Effect of intermittent subdiastolic pressure in thigh cuffs on human arterial baroreflex

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Key words:
Arterial pressure; Baroreflex; Heart rate; Respiration; Spectral analysis.

Background. **We investigated the effects of subdiastolic variations of the pressure inside the thigh cuffs on cardiovascular oscillations and arterial baroreflex sensitivity in humans.**

Methods. **During 10 min of controlled breathing at low (0.1 Hz) and high (0.25 Hz) frequencies, 30 healthy subjects underwent variations of the pressure inside the thigh cuffs (from 0 to 40 mmHg) at 0.25 and 0.1 Hz respectively; the periods of controlled breathing without cuff pressure modulation were used as a control. The frequency responses of cardiovascular signals were assessed using spectral analysis, and baroreflex sensitivity by the sequence method.**

Results. **Cuff pressure modulation at 0.25 Hz did not affect the RR interval, arterial pressure, or baroreflex sensitivity; at 0.1 Hz it did not change the RR interval and arterial pressure, but engaged (0.76 ± 0.2 of coherence) and increased the low frequency oscillations of the RR interval (from 5.6 ± 1 to 6.1 ± 0.9 ln ms^2, $p < 0.05$) and improved baroreflex sensitivity by 25% (from 14.2 ± 9 to 17.7 ± 10 ms/mmHg, $p < 0.01$).**

Conclusions. **Subdiastolic thigh cuff pressure modulation at 0.1 Hz improved the low frequency oscillations of heart rate and baroreflex sensitivity. This approach represents a new and simple non-pharmacological strategy for acutely improving baroreflex sensitivity in humans.**

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Introduction

The arterial baroreflex control of heart rate is defective in patients with heart disease[1] and may provide prognostic information in chronic heart failure[2] and after myocardial infarction[3]. This evidence has generated a growing interest in pharmacological and non-pharmacological interventions able to improve the gain of vagal arterial baroreflex control of heart rate (i.e. baroreflex sensitivity-BRS).

We have recently demonstrated in humans that changes in respiration have a profound impact on cardiovascular oscillations and BRS; i.e., the slower the respiratory rate, the higher the BRS[4]. To our knowledge, this is the only non-pharmacological approach to acutely increase human vagal baroreflex, but it requires the active collaboration of the subjects. Since thigh cuffs are able to modify venous return[5], this technique could represent a passive and external approach to modulate cardiovascular oscillations[6,7] and BRS[8-10]. In the present study we investigated the effects of the cyclic modulation of subdiastolic pressure inside thigh cuffs on the non-invasive cardiovascular oscillations and the BRS, taking into account the effect of respiration.

Methods

Subjects. We studied 30 healthy volunteers, 17 males and 13 females aged 28 ± 3 years, who gave their consent to participate. All were non-smokers and denied taking any medication. The study was approved by the local Ethics Committee.

Experimental protocol. The experiments were performed in the morning in a quiet and dimly-lit room, whose ambient temperature was kept at about 24°C. A device with pneumatic cuffs applied around the thighs was used; a closed-loop, logic-controlled valve system was used to regulate the amplitude and frequency of the pressure inside the cuffs[11]. The signals of surface ECG, arterial pressure (Finapres Model 2300, Ohmeda, Englewood, CO, USA), respiration (by means of an im-

pedance pneumograph; Hewlett Packard Model 78354C, Andover, MA, USA) and the pressure inside the cuffs were continuously acquired. After instrumentation, the subjects lay down for 10 min in a supine position and were allowed to breathe spontaneously.

The study design (Fig. 1) consisted of four periods during which breathing was controlled at a frequency of 6 (0.1 Hz) or 15 breaths/min (0.25 Hz). Between each period, the subjects were allowed to breathe spontaneously for 5 min and the self-adjustment mechanism of the Finapres was turned on. The sequence of the two breathing periods was randomly assigned. During the first and third periods, the subjects were asked to control their breathing while the cuffs were deflated (control); during the second and fourth periods, the subjects controlled their breathing at the same rate used in the previous period while the cuffs were inflated from 0 to 40 mmHg and then deflated. During the second period of breathing at 0.1 Hz, the cuffs were inflated at the frequency of 15 cycles/min (0.25 Hz); during the second period of breathing at 0.25 Hz, the cuffs were inflated at 6 cycles/min (0.1 Hz). The inflation and deflation times for the 0.15 Hz frequency were 2 s; those for 0.1 Hz were 5 s. These frequencies were chosen on the basis of the information given by these two bands during spontaneous cardiovascular oscillations.

