Evidence in the human of a hypotensive and a bradycardic effect after mouth opening maintained for 10 min

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Received: 3 February 2017 / Accepted: 9 May 2017

Abstract

Purpose We have recently shown that in humans submaximal mouth opening associated with partial masticatory movements for 10 min is followed by a small but significant and prolonged reduction of blood pressure and heart rate. We here report the effects of a fixed mouth opener.

Methods In 22 seated normotensive volunteers the effect on blood pressure and heart rate was studied in randomized order after fixed mandibular extension and after a control procedure consisting in keeping a stick between the incisor teeth (both for 10 min). Automated recordings every 10 min were done for 40 min before and 120 min following the procedure.

Results Two-way ANOVA for repeated measures on absolute values (actual recordings) and on changes from baseline revealed that, compared to controls, systolic, diastolic and mean blood pressure and heart rate were significantly lower after mandibular extension. Compared to controls, mandibular extension induced an average blood pressure drop of 2.88 mmHg (systolic), 2.55 mmHg (diastolic) and 2.42 mmHg (mean) over the entire observation period. The average decline over the central part of the observation period (30th to 80th min) was, respectively, of 3.62, 3.70 and 3.61 mmHg. The decrements of heart rate were of 2.11 and 2.66 beats per min. All these differences were statistically significant. The hypotensive and bradycardic responses persisted for 70–120 min.

Conclusions This study shows that, in normotensives, a single fixed submaximal mouth opening for 10 min is followed by prolonged albeit small reductions of blood pressure and heart rate.

Keywords Reflex, trigemino-cardiac · Blood pressure · Heart rate · Humans · Temporomandibular joint

Abbreviations

ANOVA	Analysis of variance
BP	Blood pressure
DBP	Diastolic blood pressure
HR	Heart rate
MBP	Mean blood pressure
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean

Introduction

Because of its widespread prevalence, associated cardiovascular risk and potential curability, arterial hypertension represents one of the most important disorders, worldwide.

Although pharmacological treatment and lifestyle changes represent the well-established cornerstones of hypertension treatment (see Guidelines for the management of arterial hypertension; Mancia et al. 2013), numerous alternative (non-drug, non-dietary) approaches

Communicated by Massimo Pagani.

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to lowering blood pressure have been proposed. As reviewed in 2013 in a Scientific Statement of the American Heart Association (Brook et al. 2013), procedures based on some forms of skeletal muscles exercising, have relatively stronger evidence for obtaining blood pressure lowering, compared to alternative treatments such as behavioral therapies (e.g. meditation, relaxation, yoga, etc.) or other non-invasive procedures (e.g. acupuncture, slow breathing, etc.). Procedures involving muscular exercise were distinguished, for the purpose of their effects on BP (Brook et al. 2013, 2015; Pescatello and Kulikowich 2010), in static exercise (i.e., isometric contraction without joint movement e.g., handgrip) and dynamic exercise, the latter being further distinguished in dynamic aerobic (e.g., jogging, walking, endurance) and dynamic resistance exercise (e.g., weight lifting, "exercise machines"). All these various exercise modalities have been found to reduce blood pressure not only chronically, after repeated applications (i.e., physical training), but also acutely, after a single bout of exercise. The hypotensive effect was in both cases in the order of 5–10 mmHg in hypertensive patients and somewhat less in normotensives.

The after-effects of another type of widely employed muscular activity represented by skeletal muscle stretching has been investigated by only few studies, suggesting that also this type of muscular procedure may be followed by a reduction of blood pressure both when applied chronically, i.e., after repeated application (Wong and Figueroa 2014) and acutely, i.e., after a single bout of stretching (Kruse et al. 2016). We have previously reported, in normal volunteers, that submaximal passive mouth opening associated with partial masticatory movements (dynamic mandibular extension) prolonged for 10 min, obtained by an ad hoc dilator spring device, is followed by a significant and long-lasting reduction of arterial blood pressure and heart rate (Brunelli et al. 2012). These results were, however, not replicated by an independent report by De Innocentiis et al. (2015), but were confirmed in a subsequent recent study by us (Del Seppia et al. 2016). In our studies, the BP lowering effect was on the order of 4–12 mmHg and persisted for at least 80 min. Interestingly, a similarly prolonged and even more pronounced hypotensive effect was observed in anesthetized normotensive rats after a 10 min static mandibular extension (Lapi et al. 2013, 2014).

