Effect of age and coronary heart disease on the circulatory responses to graded lower body negative pressure

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SUMMARY  Previous reports have demonstrated that haemodynamic responses to various autonomic stresses such as head-up tilt, Valsalva’s manoeuvre, face immersion, cold pressor, and static exercise are altered with increasing age and cardiac disease. In the present investigation, we compared the responses of 20 to 27 year old and 50 to 59 year old healthy men and 50 to 59 year old ambulatory coronary heart disease patients to graded lower body negative pressure (LBNP). Noninvasive methods including transthoracic impedance cardiography and venous occlusion plethysmography were used to monitor changes in stroke index, thoracic blood volume and vascular resistance. The tachycardia and stroke index decline of the older men and cardiac patients at higher levels of LBNP were similar but less than those of the younger men; we also noted greater increases in forearm and total peripheral resistance during LBNP in the two older groups than in the younger group. However, the decreases in thoracic blood volume were less in the two older groups at the higher levels of LBNP indicating that older subjects had been subjected to a lesser stress. These differences in thoracic blood volume displacement may be due to a decreased peripheral venous compliance in older subjects. When we compared responses to similar decreases in thoracic blood volume, the heart rate and stroke index changes were similar in the three groups but the exaggerated forearm vascular resistance during LBNP may be a function of the higher baseline resistance levels in these older subjects.

Autonomic responses to non-exercise as well as exercise stress important indices of functional cardiovascular capabilities and are increasingly used as guides in diagnosis and therapy of circulatory disease. For example, in experimental animals and patients in congestive heart failure, a decrease in central blood volume elicits exaggerated reflex sympathetic responses which provide an important cardiac support mechanism. Coronary heart disease patients not in failure also have altered autonomic function, eg, lesser heart rate responses to face immersion, diminished forearm vasoconstriction and heart rate responses to postural stress, and lessened heart rate changes during Valsalva’s manoeuvre compared to age-matched controls. The mechanism of these altered responses is not certain. Because of the potential for clinical use of autonomic responses in circulatory stress, it becomes important not only to delineate the mechanisms of these responses but also to define normal variations. Furthermore, recent evidence indicates that reactions to head-up tilt, lower body negative pressure and static exercise stress are significantly altered in older healthy individuals. Because the control subjects in prior clinical studies were not always age-matched, it seemed to us that some autonomic changes previously ascribed to cardiac disease may have been associated with the normal aging process.

Our objectives in the present study were: (1) to compare the haemodynamic responses of ambulatory

male coronary heart disease patients and age-matched male subjects to a graded gravitational stress; (2) to contrast the responses of these two groups with those of younger normal male subjects; and (3) to study the mechanisms involved in these responses.

We used lower body negative pressure (LBNP) because it is a convenient, controllable and comfortable technique for older as well as younger subjects. Furthermore, low levels of LBNP are thought to elicit reflexes mediated primarily by low-pressure cardiopulmonary baroreceptor systems which may play an important role in the deranged responses of the older men and cardiac patients.

Methods

Thirteen normal younger men 20 to 27 years of age, 13 normal older men, 50 to 59 years of age, and 10 male ambulatory coronary heart disease patients, 50 to 59 years of age were studied. Normal subjects had undergone a physical examination within the previous year and were free of hypertension, hyperglycaemia, hypercholesterolaemia, diabetes or any other serious systemic disease. Older normal subjects had in addition, a negative family history for death of a close relative from circulatory disease below 55 years of age, a normal chest X-ray within the past year and a recent normal exercise stress test. Coronary heart disease patients were outpatients at the Veterans Administration Medical Center, Wood, Wisconsin; they were free of valvular heart disease, hypertension or congestive failure and had coronary heart disease as evidence by history. ECG, angiographic and exercise stress test data. Six of the ten patients had a history of myocardial infarction. Of the six patients who were catheterised, three had one vessel disease, two had two vessel and one had three vessels disease. Four patients had left ventricular wall motion abnormalities; none had cardiac hypertrophy or had undergone cardiac surgery. None of the patients had abnormal diastolic pressure elevations during their exercise stress test.

