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## Carotid baroreceptor reflexes in humans during orthostatic stress

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**Orthostatic stress, including standing, head-up tilting and lower body suction, results in increases in peripheral vascular resistance but little or no change in mean arterial pressure. This study was undertaken to determine whether the sensitivity of the carotid baroreceptor reflex was enhanced during conditions of decreased venous return. We studied eight healthy subjects and determined responses of pulse interval (ECG) and forearm vascular resistance (mean finger blood pressure divided by Doppler estimate of brachial artery blood velocity) to graded increases and decreases in carotid transmural pressure, effected by a neck suction/pressure device. Responses were determined with and without the application of lower body negative pressure (LBNP) at  $-40$  mmHg. Stimulus-response curves were determined as the responses to graded neck pressure changes and the differential of this provided estimates of reflex sensitivity. Changes in carotid transmural pressure caused graded changes in R-R interval and vascular resistance. The cardiac responses were unaffected by LBNP. Vascular resistance responses, however, were significantly enhanced during LBNP and the peak gain of the reflex was increased from  $1.2 \pm 0.3$  (mean  $\pm$  S.E.M.) to  $2.2 \pm 0.3$  units ( $P < 0.05$ ). The increased baroreflex gain may contribute to maintenance of blood pressure during orthostatic stress and limit the pressure decreases during prolonged periods of such stress. *Experimental Physiology* (2001) **86.5**, 677–681.**

Orthostatic stress, as when changing body position passively from supine to upright or simulated by applying subatmospheric pressure to the lower body (lower body negative pressure, LBNP), causes a decrease in cardiac output, typically by 20–25%, but, despite this, mean arterial blood pressure does not usually fall and often actually increases (Hainsworth & Al-Shamma, 1988). The mechanism responsible for the maintenance of the blood pressure clearly must involve an increase in vascular resistance, although the stimulus responsible for the vasoconstriction remains unclear. Central to the regulation of blood pressure are the arterial baroreceptors. However, during orthostatic stress, because mean blood pressure remains relatively unchanged, unloading of arterial baroreceptors alone seems unlikely to be able to explain the observed increase in vascular resistance. Several investigators have therefore examined the hypothesis that orthostatic stress may in some way increase baroreceptor sensitivity. Results, however, have been inconsistent, with some reports indicating that baroreceptor sensitivity increased (Ebert, 1983; Victor & Mark, 1985) and others that it was not changed or even reduced (Bevegård *et al.* 1977; Abboud *et al.* 1979). In an earlier investigation from our laboratory, we suggested that LBNP had no effect on the sensitivity of baroreceptor control of vascular resistance and apparent effects were due just to non-linearities resulting from saturation of the reflex (Vukasovic *et al.* 1990).

There are many possible reasons for the previous inconsistent results. Most previous work examined effects of only one level

of change of carotid pressure which is clearly not sufficient to describe a stimulus-response relationship that would enable the point of maximum slope reliably to be deduced. Some have involved measurements of cardiac output which are used to determine total peripheral vascular resistance, but these require several minutes to perform and responses to stimulation of carotid baroreceptors tend to decline with time due to adaptation and to buffering by other reflexes (Eckberg & Sleight, 1992). It is now possible to determine vascular resistance in a limb on a beat-to-beat basis using continuous non-invasive techniques. We have found that the technique of calculating forearm vascular resistance from the ratio of finger blood pressure to blood velocity estimates using a Doppler probe over the brachial artery provides a sensitive measure of responses to postural changes and lower body suction (Brown & Hainsworth, 2000). It was the aim of the present study to use this non-invasive technique to determine responses to graded changes in carotid transmural pressure to resolve finally whether carotid baroreceptor reflex sensitivity is enhanced during orthostatic stress.

### METHODS

Studies were carried out on eight volunteer subjects (4 male) aged 21–60 (mean 35) years. All subjects were apparently healthy and none was taking any prescribed medicines. Subjects were requested to have a light breakfast on the day of the study and in particular to avoid caffeine-containing drinks. Tests were carried out in the mornings in a temperature-controlled room (22–24°C).

Written consent was obtained from the subjects and the study was approved by the Research Ethics Committee of the United Leeds Teaching Hospitals.

