Critical Analysis of Methods for Assessing Regional Blood Flow and Their Reliability in Clinical Medicine*

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The advantages and inadequacies of the currently available techniques to measure regional blood flow in the lower limbs are being reviewed. Thermodilution technique and local 133xenon washout technique have the advantage of allowing determination of blood flow during exercise, while venous occlusion plethysmography and pulsed-Doppler duplex ultrasonography only allow determination of blood flow at rest. Overall, measurements of lower limb blood flow are not highly reproducible by any technique, and the variability in measurements of regional blood flow should lead to careful interpretation of derived parameters such as vascular conductance and resistance. Determination of vascular input impedance by Fourier analysis of pressure data, recorded with high fidelity catheter, and flow velocity measurements obtained transcutaneously by Doppler ultrasonography, may offer a more accurate quantitative analysis of the characteristics of the lower limb vascular system.

The ability to measure regional blood flow is essential to develop an understanding of the factors that limit proximal aerobic capacity in normal subjects and to study the metabolism of the exercising skeletal muscles.1 Measurements of regional blood flow are more important in patients with congestive heart failure (CHF), as they experience not only a depressed cardiac output response to exercise, but also an abnormal distribution of available cardiac output to the different vascular beds.2-4 Over the past decade, it has become increasingly recognized that abnormalities of the peripheral circulation are major determinants of aerobic impairment, and thus have become a primary target of successful pharmacologic interventions.5-7 While it is unlikely that a dilated and fibrotic left ventricle (LV) with a reduced number of healthy myocytes can be stimulated to a level sufficient to return LV function to normal, promising data with long-term angiotensin-converting enzyme (ACE) inhibition suggest that, to a large extent, abnormalities of the peripheral circulation can be corrected or even prevented.8 If this latter goal can be attained, the duration of asymptomatic LV dysfunction could be substantially prolonged. To meet this therapeutic goal, a better knowledge of the molecular mechanisms responsible for the abnormal smooth muscle vascular tone in patients with CHF needs to be developed, and noninvasive measurements of vascular function need to be introduced. Accordingly, we will first review the current invasive and noninvasive techniques used to determine regional blood flow, and subsequently, we will briefly discuss our ongoing efforts to develop useful parameters of vascular function in large and small vessels.

METHODS

Thermodilution Technique

Several investigators have used the thermodilution technique with single bolus injection to measure lower limb blood flow.9-11 This technique requires a thorough mixing of injectate and blood to ensure accurate measurements. Surprisingly, while great attention was taken by the initial investigator10 to use a catheter with a curved tip and an injection orifice located in the concavity to ensure adequate mixing, subsequent investigators,10,11 except one,12 have used commercially available 5-French thermodilution catheters that are not preshaped. Whether turbulent flow can be generated in the absence of a bend in the catheter is unclear. The inability to measure lower limb blood flow at rest with the single bolus injection thermodilution technique12 suggests that mixing is inadequate with a regular 5-French catheter in conditions of low flow.

Positioning of the catheter is also an important factor in ensuring proper mixing. By advancing the catheter distally into the vein, the bolus of room temperature iced fluid will be administered retrograde against the blood stream, thereby enhancing the likelihood of turbulent flow. In contrast, advancing the catheter proximally into the vein will lead to injecting the bolus antegrade into the bloodstream, thereby decreasing the likelihood of generating turbulent flow. The position of the catheter has also important implications on the nature of the blood flow measured. When the catheter is advanced into the deep femoral vein, the flow measured is equivalent to skeletal muscle blood flow (SMBF), as the deep femoral vein contains exclusively blood from active skeletal muscles.12-14 When the catheter is positioned in the iliac vein, the flow measured stems from the skeletal muscle vasculature of the lower limbs, the anterior abdominal wall, and the great saphenous vein that drains the cutaneous tissues. The mixed nature of the iliac vein flow makes it difficult to draw any specific conclusion on the proportion of blood flow to the lower limb skeletal muscles. The position of the catheter within the vessel lumen is equally important when measuring regional blood by the single bolus injection thermodilution technique. It is essential to maintain the catheter in the central position within the vessel. Any contact between the thermistor and the vessel wall will lead to spurious results. In that regard, the distal bend of the catheter plays an important role in maintaining the portion of the catheter containing the thermistor within the full lumen of the vessel. In addition, when advanced distally into the femoral vein and tightly taped or sutured to the skin, the catheter is less prone to move during upright exercise on the treadmill or bicycle, and the risk of contact between thermistor and vessel wall is less. A last concern when using the thermodilution technique with single bolus injection is the thermistor response time of 0.5 to 1.0 s, which is quite long when compared with the transit time of the wave carrying the temperature changes. The transit time, which obviously varies with the magnitude of the blood flow, is not taken into account by commercially available computerized programs.