During the four periods, the time series of 512 beats of the RR interval, respiration, systolic and diastolic arterial pressure, and the cuff pressure were selected for subsequent analysis.

Spectral and cross-spectral analysis. Frequency domain variability was analyzed using an autoregressive method on the recorded signals. The spectral components were obtained by means of a decomposition method in order to measure the power and centered frequency of low (near 0.1 Hz) and high frequency (near 0.25 Hz) oscillations. The RR interval oscillations are expressed in ms^2 and normalized units; systolic arterial pressure and cuff pressure in $mmHg^2$; and the respiratory signals in arbitrary units. To assess the relationship between the signals, we performed cross-spectral analysis of pairwise relations and estimated the squared coherence (K^2), which evaluates the degree of correlation in the powers of two signals in the frequency band, and the phase (Φ), which quantifies the delay between signals. K^2 ranges from 0 (no relationship between the signals) to 1 (close relationship); Φ was expressed in degrees (values between -180° and +180°). When the Φ value between two signals was < 0, we considered the first signal as following the second; on the contrary, a Φ value of > 0 suggested that the first signal preceded the second. If K^2 is > 0.5, the two signals have a stable relationship for a given frequency and hence can be considered as synchronous with each other.

Baroreflex sensitivity. The time series of RR intervals and systolic arterial pressure recorded during the different periods were scanned by a computer to identify the sequences in which they concurrently increased (up sequence) or decreased (down sequence) over 3 or more beats[12]. The threshold change was set at 1 mmHg for systolic arterial pressure and at 4 ms for RR interval. A linear regression between the two variables was carried out in each individual sequence, and only those with an $r \geq 0.80$ were accepted. The automated analysis separated the values of BRS (ms/mmHg) for the up sequences (up-BRS), down sequences (down-BRS) and pooled results (BRS).

Statistical analysis. The results are given as mean values ± SD. The effect of cuff pressure modulation on the variables was assessed using Student's paired t-test. When the data were not normally distributed, they were log transformed; in the case of phase, this transformation was not possible and the effect on this parameter was tested using Wilcoxon's test. Linear regression analysis was used to assess the correlations between the changes in BRS and the changes in cardiovascular signals secondary to cuff pressure modulation. A p value of < 0.05 was considered statistically significant.

Results

The respiratory oscillations in the RR interval were closely related to respiration and concentrated in the respiratory band (Table I). As expected, BRS was higher during respiration at 6 than 15 breaths/min (20 ± 10 vs 14.2 ± 9 ms/mmHg, $p < 0.01$).

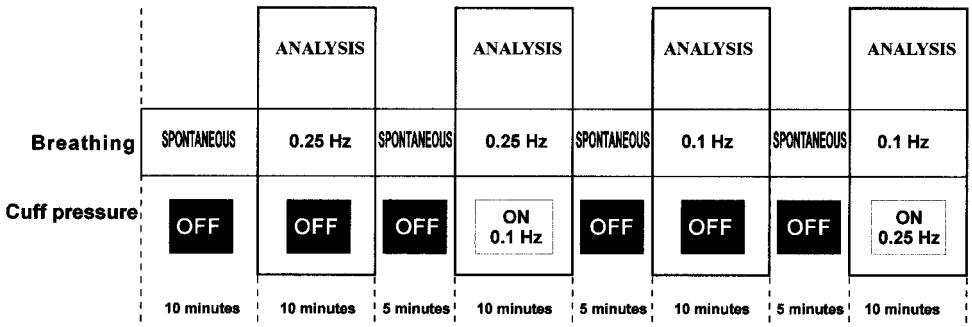

Figure 1. *Study design.*

Table I. Relations between respiration and heart rate.

	Breathing at 0.1 Hz		Breathing at 0.25 Hz	
	Control	CP at 0.25 Hz	Control	CP at 0.1 Hz
K^2 RR-RESP	0.94 ± 0.06	0.95 ± 0.05	0.95 ± 0.07	0.94 ± 0.09
Φ RR-RESP (degrees)	-47 ± 84	-53 ± 92	-43 ± 96	-44 ± 100
RSA (Hz)	0.102 ± 0.02	0.101 ± 0.03	0.251 ± 0.02	0.252 ± 0.02

Values are expressed as mean ± SD. CP = cuff pressure modulation; K^2 RR-RESP = value of squared coherence between RR interval and respiration; RSA = frequency peak of respiratory sinus arrhythmia; Φ RR-RESP = phase relation between RR interval and respiration.

