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Activity of cardiopulmonary baroreceptors, peripheral resistance and cutaneous microcirculation in patients with peripheral obstructive arterial disease

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Abstract. Arosio E, De Marchi S, Prior M, Zannoni M, Lucchese L, Lechi A (Division of Vascular Medicine and Rehabilitation, University of Verona, Italy). Activity of cardiopulmonary baroreceptors, peripheral resistance and cutaneous microcirculation in patients with peripheral obstructive arterial disease. *J Intern Med* 2000; **247**: 471–478.

Objectives. To assess the effects of cardiopulmonary baroreceptors on the haemodynamics of the humeral and common carotid arteries in patients suffering from peripheral artery disease (PAD) and to discover whether the stimulation of these receptors modifies the cutaneous microcirculation in the forearm.

Design. We studied a group of patients suffering from peripheral artery disease and two groups as controls.

Setting. Patients were examined at the ambulatory for Vascular Research, Division of Vascular Medicine and Rehabilitation, University of Verona.

Patients. We studied 15 patients with peripheral artery disease of the lower limbs at Fontaine stage II (group C), 10 free of arterial pathologies (group B) and 10 young people (group A).

Main outcome measures. We subjected the patients to passive elevation of the legs and the trunk in a horizontal position with pressure monitoring and measurement of the calibre and flow in the brachial and common carotid arteries using a colourDoppler ultrasound. We also studied the cutaneous microcirculation with laserDoppler flowmetry.

Results. During the test, arterial pressure and cardiac frequency remained constant in group A, systolic pressure values showed a slight, but statistically significant increase in group B, whilst the increase in systolic pressure values at this stage was marked in group C. Diastolic pressure values and cardiac frequency remained unchanged in all groups. The calibre of the humeral artery increased in the control groups. Carotid resistance was unchanged in the three groups. Humeral resistance during the test decreased in the two control groups whilst it increased in group C. The number of perfusion units felt in the control groups; no variations in group C.

Conclusions. Our study demonstrates, in patients with peripheral artery disease, a reduction in the activity of the cardiopulmonary baroreceptors with an increase in the humeral resistance during the test and impairment of the mechanisms of cutaneous microcirculatory vasoregulation in the forearm.

Keywords: baroreceptors, microcirculation, passive legs elevation test, peripheral obstructive disease.

Introduction

The cardiopulmonary baroreceptors (so-called low pressure receptors) are mechanoreceptors situated in the atria, the ventricles and the pulmonary vessels and are instrumental in circulatory homeostasis. Through vagal afferents they have an inhibitory effect on the vasomotor centre of the oblongata interacting at this level with fibres from the sinoaortic arterial receptors (high pressure receptors).

The activity of the cardiopulmonary baroreceptors has been studied, with partly contrasting results, in animals and in man. Investigations involving man have taken place in differing pathological conditions, such as arterial hypertension [1] and heart

failure, in which a reduced activity of the baroreceptors is probably involved in maintaining the failure itself [2]. Some studies have demonstrated a reduction in the function of the cardiopulmonary baroreceptors with ageing [3], others have shown that this function is maintained in elderly patients, but that there is a lack of integration between the high pressure and low pressure baroreceptor afferents [4]. These results are challenged by others [5], who suggest that there is a change in vascular compliance underlying the differences in the baroreceptor activity due to ageing. In ischaemic cardiac disease the reduction in sensitivity of the arterial receptors has also been related to the severity of the coronary disease [6].

We studied the functioning of the cardiopulmonary baroreceptors in patients with peripheral artery disease in relation to their effect on the haemodynamics of two large arteries, the humeral and the common carotid arteries. We also aimed to assess how a manoeuvre aimed at stimulating the cardiopulmonary receptors would modify the cutaneous microcirculation in the forearm. The stimulation of the baroreceptors was investigated with passive legs elevation and the trunk in a horizontal position. This method allowed us to increase the volume of blood in the cardiopulmonary compartment without modifying the total blood volume, and to minimize or avoid involvement of the arterial baroreceptors [7–9].

