Increased arterial stiffening and thickening in the paretic lower limb in patients with hemiparesis

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ABSTRACT

Atherosclerosis has two key components, thickening and stiffening of arterial wall. These parameters are quantified ultrasonographically by IMT (intima-media thickness) and PWV (pulse wave velocity). In the present study, we determined the FA IMT (IMT of the bilateral femoral artery) and PWV of femoral–ankle (PWV fa) and brachial–ankle (PWV ba) segments in order to examine whether the degree of atherosclerosis is different between paretic and non-paretic lower limbs in 24 patients with hemiparesis. The values of PWV fa, PWV ba and FA IMT were all significantly greater on the paretic than the non-paretic side. Furthermore, significant decreases in masses of muscle, bone and fat, determined by dual-energy X-ray absorptiometry, were observed in paretic lower limbs compared with the non-paretic side. PWV fa correlated significantly and negatively with muscle mass (r = -0.488, P = 0.0004) and tended to correlate negatively with BMC (bone mineral content; r = -0.264, P = 0.069) when statistical analyses were performed with the paretic and non-paretic sides together. Multiple regression analysis elucidated that the muscle mass was associated significantly with PWV fa and PWV ba, independent of age, duration after cerebrovascular accident, gender, bone and fat mass and FA IMT. The muscle mass was still associated with increased PWV fa and PWV ba when multivariate analysis was conducted independently in the paretic and non-paretic sides. In summary, our results indicated that arterial thickening and stiffening were greater on the paretic than the non-paretic side and suggested that a decrease of muscle mass might be associated with increased arterial stiffening in the paretic lower limb.

INTRODUCTION

It has been well documented that wasting of muscle and bone masses in the paretic limb is a prominent feature of hemiplegia and hemiparesis [1–4], because of long-standing disuse of the affected side [5–8]. Muscle wasting in the affected side causes greater vascular resistance, due to a decrease in venule density in skeletal muscle, leading to lower muscle flow rates [9]. Since it has been reported previously [10] that a decrease in muscle blood flow in the paretic side is associated with the development of insulin resistance and increased shear stress, it is possible that muscle wasting may cause the progression of local atherosclerosis in the paretic side by increasing vascular injury. Alternatively, it is known that bone loss is one of the major risk factors for the exacerbation of atherosclerosis and that the administration of a bone antiresorptive drug reverses...

The aim of the present study was to examine (i) whether or not arterial stiffening and thickening progresses preferentially in the paretic limb, and (ii) the correlation between alterations in arterial properties and muscle wasting or bone loss to elucidate the importance of these factors in an acceleration of arterial stiffening and thickening.

**METHODS**

**Subjects**

Twenty-four patients, 10 females and 14 males, were enrolled into the present study after written informed consent was obtained. The protocol was approved by the Ethics Committee of Hanwa Second Senboku Hospital. The patients were selected from in-patients at Hanwa Senboku Second Hospital, who had experienced an episode of CVA (cerebrovascular accident) at least 3 months before and were stable with regards to physical ability and daily activity. These patients were admitted to Hanwa Senboku Second Hospital for physical and occupational therapy. Hemiparesis affected the right side in 13 patients and the left side in 11 patients. The mean ± S.D. age was 68.9 ± 1.8 years, ranging from 57–86 years. The mean period after the episode of CVA was 6.21 ± 1.13 months (range, 4–24 months). Age distribution did not differ significantly between female and male patients.

**Measurements of BMC (bone mineral content), body fat mass and body muscle**

BMC, muscle mass and fat mass of both legs were measured by dual-energy X-ray absorptiometry using a Hologic QDR-1000 instrument (Hologic Inc., Waltham, MA, U.S.A.) [12]. The precision was performed by measurement of the calibration phantom, with a CV (coefficient of variation) of 0.54 % (n = 120). The CV of BMC from 10 volunteers measured twice within the same day was 0.65 %, as reported previously [13].

