Color Doppler ultrasound measurement of flow volume, flow velocity and diameter in lower extremity venous system may be indicator of tissue perfusion

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**Aims and objectives**

Peripheral arterial disease (PAD) is a condition characterized by flow-limiting atherosclerosis in the vessels supplying the lower limbs. In patients with PAD, the classical symptom, intermittent claudication which are most commonly localized to the calf, but may also affect the thigh or buttocks (1,2). Commonly identified risk factors include diabetes mellitus, coronary artery disease, hyperlipidemia, cigarette smoking, and hypertension (1). Despite a growing appreciation of its contribution to vascular morbidity and mortality, PAD remains a clinical entity that is underdiagnosed, undertreated, and understudied (3). Improving blood flow is a major therapeutic goal in patient with PAD and a number of innovative approaches beyond revascularization 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 (4).

Several modalities have been used to define affected arteries in PAD, including Doppler, computed tomography, angiography, contrast-enhanced magnetic resonance angiography, and digital subtraction angiography. 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 (5). Digital subtraction angiography is considered the 'gold standard' for assessing location and severity of PAD (6). Both X-ray angiography and magnetic resonance angiography are limited to visualizing the vascular lumen. With these techniques, macrovascular abnormalities serve 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 (4). The ankle brachial index (ABI) is a simple, noninvasive test that is helpful in determining the presence of PAD. But ABI will be '0' (zero) in patients with total large vessel occlusion so it can not give information about capillar perfusion. Transcutaneous oxygen measurements are another noninvasive measurement, which is performed to assess arterial perfusion in PAD (6). On the other hand, CDUS imaging is relatively inexpensive, easily available, and widely used noninvasive means of vessels visualization in lower extremities of patients with PAD. CDUS also provides more specific information in terms of level of occlusive disease whether there is stenosis or long segment occlusion (7).

Arterial stenosis of lower limbs is generally symmetrical and most commonly occurs in adductor canal. However, the distal part of leg and foot is less seriously affected by atherosclerosis since the popliteal artery is rich in blood supply due to collateral development (1). But sometimes collateral vessels may not have enough flow volume and blood pressure to carry on capillary perfusion. Therefore, using only arterial flow
parameters with CDUS may be inadequate for showing severe impaired tissue perfusion in patients with critical stenosis or occlusion of artery. Instead of arterial measurement with CDUS, using venous flow parameters can provide more accurate and quantitative information about capillary perfusion.

Despite the high prevalence, cost, and morbidity of lower extremity PAD, there are few effective medical therapies for the diseased limb due to some factors. First, the pathophysiology of PAD is complex and incompletely understood. While the obstruction of blood flow due to large vessel atherosclerosis is critical, the degree of hemodynamic impairment does not consistently relate to functional limitation (8).

In this study, we hypothesized that the severity of PAD can be quantified by venous color Doppler measurements of the lower extremity and those of values may be an indicator of limb tissue flow reserve in patients with PAD.
Methods and materials

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

Study population

The study comprised 72 legs of 38 patients (27 male and 11 female; mean age 58.6±14.3; age range 31-84 years old) with PAD (Table 1). Seventeen patients (14 males, 4 females; mean age 55.7±13.4; age range 34-78 years old) were smokers and twenty-one patients (14 males, 7 females; mean age 60.1±15.7; age range 31-84) were non-smokers.