Aim of the present study is to assess the effect of passive static mouth opening, obtained by inserting a dilator between the dental arches (i.e., without masticatory movements) in a group of normotensive volunteers.

Methods

Subjects

The studies were done in 22 young, normotensive healthy volunteers (University students) aged 20–31 years (25 ± 3.00 mean $\pm$ SD), 12 males and 10 females.

All subjects had been evaluated prior to the beginning of the study and were found to be free of major diseases including dental and trigeminal problems or temporomandibular disorders. Informed consent was obtained from all subjects and the study was approved by the local Ethical Committee (Comitato per lo studio del farmaco sull'uomo, Azienda Ospedaliera di Pisa).

Protocol

All sessions of the study were performed between 9:00 and 13:00 at the Outpatient Clinic of the Fondazione G. Monasterio, Pisa, where ambient temperature was controlled between 22 and 24 °C. Subjects were asked not to consume caffeine, tobacco, tea and alcohol within 2 h of the study and to void before the study. On arrival to the laboratory, an automated blood pressure recorder (Spacelabs 9027) was applied and systolic and diastolic blood pressure (SBP, DBP), and heart rate (HR) were, thereafter, recorded every 10 min throughout the study. During the entire study, subjects were comfortably seated and remained alone watching, on a laptop screen, some nature documentaries (BBC Worldwide) devoid of strong emotional contents. The volunteers made two sessions: one with mandibular extension (which will also be called "experimental procedure") and one with a control procedure that will be described below. The term "procedure" will be used to identify collectively the mandibular extension and the control procedure.

Each session lasted 170 min. During the first 40 min, four BP and HR recordings were done; the first one was discarded and the following three were averaged and the means were used as the baseline reference values. Afterwards, the procedure was applied for 10 min and subsequently BP and HR were recorded up to 120 min after the procedure (Fig. 1).

Procedures

Mandibular extension was obtained by means of a commercial mouth opener device, commonly used in dental practice (Molt; Asa Dental; Bozzano Camaiore Lucca). The instrument was applied between the upper and lower incisor teeth, maintained at a fixed opening corresponding to the 60% of the maximal interincisal distance.

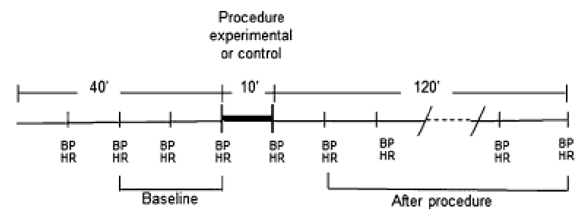

Fig. 1 Schematic representation of the protocol. Blood pressure (BP) and heart rate (HR) were automatically measured every 10 min. Baseline reference values were obtained as the mean of the second to fourth measurement recorded before the procedure, consisting in mandibular extension (experimental) or in keeping a wooden tongue depressor between the incisor teeth (control)

The control procedure consisted in keeping a sterile wooden tongue depressor (Artsana, Grandate, Como) between the upper and lower incisor teeth. This procedure was found to be devoid of any effect on blood pressure in a previous study (Brunelli et al. 2012). The two sessions were done in randomized order and were separated by a period ranging between 7 and 28 days. Subjects' "blinding" to the experimental conditions with minimization of any "expectation bias", was obtained by informing them that the aim of the study consisted in performing two procedures that were equally potentially effective in reducing blood pressure.