Subjects rested supine in a lower body negative pressure (LBNP) chamber and were fitted with ECG (lead 2) leads. The right arm was supported at heart level and a Finapres (Ohmeda, Wisconsin, USA) cuff was fitted to the middle digit. A Doppler blood velocity probe (Doptek, Chichester, UK) was held in a clamp and positioned over the brachial artery. The angle of the probe with the artery was kept as small as possible and extreme care was taken to ensure that it did not change. The cuff from an automatic sphygmomanometer (Hewlett-Packard 78325C) was fitted round the upper left arm. This provided a reference with which to calibrate the Finapres. The top was fitted to the LBNP chamber and a plate of suitable size was selected to seal the subject in the chamber at the level of the iliac crest. When required a subatmospheric pressure was created in the chamber by use of an industrial vacuum cleaner controlled by a voltage regulator.

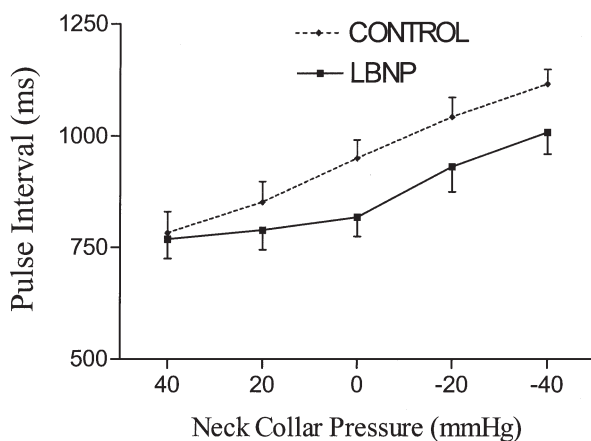
Carotid baroreceptor stimulation was changed by use of a lead collar modified from the design of Eckberg *et al.* (1975) to allow application of both positive and negative pressures. The onset of neck suction/pressure was not timed to any particular phase of the ECG. The chamber was made from sheet lead lined with neoprene foam and covered with an impermeable membrane. It was connected by wide bore tubing to a 10 litre reservoir in which the pressure (positive or subatmospheric) was controlled by a second vacuum cleaner with variable voltage control. Pressures were recorded using Statham strain gauges (P23Gb).

### Statistical analysis

Unless otherwise stated all values are reported as means  $\pm$  S.E.M. Comparisons of responses before and after the application of LBNP were performed using Student's paired *t* test.

### Procedures

Subjects rested supine for 20 min to allow steady states to be achieved. The neck chamber was then moulded to fit the contours of the subject and held in place manually. All subjects



**Figure 1**

Pulse interval during changes in neck collar pressure during baseline (control) and lower body negative pressure (LBNP). Responses to neck suction were similar in both control and LBNP conditions, whereas responses to neck pressure were reduced during LBNP.

were familiarised with the sensation and protocol of the neck collar tests before the experimental period. Tests were carried out of the cardiac responses to changes in carotid transmural pressure during held expiration. The subject was instructed to stop breathing at the normal end-expiratory point. After 5 s neck suction or pressure was applied, and after a further 5 s the neck stimulus was stopped and breathing resumed. Neck chamber pressures of  $-40$ ,  $-20$ ,  $0$ ,  $+20$  and  $+40$  mmHg were applied and the cardiac response to each stimulation was calculated as the maximum change in cardiac (R-R) interval during the stimulus, compared to the average during the 5 s period during breath-hold immediately before the onset of the stimulus. Mean values of the absolute pulse intervals during stimulation were then calculated. This procedure was repeated with the pressures applied in the reverse order after determining vascular responses.

Vascular responses were determined during normal breathing. An initial control period of 15 s of data was recorded, the stimulus was applied for 20 s, then removed and a further 20 s of control period recorded. Values of vascular resistance (index) were calculated as mean finger blood pressure (diastolic + 1/3 pulse pressure) divided by mean brachial velocity. Responses were taken as the maximum changes during the stimulation period from the means of the control periods before and after stimulation. Pressures of  $-40$ ,  $-20$ ,  $+20$ ,  $+40$ ,  $+40$ ,  $+20$ ,  $-20$  and  $-40$  mmHg were applied.

