Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2008 September ; 11(5): 580–586. doi:10.1097/MCO.
0b013e32830b5b34.

Measuring Muscle Blood Flow a Key Link Between Systemic and Regional Metabolism

Darren P. Casey, Timothy B. Curry, and Michael J. Joyner

Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905

Abstract

Purpose of review—To provide a brief overview of the main techniques to measure muscle blood flow in humans and highlight some of the strengths and weaknesses associated with each technique.

Recent findings—Peak muscle blood flow values of $300 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ are possible in humans during heavy exercise performed with small muscle mass. This value is far higher than appears in most text books. Accurate and reliable techniques are therefore essential in measuring muscle blood flow. Current invasive techniques commonly used include indicator dilution (thermo- and dye-dilution) and radiolabel tracer washout (e.g. ^{133}Xe washout) methods. While invasive techniques have provided valuable insight into tissue blood flow, non-invasive techniques such as venous occlusion plethysmography and Doppler ultrasound are frequently used and provide accurate measurements of blood flow. Newer imaging techniques (magnetic resonance imaging, positron emission tomography, and contrast-enhanced ultrasonography) promise increased resolution of measurements of local blood flow, including in discrete tissues where more classical techniques are not able to study.

Summary—Muscle blood flow is a key link in the interplay and regulation of systemic and local muscle metabolism. Recognizing the advantages and limitations of each technique is essential to translational researchers studying the effects of nutrition and metabolism on muscle blood flow.

Keywords

muscle blood flow; plethysmography; indicator dilution; Doppler ultrasound

Introduction

Skeletal muscle is the largest organ in the body and muscle contractions increase energy use and activate numerous metabolic pathways in an effort to meet the muscles' increased demand for energy. Due to the ability of muscle to increase its metabolism more than 100 fold, the rise in blood flow to active muscles can be vast and is generally proportional to the rise in metabolism. In this context, whole body and local muscle “fuel homeostasis” are linked by the cardiovascular system which transports substrate to the active muscle and removes the byproducts of contraction. Additionally, measurement of substrate flux to and turnover in both resting and active muscles frequently requires measurement of muscle blood flow.

This brief review highlights some of the main techniques to measure muscle blood flow (usually limb blood flow is used as a surrogate). General classes of techniques we focus on

include indicator dilution, venous occlusion plethysmography, and Doppler ultrasound. We will also briefly cover local techniques like ^{133}Xe washout and microdialysis along with contrast enhanced ultrasound. Key caveats for all interested in the measurement of muscle blood flow in humans is that: 1) there is no ideal technique to measure muscle blood flow in humans, 2) flow to contracting muscles can be much higher than once thought, and 3) careful consideration about what fraction of limb blood flow is going to non-muscle elements of the limb under study are required to estimate changes in muscle blood flow.

Indicator dilution methods

Indicator dilution methods for measuring blood flow include thermodilution and dye dilution are useful for performing measurements at steady state, including at rest and during maximal and submaximal exercise. First used to measure cardiac output [1, 2], they are based on the principle that infusate is diluted by blood with a corresponding change in color or temperature in proportion to blood flow.

Dye dilution most commonly uses the indicator dye indo-cyanine green and requires multiple blood samples to measure blood dye concentration with a photo-densitometer. More recently, dye dilution with indo-cyanine green has been paired with near infrared spectroscopy (NIRS) [3]. First used to study cerebral blood flow [4], it has been used to measure perfusion in other solid organs and in muscle, both at rest and during submaximal exercise [5]. Peripheral injection of indo-cyanine green can even allow simultaneous determinations of total cardiac output and regional muscle blood flow [3]. Thermodilution with iced saline can also be used to measure regional blood flow (Figure 1). A constant infusion technique removes some of the problems with using bolus injections, including response times of thermistors and the effects of dynamic exercise. Andersen and Saltin [6] first used this technique to show that maximal muscle blood flow during exercise was much higher than originally measured. Like dye dilution, thermodilution is invasive and requires expertise to use. However it does not require multiple blood sampling, spectrophotometry, and is not complicated by recirculation of dye (although care must be taken not to perform the measurements too often or too long to prevent tissue cooling). Despite their limitations, indicator dilution methods have been used for over a hundred years and are useful techniques, especially during exercise, where less invasive methods are impossible (venous occlusion plethysmography) or expensive and technically challenging (Doppler ultrasound).

