Venous flow volume measured by duplex ultrasound can be used as an indicator of impaired tissue perfusion in patients with peripheral arterial disease

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Abstract

Aim: In this study, we aimed to investigate the arterial and venous flow volume rate (FV) in order to determine the tissue perfusion using duplex ultrasonography (DU). We hypothesized that FV provides reliable information regarding tissue perfusion in patients with peripheral arterial disease (PAD).

Material and methods: The study comprised 38 patients (72 legs) with PAD. In all patients, common femoral, popliteal, anterior tibial, posterior tibial arteries and veins were examined with DU. Measurements were obtained in the supine position with 15 cm elevation of the foot to neutralise central venous pressure. The diameter, blood flow velocity, and FV of arteries and veins were measured for each patient.

Results: The FV of the common femoral artery and vein (p = 0.001), popliteal artery and vein (p = 0.003), and posterior tibial artery and vein (p = 0.008) had statistically significant differences. However, there was no statistically significant difference between the FV of the anterior tibial vein and artery (p = 0.408). The mean FV values of all veins were significantly lower than those of homonymous arteries in patients with PAD.

Conclusions: Our study showed that venous FV measured by DU can be used as an indicator of impaired tissue perfusion in patients with PAD.

Keywords: duplex ultrasonography; peripheral arterial disease, venous flow volume rate, tissue perfusion.

Introduction

Peripheral arterial disease (PAD) is a condition characterised by flow-limiting stenosis or occlusion in the vessels supplying the lower limbs. Commonly identified risk factors include diabetes mellitus, coronary artery disease, hyperlipidemia, cigarette smoking, and hypertension [1–6]. Improving blood flow is a major therapeutic goal in patients with PAD, and a number of innovative approaches beyond revascularisation have been investigated. A noninvasive technique capable of measuring tissue perfusion would be of great clinical value for assessing the severity of PAD and monitoring response to novel therapeutic interventions designed to enhance skeletal muscle perfusion [7].

Several modalities have been used to define affected arteries in PAD, including spectral Doppler ultrasonography (US), computed tomography angiography, magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). Current methods that are routinely used to diagnose PAD and evaluate its severity rely on imaging the degree of large vessel stenosis, measuring pressure gradients, or identifying abnormalities in arterial pulse-volume recordings [8,9]. Both DSA and MRA are limited to visualising the vascular lumen. These techniques use macrovascular abnormalities as a surrogate
marker of tissue ischemia, largely ignoring adaptations in cellular metabolism and within the microvasculature that develop during the evolution of vascular insufficiency and influence endorgan response [7,10]. The pathophysiology of PAD is complex and incompletely understood. Although the obstruction of blood flow is critical in the artery, the degree of haemodynamic impairment does not consistently relate to functional limitation [11].

In this study, we hypothesised that the severity of PAD can be quantified by duplex ultrasonography (DU) measurement of blood flow volume rate (FV) in the lower extremity. Values of venous FV lower than those of homonymous arterial FV may be an indicator of impaired tissue perfusion in patients with PAD. Our method relies on the measurement of returning blood FV from microvascular area. Due to the venous capillary direct connections, venous FV is influenced by microvascular environment in contrast with arterial FV. So, our aim was to verify if venous FV can be used as a reliable quantitative indicator of tissue perfusion.

**Material and methods**

The study protocol was approved by the institutional review board, and written informed consent was obtained from all participants.

**Study population**

The study comprised 38 patients (27 male, mean age 58.6 ± 14.3; age range 31–84 years, 17 active smokers) with previously diagnosed PAD by US examined between October 2013 and February 2014 in our hospital: 16 patients with mild to severe claudication (Rutherford Grade I), 10 patients with rest pain (Rutherford Grade II), and 12 patients with ischemic ulceration (Rutherford Grade III-IV). In 4 patients (3 with diabetes mellitus and one with thromboangiitis obliterans, presenting with below-knee amputation, non-healing ulcers, deep soft-tissue infection or and severe gangrene) examination was performed only in one leg. Therefore, 72 legs of 38 patients were examined. Arterial pulses of the common femoral artery (CFA), popliteal artery (PA), anterior tibial artery (ATA), and posterior tibial artery (PTA) were palpable in 59 legs.