Effects of cuff pressure modulation at 0.25 Hz. The frequency of cuff pressure was 0.247 ± 0.005 Hz. In comparison with the control period, the pressure oscillations in the cuffs at 0.25 Hz did not lead to any significant changes in the RR interval and systolic arterial pressure, nor in their variabilities (Fig. 2). There was also no significant modification in BRS (Table II).

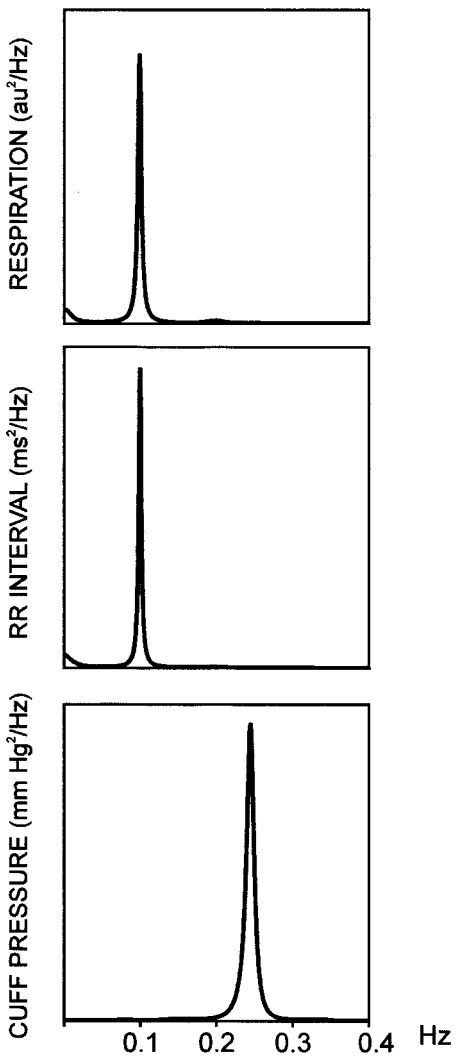

Figure 2. *Example of spectral analysis of respiratory signal, RR interval and cuff pressure during controlled breathing at 0.1 Hz. Cuff pressure modulation at 0.25 Hz does not have any frequency effect on RR interval. au = arbitrary units.*

Effects of cuff pressure modulation at 0.1 Hz. The frequency of cuff pressure was 0.097 ± 0.009 Hz. The pressure modulation inside the cuffs did not significantly modify heart rate, arterial pressure and systolic arterial pressure variability at low or high frequency (Table III), but it did induce an increase in the amplitude of heart rate oscillations in the low frequency band, whether these were evaluated as absolute values (from 5.6 ± 1 to 6.1 ± 0.9 ln ms^2, $p < 0.05$) (Fig. 3) or normalized units (from 31 ± 20 to 38 ± 23 nu, $p < 0.001$). Simultaneously, the phase relation between the RR interval and systolic arterial pressure at low frequency changed (Table III). Respiratory sinus arrhythmia increased from 6.4 ± 1.4 to 6.8 ± 1.4 ln ms^2 ($p < 0.01$) and BRS by 25% (Fig. 4). The greater the increase in heart rate oscillations in the low frequency band, the greater the increase in BRS ($r = 0.63$, $p = 0.001$).

The average K^2 between RR intervals and cuff pressure signals at low frequencies was 0.76 ± 0.2, thus demonstrating a consistent relation between the two signals, with a negative phase (i.e. cuff pressure higher than RR interval) corresponding to -51 ± 53° (Fig. 5). K^2 between RR interval and cuff pressure was significant in 22 of 30 subjects with a negative phase (i.e. cuff pressure higher than RR interval by -64 ± 41°), while K^2 between systolic arterial pressure and cuff pressure was present in 26 of 30 subjects with a phase value of -25 ± 34° (i.e. cuff pressure higher than systolic arterial pressure). In 4 of 30 subjects with low K^2 between systolic arterial pressure and cuff pressure, K^2 between RR interval and cuff pressure was low.

The comparative results of the phase analysis indicate that cuff pressure appears to precede the occurrence of systolic arterial pressure oscillations that precedes RR interval.