**PWV (pulse wave velocity)**

An automatic waveform analyser (model BP-203RPE; Colin Co, Komaki, Japan) was used to measure PWV simultaneously with blood pressure, ECG and heart sounds as described previously [14,15]. Briefly, subjects were examined in the supine position after 5 min of bed rest, with ECG electrodes placed on both wrists, a microphone for detecting hearts sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachium and ankles. The cuffs were connected to a plethymographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure. PWV was recorded using a semiconductor pressure sensor (the sample acquisition frequency for PWV was set at 1200 Hz). Volume waveforms for the brachial and ankle arteries were stored, and the sampling time was 10 s with automatic gain analysis and quality adjustment.

The time interval between the wavefront of the brachial waveform and that of the ankle waveform was defined as \( \Delta T_{ba} \) (the time interval between the brachial and ankle arteries). \( D_{ba} \) (distance between sampling points of the brachial–ankle arteries) was calculated automatically on the basis of the height of the subject. \( L_b \) (path length from the suprasternal notch to the brachium) was obtained from superficial measurements and was expressed using the following equation:

\[
L_b = 0.2195 \times \text{height of the patient (cm)} - 2.0734
\]

\( L_a \) (path length from the suprasternal notch to the ankle) was obtained from superficial measurements and was expressed using the following equation:

\[
L_a = 0.8129 \times \text{height of the patient (cm)} + 12.328
\]

Finally, the following equation was used to obtain the PWV \( ba \) (PWV of the brachial–ankle segment)

\[
PWV_{ba} = \frac{(L_a - L_b)}{\Delta T_{ba}}
\]

In the same way, the time interval between the wavefront of the femoral waveform and that of the ankle waveform was defined as \( \Delta T_{fa} \) (the time interval between the femoral and ankle arteries). The distance between sampling points of the PWV \( fa \) (PWV for the femoral–ankle segment) was calculated automatically according to the height of the subject. \( L_{fa} \) (path length from the femoral to the ankle arteries) was obtained from superficial measurements and was expressed using the following equation:

\[
L_{fa} = 0.2486 \times \text{height of the patient (cm)} + 30.709
\]

PWV \( fa \) was obtained by dividing \( L_{fa} \) by \( \Delta T_{fa} \).

Reproducibility of the PWV measurement was evaluated by repeating measurements in 17 healthy subjects on two different occasions. CVs were 1.9 % and 3.3 % for PWV \( ba \) and PWV \( fa \) respectively [15].

**Ultrasonographical measurements of FA IMT (femoral artery intima-media thickness)**

Ultrasonographical B-mode imaging of the femoral artery was performed with a high-resolution real-time ultrasonography with a 10 MHz in-line Sectas scanner (model SSD 650 CL; Aloka, Tokyo, Japan), as described previously [16,17]. To avoid inter-observer variabiliy, all IMT measurements were performed by the same examiner. Briefly, the femoral artery was scanned at the level of the bifurcation on both sides. IMT was measured in the far wall of the femoral artery at sites of the most
advanced arterial thickening as diffuse and continuous projection with the greatest distance between the lumen–intimal interface and the media–adventitial interface, but without an atherosclerotic plaque, which was defined as localized lesions of thickness more than 2.0 mm, from digitized still images of the arteries during scanning [17–19]. These interfaces were manually traced. Three still images from the same section of the artery were measured from which the mean IMT value was calculated. Reproducibility of FA IMT measurement was acceptable as shown by a CV of 3.4 %.

**Statistical analysis**

Data were analysed using the StatView 5.0 J program (Abacus Concepts, Inc., Berkeley, CA, U.S.A.). Values are means ± S.D. unless otherwise indicated. The differences in the means between paretic and non-paretic sides were analysed by Student’s t test. Correlation coefficients were calculated by simple regression analysis. Multiple regression analyses were performed to assess the association of various clinical factors with PWV fa and ba. P values < 0.05 were considered statistically significant.