Exclusions criteria were: history of lower extremity arterial surgery, asymptomatic PAD (Rutherford Grade 0), history of acute or chronic deep vein thrombosis, post-thrombotic changes, and venous insufficiency. The CFA and PA were examined 2 cm above the bifurcation, and the common femoral vein (CFV) and popliteal vein (PV) were examined 2 cm above the saphenofemoral and saphenopopliteal junction, respectively (fig 1). The ATA, PTA, anterior tibial vein (ATV), and posterior tibial vein (PTV) were examined 2 cm proximal to the ankle. The method and reproducibility of the arterial and venous haemodynamic DU evaluation have been prior published [13,14].

**Duplex ultrasonography**

DU was performed with Aplio XG (Toshiba Corporation, Japan) using a 7–12 MHz linear array transducer. Flow studies were performed by a single experienced radiologist in a temperature-controlled (21 ± 1 °C) environment after 10 min of rest to allow the muscles to achieve a resting state. All measurements were obtained in supine position with 15 cm elevation of the foot to neutralise central venous pressure. The inner vessel diameter, blood flow velocity, and FV of arteries and veins of the lower extremity were calculated for each patient. A 45–60° angle of insonation between the transducer and vessel was used to achieve the optimum color and spectral Doppler signal. Waveforms were recorded from a small sampling volume placed in the central flow stream at attempted angles of 60° relative to vessel walls. In all patients, transverse and longitudinal images of the CFA, PA, ATA, PTA and homonymous veins were obtained with gray scale US, color Doppler US, and DU, without compression. The transverse cross-sectional area (expressed in cm²) at the midpoint of the vessel was calculated automatically after the vessel edge was traced manually. The FV were calculated by multiplying the time integral value of mean flow velocity (expressed in cm/s) by the cross-sectional area of the vessel, which was assumed to be a circle [12].

The great saphenous vein, superficial femoral vein, and deep femoral vein were also imaged routinely to investigate acute or chronic deep vein thrombosis, post-thrombotic changes, and venous insufficiency. The CFA and PA were examined 2 cm above the bifurcation, and the common femoral vein (CFV) and popliteal vein (PV) were examined 2 cm above the saphenofemoral and saphenopopliteal junction, respectively (fig 1). The ATA, PTA, anterior tibial vein (ATV), and posterior tibial vein (PTV) were examined 2 cm proximal to the ankle. The method and reproducibility of the arterial and venous haemodynamic DU evaluation have been prior published [13,14].

**Fig 1.** Color duplex scan of the right common femoral vein. Longitudinal view at the level of 2 cm above the bifurcation. The cross-sectional area of lumen was measured as 0.342 cm² and the flow volume rate was calculated as 160 mL/min.
Data analysis

All DU images were analysed by a single radiologist with 10 years of experience. The values were reported as the mean ± standard deviation (SD). Statistical analysis was performed with SPSS 15.0 for Windows. The Pearson’s correlation coefficient was used to compare all the parameters with each other. A p value of < 0.05 was considered significant.

Results

The mean FV values of all vessels studied are summarised in Table I and the blood velocities and diameters for the all investigated vessels in Table II.

Correlations between the mean arterial and venous FV values for all measured vessels are detailed in Table III and between mean flow volume values, mean diameter and mean flow rate of the vessels in Table IV.

Discussions

Our study demonstrated that the noninvasive imaging of limb tissue capillary perfusion accompanied by the measurement of arterial and venous DU parameters is a useful method for evaluating the physiologic significance of PAD. We found a good correlation between FV of the arteries and the homonymous veins. Nonetheless, mean FV of the veins was always lower than the homonymous arteries in all patients with or without stenosis. Therefore, our data also revealed that venous FV values lower than those of homonymous arteries could be an indicator of impaired tissue perfusion in patients with PAD.

Table I. The mean blood flow volume of the arteries and veins studied

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Flow volume mean±SD (mL/min)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFA</td>
<td>269.81±138.99</td>
<td>0.0001</td>
</tr>
<tr>
<td>CFV</td>
<td>245.9±132.31</td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>107.22±55.82</td>
<td>0.003</td>
</tr>
<tr>
<td>PV</td>
<td>95.97±40.09</td>
<td></td>
</tr>
<tr>
<td>ATA</td>
<td>24.32±15.71</td>
<td>0.408</td>
</tr>
<tr>
<td>ATV</td>
<td>14.31±12.31</td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>18.67±13.49</td>
<td>0.008</td>
</tr>
<tr>
<td>PTV</td>
<td>15.21±12.02</td>
<td></td>
</tr>
</tbody>
</table>

