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Assessment of capillary fluid shifts during orthostatic stress in normal subjects and subjects with orthostatic intolerance

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Orthostatic stress causes, in addition to venous pooling, a loss of plasma fluid from capillaries to the dependent tissues. The rate of this loss may be one of the factors determining orthostatic tolerance. In this study we assessed the use of a multichannel impedance plethysmograph for determining changes in volume in the calf, thigh, and abdominal segments, in asymptomatic volunteers and in patients shown to have poor tolerance to orthostatic stress. Impedance plethysmography showed, for leg segments, that following head-up tilt there was an initial rapid change in volume followed after 2 to 4 minutes by an almost linear change. Results from the abdominal segment were more variable. The rate of change of leg (thigh + calf) volume was significantly correlated with the estimated loss of plasma volume derived from the changes in the concentration of plasma protein, using Evans Blue dye as the marker. Comparison of results of leg filtration rates between patients and volunteers indicated that some of the patients had abnormally high filtration rates and suggests that impedance plethysmography may have a role in assessing the possible reasons for orthostatic intolerance.

Keywords: plasma volume, orthostasis, impedance plethysmography.

Orthostatic stress results in distension with blood of dependent vessels and consequent decreases in venous return and cardiac output [1]. If the stress is sufficiently severe or prolonged, or if the subject has a poor orthostatic tolerance, then blood pressure can no longer be maintained at adequate levels and syncope occurs [2]. One of the major factors in determining an individual's orthostatic tolerance has been shown to be magnitude of blood volume [3]. This is presumably because, with a larger blood volume, more is available for filling the dependent capacitance vessels. It has also been shown that orthostatic tolerance improves if blood volume can be increased, for example by salt loading [4,5] or by exercise training [6].

Another stress encountered during orthostasis is loss of plasma volume by transudation to the tissues due to the increased capillary pressures. There have been several attempts to assess the changes in plasma volume during orthostasis by measurements of changes in concentration of blood constituents, such as haemoglobin or plasma protein, which do not leave the capillaries [8–10]. However, use of these markers is complicated by the fact that the circulation is effectively partitioned so that, although fluid is lost from dependent capillaries, this does not immediately affect the blood in the upper part of the body. It is necessary, therefore, to return subjects to supine and to allow blood to mix before estimates of changes in plasma volume can reliably be obtained [11,12]. Another problem with the invasive methods for determining plasma volume shifts is that the use of intravascular needles or catheters, which are needed to obtain blood samples, may in some people greatly reduce their tolerance to orthostatic stress [13,14]. The ideal method for assessing the loss of plasma volume would be noninvasive and would allow continuous assessment of the changes during the course of an orthostatic stress test. One simple approach is impedance plethysmography. This determines changes in volume in various segments of the body from the changes in electrical impedance when a small current is passed from wrist to ankle [15]. Changes in impedance occurring immediately after orthostasis would reflect mainly the changes in intravascular volume, but the secondary near-linear phase would be likely to be due mainly to capillary filtration [16].

In this study we evaluated the use of impedance plethysmography to determine the early loss of plasma volume following head-up tilting by comparing the results with values estimated from changes in the concentration of plasma protein using Evans blue dye as the marker. We also compared results obtained from healthy volunteers with those from patients who were shown to have reduced tolerance to orthostatic stress. The aim of this was to determine whether impedance plethysmography was likely to be of value in assessing whether excessive fluid loss could be a contributing factor in causing orthostatic intolerance in some patients.

Materials and methods

Subjects

Studies were carried out on 12 healthy volunteers, aged 20 to 67, weight 65.5 ±2.9 kg, and 14 patients with orthostatic intolerance, aged 24 to 62, weight 72.2 ±5.0 kg. None of the subjects was taking any prescribed medication or was

suffering from known cardiovascular disease. These studies were approved by the Research Ethics Committee of the United Leeds Teaching Hospitals.

Procedure

The investigation comprised two studies. In one, impedance plethysmography was used to determine the segmental volume changes to head-up tilting. The orthostatic stress test was then continued to determine the subject's orthostatic tolerance. The other study comprised the determination of plasma volume by Evans blue dye dilution and the effects of head-up tilt. The two studies were separated by an interval of at least 4 hours.