Fewer investigators have used the continuous thermodilution technique with constant infusion of injectate and dual thermistor
catheters to measure regional blood flow.12-15 The external dilution thermistor is located from 30 to 50 mm proximal to the injection orifice. The second thermistor is located inside the tubing, adjacent to the injection orifice. For each determination of blood flow, the injectate is infused through the catheter with a Harvard pump at a constant rate ranging from 40 to 60 ml/min. Regional blood flow is calculated from the formula derived by Ganz et al.16 An advantage of constant infusion of injectate over the single injection bolus is to avoid the previously described issue of long thermistor response time. Moreover, excellent mixing conditions of injectate and blood are obtained with the constant injection of injectate for blood flow ranging from 300 to 1,500 ml/min.17

Using iced injectate and a catheter with 4 side holes and an injection rate of 90 to 180 ml/min, Andersen and Saltin18 were able to validate the thermodilution technique in vitro, with constant injection at flows averaging 5.8 L/min. These investigators reported a mean coefficient of variation of 5.4%. In contrast, Haggmark et al.19 using a commercially available dual thermistor catheter and room temperature injectate, found that thermodilution within the catheter led to falsely low flows at flow rate above 300 ml/min. They modified the formula of Ganz et al.16 for flows above 300 ml/min and demonstrated the flow values obtained by the modified formula closely correlated with electromagnetically measured blood flows. Thus, the thermodilution technique, with constant injection of injectate, appears particularly suitable for measuring lower limb blood flow at rest and during submaximal exercise. However, thermoconductivity within the catheter may falsely lower measurements of blood flow during heavy or maximal exercise.

Local $^{133}$Xenon Washout Technique

As initially reported by Lassen et al.,3 SMBF can be measured by the clearance method after intramuscular injection of $^{133}$xenon; 100 μCi of $^{133}$xenon is dissolved into 0.1 ml of normal 9% saline solution and injected into the skeletal muscle; for example, in the lower limb into the lateral aspect of the quadriceps muscle at a depth of 2.5 cm, 15 cm above the patella and 2 cm lateral to midline. The 25-gauge needle is withdrawn 30 s after injection to avoid leaking of $^{133}$xenon throughout the puncture site. A small cadmium telluride semiconductor detector (RMD) is affixed over the injection depot with adhesive tape. Activity is determined every 5 s and data acquired into a microcomputer (IBM PC) that stores, displays, and analyzes the data count.20 SMBF is calculated by the following formula:

$$\text{SMBF} = \lambda (\text{slope}) \times 100 (\text{ml/100 g per min}).$$

A value of 0.7 is used for $\lambda$, the partition coefficient of xenon between muscle and blood. The slope is calculated by the computer from a least-square line fitted through the data points.

Several methodologic aspects are important to consider when applying the local xenon washout method to measurement of SMBF. First, the initial washout rate after the intramuscular injection of $^{133}$xenon leads to an overestimation of SMBF due to the trauma of injection. Thus, the first 15 min of the washout of $^{133}$xenon should be disregarded. Moreover, only the middle portion of the washout curve should be used for determination of SMBF, as the late portion of the curve is influenced by recirculation of the $^{133}$xenon due to venous arteriolar shunting by diffusion and accumulation of $^{133}$xenon in the fat tissue lining of the veins.20 Both recirculation and accumulation of $^{133}$xenon lead to an underestimation of SMBF by as much as 200%.20 This underestimation can be attenuated by peeling off the terminal portion of the washout curve. Another possible contributing factor leading to underestimation of SMBF by the $^{133}$xenon washout technique is the value of 0.7 for $\lambda$. The partition coefficient of xenon between muscle tissue and blood varies with muscle fat content, temperature, and hematocrit. A value as high as 1.0 has been proposed for $\lambda$ by Clausen and Lassen.21 A serious methodologic limitation of the $^{133}$xenon washout technique is the difficulty injecting the xenon at exactly the same site in the skeletal muscle during repeated determinations. The presence of a dual circulation in the skeletal muscle and the uneven perfusion of the different skeletal muscle fibers probably contributes to the substantial variability of baseline resting SMBF by the $^{133}$xenon washout technique.20,27 The intraindividual coefficient of variation has been reported to range from 12% to 28% with the $^{133}$xenon washout technique.28 However, during conditions of high flows, such as during exercise, the skeletal muscle appears to be more evenly perfused and the small variation in the rate of injection of $^{133}$xenon probably matters much less than during rest.3,20 Thus, while resting SMBF may not be reliably measured by the $^{133}$xenon washout technique, this method appears better suited for measurement of SMBF during exercise.