Patient medication was reduced or stopped for a sufficient period prior to testing to insure noninterference with functional responses to the tests. The dosage of beta blocking drugs was gradually reduced beginning 9 days before the experiment so that for the 2 days preceding and on the day of testing, none were taken. None of the patients were receiving digitalis; one patient was receiving isosorbide dinitrate. Patients were permitted nitroglycerin as required but none had used this drug the evening before or the day of the testing. Before the experiment each patient or subject was interviewed, a 12 lead ECG was taken, and the purpose of the study and the techniques to be used were carefully explained in order to minimise apprehension. All subjects were informed of their prerogatives and signed appropriate consent forms; the studies were approved by the Institution’s Research Committee.

Throughout the experiment a continuous effort was made to maintain a relaxed, quiet atmosphere. Room temperature was maintained at 23° to 25°C. After a 6 min control period, LBNP of either −1.33 kPa, −3.33 kPa or −5.33 kPa (−10, −25 and −40 mmHg) was induced for 3 min and then released. All subjects and patients underwent all three stresses, but in separate ‘‘runs’’—which were done in random order and with a recovery period of 6 min after each ‘‘run’’. All three ‘‘runs’’ were performed on a single subject during the same experimental session.

Before undergoing LBNP, the subject lay supine with his lower body below the iliac crests enclosed in an airtight chamber. The chamber was connected to a noise-insulated, industrial vacuum cleaner and equipped with an adjustable air release valve to permit step changes in the pressure created within the chamber. A carefully fitted saddle support prevented footward movement of the body during LBNP. The level of subatmospheric pressure created within the chamber was visually monitored with a vacuum gauge, previously calibrated with a Statham P23BC transducer (Gould Instruments, Hato Rey, Puerto Rico).

Arterial blood pressure was determined indirectly using a semiautomated auscultatory method. A microphone to record Korotkoff sounds (Narco Biosystems, Houston, TX) was placed over the left brachial artery and a pneumatic cuff, connected to an automated inflating unit, was wrapped around the upper arm and centred over the microphone. From the recording, the first positive peak deflection indicated systolic pressure and a sharp reduction in waveform or its disappearance, the diastolic. A prior comparison of this automated graphic microphone method with the conventional auscultatory method showed good agreement between the two methods in determining blood pressure. Our automated method resulted in slightly higher systolic and lower diastolic pressures than those determined by ear; the mean differences (0.4±0.32 and 0.3±0.34 kPa) were not statistically significant.

Forearm blood flow was determined by venous occlusion plethysmography using a Whitney mercury-in-Silastic strain gauge adjusted for temperature variations. The gauge was positioned around the region of greatest circumference on the right forearm. The arm was elevated 20cm above the anterior chest wall to assure adequate venous drainage during recordings. A pneumatic cuff was placed around the arm proximal to the elbow and inflated intermittently every 20 s (ie, on 10 s, off 10 s) to 8 kPa. Before the measurement period, an infant’s cuff applied to the right wrist was inflated to suprasystolic pressures to
occlude the hand circulation. Baseline forearm volume was later determined by water displacement. Forearm blood flow was estimated from the maximum rate of increase in forearm girth during venous occlusion and was expressed per 100 cm³ of forearm volume. Forearm vascular resistance was calculated as the ratio of mean arterial blood pressure and forearm blood flow. Mean arterial blood pressure was estimated as the diastolic pressure plus one-third pulse pressure.

Heart rate was derived from lead II of the ECG. Stroke index and cardiac index were estimated with a Minnesota Impedance Cardiograph model 304A (Surcom, Inc, Minneapolis, MN). The cardiograph was connected to four aluminium mylar band electrodes taped circumferentially about the subject, two around the neck and two around the lower thorax. The cardiograph signal was transmitted through the outer two electrodes and transthoracic impedance changes were recorded between the inner two. During recording intervals subjects were instructed to stop breathing after a normal inspiration. Stroke volume was determined using the formula of Kubicek, ie:

\[ \text{stroke volume, cm}^3 = \rho \frac{L^2 \cdot T}{Z_0^2} \cdot \left( \frac{dz}{dt}_{\min} \right) \]