Orthostatic stress test

This has previously been described in detail [17,18]. Briefly, the subjects had ECG electrodes attached and an automatic sphygmomanometer (Hewlett Packard 78352C, Boeblingen, Germany) fitted to one arm and a plethysmographic device (Finapres, Ohmeda, WI) attached to a finger of the other arm, which was maintained at heart level throughout the test. The test comprised 20 minutes supine, then 20 minutes head-up tilt at 60°, then while still tilted suction was applied to the body below the level of the iliac crests at −20 and −40 mmHg for 10 minutes at each or until onset of presyncope. This was defined as systolic pressure falling below 80 mmHg and accompanied by symptoms of presyncope. Orthostatic tolerance was expressed as the time from the start of head-up tilt to when presyncope occurred.

Plasma volume estimates

This was determined by Evans blue dye dilution as previously described [19]. Briefly, the subject rested supine for 30 minutes before insertion of a catheter (20G Venflon, Viggo-Spectramed, Helsingborg) into an arm vein. A precisely measured quantity of Evans blue dye (New World Trading Corp, Debary, Florida) was injected and very thoroughly washed in. Plasma volume was estimated from the series of blood samples taken at 5-minute intervals from 10 to 25 minutes after injection. The concentrations were compared with known dye concentrations made up in the subject's plasma, the data plotted, and the line drawn back to the injection time (Fig. 1).

Immediately after the fourth sample had been taken, the subject was tilted head-up by 60° for 5 minutes and was then put head-down by 10° for 4 minutes with samples of blood taken at 1-minute intervals. The change in plasma volume was estimated from the average of the concentrations of dye in the blood taken 3 and 4 minutes after head-down tilt and compared with the expected values obtained by extrapolation of the line obtained using the supine values (Fig. 1).

Impedance plethysmography

With the subject lying on the tilt-table, disposable ECG recording electrodes were placed at the lateral malleolus, lateral aspect of the knee at mid-patellar level, hip (trochanteric prominence), and on the lateral aspect of the 12th rib, to define calf, thigh, and abdominal segments. Active plate electrodes were placed on the wrist and on the dorsal surface of the foot and connected to a tetrapolar impedance plethysmograph (THRIM, UFI, Morro Bay, CA, USA) that supplied a 1mA 50 Hz alternating current. The recording electrodes were connected to the three input channels of the plethysmograph, which continuously measured the two components of impedance (resistance and reactance) of each segment to the applied current. These signals were fed into a computer and analyzed using Labview software. The THRIM was calibrated regularly by means of a simulator that provided known impedances.

Each segment was assumed to have a conical geometry. Their lengths were measured and circumferences recorded at 3-centimeter intervals so that the initial baseline volume could be calculated incrementally using a computer program.

Subjects initially rested supine on the tilt table for 20 minutes, and baseline impedance recordings were made from the three segments. Recordings were continued throughout a 10-minute period of head-up tilting (60°). The volume changes in each segment were calculated from the changes in electrical impedance, using equations that have been described previously [20].

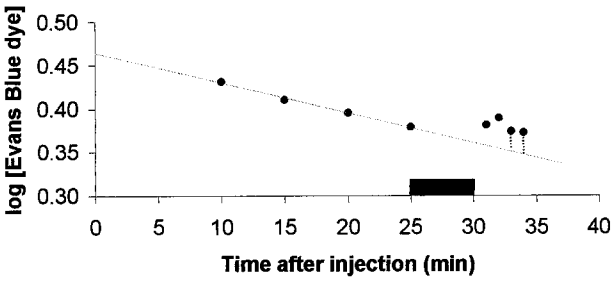

Figure 1. Example of an Evans Blue decay curve. The subject was supine until minute 25, then was tilted head-up by 60° for 5 min. At minute 30, the subject was tilted head-down by 10°. Note the uniform decay in the dye concentration until tilted. During the head-down period there was an increase in dye concentration above the extrapolated value, which stabilized between minute 33 and 34.

Results

Orthostatic tolerance, expressed as time from the start of head-up tilt, was 29.7 ± 2.5 (SE) minutes in the volunteers and significantly less ($p < 0.03$) at 22.0 ± 1.8 minutes in patients.

