50 Hz). Powers in these frequency bands quantify respectively the global power of the slowest components of variability (VLF), the magnitude of the so-called "10 sec rhythm" (LF) and the power of the respiratory component (HF).

Baroreflex function. In order to obtain an almost continuous monitoring of the baroreflex function without any intervention on the patient, we estimated the baroreflex sensitivity on the heart (BRS) from the spontaneous fluctuations of SBP and PI by applying the "sequence technique". Briefly, SBP and PI series were scanned automatically in search for spontaneous sequences of three or more consecutive heart beats in which a progressive SBP increase (increasing SBP ramp) was followed, with a one-beat lag, by a progressive PI lengthening or, *vice-versa*, in which a progressive SBP reduction (decreasing SBP ramp) was followed by a PI shortening. The slope of the regression line between SBP and PI values forming each sequence was taken as an estimation of BRS. In addition to BRS, we also computed the rate of occurrence of SBP increasing and decreasing ramps, and a recently proposed index of the baroreflex function, the baroreflex effectiveness index (BEI) [3]. BEI is defined as the ratio between the number of SBP-PI sequences (i.e., of SBP ramps followed by the respective reflex PI ramps), and the total number of SBP ramps observed in a given time window:

$$BEI = (\text{n}^\circ \text{ of PI-SBP sequences}) / (\text{n}^\circ \text{ of SBP ramps})$$

In this study, BEI was computed over a running window of 512 s length.

Statistical analysis. For the spectral powers, the significance of the differences between the before-BD and after-BD periods was assessed by paired t-test after log-transformation to obtain normally distributed data. For the BEI index, the significance of the difference was assessed by the sign test. The level of statistical significance was $p < 0.01$.

III. RESULTS

BP and PI were lower after brain death. Ensemble average (mean $\pm$ SD) of SBP and DBP decreased from 175 $\pm$ 46 to 122 $\pm$ 23 mmHg and from 84 $\pm$ 17 to 68 $\pm$ 15 mmHg respectively; the heart interval decreased from 778 $\pm$ 208 ms to 586 $\pm$ 120 ms.

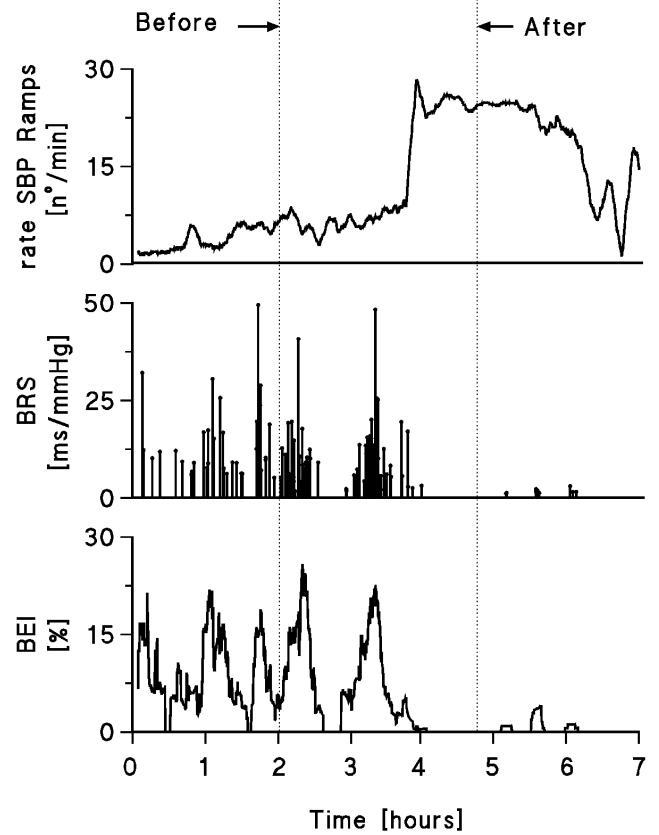


Fig. 1. Assessment of baroreflex function in one patient. From top to bottom: rate of SBP increasing or decreasing ramps; BRS estimates; BEI index. Rate of SBP ramps and BEI were estimated over a running window of 512 s. The two selected periods, before and after brain death (see text) are also shown.

