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Direct Mechanical Stimulation of Brainstem Modulates Cardiac Rhythm and Repolarization in Humans

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Abstract: Natural mechanical stimulation of the brainstem area by the blood pressure waves propagating in the adjacent arteries plays an important role in the homeostasis of the brainstem centers of cardiovascular control. However, effects of direct mechanical stimulation of this area on the cardiac elecrophysiology have never been studied in humans. In 12 patients (age: 54 ± 13 years, 5 females) undergoing microvascular decompression, the left (9 patients) or the right (3 patients) side of the ventro-lateral surface of the medulla oblongata was exposed during the surgery, and a mechanical stimulation (duration: 1 min, frequency: 1–2 Hz) of the roots of the cranial nerves and the surface of the brainstem was performed at 3–7 sites using a 2-mm metallic ball. Spatial changes in cardiac repolarization were examined using the 32-lead/192 site electrocardiographic body surface potential maps. Blood pressure was monitored using intra-arterial line. The intervals between the onset of the Q-wave and the offset of the T-wave (QTe) and between the onset of the Q-wave and the peak of the T-wave (QTp), the activation-recovery intervals (ARi), the peak T-wave amplitude, and the QRS and STT integrals were measured using custom software. During the stimulation between the caudal rootlets of the 10th nerve, the peak T-wave amplitude decreased 22% (range: 6–50%) and RR-intervals decreased from 923 ± 190 to 794 ± 111 ms compared to the recordings obtained before the stimulation ($P = .025$ and .063, respectively), whereas QTe, QTp, Ari, and the QRS- and the STT-integrals did not change. Decreased T-wave amplitudes and unchanged QT-intervals suggest that brainstem stimulation might evoke spatially inhomogenious repolarization changes. Stimulation of a localized region surrounding the caudal rootlets of the 10th nerve elicits pronounced effects on cardiac rhythm and repolarization. **Key words:** Brainstem, cardiac rhythm, cardiac repolarization, body surface mapping.

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Natural mechanical stimulation of the brainstem area by the blood pressure waves propagating in the adjacent arteries plays an important role in the homeostasis of the brainstem centers of cardiovascular control (1). In experimental studies, pulsatile stimulation and compression of this region increases blood pressure, heart rate, and peripheral sympathetic nerve activity (2). In humans, mechanical stimulation and compression of the brainstem area by adjacent arteries is often associated with hypertension and enhanced levels of circulating cathecholamines (2,3). On the other hand, separation of the brainstem area from the surrounding compressing arteries, referred to as microvascular decompression (MVD), significantly reduces blood pressure and sympathetic nervous activity in hypertensive patients (2,3).

The central role of the rostral ventrolateral medulla (RVLM) in the tonic and reflex sympathetic and cardiovascular activities explains the sensitivity of this region to mechanical stimulation (4,5). The RVLM neurons, referred to as presympathetic neurons, project directly to the sympathetic preganglionic neurons in the spinal cord, and inhibition of the RLVM neurons leads to a profound fall in arterial pressure and peripheral sympathetic activity (2).

However, functional organization of the RVLM is complex and not well understood. Viscerotopic projections of this area have been primarily studied in nonprimates whose brain architecture is different from that in primates (6). Disruption or inhibition of vagal cardiopulmonary afferents caused blood pressure rise, tachycardia, and vascular constriction, suggesting that vagal afferents exert tonic inhibitory activity on the RVLM neurons (7). Interspersed locations of the presympathetic and preganglionic vagal neurons, multiple feedback loops between the two systems, functional connections and asymmetry between the left and right sides further complicate the problem (1,7). Adding to this conundrum, the results of experimental studies with electrical stimulations of vagal afferents in animals were inconsistent, demonstrating both pressor and depressor effects (8,9).

We hypothesized that mechanical stimulation of the RVLM and the root-entry zone of the 10th nerve would activate the RVLM neurons and increase sympathetic traffic to the heart, changing cardiac rhythm and repolarization. To test this hypothesis, we used mechanical stimulations of the RVLM area in patients undergoing MVD and observed that stimulation of this region modified cardiac rhythm and repolarization patterns.

Materials and Methods

The research protocol was reviewed and approved by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from participants. In 12 patients (age: 54 ± 13 years, 5 females) undergoing MVD on the left (9 patients) or on the right (3 patients) side, the ventro-lateral surface of the medulla oblongata and the root-entry zone of the 5th–11th cranial nerves were exposed during the surgery.