in which \( \rho \) = resistivity of blood at 100 kHz (assumed constant at 135 ohm-cm), \( L \) = distance between the inner electrodes (cm), \( Z_0 \) = basic impedance between inner electrodes (Ohm), \( T \) = ventricular ejection time (s), \( \frac{dz}{dt}_{\min} \) = magnitude of peak value of the impedance derivative (Ohm·s⁻¹). The values for \( T \), \( \frac{dz}{dt}_{\min} \) and heart rate were averaged for five consecutive cardiac cycles at intervals when the venous occluding forearm blood flow cuff was deflated and paper speed was increased from 2.5 to 50 mm·s⁻¹. A heart sound microphone aided in determining ejection time.

Previous studies in other laboratories as well as our own have indicated that in the absence of left to right shunts and valvular insufficiency, the impedance method provides reliable estimates of stroke volume. Because of the marked sensitivity of electrical resistance to liquid content, alterations in baseline transthoracic impedance (\( Z_0 \)) can also be used to assess relative changes in intrathoracic blood volume. Total peripheral resistance index was estimated as the ratio of mean arterial blood pressure and cardiac index. Transthoracic impedance, ECG and heart sounds were recorded continuously; these parameters as well as blood pressure and heart rate were noted: (1) every 2 min during the 6 min control period prior to stress application, and (2) every minute during the LBNP and recovery periods. All data were recorded on a Grass model 7 polygraph (Grass Instruments, Quincy, MA) and were digitised using a Hiplot (Houston Instruments, Houston, TX) and IBM keypunch. Data were stored on magnetic discs and analysed with routine statistical software on an IBM 360 computer.

The responses of the three groups to all stresses were assessed by analysis of variance. In this fashion, significantly different responses for each variable could be revealed amongst the groups. When significance was demonstrated, analysis of variance and Student’s \( t \) tests were applied to the responses of each of the measured variables at each stress level to detect differences between any two groups. Preliminary analyses indicated that for almost all variables a steady state was achieved by the first minute of stress. We applied statistical procedures to the steady state data recorded at the second minute of LBNP stress. We considered \( P \) values less than 0.05 to be significant.

Results

The weights, heights, resting forearm girths and forearm volumes were comparable in the three groups. Resting values of stroke index and cardiac index were lower (fig 1), and those of total peripheral resistance index higher (fig 2) in older men and coronary heart disease patients compared to young men. These age-dependent differences as well as the lack of consistent differences in resting heart rate and circulating blood volume as a function of age have been reported previously.

As shown in fig 2 and 3, systolic and diastolic pressure changes during LBNP were relatively minor, even at -5.33 kPa; however, at the higher LBNP stress, there was a greater fall in mean systolic pressure in the young men.

![FIG 1 Control values and circulatory changes (delta values) at -1.33 kPa (-10 mmHg) LBNP (Mean±SEM). *, ** different from remaining group (groups) at 0.05 or 0.01 levels.](image-url)
The total peripheral resistance index and forearm vascular resistance were increased in all groups at all stress levels (fig 2 and 3). At -1.33 kPa, the forearm vascular resistance increases in the absence of blood pressure changes suggested that active and significant forearm vasoconstriction had been induced by cardiopulmonary reflexes in all three groups—and to about an equal extent in all groups. At -5.33 kPa LBNP, forearm vascular resistance increased more in both older groups compared to the younger men; the total peripheral resistance index increases were also greater in the older subjects than in young men, particularly in the cardiac patients.

Stroke index and cardiac index fell progressively with increasing LBNP in all groups. At -5.33 kPa, the decreases in these two variables were more marked in young men than in the two older groups (fig 3). These circulatory changes are generally similar to those previously reported with LBNP10-12 21 27 28 though the influence of age and coronary disease on LBNP response has not (to our knowledge) been previously studied.

The increases in baseline transthoracic impedance (Z0) were similar in the three groups at -1.33 kPa LBNP, but significantly less in the older men and coronary heart disease patients at -5.33 kPa LBNP (fig 4); this indicates a lesser caudal displacement of blood in the latter two groups and implied that a lesser stress had been imposed. In order to equalise the stresses, the cardiovascular responses of the young men at -3.33 kPa were compared with those of the two older groups at -5.33 kPa; at these points the changes in Z0 values were about similar (fig 4 and 5).