Discussion

The most frequently used method for reducing venous return is the application of lower body negative pressure while cuff modulation is considered to be less efficacious[13]. However, in our laboratory, we decided to use the cuff method because it has a number of advantages over lower body negative pressure blood pooling: no diaphragm lowering; no effects on kidney; no need

Table II. Effect of cuff pressure oscillations at 0.25 Hz on cardiovascular signals and baroreflex sensitivity.

Variable	Control	CP at 0.25 Hz	p
Heart rate			
RR interval (ms)	911 ± 170	909 ± 167	NS
RSA (ln ms^2)	8.5 ± 1	8.5 ± 1	NS
Arterial pressure			
SAP (mmHg)	123 ± 13	124 ± 15	NS
DAP (mmHg)	68 ± 11	69 ± 12	NS
MAP (mmHg)	86 ± 12	87 ± 13	NS
PP (mmHg)	54 ± 7	54 ± 8	NS
SAP at 0.1 Hz (ln $mmHg^2$)	2.7 ± 0.7	2.7 ± 0.6	NS
BRS			
BRS (ms/mmHg)	20 ± 10	19 ± 9	NS
Up-BRS (ms/mmHg)	23 ± 12	22 ± 12	NS
Down-BRS (ms/mmHg)	18 ± 9	17 ± 8	NS
Cross RR-SAP (0.1 Hz)			
K^2	0.94 ± 0.01	0.96 ± 0.06	NS
Φ (degrees)	-41 ± 24	-36 ± 50	NS

Values are expressed as mean ± SD. BRS = baroreflex sensitivity; CP = cuff pressure modulation; DAP = diastolic arterial pressure; Down-BRS = BRS of down sequence; K^2 RR-SAP = value of squared coherence between RR interval and SAP; MAP = mean arterial pressure; PP = pulse pressure; RSA = respiratory sinus arrhythmia; SAP = systolic arterial pressure; SAP at 0.1 Hz = respiratory oscillations of systolic blood pressure; Up-BRS = BRS of up sequence; Φ RR-SAP = phase relation between RR interval and SAP.

Table III. Effect of cuff pressure oscillations at 0.1 Hz on cardiovascular signals.

Variable	Control	CP at 0.25 Hz	p
Heart rate			
RR interval (ms)	848 ± 156	852 ± 164	NS
RR interval at 0.1 Hz (ln ms^2)	5.6 ± 1	6.1 ± 0.9	< 0.05
RSA (ln ms^2)	6.4 ± 1.4	6.8 ± 1.4	< 0.01
Arterial pressure			
SAP (mmHg)	118 ± 17	115 ± 16	NS
DAP (mmHg)	65 ± 12	64 ± 9	NS
MAP (mmHg)	82 ± 13	80 ± 12	NS
PP (mmHg)	52 ± 9	50 ± 11	NS
SAP at 0.1 Hz (ln $mmHg^2$)	0.77 ± 1.2	0.78 ± 1.3	NS
SAP at 0.25 Hz (ln $mmHg^2$)	1.4 ± 0.7	1.5 ± 0.8	
Cross RR-SAP (0.1 Hz)			
K^2	0.66 ± 0.2	0.67 ± 0.2	NS
Φ (degrees)	-88.5 ± 38	-62 ± 25	< 0.01
Cross RR-SAP (0.25 Hz)			
K^2	0.97 ± 0.02	0.96 ± 0.07	NS
Φ (degrees)	-20 ± 21	-16 ± 23	NS

Values are expressed as mean ± SD. SAP at 0.1 Hz and 0.25 Hz = respiratory oscillations of systolic blood pressure at low and high frequencies, respectively. Other abbreviations as in table II.

for temperature control in the chamber device; and the fact that it can be easily used[14].

In accordance with the results of previous studies[6,7], our findings confirm the absence of any effect on systolic pressure variability and show that cuff pressure modulation at 0.1 Hz, but not at 0.25 Hz, elicits a frequency response in heart rate, which we believe to be related to cuff modulation because of the high K^2 values between heart rate and cuff pressure signals. The good reproducibility of the low frequency heart rate oscillations during paced breathing[15] allows us to consider our results as being unaffected by spontaneous signal variations. From the physiological point of view, cyclic modulation of venous return has no effect on arterial pressure variability because this is buffered by heart rate reflexes in the low frequency, and by mechanical damping of the heart and thoracic vessels in the high frequency band[6].

Since the recent demonstration that the power of this component is an independent predictor of sudden death in heart failure patients[16], interest in the low frequency oscillations of heart rate variability has increased. The precise mechanism of low frequency oscillations in heart rate is still debated. Two main theories have been proposed that are not mutually exclusive[17].