Stimulation Protocol

The stimulations were performed at 1) the rootlets of the 9th, 10th, and 11th cranial nerves and 2) the surface of the brainstem between the roots. After a 1-min baseline period, we stimulated different sites consecutively using a 2-mm metallic ball (Fig. 1). A 1-min recovery period was allowed after the stimulation at each site. A sequence of software-generated beeps was used as the time markers for the stimulations. At each site, the frequency of the stimulation was increased in 0.1 Hz increments between 1 Hz and 2 Hz, so that each stimulation frequency was kept constant for 10 sec. The rootlets of the cranial nerves were stimulated at a 2-mm distance from the entry into the brainstem, because central myelin changes to peripheral myelin at this level, making the nerve fibers vulnerable to pulsatile mechanical stimulation (10).

Data Acquisition and Signal Processing

Electrocardiographic body surface potential maps (BSPM) were recorded at 1 kHz sampling frequency with a 32-lead acquisition system (CVRTI, University of Utah, Salt Lake City, UT). Baseline drift was corrected using a two-step adaptive approach described elsewhere (11). The 32 signals were transformed into 192-site maps using the method described by Lux et al. (12) QRS complexes were detected, and the intervals between the consecutive R-peaks were determined. The activation-recovery interval, the peak T-wave amplitude, and the QRS-, the STT-, and the QRST-area integrals were measured in each lead using custom software as previously described (13). Changes in the QRST-area primarily reflect repolarization dynamics, whereas changes in the QRS- and STT-areas reflect alterations in the activation and repolarization sequences, respectively (14). Thus, the 3 integrals provide relatively “clean,” independent measures of

