What is the blood flow to resting human muscle?

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1. An investigation was carried out in five healthy lean adults to assess whether forearm and calf plethysmography largely reflect muscle blood flow as measured by $^{133}$Xe and whether there is substantial variability in the blood flow to muscles located at different sites in the body.

2. Blood flow to forearm and calf flexors and extensors, biceps, triceps and quadriceps was assessed using the $^{133}$Xe clearance technique. Blood flow to forearm skin and subcutaneous adipose tissue was also measured using the $^{133}$Xe clearance technique, whereas blood flow to the forearm and calf was measured using strain gauge plethysmography.

3. The mean blood flow to different muscles ranged from $1.4 \pm 0.6$ (gastrocnemius) to $1.8 \pm 0.7$ (forearm extensor) ml min$^{-1}$ 100 g$^{-1}$ muscle ($1.4 \pm 0.6$ and $1.9 \pm 0.8$ ml min$^{-1}$ 100 ml$^{-1}$ muscle, respectively) but there were no significant differences between them. Forearm and calf blood flows ($2.7 \pm 0.3$ and $3.0 \pm 0.7$ ml min$^{-1}$ 100 ml$^{-1}$ limb tissue, respectively) were about 50% to more than 100% greater ($P<0.025$) than blood flow to the muscles within them ($1.7 \pm 0.5$ and $1.4 \pm 0.5$ ml min$^{-1}$ 100 g$^{-1}$ muscle, respectively, or $1.8 \pm 0.6$ and $1.5 \pm 0.5$ ml min$^{-1}$ 100 ml$^{-1}$ muscle, respectively). In contrast, the blood flows to 100 g of forearm skin ($9.1 \pm 2.6$ ml min$^{-1}$ 100 g$^{-1}$) and adipose tissue ($3.8 \pm 1.1$ ml min$^{-1}$ 100 g$^{-1}$) were higher than the blood flow to 100 g of forearm ($P<0.01$ and not significant, respectively).

4. Although several possibilities can explain the discrepancy between muscle blood flow measured by $^{133}$Xe and blood flow to the distal limbs measured by plethysmography, the results suggest that non-muscular blood flow, especially that to skin, is substantially greater than muscular blood flow. Indeed, the overall blood flow to the forearm could be accounted for by summation of blood flows to individual constituent tissues, which were assumed to be present in proportions typical of lean subjects. The results have important implications in the use of arteriovenous catheterization studies for assessing flux of oxygen, carbon dioxide and metabolites across the body.

INTRODUCTION

Many concepts about the metabolism of human tissues in vivo are based on studies involving the arteriovenous catheterization technique [1]. An important component of this technique is the measurement of tissue blood flow, since this allows quantification of the rate of exchange or flux of oxygen, carbon dioxide and metabolites across the tissues concerned. In the case of metabolic studies of the forearm or leg [1-16], the blood flow (measured by dye-dilution techniques or plethysmography) has frequently been assumed to be largely directed towards muscle. This assumption is largely based on anatomical considerations since muscle is usually the largest component of limbs [16-20].

However, if blood flow (ml min$^{-1}$ 100 ml$^{-1}$ tissue) to non-muscular limb tissues (skin plus adipose tissue plus bone) is substantially different from the blood flow to muscle (ml min$^{-1}$ 100 ml$^{-1}$ muscle), limb blood flow will not give accurate information about muscle blood flow. This led some workers to measure forearm blood flow (with the hand circulation excluded) before and after iontophoresis with adrenaline [16, 21, 22], which is a potent vasoconstrictor of skin blood flow. Such workers have assumed that the remaining blood flow almost entirely reflects blood flow to normal muscle. Unfortunately, such assumptions may be incorrect partly because they assume that blood flow to skin is totally suppressed, partly because they fail to consider blood flow to other limb constituents such as adipose tissue, and partly because some adrenaline may have diffused transcutaneously to produce haemodynamic effects in deeper limb tissues. Other workers [23] have also ignored adipose tissue blood flow when analysing the distribution of blood flow through the forearm.

A more direct way of assessing muscle blood flow is by measuring the clearance of $^{133}$Xe injected directly into muscle [24-30]. In general, the use of this technique in normal subjects has yielded blood flow values in the range 1.0-2.2 ml min$^{-1}$ 100 g$^{-1}$ muscle. In contrast, forearm plethysmography [4, 6, 16, 23, 25, 31-34] or dye-dilution techniques [3, 5,
7, 8, 35] in normal subjects have produced results that are usually greater than this (2-4 ml min⁻¹ 100 ml⁻¹). In one study [29] in which blood flow to calf muscle was measured with ¹³³Xe (n=24) and compared with calf blood flow measured by plethysmography, the results were twofold different [2.3±0.1 (calf) versus 1.1±0.1 (muscle) ml min⁻¹ 100g⁻¹ tissue]. In another study in which similar observations were made [28], the blood flow to the calf (2.8 ml min⁻¹ 100 g⁻¹) was 40-55% greater than the blood flow to the tibialis and gastrocnemius muscles (1.8-2.0 ml min⁻¹ 100 g⁻¹).

