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Prolonged trigemino-cardiac reflex of passive mandibular extension: evidence in normal volunteers

M. BRUNELLI[1], E. COPPI[2], D. TONLORENZI[1], C. DEL SEPPIA[3], D. LAPI[4], A. COLANTUONI[4], R. SCURI[2], S. GHIONE[3,5]

[1] CRISAF, Department of Physiopathology, Experimental Medicine and Public Health, University of Siena, Italy; [2] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy; [3] Institute of Clinical Physiology, National Council of Research (CNR), Pisa, Italy; [4] Department of Neuroscience, "Federico II", University Medical School, University of Naples, Italy; [5] Fondazione Toscana Gabriele Monasterio, Medical and Public Health Research, Pisa, Italy

ABSTRACT

Various procedures involving stimulations of facial regions are known to induce so-called trigemino-cardiac reflexes that entail a decrease of heart rate and blood pressure. We here report the effects of a specific stimulation that consists in a submaximal passive mandibular extension obtained by means of a dilatator applied for 10 minutes between the upper and lower incisor teeth, associated with partial active masticatory movements. Blood pressure and heart rate were determined in 18 young normal volunteers by a Omron M4 recorder, before (20 minutes), during (10 minutes) and after mandibular extension (80 minutes) and under control conditions (same overall duration without stimulation). While control values remained stable, mandibular extension was followed by a progressive decline of both blood pressure (up to about 12/11 mmHg) and heart rate (up to about 13 bpm), statistically confirmed by ANOVA both on absolute values and on changes from basal values. The decline of systolic blood pressure and heart rate significantly correlated with basal values. The present findings indicate that submaximal opening of the mouth, associated to partial masticatory movements, induces a prolonged reduction of blood pressure and heart rate in normotensive volunteers.

Key words
Trigemino-cardiac reflexes • Cardiovascular reflexes • Blood pressure

Introduction

The facial area is an important source of powerful autonomic reflexes that involve various systems including the cardiovascular system (Schaller et al., 2009). These reflexes are often collectively known as trigemino-cardiac reflexes, since their afferent branches are represented by trigeminal fibres.

Various procedures that involve specific stimulations of certain facial region are known to induce trigemino-cardiac reflexes that may have significant implications or applications in human (patho) physiology. Perhaps the best known, are the diving reflex, the oculo-cardiac reflex and the cardiovascular reflexes that can be induced by maxillo-facial surgery. The diving reflex is triggered by cold water contacting the skin of the face (Heath and Downey, 1990) and/or the nasal mucosa (McCulloch et al., 1999). The oculo-cardiac reflex is triggered by mechanical stimulation of orbital structures (Van Brocklin et al., 1982) and induces vagal activation (bradycardia) (Arnold, 1999). Other trigemino-car-

Corresponding Author: Dr. Sergio Ghione, Institute of Clinical Physiology and Fondazione Toscana Gabriele Monasterio, via Moruzzi 1, 56124 Pisa, Italy - Tel.: +39 050 3153230/1 - Email: ghione@ifc.cnr.it

diac reflexes, mainly of anesthesiological interest, are triggered by surgical manipulation of various deep structures of the face in maxillo-facial surgery or in brainstem neurosurgery and may induce bradycardia (up to asystolia), apnea and gastric hypermotility (Schaller, 2004, 2007; Schaller et al., 1999, 2009; Schein et al., 2009; Lübbers et al., 2010).

We here provide for the first time evidence that another procedure that involves a specific stimulation of the facial region, consisting in passive mandibular extension, produces a significant and prolonged reduction of arterial blood pressure and heart rate.

Materials and methods

Subjects

Eighteen subjects participated to the study (age range 23-30 years, 26.5 ± 2.2 mean ± SD, 5 males and 13 females). Informed consent was obtained from all subjects. All subjects were healthy and under no medical treatment. Assumption of psychoactive substances (including coffee, tea, tobacco and alcohol) was not allowed in the two hours preceding the experiment. All studies were done between 9:00 and 13:00 in the morning.