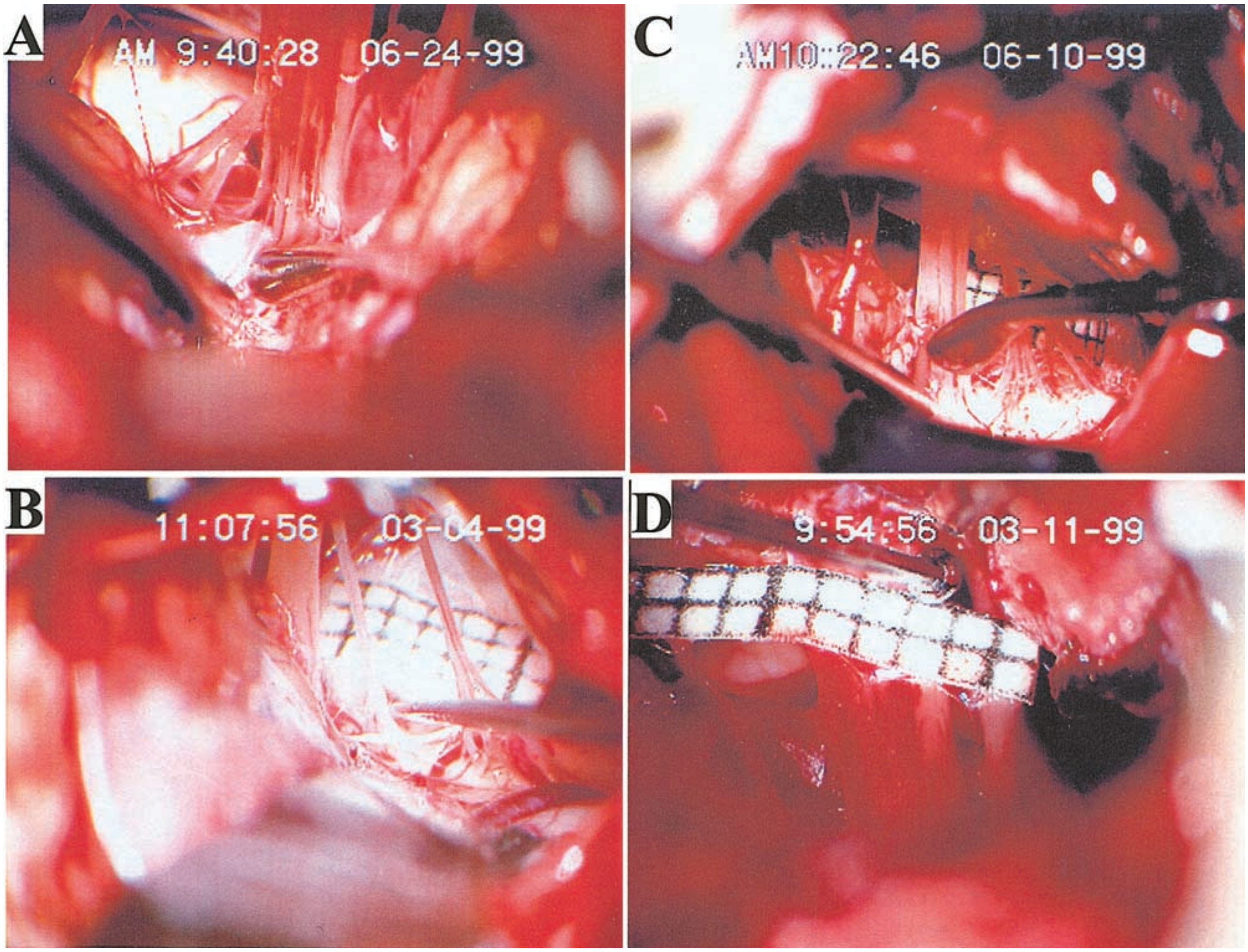


Fig. 1. Snapshots of the mechanical stimulations of the root entry zone of the 10th nerve and the RVLM area on the left side (Left Column) and the right side (Right Column). The snapshots are obtained from a 71-year old woman (A), a 56-year old man (B), a 75-year-old woman (C), and a 60-year old man (D).

cardiac activation and repolarization. Because alterations in different segments of the T-wave may reflect changes in different layers of the cardiac wall, we also calculated the intervals between 1) the onset of the Q-wave and the offset of the T-wave (QTe), and 2) between the onset of the Q-wave and the peak of the T-wave (QTp) (15). Blood pressure was monitored using an intra-arterial line.

Statistical Analysis

To estimate significance of the serial changes in cardiac rhythm and repolarization, in each subject, the values obtained during the stimulations were compared with those before the stimulations. Nonparametric Wilcoxon matched pairs test was used to minimize the effects of small sample size and unknown distribution properties. Relationships between the variables were tested using nonparametric Spearman correlations.

Results

Anatomical Differences in the RVLM Organization

The number, thickness, and localization of the rootlets of the 10th nerve varied among the subjects (Fig. 1). In most patients, the space between the rootlets was sufficiently large for accessing the surface of the brainstem ($n = 8$). In some patients, however, the smaller inter-root spaces did not allow direct access to the surface of the medulla, and the stimulations could be applied only to the rootlets of the cranial nerves (n = 4). No gross asymmetry was observed between the left and the right-side anatomy, although the number of the right-side procedures was insufficient for statistical comparisons (n = 3).

Effects of Brainstem Stimulation on Cardiac Rhythm and Repolarization

Serial isointegral maps obtained before, during, and after the stimulations in a 71-year-old woman, whose left RVLM is shown in Figure 1A, are presented in Figures 2–4. Serial QRS-area isointegral map, a gross measure of activation sequence, was unaltered during the experiments (Fig. 3). However, the repolarization properties changed drastically during the stimulation (Figs. 3–4). These changes were manifested by the inversion of the T-waves, the STT- and the QRST-integrals (from positive to negative) in the precordial region during the stimulation of the caudal rootlets of the 10th nerve (Figs. 3,4, Panels 11 and 12, Fig. 5). The negativity further increased during the stimulation of the RVLM surface (Figs. 3,4, Panels 13 and 14) and gradually resolved 40 min after the start of the stimulations (Figs. 3,4 Panel 20).

Heart rate increased during the stimulation on the left side in 4 out of 7 patients and on the right side in 1 out of 3 patients. Note, that the changes in cardiac rhythm occurred earlier than the repolarization changes (Fig. 6). Heart rate increased at the beginning of the surgical exposure of the RVLM area and remained elevated until the end of the procedure.

Patterns of Individual Electrophysiological Responses to the Mechanical Stimulations

A wide range of individual changes in repolarization and, in particular, in the peak T-wave amplitude (44%) was observed among the patients. The change in the maximum value of the STT-isointegral maps was related to the age of the patients ($r = .71$, $P = .046$), whereas other repolarization variables did not show any correlation with age or gender ($P = .14$-$.7$). We did not find any relationship between the pattern of electrophysiological response and the side of the stimulation, although the number of the patients operated on the right side of the RVLM was too small for statistical analysis (n = 3).