Patients and methods

Study population

We studied 15 patients with obliterative arterial disease of the lower limbs at Fontaine stage II (two females, 13 males, mean age 70 ± 5 years – group C), defined on the basis of pain free walking distance (measured during a treadmill test, 0% slope 4 km speed), Doppler velocimetry and digital arteriography of the lower limbs. Only two patients suffered from mild hypertension (treated with a single drug) and four suffered from diabetes which was controlled by diet. The patients underwent a cardiovascular study using ECG, echocardiography and colourDoppler ultrasound of the carotid arteries in order to exclude significant cardiovascular diseases (left ventricular hypertrophy, ischaemic heart disease, serious valve defects, carotid atherosclerosis). Patients with pulmonary pathology were also excluded. The two hypertensive patients underwent pharmacological wash-out for 3 weeks before the study.

We recruited a control group of 10 patients matched by age and sex (group B), free from arterial disease, hypertension or diabetes. Another control group, composed of 10 young patients (four males and six females, mean age 29 ± 4 years – group A) was recruited to show any changes in circulatory haemodynamics due to age rather than to arterial disease (Table 1).

All patients examined gave their informed consent before being included in the protocol.

Haemodynamic measurements

Haemodynamic measurements consisted of arterial blood pressure, heart rate, brachial and common carotid calibre, flow, resistance and wall tension, and cutaneous microcirculatory flow.

Arterial blood pressure (systolic and diastolic) and heart rate were measured at 2-min intervals with an oscillometric pressure monitor (Dinamap 845 XT; Critikon, Johnson and Johnson, Tampa, FL, USA) throughout the test. Mean arterial pressure was

Table 1 Study parameters

	Group A	Group B	Group C
Hypertension	No	No	2 (SAP > 160 mmHg)
Diabetes	No	No	4
BMI	23 ± 2	24 ± 2	24 ± 3
Cholesterol	155 ± 20 mg dL^{-1}	160 ± 30 mg dL^{-1}	165 ± 35 mg dL^{-1}
Triglycerides	102 ± 24 mg dL^{-1}	155 ± 23 mg dL^{-1}	157 ± 22 mg dL^{-1}
Smoking	No	No	No

young people – group A, elderly controls – group B, PAD patients – group C.

calculated as diastolic pressure plus one third pulse pressure.

The calibre and flow in the brachial and the right common carotid arteries were measured using a colourDoppler ultrasound with a 7.5-MHz high resolution probe (VingMed 750 CFM, Norway). The common carotid artery was measured 2 cm before the bifurcation, whilst the right brachial artery was measured at its middle third with the arm in slight abduction. The measurement of the vessel diameter was carried out using the 'frozen' image of the vessels, taking into account, as point of reference, the intima–lumen interface (4% variability). The pulsed Doppler showed the spectrum of frequencies and the machine software supplied the mean speed (expressed in cm s^{-1}) and the flow (expressed in ml min^{-1}). Measurements of vessel calibre and flow were carried out four times in 8 min during each test stage and mean values were taken into account. One operator assessed and recorded all the colourDoppler images, whilst a second operator carried out the measurements of the recorded images in blind.

The local resistance was calculated as the ratio between mean pressure and flow (expressed in mmHg mL^{-1} per s) [10].

Wall tension was calculated, following Laplace's law, by multiplying the vessel radius by the mean pressure.

Cutaneous microcirculation was studied continuously during the test using a laserDoppler flowmetry (Periflux PF 3; Perimed, Sweden). This device has a helio-neon laser which gives out light at a wavelength of 632.8 nm, transmitted by optic fibre to a probe. The probe was fixed to the volar face of the right forearm using an adhesive support. The values supplied by the machine were expressed in perfusion units (PU) and we considered the mean value for each period of the test.

Activation of cardiopulmonary baroreceptors

The stimulation of the baroreceptors was investigated by increasing the volume of blood in the cardiopulmonary compartment with passive legs elevation (60 degrees) whilst the trunk was kept in a horizontal position. This stimulus was maintained for 8 min. This method has been proved to activate cardiopulmonary baroreceptors without modifying the total blood volume, and to minimize or avoid involvement of the arterial baroreceptors [7–9].

Study protocol

The study was carried out during hospitalization in the case of patients with arterial disease and as outpatients for the control groups, at 09.00 hours in a comfortable environment and at a constant temperature (22 ± 1 °C). After a 10-min period of stabilization in supine position, haemodynamic measurements were performed for 8 min (basal values), then for 8 min during passive legs elevation (test values) and finally for 8 min after regaining the original supine position (recovery values).

The position taken up during the test did not cause the patients particular discomfort.

Statistical analysis

The data are expressed as mean ± SD and the statistical analysis was carried out using analysis of variance (ANOVA; SPSS, SPSS Italia srl, Italy) followed by posthoc *t*-test (values of $P < 0.05$ were considered to be significant).