Procedures

Design of the studies

All subjects undertook two sessions, one with and one without a 10 minutes-lasting mandibular extension (ME, to be described below) in random order, and 14 repeated an additional third control session, that consisted for 8 subjects in chewing for 10 minutes a soft gum and for 6 subjects in keeping an ice stick for 10 minutes between the medial incisor teeth. The interval between the sessions was one week. Blood pressure and heart rate were measured before ME or control treatments for 20 minutes, and for subsequent 80 minutes, after ME or control treatment. Five pre-treatment measures were obtained and the average of the last 3 was used as basal reference measurement. Post-treatment measures were obtained immediately after ME or control treatment and after 5, 15, 30, 50 and 80 minutes. Measurements were obtained manually by the same observer with an automatic blood pressure recorder (OMRON M4, Lacciarella (MI), Italy). During the entire period subjects were seated in a comfortable chair in a quiet room watching scientific documentary films that were devoid of emotional impact.

Description

ME was obtained by a self-developed U-shaped folded steel spring device that was inserted between the upper and the lower medial incisor teeth (see Fig. 1). The degree of mouth opening obtained, as measured by the interincisal distance, was of 4 cm and was in all subjects lesser than their maximal active mouth opening capacity. All subjects were asked to make partial masticatory-like movements, by compressing and relaxing the spring, the interincisal distance varying between a maximum of 4 cm and a minimun of 2 cm. The procedure was readily acceptable to all participants without inducing any perceived masticatory fatigue or other discomfort, besides, for a few subjects, a slight nuisance due to salivation.

The effects of ME was compared against three different procedures: 1) no treatment at all, defined as "controls"; 2) chewing for 10 minutes a soft chewing gum with low resistance (Brooklyn, Perfetti, Lainate Italy) without particular indication on masticatory frequency or laterality; 3) keeping for 10 minutes, between the upper and the lower medial incisor teeth, an ice stick. Procedures 2) and 3) were done respectively in 8 and 6 different subjects.

Statistical analysis

Blood pressure and heart rate data were analyzed with a repeated-measure analysis of variance (ANOVA) with two within-factor variables: treatments (mandibular extension *vs.* control sessions) and sequence. A one within-factor repeated measure ANOVA was also used to compare separately, the trend in the two sessions (mandibular extension and control sessions). When statistically significant differences were obtained, post-hoc comparisons were done by applying Tukey correction. Linear trend was evaluated with linear regression and linear association by Pearson correlation coefficients. A statistical significant effect was defined when the level of significance was $P < 0.05$. All analyses were run with the statistical packages Sigma Stat statistical software, version 3.5 (Jandel Corporation San Mateo, CA).

Fig. 1. - Mandibular extension as obtained by a self-developed U-shaped folded steel spring device inserted between the upper and the lower medial incisor teeth.

Results

Table I reports the values of the mean and the standard deviation of blood pressure and heart rate of all subjects (n = 18) studied in the control and in the ME sessions. The overall ANOVA revealed a significant main effect of treatment (control versus ME) on SBP ($F_{1,17} = 5.390$, $P = 0.033$), a significant main effect of sequence on SBP ($F_{6,102} = 8.736$, $P < 0.001$) and HR ($F_{6,102} = 11.734$, $P < 0.001$), and a significant interaction of sequence for treatment, on SBP ($F_{6,251} = 9.598$, $P < 0.001$), DBP ($F_{6,251} = 6.798$, $P < 0.001$) and HR ($F_{6,251} = 9.738$, $P < 0.001$).

Analyzing separately the performance of the control session and ME session, one-way repeated ANOVA did not reveal any statistical significant effect for the control session, whereas, for the ME session it showed a significant effect on SBP ($F_{6,102} = 15.212$, $P < 0.001$), DBP ($F_{6,102} = 7.147$, $P < 0.001$) and HR ($F_{6,102} = 16.178$, $P < 0.001$), all of which decreased.