Color Doppler Ultrasonography

Color Doppler US (CDUS) was performed with AplioXG (Toshiba Corporation, Japan) using a 7-12 MHz linear array transducer. Flow studies were performed by a single radiologist in a temperature-controlled (21±1 °C) environment. All measurements were obtained in supine position with 15 cm elevation of foot to neutralize central venous pressure. Luminal diameter, blood flow velocity and flow volumes of arteries and veins were calculated on transverse and longitudinal planes for each patients. The angle of insonation of 45-60° between the transducer and vessel was used to achieve the optimum color and spectral Doppler signal. In all patients, transverse and longitudinal images of common femoral, popliteal, anterior tibial and posterior tibial arteries-veins of lower extremity were obtained with gray scale ultrasoundography and color Doppler ultrasonography (CDUS) without compression. The proximal medial saphenous and superficial-profunda femoral veins were also imaged routinely. Common femoral artery and popliteal artery were examined one centimeter above the bifurcation, common femoral vein and popliteal vein were examined one centimeter above the saphenofemoral and saphenopopliteal junction, respectively. Anterior and posterior tibial artery and vein examined at the level of ankle. The method and reproductibility of venous hemodynamic CDUS evaluation thus conducted have been presented.

Data analysis

All CDUS imagings were analyzed by an experienced radiologist with 10 years of experience.

The parameters were compared between sexes, ages, and CDUS measurements. The values were reported as the mean ± standard deviation. Statistical analysis was performed with the SPSS 15.0 for Windows. The Mann-Whitney U test, Pearson and Spearman's correlation were used to compare the parameters. A p value of < 0.05 was considered significant.
Table 1: The mean age values with standard deviation of the patients according to the genders.

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>%</th>
<th>Mean±SD</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>11</td>
<td>28,9</td>
<td>58,82±15,65</td>
<td>31</td>
<td>83</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>71,1</td>
<td>58,5±13,98</td>
<td>31</td>
<td>84</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>100,0</td>
<td>58,59±14,27</td>
<td>31</td>
<td>84</td>
</tr>
</tbody>
</table>

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Results

Arterial pulses of common femoral, popliteal, anterior tibial and posterior tibial arteries were detected in 59 legs and were not detected in 13 limbs. No patient had a venous thrombosis demonstrated by duplex ultrasound. The mean flow volume values for common femoral, popliteal, anterior tibial and posterior tibial arteries-veins in patients with PAD were summarised in Table 2. The flow volume of common femoral artery-vein (p=0.0001), popliteal artery-vein (p=0.003), and posterior tibial artery-vein (p=0.008) were statistically significant correlated in all patients. Also, out of anterior tibial vein, all measured vessels flow volumes were correlated with others (p<0.05) (Table 3). We didn’t find correlation between the volume flow of anterior tibial vein with CDUS measurements of other vessels. There was also negative correlation between smoking with posterior tibial artery diameters (p=0.003). The diameters of crural vessels and flow volume of anterior tibial artery were significantly reduced in smokers. There were significantly correlation for flow volume between popliteal artery with crural vessels in non-smokers (p<0.05). We did not find any correlation for flow volume between popliteal artery and crural vessels in smokers.
Table 2: Displaying mean values with standard deviation of arterial and venous measurements of lower extremity with minimal and maximal values for all patients.

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Table 3: Correlation of the arterial and venous flow volume for all measured vessels.

<table>
<thead>
<tr>
<th>Vessels</th>
<th>CFA</th>
<th>CFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>0.040</td>
<td>PA</td>
</tr>
<tr>
<td>ATA</td>
<td>0.000</td>
<td>0.342</td>
</tr>
<tr>
<td>PTA</td>
<td>0.010</td>
<td>0.009</td>
</tr>
<tr>
<td>CFV</td>
<td>0.000</td>
<td>0.212</td>
</tr>
<tr>
<td>PV</td>
<td>0.000</td>
<td>0.003</td>
</tr>
<tr>
<td>ATV</td>
<td>0.309</td>
<td>0.268</td>
</tr>
<tr>
<td>PTV</td>
<td>0.017</td>
<td>0.011</td>
</tr>
</tbody>
</table>

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Conclusion

In the current study, we have demonstrated that noninvasive imaging of limb tissue reserve with measuring venous CDUS parameters that can be used to evaluate the physiological significance of PAD. The findings of our study showed that venous flow volume might be an indicator of impaired tissue perfusion in patient with PAD. The absence of statistically correlation between the volume flow of anterior tibial vein with CDUS measurements of all other vessels in all patients, and between the measurements of popliteal artery and crural vessels in smokers, showed that the diameters and flow volumes of crural vessels may be also an indicator of impaired tissue perfusion. The discrepancy between anterior tibial artery flow volume and anterior tibial vein flow volume indicates that venous CDUS can also assess the contribution of the alternate sources of perfusion, such as large artery inflow, collateral vessels, redistribution from other tissues and nonnutritive pathways.