Statistical analysis

Blood pressure and heart rate data were analyzed both as absolute values (i.e., actual recorded values) and as changes from baseline (i.e., differences between the absolute values and the baseline values of their corresponding session). Mean blood pressure (MBP) was calculated using the standard equation MBP = DBP + 1/3 (SBP − DBP).

Variables were summarized as mean ± standard deviation (SD) and plotted as mean ± standard error of the mean (SEM). Statistical analysis was done using one-way and two-way analysis of variance (ANOVA) for repeated measures. One-way ANOVA was applied on absolute values separately in control and experimental sessions to test differences over time. Two-way ANOVA for repeated measures, with procedure (control vs. experimental) as between-factor and sequence (time) as within-factor variables, was applied on data recorded after procedure in both the absolute values and the changes from baseline. When the ANOVA revealed a statistically significant effect ($P < 0.05$), the Holm Sidak test was made for "post hoc" comparisons. All analyses were done with the statistical package Sigma Stat, version 3.5 (Jandel Corporation San Mateo, CA).

During the after-procedure period the mean of all values of the changes from baseline were computed over the entire 2 h observation period, and over the central 1 h (from the 30th to the 80th min, included) and compared (by *t* paired test) between control and experimental procedure. Simple regression analysis was finally done to evaluate the relation between mean BP changes and baseline values. These analyses were done using the software R.

Results

All procedures were readily acceptable to all participants without inducing any perceived discomfort, apart, for a few subjects, a slight nuisance due to salivation.

Baseline levels of SBP, DBP, MBP and HR were almost identical for the control and experimental sessions. At baseline, SBP was 113.6 ± 9.4 and 114.2 ± 11.6 mmHg; DBP was 68.6 ± 7.4 and 68.9 ± 7.0 mmHg; MBP was 83.6 ± 7.0 and 84.0 ± 7.5 mmHg; HR was 70.9 ± 10.5 and 68.7 ± 10.3 bpm, for the control session and the experimental session, respectively.

The results of one-way ANOVA for repeated measures on absolute values and of two-way ANOVA for repeated measures on absolute values (Fig. 2) and on changes from baseline (Fig. 3) are reported in Table 1. As shown by the table, one-way ANOVA, done separately on control and experimental session, revealed, for BP, no significant changes over time in the control session and statistically significant changes in the experimental session. For HR, a significant effect was observed in both sessions. As regards two-way ANOVA, after the procedure, BP and HR values varied over time, as indicated by a significant effect of sequence, and were different after control procedure and mandibular extension, as indicated by a significant effect of procedure. All these effects were statistically significant with the only exception of the effect of treatment on the absolute values of SBP that, although formally statistically non-significant ($P = 0.058$), was very close to the significance level.

Figures 2 and 3 show the time course for absolute values and for changes from baseline, respectively, plotting the mean ± SEM of SBP, DBP, MBP and HR.

As shown in the figures, for SBP, DBP and MBP, the time-courses after the control procedure and mandibular extension were very similar for the first 3–4 measurements, i.e., the baseline value, the measurement done at the end of the procedure and the following one or two recordings. Thereafter, the trend was divergent, tending to decrease after mandibular extension and increase after control procedure. The BP decline after mandibular extension reached a nadir at about 40–70 min after the end of the procedure and returned to the control values at 100–120 min. HR values stably decreased after both mandibular extension and control procedure, although less in the latter condition.