Results

During the test arterial pressure and heart rate remained constant in the young control group, systolic pressure values showed a slight, but statistically significant increase in the elderly control group, whilst the increase in systolic pressure values at this stage was marked in the group with arterial

Table 2 Arterial pressure and heart rate (mean ± SD)

Group	Basal	Test	Recovery
heart rate	65 ± 11	65 ± 12	65 ± 12
SAP (mmHg)	110 ± 15	112 ± 13	110 ± 15
DAP (mmHg)	63 ± 5	64 ± 6	63 ± 5
heart rate	67 ± 5	68 ± 7	66 ± 5
SAP (mmHg)	135 ± 13	140 ± 12*	134 ± 15
DAP (mmHg)	75 ± 5	76 ± 5	74 ± 5
heart rate	63 ± 8	63 ± 8	63 ± 10
SAP (mmHg)	147 ± 16	157 ± 19**	148 ± 15
DAP (mmHg)	73 ± 4	74 ± 7	72 ± 6

Young people – group A; elderly controls – group B; PAD patients – group C. *$P < 0.05$, **$P < 0.005$.

disease. In all the groups diastolic pressure values and heart rate remained unvaried (Table 2).

The calibre of the humeral artery was significantly higher in the elderly patients (groups B and C vs. A; $P < 0.05$). It showed an increase in the control groups during the test (group A: 0.34 ± 0.02 vs. 0.33 ± 0.02 cm – group B: 0.41 ± 0.03 vs. 0.38 ± 0.01 cm; $P < 0.05$) with a return to initial values during recovery. In the group with arterial disease no variation in calibre was recorded (Fig. 1).

The measurements of resistance calculated for the cerebroafferent vessels were unchanged in the three groups. During the test the humeral resistance showed a statistically significant reduction in the two control groups, whilst there was a significant increase in the group with arterial disease, which remained slightly raised, though not to a statistically significant degree, during recovery (Fig. 2).

The tension applied to the wall as calculated for the carotid arteries was unchanged in the control groups, whilst it was significantly raised during the test in the group with arterial disease (37.6 ± 7 vs. 35.5 ± 6 mmHg $\times$ cm; $P < 0.005$; Fig. 3).

The laserDoppler perfusion monitor showed a fall in the perfusion units recorded in the young control group during the test (5.4 ± 1.5 vs. 7.22 ± 1.4 PU; $P < 0.005$) with recovery at the end. The elderly control group also showed a significant fall (5.7 ± 0.4 vs. 7.2 ± 1.4 PU; $P < 0.05$) with no significant recovery at the end. During this stage there was a reduction in the flow which nearly reached significance when compared to the basal level. The group with arterial disease displayed higher perfusion values than the controls ($P < 0.05$) at all stages of the study and there were no statistically significant variations during the test (8.9 ± 3.0 vs. 9.6 ± 3.0 PU; Fig. 4).

Discussion

In our study we adopted passive elevation of legs, keeping the trunk in a horizontal position; this test is considered, in the literature, a manoeuvre able to elicit the activation of the cardiopulmonary baroreflex without interfering significantly with the arterial high pressure baroreceptors [7, 8] and without causing discomfort. In studies in which the index of sensitivity of the baroreceptors has been directly assessed by pharmacological stimulation this stimulus is considered elective on the cardiopulmonary receptors when the arterial pressure and cardiac frequency values remain unchanged [7].

Cardiac frequency and diastolic pressure values in the control groups remained substantially stable during the test, confirming the lack of stimulus of the arterial receptors, whilst there was a statistically significant increase in systolic pressure values only in the group with arterial disease. In other studies a similar increase has been found in hypertensive patients in the presence of left ventricular hypertrophy and this has been attributed to reduced arterial compliance [8].