Plethysmography

Noninvasive measurement of limb blood flow can be obtained by venous occlusion plethysmography. Currently, the changes in limb volume are most often determined by using a mercury-in-rubber strain gauge rather than a water plethysmograph. Changes in limb circumference are assumed to be linearly related to limb blood flow. The limb blood flow measured by venous occlusion plethysmography is nonspecific and includes flows from cutaneous and subcutaneous tissues, skeletal muscles, bones, and tendons. The overall reliability of the venous occlusion plethysmography method has been reported to range from 6% to 25%.28,29 The major inconvenience of this method is that limb blood flow cannot be measured during exercise as the motion artifacts introduced by the exercise prevent reliable readings. Nevertheless, hyperemic response to ischemia following arterial occlusion for 5 to 10 min or immediately after exercise can be measured and provides indirect information on the vasodilatory response of the limb skeletal muscle vasculature to exercise. A limitation of the venous occlusion plethysmography method is the variability of repeated limb blood flow measurement performed at intervals ranging from days to weeks. Physiologic variability in limb blood flow probably accounts for at least two thirds of the variation in measurements obtained with venous occlusion plethysmography. Such variation hinders sequential evaluation of a pharmacologic intervention in view of the shifting baseline measurement. Normalization of the pharmacologic response to peak reactive hyperemia produced by 10 min of arterial occlusion can obviate the problem of nonsteady baseline measurements. Despite these limitations, plethysmography is the most widely used technique to measure limb blood flow.30

Pulsed Doppler Duplex Scanner Ultrasonography

Lower limb blood flow can be noninvasively measured by combining two-dimensional ultrasonography that produces a 90° sector real-time image, and range-gated pulsed Doppler that produces Doppler-shift spectrum of the blood in the common femoral artery.30,31 Therefore:

$$V = \Delta f \times C2 \times f \times \cos \theta (\text{cm/s})$$

where $V =$ blood velocity; $\Delta f =$ Doppler shift spectrum; $\theta =$ angle between the sound beam axis and the velocity vector in degrees; $f =$ frequency of transmitted ultrasound in hertz; and $C =$ velocity of sound in tissue media in centimeters per second. Duplex ultrasound systems, now commonly available, allow fairly accurate determination of the incident angle $\theta$, with an error of less than 5%.

$$\text{Flow} = \bar{V} \times \pi D^2 / 4 \times 60$$

where $\text{flow} =$ common femoral artery blood flow; $\bar{V} =$ mean blood flow velocity average over a cardiac cycle; $D =$ diameter of the common femoral artery in centimeters.

As pointed out by the second formula, a very precise measurement of the vessel diameter is required to accurately determine lower limb blood flow by pulsed-Doppler duplex scanner ultrasonography. Moreover, this method does not permit measurement of lower limb flow during exercise. Like venous occlusion plethysmography,
pulsed-Doppler duplex scanner ultrasonography allows only indirect assessment of the vasodilatory response to exercise by measuring the hyperemic response to ischemia after exercise.  

**Alternative Approaches**

The choice of a method to measure regional blood flow is, to a large extent, dependent on the circumstances and the rationale for measuring regional flow. When concerned with blood flow during exercise, the choice is between the thermodilution technique and the local 133xenon washout technique, as both venous occlusion plethysmography and pulsed-Doppler duplex scanner ultrasonography cannot be used. In view of the invasive nature of the 2 former techniques, one should really question the need for measurement of regional blood flow. When attempting to determine the mechanisms of an improved aerobic capacity, direct measurement of maximal lower limb blood flow or SMBF may not be essential, as lower limb blood flow can be indirectly assessed during maximal exercise. In normal subjects, there is very close linear relationships between lower limb blood flow and systemic oxygen uptake during graded exercise. Nevertheless, maximal oxygen uptake can be increased, in the absence of increased limb blood flow, by a greater widening of the arteriovenous oxygen difference, as observed after physical training.

**DISCUSSION**

Retrograde catheterization of the deep femoral vein with a small flexible polyethylene catheter allows measurement of oxygen content in the deep femoral vein. In the absence of a change in arterial oxygen content, deep femoral vein oxygen content closely reflects the extraction of oxygen by the active skeletal muscles. An increase in maximal oxygen uptake is, in the absence of a change in femoral venous oxygen content, secondary to a greater SMBF in the lower limbs, assuming that arterial oxygen is unchanged. Moreover, even when oxygen content decreases in the deep femoral vein, one should be able to comment on potential alterations in SMBF by comparing the relative changes in proximal oxygen uptake and arteriovenous oxygen difference. While direct invasive quantification of SMBF during exercise has the advantage of allowing calculations of changes in vascular conductance during exercise, these calculations are not precise due to the relative inaccuracy of the methods used to measure regional blood flow.

To better define the abnormalities of the lower limb skeletal muscle vasculature present in patients with hypertension, CHF, diabetes, and hypercholesterolemia, and to precisely quantify potential changes brought on by physical conditioning and pharmacologic interventions, we became interested in studying vascular impedance in the superficial femoral artery. By directly recording arterial pressure using a high-fidelity 2-French Millar catheter advanced distally into the artery, and by transcutaneously measuring Doppler blood flow velocity using a system (Hewlett Packard Sonos 100) input impedance of the lower limb skeletal muscle vasculature can be defined in terms of impedance modulus and phase angle by Fourier analysis. The changes in impedance modulus and phase angle recorded in a patient with CHF prior to and after administration of 10-4M of nitroglycerin into the femoral artery are illustrated in Figure 1. While this methodology has the advantage of precisely quantifying the characteristics of the skeletal muscle vascular system without relying on precise measurement of vessel diameter, it still has the inconvenience of being invasive.

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Methods for Assessing Regional Blood Flow (Lejtemt et al)