Statistical Analysis of the Electrophysiological Responses in the Studied Group

The results are summarized in Table 1. During the stimulation between the caudal rootlets of the 10th nerve, the peak T-wave amplitude decreased (normalized difference: 22%, $P = .025$), RR-interval shortened, whereas QT-interval, the activation-recovery interval, and the QRS- and the STT-integral did not change significantly. No changes were detected in the blood pressure readings during the stimulation.

Discussion

Main Results and Comparison With Previous Studies

Mechanical stimulation of the RVLM surface and the caudal rootlets of the 10th nerve increased the heart rate and modified repolarization patterns. These changes were found during the stimulations on the left side and the right side of RVLM.

Although brainstem centers of sympathetic and parasympathetic system have been extensively studied in animal models, data from human studies are scarce. In non-primate animals, cardiac sympathetic premotor neurons and centers of parasympathetic cardiovascular control (the nucleus of the solitaty tract and the nucleus ambiguus) are located close to each other (16,17). Therefore, stimulation of this area may change both sympathetic and vagal traffic to the heart. As a result, a variety of changes in heart rate, including cardiac arrhythmias (18), and repolarization (T-wave amplitude and QT-interval) may occur in patients with acute cerebrovascular events (6). However, no association between specific ECG changes and regional cerebrovascular abnormalities has been reported in humans.

Mechanical Stimulation of the Brainstem and Cardiac Electrophysiology. Viscerotopic organization of the vagus nerve has not been systematically studied in humans. In cats, cardiodecelerator fibers are located in the caudal rootlets of the 10th nerve (9). Stimulations of the caudal rootlets of the 10th nerve in our study also induced changes in the heart rate, which suggests that the caudal rootlets of the 10th nerve play an important role in the cardiac chronotropic control in humans. However, in contrast to the negative chronotropic effect