As shown in fig 5, when compared on the basis of equivalent increases in impedance (Z0) (i.e., compara-
ble decreases in thoracic blood volume), there were no significant differences in mean heart rate, stroke index or cardiac index responses among these groups. However, the greater increases in total peripheral resistance index at -1.33 kPa LBNP (fig 2) and in the total peripheral resistance index and forearm vascular resistance at -5.33 kPa LBNP (fig 5) in the two older groups persisted undiminished even when the stresses were compared at similar levels of thoracic blood volume decreases.

In fig 6, we plotted the mean control total peripheral resistance index values prior to initiation of LBNP against the corresponding mean change in total peripheral resistance index for each group and each stress level. The graph illustrates that starting from higher control total peripheral resistance index levels, the older men and coronary heart disease patients had exaggerated increases in the total peripheral resistance index during LBNP.

Discussion

Transthoracic electrical impedance, when carefully applied, can be used to monitor changes in both intravascular and extravascular thoracic fluid volume in man.20-23 The lesser increased in transthoracic impedance in the present study strongly suggest a lesser caudal sequestration of thoracic blood volume in older subjects and coronary patients during higher levels of LBNP.

The lesser thoracic blood volume displacement in older subjects during intense LBNP may be associated with a decreased capacitance of the peripheral vascular bed; the latter may, in turn, be due to a heightened venuconstrictor tone or an alteration in vascular wall structure.26 Such an alteration in venous capacitance could be an important factor in the circulatory response, not only to LBNP, but also the assumption of the upright position or to Valsalva’s manoeuvre, since all of these stresses involve displacement of central blood volume to the periphery. None of our subjects had visually detectable varicose veins.

A report by Montgomery et al.27 indicates that LBNP produced less peripheral dislocation of central blood volume in women than men; thus, sex as well as age may be a significant factor in blood volume displacement in certain types of preload stresses. These results underline previous admonitions that when examining autonomic responses of cardiac patients to circulatory stresses, serious consideration must be given to normal variations due to age and sex.

The noninvasive methods used in the present study indicated that there were lower resting values of stroke index and cardiac index and higher resting values of total peripheral resistance index in older men and cardiac patients compared to younger men. These baseline cardiovascular changes have been demonstrated in previous studies.24-26 It is noteworthy that the resting forearm vascular resistances were similar in the three groups (fig 2) suggesting that the higher resting total peripheral resistance index in the older men and still higher levels in the cardiac patients may be associated with increased vascular resistance levels in tissues other than forearm skeletal muscle and skin. The kidney may contribute to this higher resting peripheral resistance since it has been reported that with advancing age there is an exaggerated decrease in renal blood flow and an increase in renal vascular resistance which is disproportionate to that of other beds.29

The LBNP responses of cardiac patients were very similar to those of older men; the results suggest that compared to younger men, the difference in response of ambulatory cardiac patients to LBNP are primarily ascribable to age.

As previously noted by other investigators, the increases in forearm vascular resistance at -1.33 kPa LBNP in the absence of any change in arterial blood pressure suggest an involvement of the low pressure cardiopulmonary receptors independent of the high pressure arterial baroreceptors.11,12,26 Furthermore, in dogs nonhypotensive haemorrhage activates cardiopulmonary baroreflexes without altering carotid sinusafferent nerve activity.31 In our study, beginning from similar control levels, the forearm vascular resistance increases in the three groups at -1.33 kPa were similar. Since at this stress level, the thoracic blood volume displacements were equivalent, it would appear that the reflex vasoconstrictor effects in forearm vascular beds due to decreased activity of cardiopulmonary baroreceptors were about equal in the three groups.