To get an idea of the extent of these effects, the mean of the values of the changes from baseline of SBP, DBP, MBP

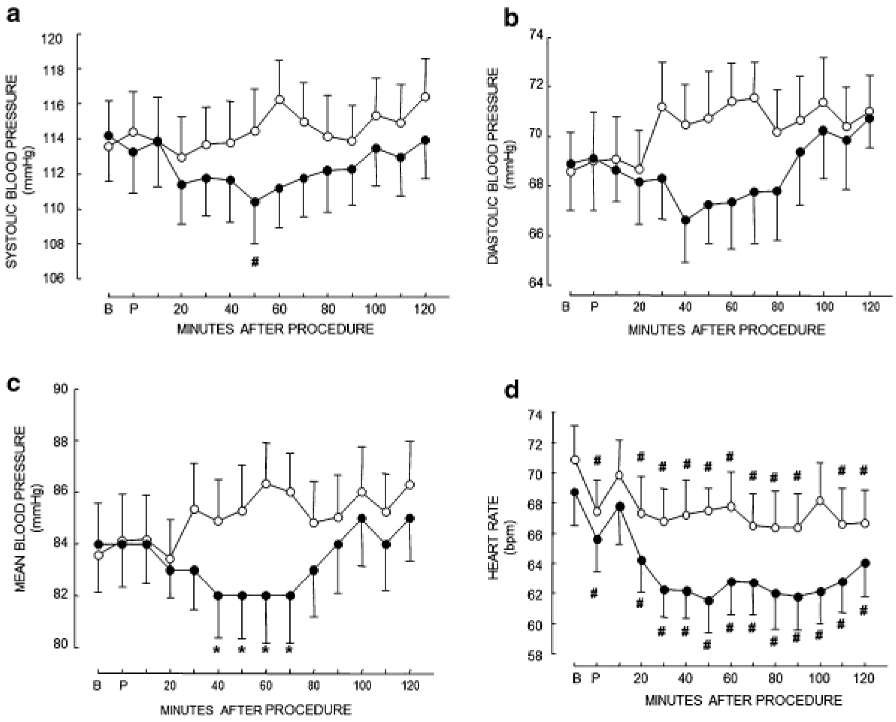

Fig. 2 The time-courses of the absolute values (mean ± SEM) in normotensive volunteers after the control procedure (*empty circles*) and after mandibular extension (*filled circles*) are represented for systolic blood pressure (**a**), diastolic blood pressure (**b**), mean blood pressure (**c**) and heart rate (**d**). "*B*" indicates the baseline value and "*P*" the value recorded at the end of the 10 min control or experimental (mandibular extension) procedure. *Hashes* (#) indicate significant differences from baseline values in post hoc comparisons after one-way ANOVA done separately in controls and experimentals. *Asterisks* (*) indicate significant differences between control and experimental procedures in post hoc comparisons after two-way ANOVA. Other explanations in the text