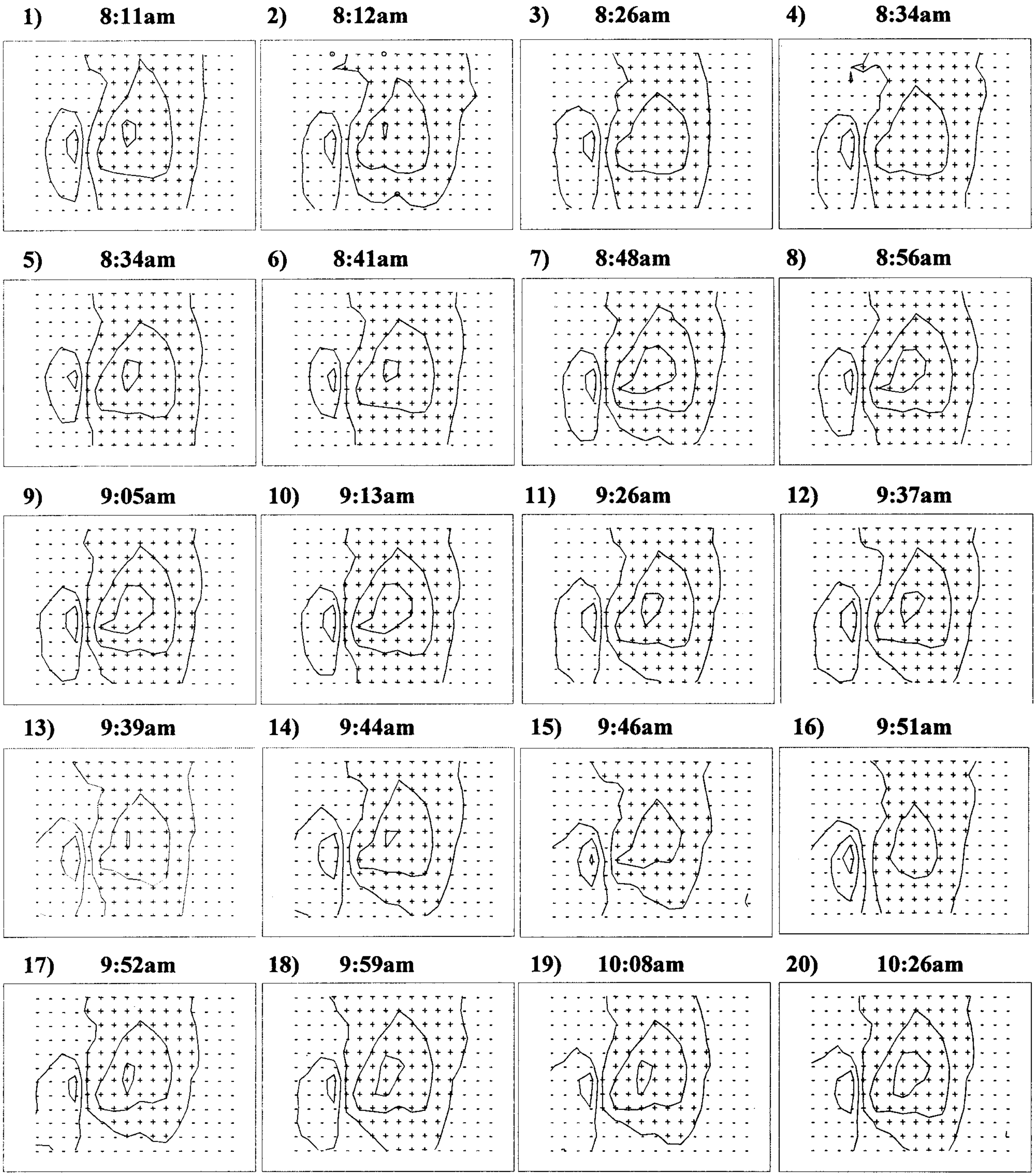
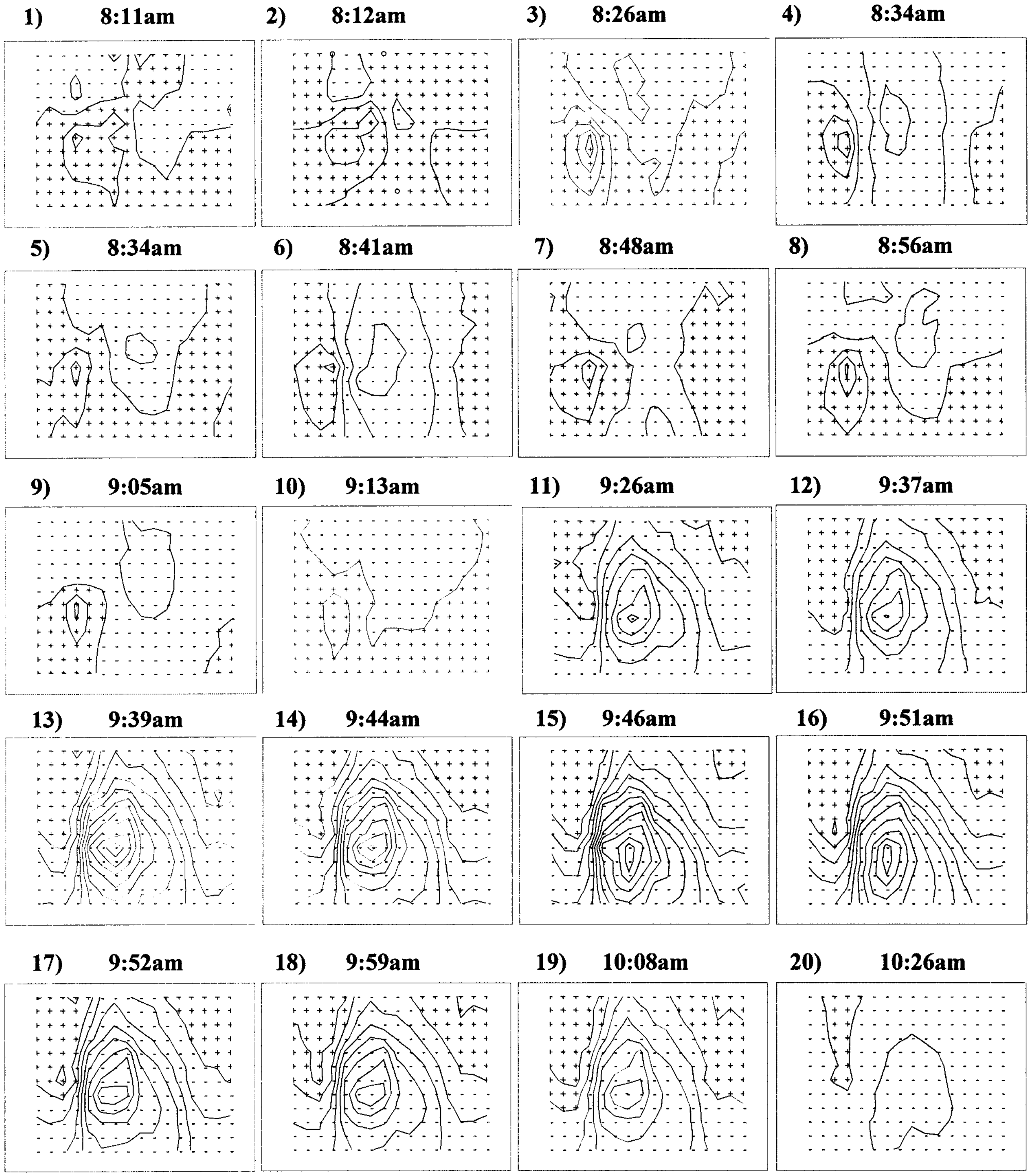