Assessment of fluid shifts by impedance plethysmography and Evans blue dye correlation

Immediately following head-up tilt there were rapid changes in impedance in all segments studied. Changes were greatest in the first minute and after 2 to 4 minutes the relationship between impedance (volume) and time became linear. An

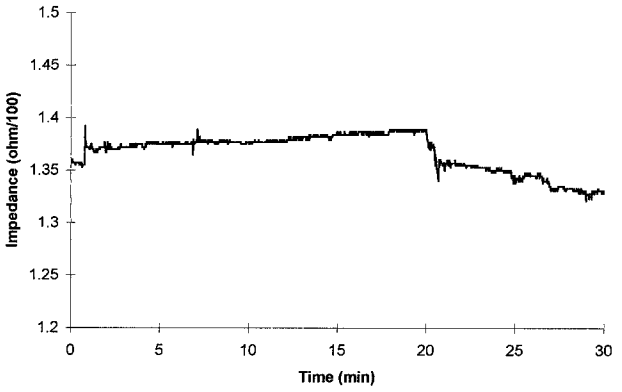

Figure 2. Original trace showing the calf segment impedance changes during a tilt test. Time 0 to 20 minutes is supine rest, 20 to 40 minutes is head-up tilt.

example from one subject is shown in Figure 2. The average changes in all three segments from all subjects are shown in Figure 3. We found the changes in the abdominal segment to be much less stable than in the other two segments and it was considerably influenced by respiration. We therefore assessed the volume changes in the leg only and compared the steady-state change estimated at 4 to 6 minutes after tilt with the calculated loss of plasma fluid during 5 minutes of tilt. These data are compared in Figure 4. There was a highly significant correlation between the estimates of increase in leg volume and total loss of plasma volume in the patients and volunteers.

Comparison of changes in leg volumes in patients and volunteers

Estimates of changes in volumes of both segments were made between 4 to 6 minutes and 4 to 10 minutes after head-up tilt. The values for both segments and both periods of assessment were greater for the patients than for the controls (Table 1). The total changes in the leg volumes in the two groups of subjects for 10 minutes of head-up tilt are shown in Figure 5. There was little difference in the initial volume change, but the slope of the steady-state change was greater in the patients.

Although comparison of the group responses showed differences, there was considerable individual variation and overlap between results of patients and volunteers (Fig. 4). However, the volunteers all had a rate of change of volume of 26 ml/min or less. Seven of the patients gave results within this range and seven gave larger values. There was, however, no significant correlation between the rate of volume change and the time to presyncope.

Discussion

The principal aim of this study was to determine whether impedance plethysmography, applied to calf, thigh, and abdominal segments, was likely to be of value in assessing the early loss of plasma volume during orthostasis. The likely usefulness of the method was examined in two ways: first,