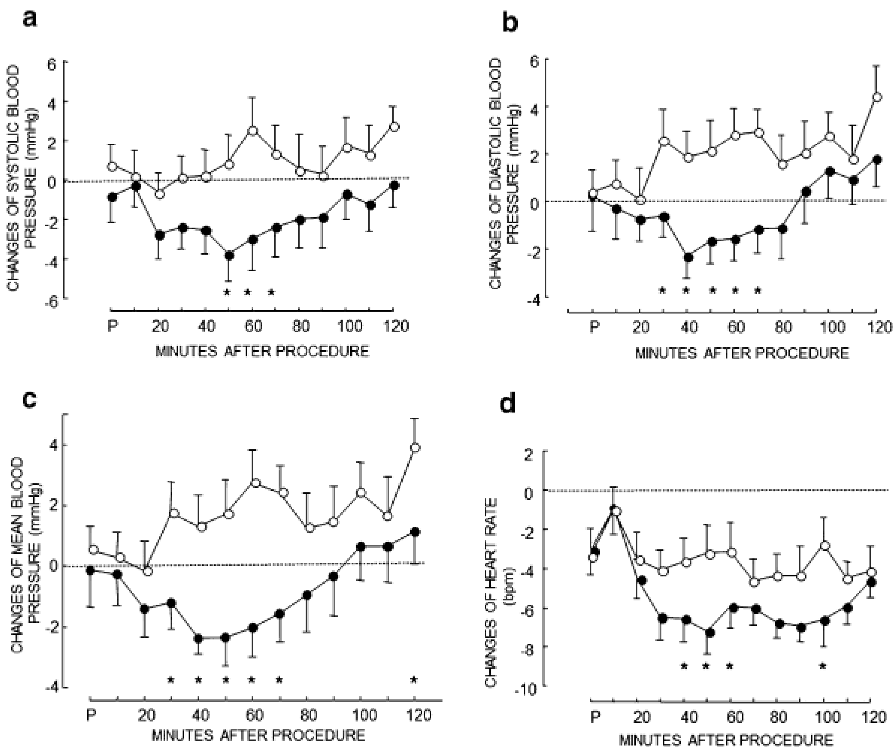

Fig. 3 The time-courses of the changes (differences) from baseline (mean ± SEM) after mandibular extension in normotensive volunteers after the control procedure (*empty circles*) and after mandibular extension (*filled circles*) are represented for systolic blood pressure (**a**), diastolic blood pressure (**b**), mean blood pressure (**c**) and heart rate (**d**). "*P*" indicates the difference between the baseline value and the value recorded at the end of the 10 min control and experimental (mandibular extension) procedure. *Asterisks* indicate significant differences between control and experimental procedures in post hoc comparisons. Other explanations in the text

Table 1 Summary of the results of one-way and two-way repeated measure ANOVA (*F* and corresponding *P* values)

	SBP	DBP	MBP	HR
One way ANOVA				
On absolute (recorded) values				
Control session	$F_{21,273} = 1.39$; $P = 0.165$	$F_{21,273} = 1.26$; $P = 0.235$	$F_{21,273} = 1.61$; $P = 0.082$	$F_{21,273} = 2.22$; $P = 0.009$
Experimental session	$F_{21,273} = 1.82$; $P = 0.040$	$F_{21,273} = 1.81$; $P = 0.042$	$F_{21,273} = 2.29$; $P = 0.007$	$F_{21,273} = 7.37$; $P < 0.001$
Two way ANOVA				
On absolute (recorded) values				
Effect of procedure (control vs experimental)	$F_{1,231} = 4.01$; $P = 0.058$	$F_{1,231} = 5.19$; $P = 0.033$	$F_{1,231} = 6.25$; $P = 0.021$	$F_{1,231} = 8.27$; $P = 0.009$
Effect of sequence (time)	$F_{11,231} = 2.23$; $P = 0.014$	$F_{11,231} = 2.52$; $P = 0.005$	$F_{11,231} = 3.11$; $P < 0.001$	$F_{11,231} = 3.52$; $P < 0.001$
Interaction effect (procedure × sequence)	$F_{1,231} = 1.37$; $P = 0.187$	$F_{1,231} = 1.10$; $P = 0.365$	$F_{1,231} = 1.50$; $P = 0.132$	$F_{1,231} = 1.24$; $P = 0.260$
On changes from baseline				
Effect of procedure (control vs experimental)	$F_{1,231} = 6.44$; $P = 0.019$	$F_{1,231} = 7.09$; $P = 0.015$	$F_{1,231} = 9.21$; $P = 0.006$	$F_{1,231} = 5.56$ $P = 0.028$
Effect of sequence (time)	$F_{11,231} = 2.28$; $P = 0.014$	$F_{11,231} = 2.48$; $P = 0.006$	$F_{11,231} = 2.99$; $P < 0.001$	$F_{11,231} = 3.52$; $P < 0.001$
Interaction effect (procedure × sequence)	$F_{1,231} = 1.37$; $P = 0.187$	$F_{1,231} = 1.06$; $P = 0.396$	$F_{1,231} = 1.63$; $P = 0.091$	$F_{1,231} = 1.24$; $P = 0.260$

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate

Table 2 Mean changes from baseline after control procedure and after mandibular extension