**RESULTS**

**Comparison of arterial stiffening and thickening and various body components between paretic and non-paretic lower limbs**

The values of PWV fa, PWV ba and FA IMT were all significantly increased (by 9.0 ± 2.3, 10.5 ± 2.2 and 10.3 ± 3.0 % respectively) on the paretic side compared with the non-paretic side (Figure 1). Figure 2 shows the comparison of body components between the paretic and non-paretic lower limbs. Muscle mass, BMC and fat mass on the paretic side were all significantly decreased by 10.7 ± 2.4 %, 41.9 ± 3.5 % and 5.4 ± 1.8 % of the respective values on the non-paretic side.

**Correlations between muscle mass, BMC and fat mass in lower limbs**

Muscle mass in lower limbs correlated significantly and positively with BMC (r = 0.568, P < 0.0001) and fat mass (r = 0.41, P = 0.0161) in lower limbs when analysis was performed together with the paretic and non-paretic sides. However, BMC failed to correlate with fat mass (r = 0.025, P = 0.865).

**Correlations between markers of arterial stiffening and thickening and body components in lower limbs**

Table 1 shows that PWV ba correlated significantly and positively with PWV fa (r = 0.924, P < 0.0001), although
Figure 3  Correlation between PWV ba and muscle mass (a), bone mineral content (b) and fat mass (c) in patients with hemiparesis/hemiplegia

Table 2  Multiple regression analysis of factors independently associated with PWV ba and PWV fa in both the paretic plus non-paretic sides in hemiparetic patients
Values are standard regression coefficients. $R^2$, multiple coefficient of determination. *$P < 0.05$ and **$P < 0.01$.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>PWV fa</th>
<th>PWV ba</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.050</td>
<td>0.178</td>
</tr>
<tr>
<td>Duration after CVA</td>
<td>−0.126</td>
<td>−0.059</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>−0.627**</td>
<td>−0.670**</td>
</tr>
<tr>
<td>BMC</td>
<td>0.045</td>
<td>0.069</td>
</tr>
<tr>
<td>Fat mass</td>
<td>−0.025</td>
<td>0.067</td>
</tr>
<tr>
<td>FA IMT</td>
<td>−0.031</td>
<td>−0.078</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.259*</td>
<td>0.382*</td>
</tr>
</tbody>
</table>

Neither PWV ba nor PWV fa correlated significantly with FA IMT. PWV ba correlated significantly and negatively with muscle mass ($r = −0.589, P < 0.0001$) and BMC ($r = −0.342, P = 0.017$), but not with fat mass ($r = −0.158, P = 0.283$) (Figure 3). PWV fa had a significant and negative correlation with muscle mass ($r = −0.488, P = 0.0004$), a tendency towards a negative correlation with BMC ($r = −0.264, P = 0.069$), but no correlation with fat mass ($r = −0.153, P = 0.1154$). FA IMT did not correlate significantly with muscle mass, BMC or fat mass.

Multiple regression analysis of factors independently associated with PWV ba and PWV fa in hemiparetic patients
Table 2 shows the multiple regression performed with the paretic and non-paretic sides together. Muscle mass was associated significantly with increased PWV ba and PWV fa, independent of age, duration after CVA, BMC, fat mass and FA IMT when the analysis was conducted in both paretic and non-paretic limbs. Even when the association of those parameters with PWV fa and PWV ba were examined independently in the paretic and non-paretic limbs, muscle mass was again significantly and independently associated with PWV ba on either side. Likewise, PWV fa was also significantly and independently associated in the paretic limb, and tended to be associated with PWV fa in the non-paretic limb (Table 3).

DISCUSSION
A marked decrease in blood flow in the affected limb is commonly observed in the patients with hemiplegia/hemiparesis following CVA [20]. In the present study, we have elucidated structural abnormalities of the femoral artery in the paretic limb characterized by increased arterial stiffening and thickening, as shown by increased PWV ba, PWV fa and FA IMT. Since IMT and PWV provide a relevant assay for quantifying arterial thickening and stiffening respectively, our data clearly indicated that arterial thickening and stiffening were both increased in paretic lower limbs compared with the non-paretic side. Furthermore, we have demonstrated that decreased muscle mass may be one of the major factors for increased arterial stiffening of paretic lower limbs in patients with hemiparesis/hemiplegia.