Fig. 2 shows the time-course of the changes of BP and HR values from basal values (i.e. the mean differences between the individual values and their basal values). As shown in the figure, while in the control session BP and HR remained essentially stable, in the ME session a progressive reduction of BP and HR was observed that persisted up to the end of the recording (i.e. 80 min). The overall ANOVA revealed a significant main effect of treatment (control versus ME) on SBP ($F_{1,17} = 11.790$ $P = 0.003$), DBP ($F_{1,17} = 24.429$, $P < 0.001$) and HR ($F_{1,17} = 13.103$, $P = 0.002$), a significant main effect of sequence on SBP ($F_{6,102} = 8.736$, $P < 0.001$) and HR ($F_{6,102} = 11.734$, $P < 0.001$), and a significant interaction of sequence for treatment, on SBP ($F_{6,251} = 9.598$, $P < 0.001$), DBP ($F_{1,251} = 6.798$, P < 0.001) and HR ($F_{1,251} = 9.738$, $P < 0.001$). Post hoc comparison revealed, that throughout the session, starting from 5 min for DBP and starting from 10 min for SBP and HR, values were significantly lower after ME compared to control condition. At 80 min this difference was of about 12 mmHg for SBP, 11 mmHg for DBP and 13 bpm for HR.

A significant inverse correlation was found for SBP and HR (but not for DBP) between individual basal values and their maximal decline (i.e. at the nadir) observed after mandibular extension (Fig. 3).

Table II and III show the mean and standard deviation of BP and HR in the two subgroups who made an additional session in which the effect of chew-

Table I. - Blood pressure and heart rate in the control and in the mandibular extension sessions.

		Basal	Time zero	5 min	15 min	30 min	50 min	80 min
Control (n = 18)	SBP (mmHg)	110.0 ± 10.76	106.9 ± 11.98	107.5 ± 12.02	108.9 ± 10.82	109.9 ± 11.36	110.5 ± 9.58	110.5 ± 10.64
	DBP (mmHg)	74.4 ± 8.17	73.9 ± 11.11	74.7 ± 11.47	75.2 ± 9.69	75.6 ± 10.29	75.3 ± 7.48	76.0 ± 7.40
	HR (beats/min)	75.5 ± 12.92	74.1 ± 11.62	75.0 ± 11.77	75.8 ± 10.50	75.6 ± 10.78	75.4 ± 7.88	76.2 ± 7.84
ME (n = 18)	SBP (mmHg)	111.0 ± 10.47	107.0 ± 9.55	104.8 ± 8.70	101.5 ± 7.82	102.9 ± 9.00	99.6 ± 8.51	98.8 ± 8.64
	DBP (mmHg)	79.8 ± 7.94	77.5 ± 8.29	76.2 ± 8.25	74.4 ± 10.04	74.0 ± 8.50	72.1 ± 9.32	71.8 ± 8.41
	HR (beats/min)	81.9 ± 14.07	78.2 ± 14.74	77.4 ± 13.33	74.6 ± 13.04	74.3 ± 12.77	70.2 ± 10.89	69.7 ± 11.27

Mean values (± standard deviations) of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in the control and in the ME sessions. Basal values refer to the last three out of the initial five recordings. Time zero values are those recorded at the end of the subsequent ten minutes, during which mandibular extension was made in the ME session (and nothing was done in the Control session), and the following time values refer to minutes passed after time zero, i.e. after cessation of ME in the ME session. For further detail see Materials and Methods.

ing a soft gum (8 subjects) or keeping an ice stick between the medial incisors (6 subjects) for 10 minutes were compared to control. ANOVA did not reveal any statistically significant effect.

Discussion

This study demonstrates that submaximal passive mouth opening, obtained by means of a spring device applied for 10 minutes between the upper and lower incisor teeth and associated with partial active masticatory movements, induces a significant and persistent reduction of BP and HR. To the best of our knowledge, we are not aware of a previous description of this effect, which, conversely was also observed by us in the anesthetized rat (Lapi et al., 2011, 2013).

As regards the time-course of the hypotensive response following ME, the onset was found to occur within the initial 5 to 10 minutes, and BP and HR were still slightly declining at the end of the observation period of 80 minutes. The hypotensive response following ME observed in the human is similar to the one we observed in the anesthetized rat (Lapi et al., 2011, 2013).

This study and the one on the rat provide some indication on the mechanisms underlying the hypotensive effect following ME. The fact that BP reduction is associated to a concomitant HR reduction would in fact point against an exclusively peripheral vasodilator effect (that would induce tachycardia) but rather for a central (possibly sympathoinhibitory) effect on the central bulbar vasomotor centre (Guyton et al., 1969).