Parameters	Entire period (2 h)				Central period (1 h)			
	C	M	M − C	*P*	C	M	M − C	*P*
SBP (mmHg)	0.97	−1.92	−2.88	0.019	0.96	−2.66	−3.62	0.008
DBP (mmHg)	2.16	−0.40	−2.55	0.015	2.33	−1.38	−3.70	0.001
MBP (mmHg)	1.64	−0.78	2.42	0.009	1.87	−1.73	−3.61	0.0004
HR (bpm)	−3.59	−5.71	−2.11	0.028	−3.83	−6.49	−2.66	0.015

Mean changes from baseline of systolic (SBP), diastolic (DBP) and mean blood pressure (MBP) and heart rate (HR) averaged over the entire observation period (2 h) and over the central part of the observation period (1 h: 30–80 min, included) following the control (C) procedure and mandibular extension (M). M − C = difference between the average of values after mandibular extension and the average of values after control procedure and *P* the statistical significance by paired *t* test

and HR following the control procedure and mandibular extension are reported in Table 2. As shown in the table, the average changes from baseline observed after mandibular extension minus those observed after control procedures were always negative (in the order of 2–4 mmHg) and always statistically significant (by *t* paired test).

Simple regression analysis examining the relationship between mean BP changes after mandibular extension and baseline values revealed a significant inverse relation for SBP ($P = 0.007$; Fig. 4) but not for DBP and MBP. No significant relations were observed after control procedure.

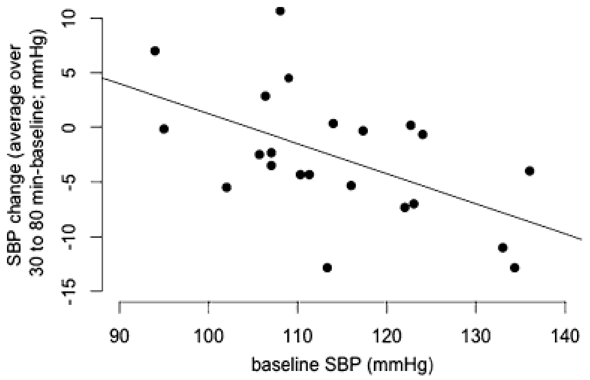

Fig. 4 Relationship between the baseline values of systolic blood pressure (SBP; *x*-axis) and the differences between SBP after mandibular extension, averaged over the interval from 30 to 80 min, minus the corresponding baseline value (*y*-axis). The regression line is also reported ($R^2 = 0.31$, $P = 0.007$)

Discussion

This study demonstrates that, in normotensive humans, submaximal mouth opening obtained by means of a fixed dilatator applied for 10 min between the upper and lower incisor teeth is followed by a significant, but small, and prolonged reduction of arterial blood pressure and heart rate.

The present results confirm and extend those of two previous reports by us in normal volunteers (Brunelli et al. 2012; Del Seppia et al. 2016), in which mandibular extension was obtained by a somewhat different dilator device. These results were, however, not confirmed in a recent independent study (De Innocentiis et al. 2015). In all these studies the dilator was represented by a "spring device", that permitted partial masticatory movements, whereas in the present study mouth opening was fixed. For simplicity the two procedures will be referred to as dynamic and static mandibular extension, respectively.

The rationale for trying a static rather than dynamic device is the observation that static mandibular extension in the anesthetized normotensive rat was found to be followed by a remarkable hypotensive effect, of about 20–25 mmHg (Lapi et al. 2013, 2014).

However, our findings did not fulfill the expectation of a more pronounced hypotensive effect in the human of static compared to a dynamic mandibular extension, being in fact in the order of 2–4 mmHg and similar or slightly less than that observed after dynamic mandibular extension (Del Seppia et al. 2016). It is interesting to observe that, at least for SBP, the decrement induced by static mandibular extension correlated with baseline values (i.e., the higher the baseline values, the greater the hypotensive effect), suggesting that the effect would be perhaps more significant in hypertensive patients. We are currently investigating this aspect.