Experimental evidence from histopathologic and clinical studies suggests that skeletal muscle is not a passive bystander during development of PAD. The vascular system can not be taken as a simple pipe system (4,9). Mann suggested that 'blood goes to where there is necessity'(10). Carbon dioxide, lactis acid, adenosine, histamine, hydrogen ions, potassium and nitric oxide (produced in ischemic area) control capillar flow (11). Our method relies on the measurement of returning blood volume flow from microvascular area. It is uniquely suited for evaluating the physiologic impact of PAD because it can directly assess microvascular flow which can originate from multiple sources, including stem artery inflow, collateral vessel networks, or redistribution from other limb tissues and nonnutritive pathways.

Failure to arterial pulse palpation is not a real indication for angiographic imaging in patients with PAD. The capillary perfusion can be carry on thanks to collateral vessels in spite of total occlusion in a large vessel. The cardiovascular surgeons decide the surgery for tissue ischemia. Current methods that are routinely used to diagnose PAD, rely on imaging the degree of large vessel stenosis and measuring pressure gradients, do not measure capillary blood volume and are limited in their ability to evaluate small vessel disease and the influence of collateral perfusion (5). A noninvasive methods of tissue perfusion and flow reserve imaging can provide information on the physiologic impact of the disease and could improve the management of patients with PAD. But current methods such as positron emission tomography and contrast-enhanced magnetic resonance imaging can be used to evaluate limb perfusion, do not meet many of requirements needed for routine patient screening such as low cost, portability, and rapid protocol implementation necessary for high throughput (5,6,8).CDUS imaging is relatively inexpensive, easily available, and widely used noninvasive method of vascular assesment in lower extremities of patients with PAD. But, imaging the anatomic severity of stenosis or measuring the Doppler pressure gradient is often unreliable for quantifying disease severity in the presence of diffuse stenosis or multiple sequential lesions.
Plethysmography and ankle brachial index measurements can provide information on the physiologic impact of diffuse large-vessel disease, but they are not sufficient for evaluating microvascular disease and can be inaccurate in patients with severely reduced vascular compliance that occurs with aging and hypertension (5,12).

The reasons why direct assessment of tissue perfusion by venous volume flow CDUS may be more accurate for noninvasively assessing PAD than techniques that rely on pressure gradients or flow within the large vessels. Venous flow volume returning to systematic circulation can derive from several sources other than the major limb inflow vessel. In the proximal extremities, there is an extensive and preexistent circuit of medium- and large-size arteries that are 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 that exist within the muscle. Flow redistribution occurs during modest exercise and physiologic hyperinsulinemia (5-9). Consequently, venous flow volume imaging on CDUS is likely to provide more accurate information on the total physiologic impact of PAD by taking into account all sources of flow.

The disturbance in peripheral tissue perfusion of patient with PAD may be underestimated leading to delayed vasculary surgery and/or medical treatment. Measurement of arterial flow measurement with CDUS, should be combined with investigations of concomitant venous flow parameters, especially venous flow volume in order to get an adequate estimation of peripheral tissue perfusion in patients with PAD. Because it measures direct tissue perfusion with venous flow volume value that is likely to be more accurate for assessing the severity of PAD and the combined effects of large-and small-vessel disease and collateral perfusion. The discrepancy between large arterial inflow and venous blood flow indicates that venous CDUS can assess the contribution of the alternate sources of perfusion. The contribution of these alternative sources to flow reserve was also detected by returning venous flow volume measurement by CDUS. Further studies will be needed to examine in a large group to determine the cut-off values for diameter, velocity and flow volume of limb veins.
References