Fig. 2. Serial QRS-isointegral maps in a 71-year-old woman, whose RVLM is shown in Figure 1A: 1) before the surgery starts, the subject is under general anesthesia in the operating room, 2–6) opening the skin and the scalp, 6) opening the dura, 7–10) opening the brainstem region, 11–12) stimulation of the rootlets of the 10th nerve, 13–14) stimulation of the surface of RVLM, 15–16) Valsalva maneuvers, 17–18) closing the dura, 20–21) closing the skin.

observed in animal models, the stimulation paradoxically increased the heart rates in our study. The discrepancy could be explained by different experimental settings. In animal models, the nerves were severed at the beginning of the experiment, and only the distal part of the nerve was stimulated leaving the afferent traffic to the brainstem unmodified (9). In our study, stimulation of the intact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16) 9:51am
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19) 10:08am
20) 10:26am

Fig. 3. Serial STT-isointegral maps. See the caption in Figure 2 for details.

rootlets of the 10th nerve could have affected the afferent fibers that provide tonic inhibition of the presympathetic neurons in RVLM (1). Disruption of this natural inhibitory feedback mechanism would result in the increased sympathetic traffic to the heart, which, in turn, would increase the heart rate. Consistent with this hypothesis, the stimulation caused a decrease in the peak T-wave amplitude, which corresponds to an increased cardiac sympathetic activity (13). Furthermore, the gradual devel-