TABLE I
MEAN ($\pm$ SE) OF SPECTRAL POWER IN 3 FREQUENCY BANDS
A * INDICATE A SIGNIFICANT DIFFERENCE ($P < 0.01$)
BETWEEN BEFORE-BD AND AFTER-BD CONDITIONS

Frequency Bands	SBP(mmHg ²)		DBP(mmHg ²)		PI(ms ²)	
	Before	After	Before	After	Before	After
VLF	7.5 $\pm$ 2.5	5.2 $\pm$ 1.6	2.8 $\pm$ 0.9	1.4 $\pm$ 0.4	488 $\pm$ 170	30 $\pm$ 16*
LF	4.6 $\pm$ 1.4	0.2 $\pm$ 0.1*	2.3 $\pm$ 0.9	0.1 $\pm$ 0.03*	353 $\pm$ 161	2 $\pm$ 1*
HF	15 $\pm$ 5	4.4 $\pm$ 1.2	5.2 $\pm$ 1.5	0.9 $\pm$ 0.2*	2103 $\pm$ 918	0.9 $\pm$ 0.2*

Blood pressure and heart rate variability. Table I shows mean values ($\pm$ SE) over the group of the powers in the 3 bands. The VLF power did not change significantly for SBP and DBP, indicating that a consistent fraction of the slower components of blood pressure variability was still present after the brain-stem death. By contrast, PI power dramatically and significantly decreased in this band. The LF power decreased significantly for all SBP, DBP and PI series, showing that the "10-sec rhythm" was still present few hours before the occurrence of brain-stem death, and almost disappeared after brain death. The HF power decreased significantly for DBP and PI; the reduction was consistent for SBP too ($p = 0.013$).

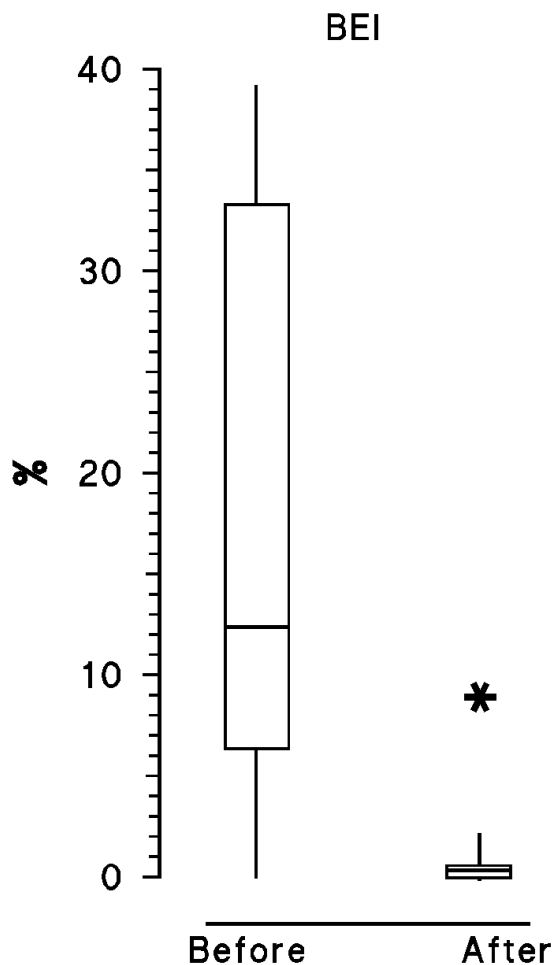


Fig. 2. Box-and-whiskers plots of BEI distributions before and after brain death. Each box represents the middle 50% of the data, with the central line at the median, and the whiskers extending to minimum and maximum values of the data. The "*" indicates that the two distributions differ at a significance level $p < 0.01$

TABLE II
MEAN ($\pm$ SE) OF BAROREFLEX SENSITIVITY BRS,
AND RATE OF OCCURRENCE OF SBP RAMPS
BEFORE AND AFTER BRAIN DEATH

	Before	After
BRS [ms/mmHg]	10.7 (2.6)	not assessed†
SBP-ramps rate [n°/min]	10.6 (1.9)	12.9 (1.7)

†not enough spontaneous SBP-PI sequences were found to estimate BRS (see text)

Baroreflex function. Figure 1 shows an example of continuous assessment of the baroreflex function in one subject. After brain death not only the values, but also the number of BRS estimates dramatically decreased, although in this patient the loss of the brain stem was associated with an augmented rate of SBP ramps (i.e., an increase in the number of SBP spontaneous transients that the sequence technique

considers as the probe input to the baroreceptors for evaluating BRS).