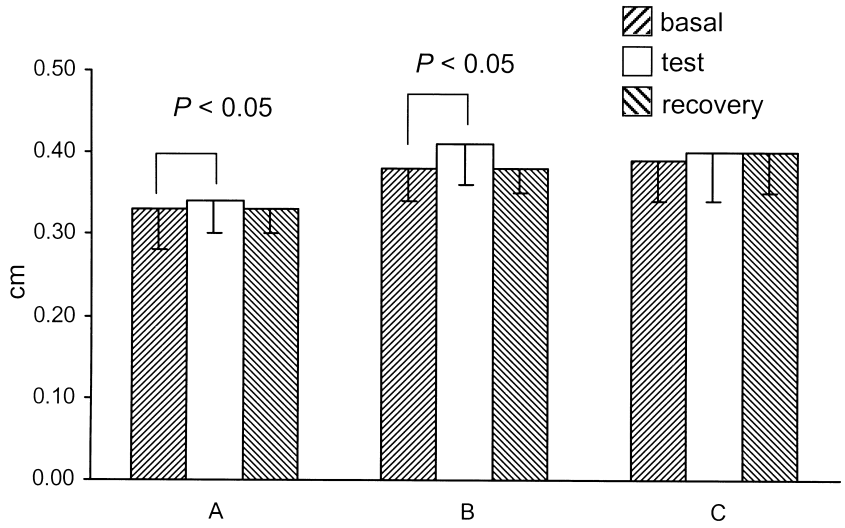

Fig. 1 Changes (mean ± SD) in humeral diameter in the three groups before, during and after the test (young people – group A, elderly controls – group B, PAD patients – group C).

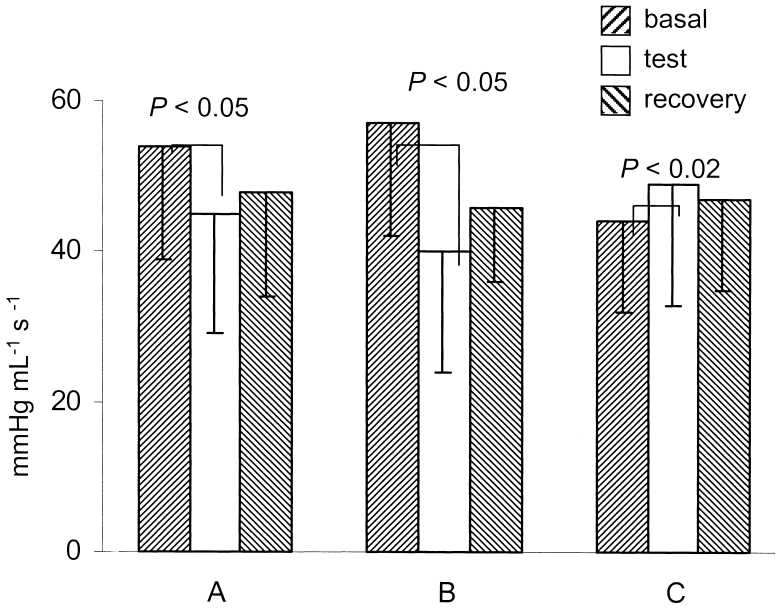

Fig. 2 Changes (mean ± SD) in humeral resistances in the three groups before, during and after the test (young people – group A, elderly controls – group B, PAD patients – group C).

In patients with arterial disease it seems that the role of angiosclerosis of the humeral artery is of significance in the increase in systolic pressure. This finding is associated with a substantial lack of variation of arterial calibre, due mainly to a significant reduction in arterial compliance and probably to reduced endothelial function which mediates the flow-dependent arterial dilation [11]. In the two control groups the humeral calibre increases during passive elevation of the lower limbs test in relation to the increase in the flow [12] and to the modulation of the output of the cardiopulmonary baroreceptors [9] which presumably induce dilation by reducing the sympathetic tone.

Systolic pressure values at rest in the group of patients with obliterative arterial disease are slightly elevated; this is due to the presence of two patients with isolated systolic hypertension and a patient with only borderline values. The other patients of the group show systolic values within the normal range. Thus the prevalence of isolated systolic hypertension in this group is comparable to that of