At the higher levels of LBNP, forearm vascular resistance increases were substantially greater in the older groups than in the young men. About 60% of the
maximum forearm vascular resistance attained at 
-5.33 kPa of LBNP was achieved at -1.33 kPa LBNP
in the younger men; this ability of low-pressure
cardiopulmonary baroreceptors to invoke a near max-
umum constriction of the forearm vascular bed has
already been noted. In contrast to this, the mean
forearm vascular resistance values in older men
and coronary heart disease patients increased at a distinctly
greater rate than did the values in young men at higher
levels of LBNP. For example, starting from similar
baseline resistance levels, forearm vascular resistance
increased 116% over control in older men and 155%
over control in coronary heart disease patients but only
53% over control in young men at equivalent displace-
ments of thoracic blood volume. It is possible that an
error in calculating forearm vascular resistance may
have occurred if older subjects had unequal arterial
perfusion of the arms since blood pressure was
recorded from the left arm and forearm blood flow was
determined in the right arm.

The differences in the calculated total peripheral
resistance index responses among the three groups at
all levels of LBNP were notable. Compared with
young men, there was in the older groups a consistent
trend toward greater increases in total peripheral
resistance index at both low and high levels of LBNP.
Interestingly, at -1.33 kPa, when forearm vascular
resistance changes were similar between the groups,
the total peripheral resistance index increases were
greater in the older groups. Thus, it would appear that
other tissue resistances must have increased more in
the older subjects than in the younger men. The
splanchnic region may be involved in this exaggerated
response since at low levels of LBNP there is, in
addition to the forearm, an apparent vasoconstriction
in the splanchnic region. We

What is the mechanism for this disproportionate
response in the older groups during LBNP? With increasing age there is a gradual increase in
resting muscle sympathetic activity in man. We
therefore considered the possibility that the exagger-
ated resistance responses of the older groups may have
been due to a greater resting neural tone of the
peripheral vasculature in these groups. Myers and
Honig demonstrated that gradual increases in base-
line neurogenic tone diminishes the delta resistance
response to repeated identical vasoconstrictor stimuli,
that is, a negative relationship. However, our data revealed
a positive relationship in that higher resting total
peripheral resistance in the older groups was associ-
ated with an exaggerated delta resistance response (fig
6); thus an age-related change in baseline neural
vascular tone does not account for our findings.

It is more likely that a change in the morphology of
the peripheral vessels in the older groups may best
explain our data. Folkow et al. have suggested that
increased arterial wall thickness (such as occurs with
age) predisposes precapillary vessels to a greater
resistance response; in this situation, an increased
wall thickness to lumen ratio may magnify luminal
narrowing because of the Poiseuille (radius to the
fourth power) relationship.

Aside from an anatomical predisposition, a height-
ened resistance response in the older men and coronary
heart disease patients might also be associated with
other neural or circulatory changes. There is, for
example, an increased plasma catecholamine con-
centration in older subjects both at rest and in response
to static exercise and postural stress. Thus, it is
possible that heightened resistance responses in the
older groups may result from an increased responsiv-
ess of vascular smooth muscle to baseline or stress
levels of neural and humoral stimuli.

As mentioned above, previous studies on older
subjects and cardiac patients have revealed altered
cardiovascular responses to head-up tilt, LBNP, Val-
salva's manoeuvre and face immersion; these
changes have usually been ascribed to a diminished
sensitivity of arterial baroreflexes or lesser cardiac
responses to catecholamines. However, in the present
study, the heart rate, stroke index and cardiac index
responses of our older subjects and coronary patients
during equivalent decreases in thoracic blood volume
were quite similar to those of the younger subjects.
Thus, the degree of thoracic blood volume displace-
ment in the older subjects may have significantly
influenced the cardiac response to LBNP. The nature
of our study did not permit us to reach any conclusion
regarding the possible effect of age and coronary
disease on cardiac contractility.

In summary, our data suggest: (1) the previously
described deranged cardiovascular responses of
coronary heart disease patients to decreases in cardiac
preload may be due primarily to normal aging; (2) the
decreased haemodynamic response to postural stress
previously reported in older subjects and cardiac
patients is due—at least in part—to a lesser peripheral
sequestration of blood in the older individuals; and (3)
the greater increases in total peripheral resistance
index in older individuals during LBNP may be a
function of their higher resting levels of peripheral
vascular resistance compared with younger men.

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Circulatory effects

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