Being this a seemingly novel phenomenon, several aspects remain to be elucidated. A first point regards the structure involved in the afferent limb of this reflex. Although we cannot exclude other afferent mechanisms, such as the mechanical stress of some adiacent structure (e.g. the carotid arteries, the jugular veins, the ganglion of Gasser etc.), the simplest and probably most likely hypothesis is an involvement of the mechanoceptors within the masseter activated by muscular stretching and leading to a consequent trigeminal afferent stimulation. In fact, hypotension and bradycardia have been observed (along with other symptoms such as apnea and gastric hypermotility) after central or peripheral stimulation of any of the sensory branches of the trigeminal nerve. Clinically, these reflexes are collectively defined as trigemino-cardiac reflexes and have been reported to occur during craniofacial surgery, manipulation of the trigeminal nerve/ganglion and during surgery for lesion in the cerebellopontine angle, cavernous sinus, and the pituitary fossa (Schaller et al., 1999; Schaller, 2007; Schaller et al., 2008, 2009). Further studies, in particular in the experimental animal, are needed to assess whether the hypotensive response to mandibular extension is a special form of a trigemino-cardiac reflex.

For several aspects the hypotensive response to mandibular extension reminds us of the so-called postexercise hypotension (PEH), i.e. the sustained reduction in arterial blood pressure that is observed after a single bout of large-muscle, mild to moderate dynamic exercise, including walking and running, leg cycling and swimming (Kenney and Seals, 1993; MacDonald, 2002). In fact, several features

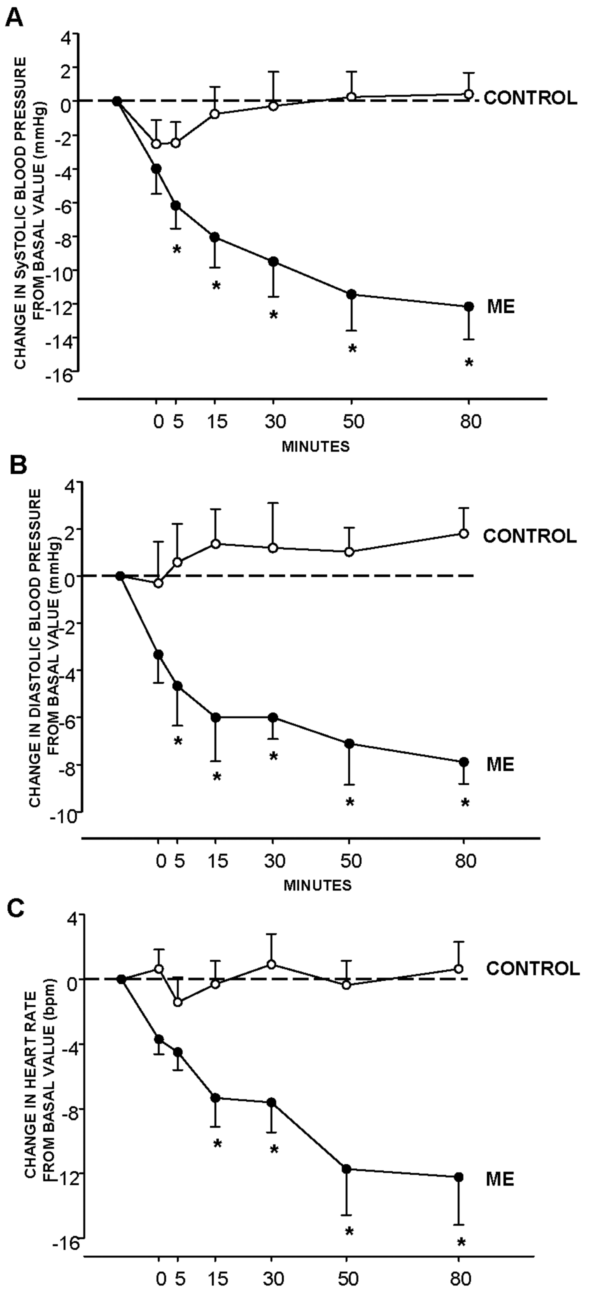

Fig. 2. - Time course of the changes from basal values of systolic (A) and diastolic (B) blood pressure and heart rate (C) after mandibular extension (ME, full symbols) and in control condition (empty symbols). Basal values refer to the means of the last three out of the initial five recordings. Time zero (0) values are those recorded at the end of the subsequent ten minutes, during which mandibular extension was made in the ME session (and nothing was done in the control session), and the following time values refer to minutes passed after time zero, i.e. after cessation of ME in the ME session. For further detail see Materials and Methods. All values are means ± SEM. Asterisks indicate a statistically significant difference ($P < 0.05$, Tukey corrected post-hoc analysis), between ME and control session, in BP and HR changes from basal value.