Venous occlusion plethysmography (VOP)

Venous occlusion plethysmography is a common technique used to assess the various areas of vascular biology in humans and a recent historical review has described the origins of the technique, fundamental observations made with it, and its continued utility [7]. The general idea behind VOP is that a pneumatic cuff is inflated ($\sim 40\text{--}50\text{ mmHg}$) around the upper arm or thigh to occlude blood flow in the veins without impeding arterial inflow. A second cuff is placed at the level of the wrist or ankle and inflated to suprasystolic pressure to exclude blood flow to the hand and foot, respectively. Blood flow is measured as linear increases in forearm volume over time and is thought to be proportional to the rate of arterial inflow [8]. Mercury-in-silastic strain gauges placed around the widest part of the limb where flow is to be measured are commonly used to detect changes in limb circumference and the calculation of the corresponding percentage increase in volume changes (Figure 2).

The use of VOP has provided several fundamental observations and advanced our understanding of limb blood flow responses to exercise in humans. This technique has provided critical information regarding the dynamics and timing of muscle blood flow at the onset of exercise, mechanisms responsible for changes in muscle blood flow during exercise, and the balance between vasoconstricting and vasodilating substances contributing

to the regulation of muscle blood flow at rest and during exercise [7]. It should be noted that, measurements of blood flow during exercise using plethysmography can underestimate the true response to exercise. Using plethysmographic techniques blood flow to exercising muscle has been shown to increase 10- to 20-fold, whereas studies using thermodilution techniques suggest that blood flow to active human muscles can increase 50- to 100-fold [7]. The fact that the plethysmography measurements are made during brief pauses in the contraction and because the limb is typically above heart level likely explain these discrepancies observed between techniques.

The use of venous occlusion plethysmography has also been utilized to establish maximal vasodilator responses following reactive hyperemia, as well as in conjunction with brachial arterial infusion of drugs to study the pharmacology of blood vessels in humans. These studies have provided useful information regarding the role of the vascular endothelium in health and disease. Indeed, patients with established risk factors for cardiovascular disease (i.e. hypertension, hyperlipidemia, aging) demonstrate blunted dose response curves to acetylcholine that are indicative of endothelial dysfunction [9-11]. Interventions such as aerobic exercise [10, 12, 13], weight loss [14], and administration of antioxidant vitamins [13, 15] have been shown to improve endothelial function in these patient populations.

Doppler ultrasound

The introduction of Doppler ultrasound has provided a method for continuous determination of blood velocity in conducting vessels that are the main suppliers of blood to a specified region. Most commonly this technique is used to measure flow in the brachial or femoral artery, including studies done during exercise (Figure 3). The velocity of flow through a large artery can be calculated from the Doppler frequency shift that occurs as transmitted ultrasound waves of a specific frequency are reflected by the erythrocytes passing through the vessel [16]. Measurement of the arterial diameter along with the blood velocity is needed for the determination of blood flow. Most ultrasound transducers have the capability of measuring both variables. Blood flow is commonly calculated by multiplying mean blood velocity (cm s^{-1}) by the cross-sectional area of the artery (cm^2) then multiplied by 60 to present values as milliliters per minute (ml min^{-1}). The insonation angle used for measuring velocity is critical in obtaining accurate flow estimates. It is recommended that using lower insonation angles ($\sim 60^\circ$) will limit the error that may be induced in the flow estimate [17].