Being the hypotensive effect of mouth opening a seemingly novel phenomenon, several aspects remain to be elucidated at a pathophysiological level. One point regards the anatomical structures involved in the afferent limb of this reflex. The simplest and probably most likely hypothesis is an involvement of the mechanoceptors within the masseter muscle activated by passive stretching, although one cannot exclude the involvement of some adjacent structure (e.g., the carotid arteries, the jugular veins, the ganglion of Gasser, etc.). The fact that in the normotensive rat the cardiovascular effects of mandibular extension were found to be abolished by bilateral peripheral trigeminal section indicates a role of the cranial nerve as the afferent limb of this response and suggests that this effect is part of the so-called trigemino-cardiac reflexes. The trigemino-cardiac reflex was first described by Kumada et al. (1977) in the rabbit and extensively studied, in the humans especially during neurosurgical operations, by Schaller and coworkers (Schaller 2004; Schaller et al. 2008, 2009; Chowdhury et al. 2015; Meuwly et al. 2015a, b).

Several evidence have demonstrated that short-term reductions of blood pressure occur acutely after various types of even a single or brief bouts of muscular exercise, including dynamic aerobic exercise (e.g., walking), dynamic resistance exercise (e.g., weight lifting) or isometric resistance exercise (e.g., handgrip) (Brook et al. 2013, 2015; Kenney and Seals 1993; Pescatello and Kulikowich 2010). Although the cardiovascular responses during a single skeletal muscular stretching (Gladwell and Coote 2002; Fisher et al. 2005; Venturelli et al. 2017) and the cardiovascular effects of stretch training programs (Cortez-Cooper et al. 2008; Wong and Figueroa 2014) have been investigated in several reports, to the best of our knowledge, only one study (Kruse et al. 2016) has focussed its attention on the cardiovascular after-effects following a single skeletal muscular stretching. In that study conducted in young normotensive volunteers, in whom the cardiovascular effects following passive stretching of the calf muscles for four min was examined for ten min, a significant reduction of BP by about 4–7 mmHg was reported. Compared to the latter study, our results conducted on a different muscle (the masseter) demonstrated a perhaps somewhat smaller decline of BP, with a slower onset but with a markedly prolonged duration.

Finally, looking at the HR effects of mandibular extension, it may be interesting to note that hypotension is accompanied by a concomitant reduction of HR rather than an increase of HR that could be expected as a reflex hemodynamic effect. The prolonged reduction in BP without evidence of baroreflex-mediated compensatory increase in HR may suggest that mandibular extension may result from a prolonged resetting of the operating point of the arterial baroreflex to a lower pressure (Minami et al. 2006). This effect could possibly result from a reflex efferent sympathetic inhibition and vagal enhancement secondary to afferent trigeminal input (Kumada et al. 1977). Sympatho-vagal autonomic balance, sympathetic cardiovascular function and baroreceptor regulation can be assessed by various techniques (Pagani et al. 1988; Grassi et al. 2015), which, however, were not available in this study. A further limitation of our study could consist in the effects of swallowing, which could have occurred during the procedure. Swallowing is a complex motor process (Massey 2006) associated also with cardiovascular responses (Gandevia et al. 1978). However, in our study automatic and volitional saliva swallowing was made difficult (if not impossible) by the concurrent forced opening of the oral cavity, though we did not control for swallowing attempts.

Conclusions

In conclusion, our study provides further evidence that a relatively brief submaximal opening of the mouth obtained by an ad hoc dilator induces a prolonged, albeit small, reduction of blood pressure in normotensive volunteers.

Studies under controlled conditions on larger samples by independent laboratories are needed, as well as studies on free-living conditions and on hypertensive patients. In addition, and perhaps more importantly, studies are required to ascertain whether the hypotensive response could be improved by optimizing the different components of mandibular extension (i.e., method used, duration, intensity and repetition).

Acknowledgements We are grateful to the study volunteers for their participation. We also thank Fabrizio Minichilli for statistical support and Giuseppe Federighi for technical assistance.

Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest.

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