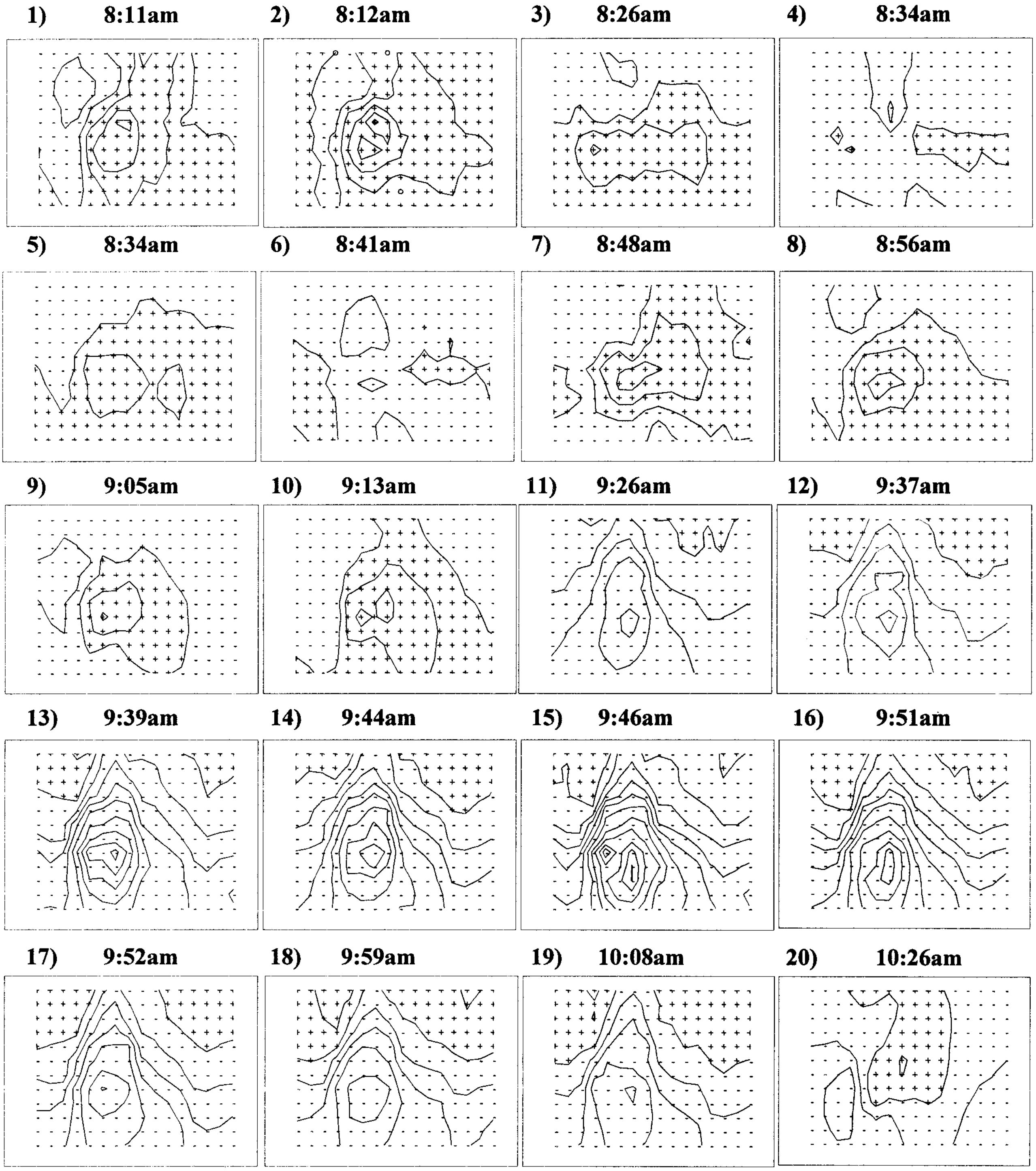

Fig. 4. Serial QRST-isointegral maps. See the caption in Figure 2 for details.

opment and resolution of the repolarization changes is not inconsistent with the slow response of the sympathetic nervous system that contrasts with the faster and more abrupt parasympathetic effects (6). A gradual increase in heart rate and sympathetic nerve activity was also reported during mechanical stimulation of the RVLM in rats (19).

The RR-intervals and the T-wave amplitudes decreased during the stimulation, whereas the QT intervals did not change significantly. This suggests

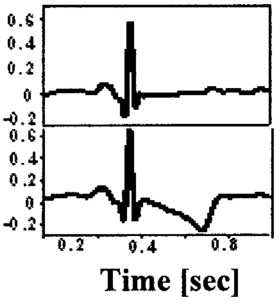

Fig. 5. ECG in lead V4 before (Top Panel) and after (Bottom Panel) the mechanical stimulation of the left RVLM in a 71-year-old woman whose brainstem is shown in Figure 1A.

that the repolarization changes evoked by the stimulation were spatially inhomogeneous. Because sympathetic stimulation and repolarization inhomogeneity play a major role in arrhythmogenesis (20) and because stimulation of the RVLM was associated with initiation of arrhythmias in animal models (21), our results suggest that natural stimulation of the RVLM area by the blood pressure waves, propagating in the adjacent arteries, may be proarrhythmic. Our findings may also explain some mechanisms of the cardiac arrhythmias that accompany acute cerebrovascular events (18).

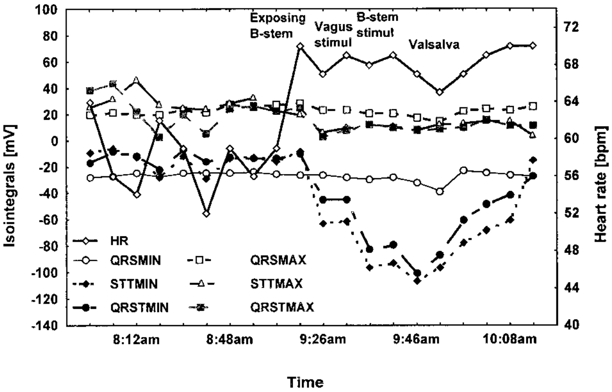

Fig. 6. Changes in heart rate and cardiac repolarization during the procedure in a 71-year old woman, whose left RVLM is shown in Figure 1A. Note, pronounced changes in the minima of STT- and QRST-isointegral maps during the stimulations. Changes in heart rate occurred earlier than the repolarization changes (during the surgical exposure of the RVLM area). HR, heart rate; B-stem, Brainstem; stimul, stimulation. QRSmin/QRSmax, STTmin/STTmax, QRSTmin/QRSTmax = minimum/maximum values of the corresponding isointegral maps.