Table II. The blood velocities and diameters for the all investigated vessels

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Velocity(cm/s)</th>
<th>Diameter(mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean±SD min-max</td>
<td>mean±SD min-max</td>
</tr>
<tr>
<td>CFA</td>
<td>74.61±31.55 0-147</td>
<td>6.99±1.65 0-10.8</td>
</tr>
<tr>
<td>CFV</td>
<td>25.6±12.3 4.2-77</td>
<td>7.2±2.16 3.2-14</td>
</tr>
<tr>
<td>PA</td>
<td>41.29±17.07 8.8-98</td>
<td>5.7±0.95 3.7-8.6</td>
</tr>
<tr>
<td>PV</td>
<td>16.2±11.19 3.3-83</td>
<td>6.08±1.4 3.5-9.4</td>
</tr>
<tr>
<td>ATA</td>
<td>35.49±19.79 3.6-87</td>
<td>2.51±0.61 0.5-4.5</td>
</tr>
<tr>
<td>ATV</td>
<td>7.89±3.52 2.6-23</td>
<td>2.39±0.87 0.9-6.1</td>
</tr>
<tr>
<td>PTA</td>
<td>30.81±22.78 0-132</td>
<td>2.37±0.75 0.3-9.3</td>
</tr>
<tr>
<td>PTV</td>
<td>9.3±6.36 2.6-42</td>
<td>2.44±0.69 1.3-5.4</td>
</tr>
</tbody>
</table>

Table III. Correlations of the mean arterial and venous flow volume rate values for all measured vessels.

<table>
<thead>
<tr>
<th>p value</th>
<th>CFA</th>
<th>PA</th>
<th>ATA</th>
<th>CFV</th>
<th>PTA</th>
<th>PV</th>
<th>ATV</th>
<th>PTV</th>
</tr>
</thead>
</table>

*The Pearson’s correlation coefficient was used to compare all the parameters with each other. **A p value of < 0.05 was considered significant.

Table IV. Correlations of the mean flow volume values with the mean diameter and mean flow rate of the vessels (all the correlations were statistically significant p<0.05).

<table>
<thead>
<tr>
<th>Mean flow volume</th>
<th>AFA</th>
<th>MD of AFV</th>
<th>PTA</th>
<th>MFR of PTV</th>
<th>PV</th>
<th>MFR of PTA</th>
<th>MFR of PTV</th>
<th>ATA</th>
<th>MD of PTV</th>
<th>MFR of ATV</th>
<th>AFV</th>
<th>MD of ATA</th>
<th>MD of PTV</th>
<th>MFR of ATA</th>
<th>PA</th>
<th>MD of ATA</th>
<th>MD of PTV</th>
<th>MFR of PV</th>
<th>MFR of ATA</th>
</tr>
</thead>
</table>
| MD: Mean diameter, MFR: Mean flow rate, CFA: common femoral artery, CFV: common femoral vein, PA: popliteal artery, PV: popliteal vein, ATA: anterior tibial artery, ATV: anterior tibial vein, PTA: posterior tibial artery, PTV: posterior tibial vein,
mal, > 0.40 to <0.90 reflects mild to moderate PAD, and ≤ 0.40 suggests severe arterial occlusive disease [15]. A value of ≈ 0.90 is accepted as normal but this situation can be encountered in a patient with a value of ABI 100 mmHg/110 mmHg and also in a patient with heart failure and hypotension, with ABI: 50 mmHg/55 mmHg. But the second patient with 50 mmHg ankle pressure had a risk for tissue ischemia. Current methods such as positron emission tomography and contrast-enhanced magnetic resonance imaging can be used to evaluate limb perfusion, but cannot be used for routine patient screening, [8,10,12]. Plethysmography can provide information about the physiologic impact of diffuse large-vessel disease, but this is not sufficient for evaluating microvascular disease [8,16]. Current methods do not measure capillary blood volume and are limited in their ability to evaluate small-vessel disease and the influence of collateral perfusion [8]. Imaging of tissue perfusion and capillary FV with a noninvasive radiologic method can provide information about the pathophysiologic severity of the disease and could improve the management of patients with PAD. Using only arterial flow parameters such as degree of stenosis or blood flow rate with DU is inadequate for showing severe impaired tissue perfusion in patients with critical stenosis or arterial occlusion. In addition to arterial DU, measurement of venous FV can provide more accurate and quantitative information about capillary perfusion. We suggest that arterial and venous FV measurement is necessary for peripheral arterial intervention and lower values of venous FV compared with arterial FV may indicate impaired capillary perfusion.