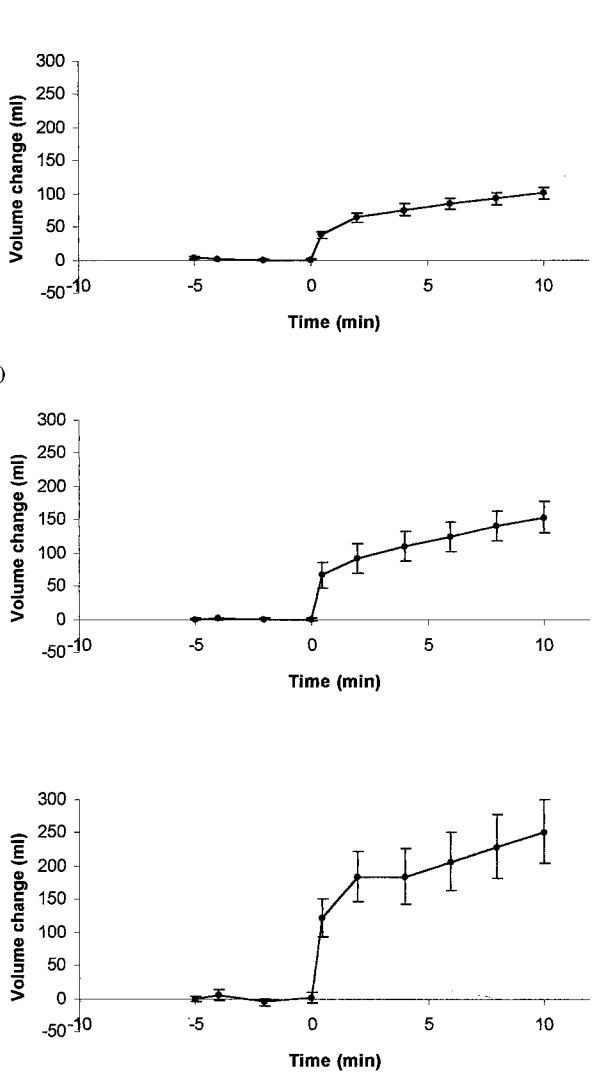

Figure 3. Volume changes during head-up tilting in **(A)** calf, **(B)** thigh, and **(C)** abdomen segments for all subjects.

by comparing it with a different method that was dependent on measuring changes in plasma protein concentration and, secondly, by seeing whether it could detect differences between results from healthy volunteers and those from patients known to have poor orthostatic tolerance. The impedance plethysmography method did provide stable results from the high and calf segments that correlated with the plasma protein method. However, results from the abdominal segments were more variable and are probably not very useful. The unreliability of these results is probably related to changes in the geometry of the abdomen when position is changed, and the movement artefacts due to respiration.

Although there was a good correlation between results obtained by the two methods there was considerable scatter, and impedance plethysmography applied to the leg provided smaller estimates of fluid shifts than those provided by the Evans blue technique. Both methods rely on a number of unproven assumptions and it is not possible to consider either of them to be more accurate than the other. Use of the Evans blue method provides reliable estimates of plasma

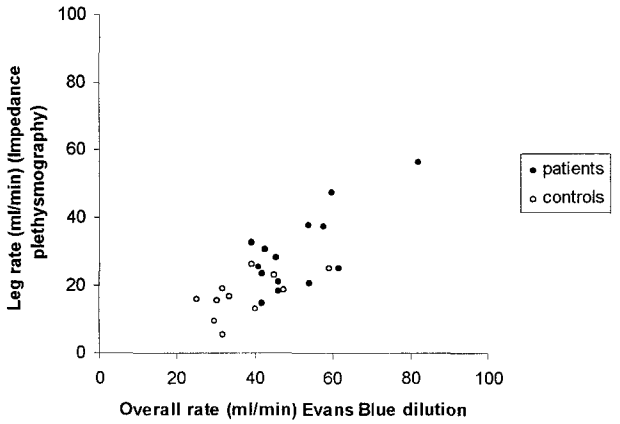

Figure 4. Relationship between overall rate of volume change calculated by Evans Blue concentration and the rate of volume increase in two legs calculated by impedance plethysmography using values of rate of change of volume between 4 and 6 minutes. There was a highly significant correlation between the two estimates ($r = 0.79$, $p < 0.001$).

volume [19] but in assessing changes in plasma volume it is necessary to assume that the rate of removal of the dye from the blood is unaffected by the procedure so that changes in concentration from the expected values are due only to fluid shifts. It is possible that if splanchnic perfusion alters with a change in body position, the rate of removal of dye may change. Another assumption is that the "plateau" values of dye concentration 3 to 4 minutes after the end of the tilt represents a true mixed value of blood from both upper and lower parts of the body. The values at 1 and 2 minutes tend to be higher (Fig. 1), suggesting that at that time the blood sampled is disproportionately influenced by blood returning from the dependent regions. The method also assumes that for 4 minutes after the end of the period of orthostatic stress only a small proportion of filtered fluid would have been reabsorbed. This is probably reasonable, as the pressure gradients for reabsorption would be much smaller than those for filtration during orthostasis.

There are also potential errors with impedance plethysmography. One assumption is that there is a clear demarcation between the initial volume change, assumed to be due to distension of capacitance vessels, and the delayed effect, assumed to be due to capillary filtration. It has been suggested that during orthostasis, the most rapid rate of filtration occurs in the first few minutes [9]. By ignoring this initial phase and assuming that the volume change is solely due

Table 1. Rates of overall leg volume increase, as measured between minutes 4 to 6 and 4 to 10 of head-up tilting. Note the significantly higher rates in the patients.