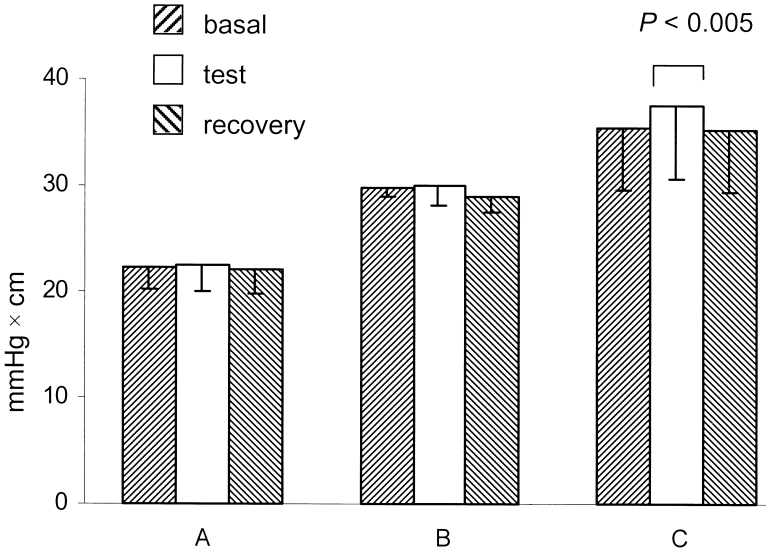

Fig. 3 Changes (mean ± SD) in carotid artery wall tension in the three groups before, during and after the test (young people – group A, elderly controls – group B, PAD patients – group C).

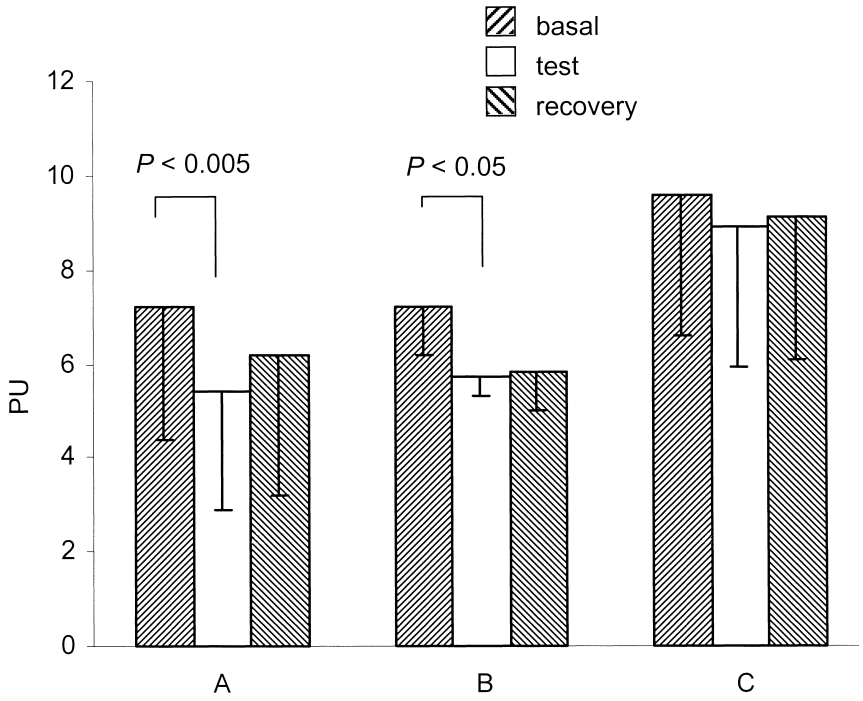

Fig. 4 Changes (mean ± SD) in perfusion unit recorded by mean of laserDoppler flowmetry in the three groups before, during and after the test (young people – group A, elderly controls – group B, PAD patients – group C).

the general age-matched population. Since the profile of parameters measured and calculated in patients with isolated systolic hypertension was similar to that of other patients of the group, we have considered that this clinical condition does not relevantly affect their test response.

The stimulation of the cardiopulmonary baroreceptors with the test produces, as expected, a significant fall in peripheral resistance in the arms in the two control groups because of activation of the inhibitory reflex on the vasoconstrictor tone. However, this does not take place in the group with arterial disease, where the calculated peripheral resistance increases with the increase in systolic arterial pressure.

The increase in humeral peripheral resistance and systolic pressure values in patients with arterial disease is probably due both to reduced compliance of the humeral artery, and to a lack of vasodilatation in the face of an increase in cardiac output due to augmented intrathoracic blood volume.

Several studies of hypertensive patients have suggested that there is an impairment of the tone regulation of small calibre veins in response to an increased venous return. The veins are presumably unable to significantly reduce their tone [13] and the absence of a buffering function in the veins would therefore produce an increase in cardiac output [7]. This condition of reduced venous compliance has also been demonstrated in patients with a family history of hypertension [14], which appears in this case as a relatively early condition of impaired vessel regulation. By analogy, we find it plausible to suggest that in patients with arterial disease there is a modification of the reactivity of the cardiopulmonary baroreceptors, with a reduction in their sensitivity consequent to or concomitant with a loss of the viscoelastic properties of the venous vessel in the cardiopulmonary compartment. This hypothesis is worth evaluating with studies of the venous tone and distension in this district.