The distal part of the leg and foot is less seriously affected by atherosclerosis, because the PA is rich in blood supply due to collateral development [17]. Nevertheless, sometimes collateral vessels may not have enough FV and blood pressure to carry out capillary perfusion that may lead to tissue ischemia. Experimental evidence from histopathologic and clinical studies suggests that the skeletal muscle is not a passive bystander during the development of PAD. The vascular system cannot be considered a simple pipe system [7,18]. Mann et al suggested that “blood goes to where there is necessity” [19]. Carbon dioxide, lactic acid, adenosine, histamine, hydrogen ions, potassium, and nitric oxide (produced in the ischemic area) control capillary flow [20]. Our method relies on the measurement of returning blood FV from the microvascular area. It is uniquely suited for evaluating the physiologic impact of PAD, because venous FV directly assesses capillary flow, which can originate from multiple sources, including stem artery inflow, collateral vessel networks, or redistribution from other limb tissues and nonnutritive pathways other than homonymous main artery inflow.

Pulselessness and intermittent claudication do not constitute an indication for angiographic imaging or intervention in patients with PAD. In spite of total occlusion in a large vessel, capillary perfusion can be carried out thanks to collateral vessels. Cardiovascular surgeons decide whether to perform the surgery for tissue ischemia [21–23]. Therefore, indirect evaluation of tissue perfusion by venous FV is a more reliable noninvasive technique compared with other techniques which rely on velocity or pressure gradients within the large vessels. Although the destination of the blood in the ascending aorta is uncertain, it is clear that the origin of the blood in the coronary sinus comes from the myocardium. Venous flow directly indicate the target tissue flow but arterial flow can go anywhere other than target tissue [21]. Venous FV returning to systemic circulation can derive from several sources other than the major limb inflow vessel. In the proximal part of the lower extremity, there is an extensive and preexistent circuit of medium- and large-size arteries capable of providing collateral flow in the presence of stem-vessel stenosis. Muscle perfusion can also be augmented by redistribution of flow from other limb tissues and from nonnutritive channels within the muscle [8,12–18].

The lack of statistical correlation between the FV of ATV and the DU measurements of all other vessels show that FV of ATV may also be indicators of impaired tissue perfusion. The discrepancy between the FV of ATA and ATV indicates that venous FV can also assess the contribution of the alternate sources of capillary perfusion. We identified 15 mL/min as the lowest mean FV value for crural vessels and proposed it as a cut-off FV value for tissue ischemia in cruris. Instead of detection of arterial stenosis, arterial and venous FV measurement with DU is mandatory for the detection of ischemic regions.

To the best of our knowledge, this is the first study that presents the findings of dynamic venous DU with the FV in patients with PAD. Our results showed the FV of lower extremity veins were significantly lower than homonymous arteries in this category of patients. The results of this study suggested that FV of peripheral venous system can be an indicator of impaired tissue perfusion in PAD patients.

There are some limitations in this study. Firstly, the difficulty in the measurement of FV in small vessels and compressible veins cause a limitation. If we did not see intraluminal color in the smaller vessels due to slow flow, we performed B-flow imaging for measurement of FV and we tried to perform venous DU without any compression especially for small superficial crural veins. Secondly, the present study reports our initial experience with blood FV values of lower extremity vessels of patients with PAD in a small sample. Further studies us-
Venous flow volume measured by duplex ultrasound can be used as an indicator for the FV, diameter, and velocity of limb veins.

Conclusions

Consequently, as an indicator of tissue perfusion, venous FV imaging by DU provides more accurate information regarding the total physiologic impact of PAD by taking into account all sources of flow. We showed that lower FV compared with arterial FV indicate impaired tissue perfusion and there is no need for intervention when venous FV is sufficient. The disturbance in peripheral tissue perfusion in patients with PAD may be underestimated, leading to delayed vascular surgery and/or medical treatment. Future studies with a larger group of patients are required in order to determine cutoff values for the FV, diameter, and velocity of limb veins.

Conflict of interest: none

References