	Controls ($n = 12$)	Patients ($n = 14$)	p
Rate of volume change, 4–6 minutes (ml/min)	8.48 ± 0.81	15.06 ± 1.55	<0.01
Rate of volume change, 4–10 minutes (ml/min)	8.41 ± 1.02	14.22 ± 1.43	<0.01

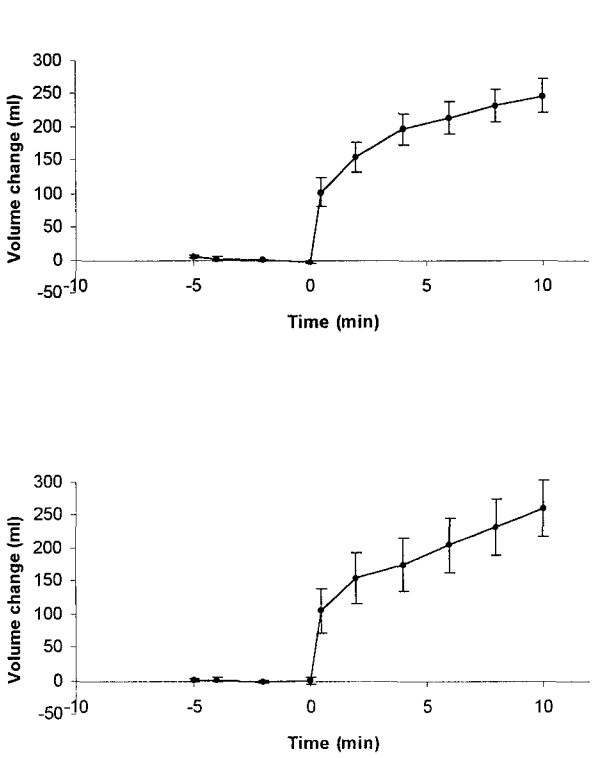

Figure 5. Mean leg volume changes during 10 minutes of head-up tilting in **(A)** controls and **(B)** patients with poor orthostatic tolerance. Note that the initial volume changes were similar but that after about 4 minutes the rate of change was greater in the patients. The standard error bars indicate greater variability in the patients.

to intravascular changes the net filtration rate may have been underestimated and this may at least partly explain the difference between values by impedance plethysmography and dye concentration. Nevertheless the rates of change of volumes in both leg segments after 4 minutes of head-up tilt were remarkably constant.

Another explanation for the lower net values of fluid loss estimated by impedance plethysmography is that the values excluded changes in the feet and abdomen. Since the feet are subjected to the greatest hydrostatic pressures during orthostasis [21], their exclusion is likely to have a significant effect on the estimate of the overall volume change. The method was not satisfactory for making accurate estimates of abdominal volume changes and, as seen in Figure 3, abdominal volume did change, so that neglecting this would underestimate the total rate of plasma loss. Despite the limitations of plethysmography for assessment of fluid changes, this method is likely to be of value in the examination of reasons for poor orthostatic tolerance. There was overall a significant difference in the estimated filtration rates between patients and volunteers, although there was no significant correlation between the filtration rate and time to presyncope. However, we consider that the finding of a difference between the groups is not the most useful way of considering these data. There was clearly an overlap between the groups but, while results of some of the patients were similar to those of the controls, results from others were clearly different. Of the 14 patients studied, seven had

filtration rates that lay outside the range of values obtained from the controls. This suggests that in these patients an abnormally high filtration rate could make a significant contribution to their orthostatic intolerance, whereas in others it was relatively unimportant.

Other studies have also shown that measurements of fluid shifts may be of value in studies of orthostatic tolerance. For example, it has been demonstrated that capillary filtration can be influenced by postural deconditioning [22] or endurance training [23]. The findings in the present study of differences in estimates between some of the patients and the volunteers indicates at least that the method is worth further evaluation in patients and could be of use in the assessment of the mechanism of action of various therapeutic interventions, for example salt loading, exercise training, or vasoactive drugs.

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