After completion of the baroreceptor tests, LBNP was set at  $-40$  mmHg and after 10 min, the baroreceptor tests were repeated.

## RESULTS

### Pulse interval responses

Increasing carotid transmural pressure by neck suction resulted in prolongation of the pulse interval and decreasing transmural pressure by neck pressure resulted in a reduction in pulse interval. The relationship between pulse interval and stimulus intensity is illustrated in Fig. 1 and shows that similar changes in pulse interval were obtained in response to both increases and decreases in carotid transmural pressure. Application of LBNP caused an average increase in heart rate of 11 beats  $\text{min}^{-1}$  and a decrease in pulse interval of 210 ms (Table 1). During LBNP the responses to increases in baroreceptor stimulation (neck suction) were very similar to those seen in the absence of LBNP; the lines are approximately parallel. However, responses to neck pressure were smaller, and at  $+40$  mmHg neck chamber pressure the pulse interval values were not affected by the LBNP. The sensitivity of the carotid cardiac reflex, expressed as the maximum slope of the stimulus-response relationship, was not affected by LBNP: the sensitivities without and during LBNP were  $3.9 \pm 0.6$  and  $4.1 \pm 0.8$  ms  $\text{mmHg}^{-1}$  ( $P > 0.05$ ).

### Vascular resistance responses

Forearm vascular responses to changes in carotid transmural pressure before LBNP were not linear. Responses to neck pressure were greater than those to neck suction (Fig. 2). LBNP resulted in a 61% increase in vascular resistance and a small increase in mean arterial blood pressure (Table 1). During LBNP, the vascular responses to neck suction were not greatly altered. The responses to neck pressure (baroreceptor unloading), however, were greater (Fig. 2). Linear

**Table 1. Cardiovascular variables without (baseline) and 10 min following onset of lower body negative pressure at -40 mmHg (LBNP)**

	Baseline	LBNP	$\Delta$	<i>P</i>
Heart rate (beats min <sup>-1</sup> )	64.5 ± 2.5	75.8 ± 4.0	+11.3 ± 2.4	< 0.005
Pulse interval (ms)	939.3 ± 43.7	728.7 ± 56.0	-210.5 ± 21.2	< 0.0001
Mean pressure (mmHg)	85.9 ± 2.3	90.2 ± 2.5	+4.3 ± 1.6	< 0.05
Vascular resistance (units)	15.3 ± 1.2	24.7 ± 1.5	+61.4%	< 0.001

Mean values ± S.E.M. shown for 8 subjects.

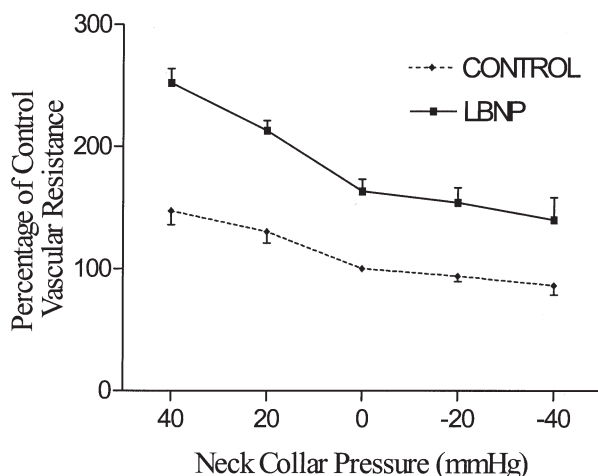
regression of the responses to neck pressure showed a near doubling of the slope from  $1.18 \pm 0.28$  to  $2.22 \pm 0.32$  units mmHg<sup>-1</sup>. The enhancement of the reflex gain is also shown in Fig. 3, which shows the differential of the mean curves derived by fitting sigmoid functions to the points at each carotid transmural pressure.