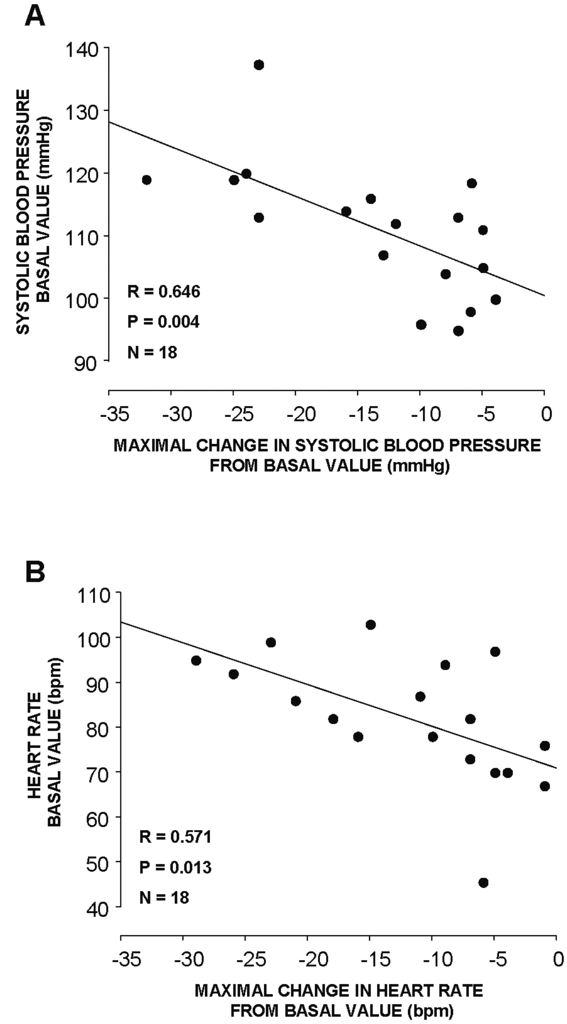

Fig. 3. - Linear regression: maximal changes observed, within 80 minutes after mandibular extension, in the 18 subjects studied *vs.* basal values. Panel A refers to systolic blood pressure and panel B to heart rate.

of the hypotensive response following dynamic exercise are remarkably similar to those reported here: a stimulus duration of at least 10 minutes to be effective (Mac Donald, 2000), a long-lasting hypotensive effect of at least two hours (but possibly more) (MacDonald, 2002), a magnitude of the response of 8 to 10 mmHg for SBP and of 3 to 5 mmHg for DBP in normotensive humans (Kenney and Seals, 1993; MacDonald, 2002).

Even assuming that the hypotensive response following ME falls within the field of post-exercise hypotension, one should note several peculiarities. Post-exercise hypotension has been observed, firstly, mainly after dynamic exercise, and to a lesser extent after static exercise, but – to our

Table II. - Blood pressure and heart rate in the control and in the chewing gum sessions.

		Basal	Time zero	5 min	15 min	30 min	50 min	80 min
Control (n = 8)	SBP (mmHg)	110.6 ± 9.13	107.6 ± 10.36	108.0 ± 9.62	107.7 ± 9.67	108.7 ± 9.86	110.0 ± 8.64	110.0 ± 9.51
	DBP (mmHg)	73.7 ± 6.54	72.9 ± 9.71	73.2 ± 8.47	75.2 ± 10.53	75.1 ± 8.34	76.1 ± 7.59	75.3 ± 8.11
	HR (beats/min)	75.4 ± 11.88	76.9 ± 11.07	74.8 ± 12.97	77.3 ± 14.29	77.6 ± 13.41	75.8 ± 12.98	76.8 ± 13.32
Chewingum (n = 8)	SBP (mmHg)	107.8 ± 10.19	105.5 ± 6.65	105.4 ± 4.78	105.5 ± 6.07	108.1 ± 7.94	106.5 ± 7.15	106.5 ± 4.66
	DBP (mmHg)	76.7 ± 9.27	77.5 ± 4.81	74.5 ± 7.39	74.1 ± 5.30	78.0 ± 7.17	79.3 ± 9.30	80.7 ± 8.90
	HR (beats/min)	78.4 ± 11.93	77.9 ± 13.74	76.0 ± 10.17	75.4 ± 7.82	76.4 ± 10.14	77.9 ± 10.62	78.6 ± 12.36