Before brain death our group of patients was characterized by an extremely wide range of individual BRS values, spanning from 0 to 30 ms/mmHg, possibly reflecting the variety of their clinical conditions. It is worth noting, however, that when the individual estimates were averaged over the whole group (table II), the average BRS value was not too far from the average values observed in healthy subjects in awake condition (around 12 ms/mmHg) [2]. After brain death, BRS could not be estimated because of the very-low number of SBP-PI sequences found after brain death. Indeed, the average rate of spontaneous sequences fell from one every 27 seconds (in the before-BD segment) to one every 25 minutes (in the after-BD segment), and no sequences at all were found in three subjects after brain death. By contrast, the number of SBP ramps slightly increased after brain death (table II): on average more than ten short-term SBP transients per minute were found both before and after brain death.

Values of BEI before and after brain death are shown in figure 2, which points out a dramatic and significant reduction of this index after the occurrence of brain death.

V. CONCLUSION

Spectral analysis and the continuous monitoring of the baroreflex function showed the maintenance of baroreflex sensitivity and effectiveness near to normal values up to few hours before brain death, and that changes occurring with brain-stem death are well discernible, appearing as a marked fall in the indexes of baroreflex spontaneous activity, accompanied by a fall in the LF power of BP and in the overall HR spectrum.

An established hypothesis to explain the LF power is that a "ten-second rhythm" is generated by a resonance phenomenon due to time constants and delays of the baroreflex loop [5]. Thus, the loss of the LF power of SBP, DBP and PI we observed in our patients after brain death are likely to reflect the opening of the baroreflex loop induced by the deactivation of cardiovascular centres in the brain stem.

The baroreflex sensitivity and effectiveness index were remarkably high before brain death and, on average, close to values reported in normal subjects. Their values, however, showed a high between-subject variability. This may be explained by considering that if higher centres of the brain are lost or damaged but the brain stem is intact, then the baroreceptors reflex might still work efficiently, with sensitivity and effectiveness even greater than in healthy condition, given the absence of potential inhibitory influences coming from higher centres. However, it is also possible that in some of our patients the brain stem was partially and progressively damaged also before the brain death, and that the cardiovascular centres of the brain stem were already suffering. This might justify the wide distribution of values we observed before brain death. In this context, it may be of

interest considering the case of one subject who showed values of BRS and BEI very close to zero even before brain death. This patient was also characterized by very low values of PI power at 0.1 Hz even before brain death (while the blood pressure powers were similar to those observed over the whole group). In this patient most of the brain-stem reflexes used for the diagnosis of brain death were clinically absent even during the before-BD period, with the only exception of a gasping breath. Thus, it is likely that in this subject the cardiovascular centres of the brain stem were partially damaged, and the autonomic control on the heart was almost completely lost already before brain death, while a residual vasomotor control on blood pressure was still present.

In conclusion, our study suggests that the continuous monitoring of cardiovascular reflexes may support the diagnosis of brain-stem death, similarly to what is actually done with other brain-stem reflexes. It should also be considered that while brain-stem reflexes traditionally used for the diagnosis of brain death can be checked only periodically, and require a perceptive and experienced physician for reliable testing, the techniques used in this study allow an automatic and continuous monitoring during the whole period of hospitalisation in the intensive care unit. Obviously, caution is needed while using these indexes in patients under such deranged clinical conditions. Indeed, it should be considered that before the onset of brain death a possible concurrent impairment of cardiovascular centres of the brain stem may cause alterations of BP and HR variabilities and a deactivation of the baroreceptors reflex. On the other hand, specific pharmacological therapies or neurological alterations occurring in these subjects may also affect BP and HR variability and may exert inhibitory effects on baroreflex function. Notwithstanding these limitations, our

data indicate that the running evaluation of the spectral components of BP and HR variabilities and of the baroreflex function might become an additional tool for monitoring the brain-stem state and for confirming the diagnosis of brain stem death.

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