Since ideal velocity measurements are obtained when the limb and artery are in a fixed position, thus minimizing motion and potential insonation failures, earlier studies mainly relied on blood flow measurements during intermittent static contractions [18, 19]. However, several studies have demonstrated the use of Doppler ultrasound to measure blood flow responses during dynamic submaximal exercise in the leg [20-22] and forearm [23-25]. Studies during dynamic leg exercise have led to observations that relative and absolute blood flow during exercise is reduced in conditions such as aging [20, 26] and chronic heart failure [27] and these observations are in general agreement with indicator dilution measurements [28-30]. Interestingly, blood flow to exercising forearm was previously reported to be largely unaffected by aging using plethysmography, a technique that measures flow during brief pauses in contraction [31]. This highlights the need for continuous measurements of flow to correctly identify differences that come with aging and other conditions that would potentially limit the blood flow response to exercise. However, it should be noted that recent evidence using Doppler ultrasound techniques suggests that aging induces limb specific alterations in exercise blood flow, which result in reductions in leg blood flow during exercise but do not impact forearm blood flow [26].

In addition to measuring changes in blood flow during exercise, the use of Doppler ultrasound has proven to be advantageous for reactive hyperemia studies. Ultrasound is

frequently used in the detection of impaired endothelial dependent dilation, as measured by flow mediated dilation (FMD). The general principle of FMD is that increasing flow in an artery will lead to shear stress along the endothelial wall and subsequent dilation. Typically the flow stimulus is created by inflating a pressure cuff on the forearm to suprasystolic pressures (usually 50 mmHg above systolic pressure) for five minutes. This results in ischemia and dilation in the downstream resistance vasculature. Upon cuff deflation there is an increase in flow and shear stress through the artery (reactive hyperemia), which results in dilation [32]. FMD studies are usually performed in large conduit vessels such as the brachial or femoral arteries. Doppler ultrasound allows for simultaneous imaging of the artery combined with a pulsed Doppler velocity signal. The combination of these two measurements provides the potential for determining the artery diameter as well as the estimation of the blood flow and shear stress.

The FMD response has been shown to be attenuated in various conditions, including aging and cardiovascular disease [33, 34]. However, it is questionable whether FMD is decreased in these populations due to endothelial dysfunction or to a potential decreased stimulus (i.e. decreased blood flow or shearing following cuff deflation). Therefore normalizing the FMD response to the stimulus following deflation is critical in comparing different populations and determining the clinical usefulness of FMD [35].

Additionally, increased sympathetic nervous system activity can blunt the FMD response [36]. Therefore, in studies evaluating FMD as an indicator of endothelial dysfunction, the strong effect of sympathetic activity on FMD should be considered. For a detailed and excellent review on the guidelines, mechanisms responsible for FMD response, and the clinical utility of FMD testing see Pyke and Tschakovsky [37].

Local blood flow measurements

A number of different techniques have been utilized to measure local tissue blood flow, most dependent on measuring the appearance or disappearance of various tracers, including radioactive isotope clearance (e.g. ^{133}Xe) and ethanol from microdialysis fibers. ^{133}Xe clearance has the capability of measuring blood flow in discrete tissues with small arterial supplies and can be used to measure blood flow to non-muscle tissues such as adipose tissue [38]. It has also been used to measure regional muscle blood flow in response to various conditions such as water immersion [39] and exercise [40]. However, it is limited in its ability to be used for repetitive measurements due to inaccuracy in injected the tracer in the same spot and also by variable perfusion at rest [41], although the increased blood flow during exercise results in a more consistent circulation. Newer imaging techniques such magnetic resonance imaging (MRI) [42], near infrared spectroscopy (NIRS) [43], and positron emission tomography [44] are all being adapted to measurements of blood flow. NIRS utilizes the different absorption of near-infrared light by oxygenated and deoxygenated hemoglobin and from the dynamic absorption pattern, blood flow can be estimated. NIRS in combination with indo-cyanine green, which absorbs light, has compared favorably with other indicator dilution methods of measuring blood flow [3]. MRI uses phase shift of blood protons to calculate instantaneous blood velocity throughout the cardiac cycle and flow in multiple vessels can be obtained simultaneously with precise knowledge of the anatomical location of the measurements. Using this technique, measurements of femoral artery blood flow during low-intensity exercise have been made (Figure 4) and it has been shown that femoral artery blood flow is impaired in persons with diabetes during exercise [42]. These newer imaging techniques offer the promise of measurements of local blood flow in regions that have not been able to be easily measured before and at very high resolution. While they require sophisticated and expensive equipment and analysis they are clearly emerging as important tools.