## DISCUSSION

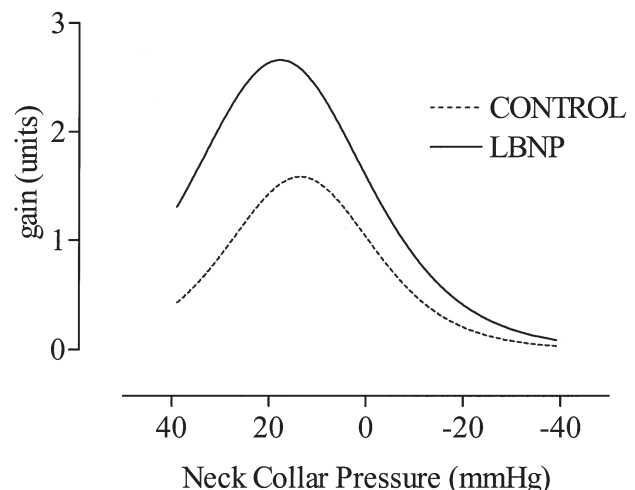
Application of positive or negative pressure to the region of the neck overlying the carotid arteries is now a widely used method of altering the stimulus to the sinus baroreceptors. It has advantages over other methods, such as injections of vasoactive agents, in that not only are discrete stimuli applied to the baroreceptors, but, because the method does not directly influence vascular tone, it is also possible to study the vascular as well as the cardiac responses. The disadvantage of the technique is that only one group of baroreceptors is directly stimulated; others including aortic (Eckberg & Sleight, 1992) and coronary receptors (Drinkhill *et al.* 1993)

would still be able to buffer any response. Due to this, and possibly due to adaptation of the carotid receptors themselves, responses to changes in neck pressure tend to be transient. Cardiac responses are usually greatest in the first one or two beats after the start of the stimulus, and vascular responses, being of slower onset, are maximal at 10–15 s. Cardiac responses are also greater in the absence of respiration (Eckberg, 1976) and so, to maximise the responses, we did this part of the study during held expiration. Clearly, for the study of the much slower vascular responses it is not possible to continue breath-holding for a sufficiently long period, so we undertook this during normal respiration.

We used lower body negative pressure to simulate standing or upright tilting. The stress of LBNP at -40 mmHg, in terms of its effect on cardiac output, is very similar to that of passive head-up tilting to 60 deg (Al-Shamma & Hainsworth, 1987): both decrease cardiac output by about 25%. Assessments of volume shifts show these also to be similar (Musgrave *et al.* 1971). The advantage of LBNP is that the study can be undertaken without changing the position of the subject. Thus, from a practical point of view, the positions of the various probes, particularly the Doppler probe, would not change. Also there would be no difference in hydrostatic

**Figure 2**

Percentage changes in vascular resistance during changes in neck collar pressure during baseline (control) and lower body negative pressure (LBNP). Vascular resistance during the control condition with zero collar pressure was taken as 100%. Responses to neck suction were not significantly altered by LBNP, whereas the responses to neck pressure were greater during LBNP than during baseline control.

**Figure 3**

Differential curves of vascular resistance responses to changes in neck collar pressure. There was near doubling of the gain during LBNP compared to the baseline condition.

pressures due to changes in the relative positions of the various cardiovascular reflexogenic areas.

The results of the present study have shown that the immediate change in pulse interval to unloading of carotid baroreceptors (neck pressure) was much smaller during LBNP. The response to increasing carotid transmural pressure, however, was unaffected. These results confirm those that were reported earlier (Vukasovic *et al.* 1990). The interpretation is that there is no interactive effect, but purely additive summation. The smaller response to neck pressure during LBNP is likely to be due to non-linearity in the efferent pathway of the reflex. The curves relating pulse interval to carotid transmural pressure over the range above resting blood pressure were parallel. There was certainly no suggestion of any potentiation of the response during LBNP. Responses of heart rate, however, are of little importance in the maintenance of blood pressure during orthostatic stress (Hainsworth, 2000).

The main mechanism responsible for the maintenance of blood pressure when cardiac output is decreased is an increase in peripheral vascular resistance. In the present study we recorded blood pressure and velocity to calculate an index of resistance in the forearm. We have used this technique in earlier investigations (Brown & Hainsworth, 2000) and have found it to provide convenient and reliable values for changes in resistance in the region. The advantages of this method over the more established technique of plethysmography are that it provides continuous, beat-to-beat estimates of resistance and does not require intermittent obstruction of the venous outflow. The disadvantage is that it does not provide an absolute value for flow or resistance, as the diameter of the artery insonated is not known.