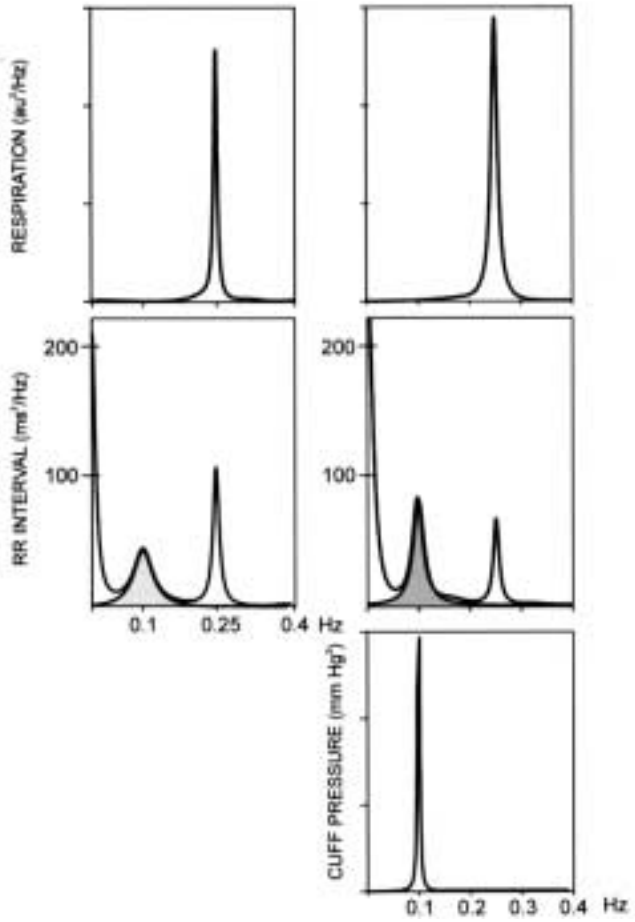

Figure 3. Left: *spectral analysis of respiratory signal* (upper panel) *and RR interval* (middle panel) *during controlled breathing at 0.25 Hz in the same subject.* Right: *spectral analysis of respiratory signal* (upper panel) *and RR interval* (middle panel) *and cuff pressure* (bottom panel) *during controlled breathing at 0.25 Hz and cuff pressure modulation at 0.1 Hz in the same subject. During cuff pressure modulation at 0.1 Hz the low frequency component* (dark area) *of the RR interval increases.*

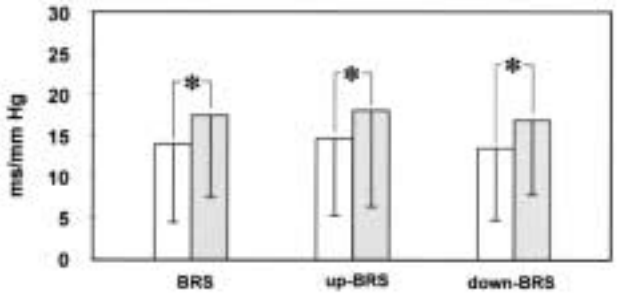

Figure 4. *Effect of cuff pressure modulation at 0.1 Hz on arterial baroreflex sensitivity (BRS) for both the up sequence (up-BRS) and the down sequence (down-BRS).* White bars = *control condition;* dark bars = *cuff pressure modulation at 0.1 Hz. * p < 0.05.*

According to the central theory, this component is the result of the activity of a central nervous system oscillator. The peripheral (or baroreflex) theory explains this oscillation as a result of a resonance phenomenon due to a phase lag in the slow sympathetic control loop of the arterial baroreflex; in fact, the peak at 0.1 Hz is