A hypothesis suggesting the resetting of the arterial baroreceptors in relation to variations in the viscoelastic properties of the vessel wall has been suggested in the literature [15]. Some experimental data are also given in studies of the physical properties of the vein in relation to baroreceptor resetting [16]. Some studies on hypertensive patients with left ventricular hypertrophy have shown a reduction in the activity of the cardiopulmonary baroreceptors and a relative restoration of this after regression of the hypertrophy [8]. Although there was no evidence of left ventricular hypertrophy or serious ischaemic heart disease in our patients, it is

likely that an initial condition of reduced myocardial compliance could contribute to a reduction in baroreceptor activity through a mechanism similar to that found in hypertensives.

There are contrasting results concerning the role of low pressure receptors in the control of cutaneous flow. Some studies have shown that this is little influenced by the activation of cardiopulmonary receptors [17, 18], whilst others attribute an important role to the stimulation of this system in determining active cutaneous vasodilatation [19].

Several studies have documented the presence of an increase in cutaneous precapillary resistance following vein distension produced by a downward sloping position of the limb (venoarteriolar reflex). This mechanism, which is mediated by an axonal reflex, seems to protect the microcirculation from increases in capillary pressure. The consequent reduction in capillary flow can be measured using laserDoppler flowmetry [20]. In some studies, but not in others [21], this reflex appears to be reduced with ageing [22] and is significantly reduced or almost eliminated in patients with arterial disease, in proportion to the severity of atherosclerosis [23]. The test adopted increases the distension of the vein tree in the arms by producing an intrathoracic compartmentalization of the blood volume. This manoeuvre thus stimulates the venoarteriolar reflex at the cutaneous level and brings about a reduction in the perfusion units.

Two conditions can therefore be recorded during the test which are theoretically capable of modulating the cutaneous flow. One is connected to the stimulation of cardiopulmonary receptors; the other is a local condition mediated by the axonal reflex. We consider that the reduction in dermal flow recorded in the control groups can be attributed mainly to local activation of the venoarteriolar reflex.

We hypothesize that the lack of response of the venoarteriolar reflex to the test in patients with arterial disease may be related to a modification of the venular capacity and reactivity rather than to a lack of vasoconstriction, since the vascular homeostasis in these patients is more prone to respond to vasoconstrictor stimulation. In patients with arterial disease, a reduced function of the venoarteriolar reflex, particularly in the lower limbs, has been described in the literature [23]. However, these patients did not show clinical signs of neuropathy.

We observed a higher number of perfusion units in patients with arterial disease during laserDoppler flowmetry, both in basal conditions and after stimulation, compared with the control groups. This find was unexpected and would seem to be due to a functional (or perhaps anatomical) alteration in microcirculation. This difference is difficult to interpret: one possible cause is the increased production of NO found in arterial disease which affects the microcirculation of the forearm [24]; another cause could be an increased activity of the artero-venous anastomosis which may accompany the increase in peripheral resistance at the cutaneous level.

In conclusion, with reference to the age differences, in the elderly control group there is a predictable increase in systolic pressure during the manoeuvre of stimulation which can be related to reduced arterial compliance. There is also a slower return of the cutaneous microcirculatory flow to base values after the test. This finding is probably due to a slower mechanism of restoration of the original vessel modulation.

With reference to patients with arterial disease, data from our study show a reduction in the activity of cardiopulmonary baroreceptors. These findings suggest the need for more detailed studies of the changes in the pulmonary venous bed and cardiopulmonary baroreceptors which take place in patients with arterial disease. In this perspective, these patients may turn out to have vascular disease in a wider sense, showing how arterial disease can be linked to serious morphofunctional changes in the venous compartment as well as in the baroreceptor structures connected to it. It would be particularly important to obtain data about the baroreceptor structures at histological and neurophysiological levels. Finally, the lack of activation of the venoarteriolar response in the cutaneous microcirculation of the arm in patients with arterial disease subjected to the passive legs raising test suggests that, even at this level, the physiological mechanisms of regulation of vasomotility are impaired. The delayed return to baseline of resistance in smaller arteries may well play a role in extending the recovery time of cutaneous flow. Moreover, our finding that the profiles of elderly healthy patients and patients with arterial disease are similar suggests that this mechanism can realistically be attributed to phenomena linked to ageing.

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