Radiolabelled microspheres have been used extensively in animal studies to measure local and regional blood flow [45] but are not used in human research. However, a similar technique that uses ultrasonography has recently been used in the assessment of the skeletal muscle microcirculation and may have wide-spread applications. Contrast-enhanced ultrasonography (CEUS), originally used to assess myocardial perfusion [46] has been adapted for the quantification of skeletal muscle perfusion [47]. To quantify tissue perfusion by ultrasonography, intravenous application of a contrast agent (microbubbles) is required. In general, an acoustic signal is obtained from intravenously infused microbubbles of inert gas that are about 1-5 μm in size. The acoustic properties of microbubbles results in their bursting when impacted by high-energy ultrasound pulses, which in turn emits a signal [48]. A series of images are collected over a given period of time in a specified region of interest and a replenishment curve is generated that describes the refilling rate and the volume of microvasculature filled by microbubbles [48]. The curves typically demonstrate an early rise in signal intensity, a short maximum, and a slow, exponential decay from which absolute perfusion parameters can be quantified.

The ability of CEUS to detect perfusion deficits over a range of populations with known microvascular pathologies is yet to be determined. Duerschmied and colleagues [49] demonstrated the utility of CEUS in the detection of perfusion deficits at rest and after calf exercise in patients with peripheral arterial disease. However, the clinical significance of this finding is unclear. CEUS has the advantages of being highly sensitive, even to blood flow within capillaries, is noninvasive, and can be used during voluntary exercise. Additionally, CEUS has great potential for clinical implementation because of its portability, low cost, and requirement for equipment already in place in most vascular laboratories. Limitations to the technique include; 1) perfusion has to be measured at a single representative muscle region and therefore, may not reflect representative results for the whole muscle group, and 2) CEUS data acquisition lasts for 90-120 seconds, therefore, real-time measurement of perfusion is not possible [47].

Conclusion

A number of techniques are available to assess muscle blood flow in humans. Most commonly used techniques rely on measures of limb blood flow with estimates about changes in muscle flow requiring careful consideration of a set of assumptions about how various interventions influence flow to other (especially skin) tissues. Indicator dilution and Doppler ultrasound probably provide the best absolute measures of flow, but they are both expensive and require operator skill, and indicator dilution techniques are invasive and do not provide beat to beat information. Venous occlusion plethysmography is relatively inexpensive and non-invasive, but can only be used at rest and absolute values of flow are problematic. Microdialysis and Xenon washout can be highly localized but have a slow time course and there are concerns about absolute flow values and tissue damage associated with the technique. As noted earlier in the paper there is no gold standard for measuring muscle blood flow in human limbs. Recent advances in technology, particularly in imaging, offer the promise of even more comprehensive studies of the metabolic control of blood flow.

Acknowledgments

The authors thank Sophie Lalande, PhD and Christopher Johnson at Mayo Clinic, Rochester, MN for their time and help with figure preparation.

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Figure 1.

A schematic illustration of the experimental set-up for blood flow measurements by a constant infusion thermodilution technique. (Adapted from [Ref 6], permission pending)

Figure 2.
Schematic illustrating the general setup for measuring forearm blood flow using venous occlusion plethysmography and a sample tracing produced from the measurement.

Figure 3.

Use of Doppler ultrasound during rhythmic forearm exercise. A) Ultrasound image of the brachial artery and blood velocity waveforms during forearm exercise. B) Computer acquired brachial artery mean blood velocity waveforms during rhythmic forearm contractions. Arrows indicate onset of muscle contraction.

Figure 4.

Representative MRI derived time-flow curves of the femoral artery at rest and during submaximal exercise (consisting of leg extensions) in a healthy individual. (Unpublished data from the study by Lalande et al. [42]. Figure provided by Dr. S. Lalande and used with permission)