Mean values (± standard deviations) of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in the control session and in an additional session in which the effect of chewing a soft gum for 10 minutes were done. Control values refer to the control session in the 8 subjects who performed the chewing gum session. For other explanations, see legend of Table I.

Table III. - Blood pressure and heart rate in the control and in the ice stick sessions.

		Basal	Time zero	5 min	15 min	30 min	50 min	80 min
Control (n = 6)	SBP (mmHg)	109.3 ± 14.95	103.8 ± 12.81	104.7 ± 14.31	107.2 ± 9.64	106.7 ± 7.23	109.2 ± 7.96	108.3 ± 8.80
	DBP (mmHg)	70.2 ± 7.94	65.5 ± 10.31	68.3 ± 14.05	70.0 ± 9.53	66.8 ± 9.22	69.5 ± 8.02	72.3 ± 7.42
	HR (beats/min)	75.0 ± 10.62	73.8 ± 8.77	70.2 ± 6.88	70.0 ± 7.27	70.7 ± 11.00	70.7 ± 8.73	71.5 ± 7.20
Stick (n = 6)	SBP (mmHg)	107.8 ± 11.70	107.2 ± 12.42	106.7 ± 12.89	107.5 ± 11.45	108.2 ± 10.93	107.8 ± 10.55	107.8 ± 11.39
	DBP (mmHg)	78.2 ± 5.31	77.5 ± 4.55	77.7 ± 5.13	78.8 ± 4.58	77.5 ± 4.09	76.7 ± 4.68	76.7 ± 4.78
	HR (beats/min)	74.3 ± 13.25	72.8 ± 12.59	74.5 ± 11.90	74.0 ± 12.90	75.7 ± 13.47	74.7 ± 13.49	75.0 ± 12.25

Mean values (± standard deviations) of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in the control session and in an additional session in which the effect of keeping an ice stick between the medial incisors for 10 minutes were done. Control values refer to the control session in 6 subjects who performed the ice stick session. For other explanations, see legend of Table I.

knowledge – not after muscular stretching, and, secondly, after exercising large muscles, such as those of the limbs, but – to our knowledge – not a relatively small, albeit important muscle such as the masseter.

In addition, in post-exercise hypotension, during the exercise that precedes BP reduction, an increase in blood pressure generally occurs, so that the ensuing BP fall could be considered as some sort of "rebound" hypotensive response to the exercise-induced BP increase. In our case, on the other hand, the stimulus after which a hypotensive response occurs, (i.e. masseter strectching) is not, per se, associated with a BP increase. As regards heart rate reduction following ME, we can only hypothesize that mouth opening may activate the vagal cardio-modulating centre.

Some limitations of the study should be mentioned. Firstly, the measurement of BP could have benefitted of a beat-to-beat measurement rather than a "spot" measurement.

Secondly, since the applied stimulus consisted in reality in two concomitant stimuli (i.e. submaximal opening of the mouth and partial masticatory movements), the study does not allow to dissect between the effects on BP and HR of these two procedures. Although further studies are needed to address this point, it may be interesting to note that a hypotensive and bradycardic effect similar to that observed in the human was found in the anesthetized rat in which only submaximal passive mouth opening was applied (Lapi et al., 2011, 2013).

In conclusion, our study provides evidence that submaximal opening of the mouth, associated to partial masticatory movements induces a prolonged reduction of blood pressure by about 5-10 mmHg in subjects in the normotensive range. The finding that, in the normotensive range, the magnitude of the hypotensive response following ME is all the greater, the higher the baseline pre-ME values are, is a promising indication that this procedure may be even more effective in hypertensive patients. What is the magnitude of this effect in hypertensive patients and whether this or a similar procedure may find an application as a non-pharmacological aid in arterial hypertension remains, however, to be established.

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