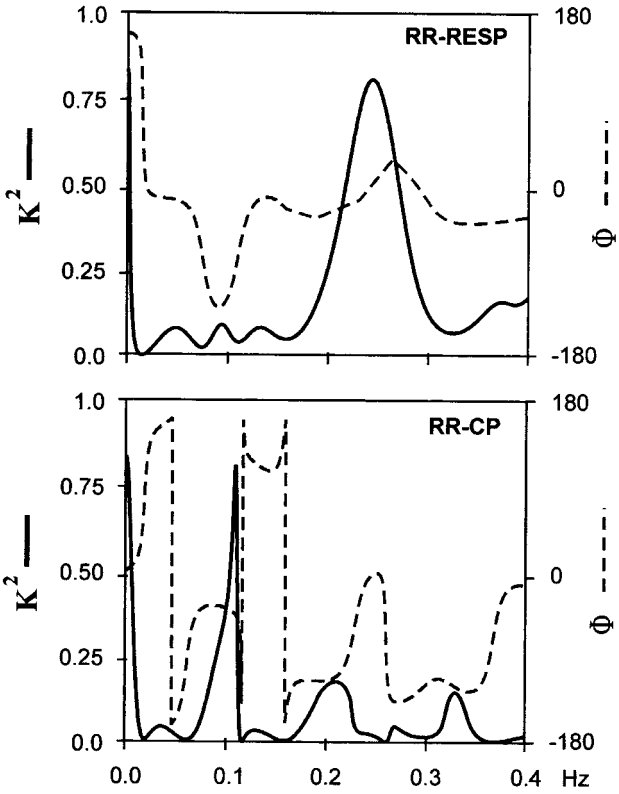

Figure 5. *Cross-spectral analysis between the RR interval and respiratory signal (RR-RESP)* (upper panel)*, and between the RR interval and cuff pressure (RR-CP)* (bottom panel). *Note that the RR interval oscillations in the high frequency band show strong coherence (K^2) with the respiratory signal, whereas those in the low frequency band show strong coherence with CP.* Φ = *phase relation.*

evident if arterial baroreflex is relatively intact[18]. The present study, as well as that by Triedman and Saul[6], suggests that the venous perturbation could exert an influence on the origin of the low frequency component of heart rate variability.

The improvement of BRS secondary to the reduction in venous return may be explained by two main mechanisms. The first one hypothesizes that a reduction in venous return deactivates cardiopulmonary baroreceptors and, as a consequence, removes the inhibitory effect of cardiopulmonary baroreceptors on the arterial baroreflex control of heart rate[8-10]. However, this mechanism is not supported by the results of other investigations[19-22]. The second is represented by the mechanical engagement of baroreflex demonstrated by the fact that low frequency variations in venous return may change cardiac output (and thus arterial volume), and that this may affect arterial BRS. This hypothesis is supported by the finding that non-hypotensive hypovolemia reduces the area of the aortic pulse[23] and the diameter and hemodynamics of the carotid artery[24,25]. In the present study, the bivariate spectral analysis (K^2 and phase analysis) allowed us to establish a phase relationship between cuff pressure modulation, systolic pressure and heart rate oscillations and, therefore, the timing between the three signals. The phase values indicate that cuff pressure mainly af-

fects systolic pressure oscillations and secondly heart rate.

We cannot exclude the possibility that our results may have been influenced by the activation of intramuscular mechanoreceptors; however, if this had been the case, we would have seen a reduction in BRS[26]. For a similar reason, we can also exclude the possibility that our results were the consequence of veno-arterial reflexes in the legs[27] or muscle metaboreflexes[28]. The activation of these latter reflexes may also be excluded by the fact that no exercise was performed in this study. Moreover, the effects on BRS do not seem to be due to a direct effect of the cuffs on the arterial conduit: the thigh is not a baroreflex area[29], and subdiastolic thigh cuff pressure decreases total peripheral conductance by only ~ 4%[30]. Furthermore, if mechanical effects on the arterial conduit played a role in the genesis of our results, it is unclear why there was an increase in BRS when modulating cuff pressure at 0.1 Hz and not at 0.25 Hz.

The main limitation of this study was the absence of any measurement of central venous pressure in order to evaluate the gain between cuff pressure and central venous pressure, and between central venous pressure and cardiovascular parameters. However, in a pilot study[11], we found effects on cardiovascular signals that were close to those previously reported[6], suggesting a relationship between heart rate variability and cyclic venous occlusion of the legs.

Although this study was performed in normal subjects, the short-term increase in BRS may be potentially useful in patients with cardiovascular diseases and altered autonomic control of heart rate. In particular, it would be very interesting to evaluate the short- and long-term effect of tight cuff pressure modulation in patients with heart failure in whom moderate low frequency variability of heart rate[16] and BRS[2] have been associated with a poor prognosis.

In conclusion, our study offers the first demonstration that subdiastolic pressure oscillations inside thigh cuffs influence low frequency oscillations of heart rate and improve arterial BRS. Cuff devices may have potential applications in cardiovascular diseases as a means of exploring and modulating neurally mediated heart rate control.

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