Wasting of muscle is a prominent feature of hemiplegia/hemiparesis. Previous reports demonstrated that
the muscle blood flow, measured using a radioisotope \(^{133}\text{Xe}\)-clearance method [21], was decreased significantly in the paretic limb. As muscle mass decreases, vascular resistance becomes greater, leading to lower muscle flow rates in the affected limbs [22]. Increased shear stress, due to increased vascular resistance, may contribute to the progression of local atherosclerosis in the paretic side by increasing vascular injury [23].

An increase in basal vascular resistance in the hindlimb of the sedentary spontaneously hypertensive rats is significantly decreased after training [24]. Its mechanism is explained by training-induced increase of venule density in skeletal muscle. Alternatively, physical exercise may exert its effect on vascular function by decreasing insulin resistance. Asymmetrical training of the upper limbs is accompanied by a greater distensibility of the middle-sized arteries of the more trained side [25]. Previous studies have reported improved vascular endothelial function in the upper limb after hand-grip exercise training in the patients with congestive heart failure [26,27], suggesting that the beneficial effect of training on vascular endothelial function may be localized to the side where muscle mass is increased.

Previous work has demonstrated that hindlimb unloading rapidly diminishes blood flow to the femoral and tibial metaphysis (cancellous bone), diaphysis (cortical bone), and marrow [28] that appears to coincide with a diminished mineral apposition rate, density and mass of both cortical and cancellous bone observed in hindlimb unloading in rats [29–35]. The hypothesis was proposed that the hindlimb-unloading-induced decrease in blood perfusion to bone leads to bone loss by both stimulating bone resorption and inhibiting bone formation. It is possible that the hindlimb-unloading-induced decreases in blood flow and increases in shear stress alter vascular endothelial cell release of NO (nitric oxide) and PGI\(_2\) (prostaglandin I\(_2\)), which could subsequently modify the focal balance between osteoblast and osteoclast activity. Furthermore, the acute increase in blood flow to the bones of the forelimb, shoulder and head appears to coincide with some reports of increased bone mass in hindlimb unloading in rats [33]. Therefore a correlation between PWV and BMC may suggest that decreased blood flow may cause bone loss in the affected side of hemiparetic patients. Another possibility is that enhanced release of calcium from bone in the paretic lower limb may enhance atherosclerosis locally, since etidronate, a bone antiresorptive bisphosphonate, was reported to reverse atherosclerosis in diabetic patients [36].

Multiple regression analysis elucidated that the muscle mass was significantly associated with PWV fa and PWV ba, independent of age, duration after CVA, bone and fat mass and FA IMT (Table 2). Furthermore, even when multiple regression analysis was performed independently in the paretic and non-paretic sides, muscle mass still emerged as an independent factor associated with PWV fa and PWV ba (Table 2). However, bone mass failed to appear as an independent factor associated with PWV fa and PWV ba. These data clearly indicated that the decrease of muscle mass may be a factor independently associated with accelerated atherosclerosis in paretic limbs of hemiparetic patients.

The limitation of the present study is that it is purely observational, since it is possible that increased PWV may cause a decrease in muscle blood flow, resulting in the decrease of muscle mass. Furthermore, since the alteration of arterial properties demonstrated in the present study only increased arterial thickening and stiffening in paretic lower limbs, as reflected by increased IMT and PWV, there is no direct histopathological evidence that increased IMT or PWV in paretic lower limbs is due to atherosclerosis. Therefore it is possible that the arterial stiffening and thickening of the femoral artery in paretic lower limbs might be the result of another non-atherosclerotic arteriopathy.

In summary, our results indicated that the decrease in muscle mass is a major factor independently associated with the local increase in arterial thickening and stiffening in paretic limbs of hemiparesis/hemiplegia patients.

REFERENCES


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