Table 1. Changes in the Cardiac Rhythm and Repolarization during Mechanical Stimulation of the Brainstem

Parameter	Baseline	Stimulation	P
Min QRSi [mV*ms]	−30.3 ± 13.8	−32.8 ± 9.3	.58
Max QRSi [mV*ms]	44.2 ± 38.1	41.4 ± 31.0	.78
Min STTi [mV*ms]	−19.4 ± 13.4	−26.7 ± 30.6	.89
Max STTi [mV*ms]	102.4 ± 71.8	77.8 ± 34.9	.40
Min QRSTi [mV*ms]	−31.9 ± 19.4	−36.0 ± 24.8	.89
Max QRSTi [mV*ms]	121 ± 76.2	94.0 ± 48.6	.48
RR-interval [ms]	923 ± 190	794 ± 111	.063
Peak T-amp [mV]	0.76 ± 0.49	0.58 ± 0.42	.025
Max QTe [ms]	432 ± 67	422 ± 55	.89
Max QTp [ms]	345 ± 52	336 ± 53	.67

Max/min = the maximum/minimum value of the corresponding integrals over 192 leads, QRSi, STTi, QRSTi = integrals of the corresponding parameters, peak T-amp = peak magnitude of the T-wave, QTe = interval between the onset of the Q-wave and the offset of the T-wave, QTp = interval between the onset of the Q-wave and the peak of the T-wave.

Functional Asymmetry between the Left and the Right RVLM and the Rootlets of the 10th Nerve. In cats, high-resolution functional mapping of RVLM with microinjections of sodium glutamate to activate selective neurons showed that the sinoatrial node is driven primarily by the premotor sympathetic neurons on the right side of RVLM (21). In rats, however, the heart rate responses to mechanical stimulations on the right and on the left side of RVLM were identical (19). In humans, functional asymmetry and sensitivity of the RVLM with respect to mechanical stimulations on the left and the right sides has been debated (1,19). Although the sample size in our study was insufficient for statistical assessment of the left-side and right-side asymmetry, we did not observe any major unilateral differences in the responses of cardiac rhythm and repolarization. An increase in heart rate after the stimulations of the left RVLM and the caudal rootlets of the left vagus nerve suggests that the stimulation could spread to the presympathetic neurons on the other side of the medulla. However, the exact mechanism of this phenomenon requires further study.

Individual Sensitivity of RVLM to Mechanical Stimulation. A wide range of individual responses of cardiac rhythm and repolarization was observed in our study. Among the factors that may account for the observed variability are 1) individual differences in the sensitivity of RVLM and the rootlets of the 10th nerve to mechanical stimulations (2), 2) individual sensitivity of the cardiac electrophysiological responses, and 3) the differences in the stimulation intensity. Our results cannot be used to determine the exact contributions of these factors. However, because the intensity of the stimulations was controlled by an experienced neurosurgeon, it is more likely that individual differences in the sensitivity of RVLM and in cardiac electrophysiological properties caused the intersubject variability of responses to mechanical stimulations.

Limitations

Although we used a small-sized metallic ball to stimulate the brainstem, mechanical stimulation could radiate to other areas. Surgical manipulations in the vicinity of the brainstem area could have affected the RVLM even before the start of the stimulation (Figure 3, Panel 11). Moreover, the intensity of the manual mechanical stimulation was not precisely controlled. Direct electrical stimulations might be useful for making the stimulations more focused and accurately controlled.

The small size of the group was not sufficient for statistical analysis of the relationship between the side of the stimulation and the responses of cardiac rhythm and repolarization. Studies in larger groups are required to answer the questions about functional asymmetry of RVLM in humans.

Conclusions

Stimulation of a localized region of RVLM between the caudal rootlets of the 10th nerve elicits pronounced effects on cardiac rhythm and repolarization. The changes occur during the stimulations of both the left and the right RVLM. The magnitudes and the patterns of the cardiac responses are highly variable among individuals.

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