The response to changes in carotid transmural pressure in the absence of LBNP were quite small. The full range of applied pressures, from +40 to -40 mmHg, which allowing for an 85% transmission to the carotid sinus (Eckberg, 1976; Ludbrook *et al.* 1977) would be equivalent to carotid pressures of 52–120 mmHg, caused vascular resistance to decrease by about 36%. Differentiation of the stimulus–response curve revealed that the peak gain of the reflex was 1.2 units mmHg<sup>-1</sup>. During LBNP, however, the overall response was greater and the peak gain of the reflex was significantly increased to 2.2 units mmHg<sup>-1</sup>.

The first question to consider is: does the increased response to baroreceptor stimulation mean that the reflex sensitivity is increased? The results indicate that it is. The increase in sensitivity is not due to non-linearities of the reflex and, therefore, can only be due to an interactive effect. These results differ from our previous report (Vukasovic *et al.* 1990) in which we found that although overall responses were greater during LBNP there was no difference in the maximum slope and we suggested that this was just due to non-linearity of the stimulus–response relationship. There are a number of differences in experimental technique. In the earlier study we were recording changes in the 2–3 min following the application of carotid pressure change, when responses are

likely to have declined, whereas in the present study continuous recordings of pressure and flow were made to allow peak responses to be studied. In the earlier study we obtained only one level of neck suction and one of neck pressure making it impossible to define reliable stimulus–response curves; in this study curves were defined from 5 points.

The mechanism(s) responsible for enhancing the sensitivity of the carotid baroreceptor–vascular resistance reflex during LBNP are unknown. LBNP draws blood from the thoracic region to below the diaphragm. Thus, the distension of low pressure intrathoracic receptors, the so-called ‘cardiopulmonary receptors’, would be decreased while that of possible vascular receptors in the subdiaphragmatic regions would be increased. There is a widely held view that the main influence is through the ‘cardiopulmonary receptors’ (Ebert, 1983; Victor & Mark, 1985; Pawelczyk & Raven, 1989). This view was reinforced by the finding that LBNP induced a much smaller increase in vascular resistance in patients with transplanted, and therefore denervated, hearts than in normal subjects (Mohanty *et al.* 1987). However, against this opinion are the findings from controlled animal preparations that discrete decreases in distension to any of the low pressure areas within the thorax do not increase vascular resistance. Atrial receptors have little or no effect on vascular resistance (Linden & Kappagoda, 1982), and unloading of pulmonary vascular receptors would be expected, if anything, to result in vasodilatation (Ledsome & Kan, 1977; McMahan *et al.* 1996). Changes in ventricular distension have very little effect and only when grossly distended (Wright *et al.* 2000). In fact the only vascular receptors within the intrathoracic region that appear capable of inducing large vascular responses are the coronary arterial receptors and these seem to function as high pressure arterial baroreceptors (McMahan *et al.* 1996). Even the evidence from transplanted patients has been questioned, as other studies undertaken after patients had had longer to recover from the transplant surgery indicated that arterial baroreceptors were much more important than ‘cardiopulmonary receptors’ in cardiovascular control (Jacobsen *et al.* 1993).

We feel that, rather than the unloading of ‘cardiopulmonary receptors’, an alternative, plausible mechanism may be that during LBNP the vasoconstriction and augmented baroreceptor sensitivity may actually be due to a reflex or reflexes elicited by distension of subdiaphragmatic vessels. In support of this Doe *et al.* (1996) showed in dogs that moderate distension of the subdiaphragmatic circulation did cause a reflex vasoconstriction and, furthermore, also enhanced the baroreceptor reflexes in much the same way as seen in the present experiments. This mechanism, however, has not yet been demonstrated in humans and, although they are compatible with this suggestion, the present experiments do not prove that subdiaphragmatic reflexes are responsible.

The other question to consider is what is the significance of these results? We believe that they provide an explanation as to why vascular resistance is enhanced during orthostatic

stress despite mean arterial blood pressure not decreasing. Baroreceptors are very sensitive to small changes in pulse pressure (Ead *et al.* 1982) and, if responses are amplified as seen in the present paper, this could explain the remarkable stability of blood pressure during large decreases in cardiac output. The increase in sensitivity could also protect against further falls in blood pressure during more prolonged orthostatic stress.

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