These observations prompted us to consider in more detail the distribution of blood flow to the forearm, since the forearm arteriovenous catheterization technique is frequently used to assess muscle metabolism in vivo [1]. The study aimed to (a) measure the blood flow to forearm and calf muscles (using the ¹³³Xe technique) and compare it with the results of forearm or calf plethysmography obtained at the same time under the same conditions; (b) assess the contribution of non-muscular components of the forearm to the total forearm blood flow; and (c) assess the variability in blood flow to different muscles of the body.

MATERIALS AND METHODS

Five healthy young adult males (age 36±4 years, weight 68.7±4.5 kg, height 171.8±4.7 cm, body mass index 23.2±0.8 kg/m², means±SD) were studied in the fasted state. The skinfold thicknesses were measured over the biceps, triceps, supra-iliac, medial calf. Bioimpedance measurements were made using a Holtain prototype machine (Holtain Ltd, Crosswell, Crymych, Dyfed, Wales, U.K.) as described by Fuller and Elia [37]. Body composition was assessed from skinfold thicknesses (sum of biceps, triceps, subscapular and supra-iliac [36]) and from bioimpedance using the Holtain equation [37] assuming that water contributes 73% of fat-free mass. The mid-forearm cross-sectional area of the skin and subcutaneous adipose tissue combined were calculated on the basis of the formula given by Martin et al. [38]. Blood flow measurements were made in a room maintained at 25±0.5°C. The measurements began after the subjects had rested in a recumbent position for at least half an hour. Blood flow to the muscle was studied by the radioactive ¹³³Xe clearance technique [24]. ¹³³Xe dissolved in sterile saline was obtained from Amersham (Amersham, Bucks, U.K.) and approximately 75 µCi was injected intramuscularly to a depth of about 10 mm using the fine-bore needle of an insulin syringe. The radioactivity at the site was measured by a sodium iodide detector placed at least 30 cm away from the site. The blood flow was calculated from the decay constant and the partition coefficient for ¹³³Xe (tissue/blood, 0.7 g/g) using standard methods [24]. After an initial 10-15 min which were allowed to overcome the possible effects of traumatic hyperaemia and possible loss of the ¹³³Xe from the injection tract, loss of radioactivity from the injection site was approximately mono-exponential.

The ¹³³Xe injections were made into the following muscles: brachioradialis (elbow flexor), extensor digitorum (wrist extensor), biceps (forearm flexor), triceps (forearm extensor), quadriceps (knee extensor), gastrocnemius (foot flexor) and tibialis (foot extensor). The sequence of injections was random and made in such a manner that there was no interference from a distal site to a proximal site, or from one side of the body to the other.

Forearm and calf blood flows were also measured by mercury-in-rubber strain gauge plethysmography [D E Hokanson Inc–PMS (Instruments) Ltd, Maidenhead, Berks, U.K.]. A sphygmomanometer cuff was placed just above the antecubital fossa (or above the popliteal fossa) and inflated to 55 mmHg, cutting off venous return, so that arterial inflow could be recorded by the plethysmograph. The strain gauge was applied around the forearm and kept under minimal tension at a constant position throughout the study (i.e. it did not roll or constrict the limbs). The limbs rested on folded towels which were placed below the position of the plethysmograph. Hand and wrist (or foot and ankle) blood flow was excluded by the inflation of a paediatric cuff at the wrist or ankle to about 200 mmHg, 2 min before the measurement. Three measurements of forearm blood flow were made and the mean value was calculated. No significant differences between sequential measurements were found. Forearm blood flow was measured at the same time as the ¹³³Xe blood flow measurements on forearm muscles, and calf blood flow was measured at the same time as the ¹³³Xe measurements on calf muscles. The procedures involved with plethysmography had no detectable effect on the loss of ¹³³Xe from the muscles within the forearm or calf. Furthermore, in separate studies we have shown that occluding the wrist for a period of up to 5 min had no detectable effect on the loss of ¹³³Xe injected into muscle. In addition, there was no detectable effect of intermittent cuff occlusion (55 mmHg) of the upper arm, as used in this study (or continuous occlusion at 55 mmHg for 1 min), on the loss of ¹³³Xe from forearm muscle.

Blood flow to the skin on the ventral surface of the forearm was also measured in four of the subjects by the ¹³³Xe clearance technique [39] on a separate occasion under the same conditions. Finally, blood flow to subcutaneous adipose tissue was measured [25] on the ventral surface of the mid-forearm by the same technique in the same subjects. ¹³³Xe (50 µCi) was used for injection in these studies. In calculating blood flow, the ¹³³Xe partition coefficient (tissue/blood, g/g) was assumed to be 0.7 for skin [39] and 8.5 for adipose tissue (the mean value of 8.2 and 8.7 obtained in two
Table 1. Regional blood flow. Values are means ± SD. Statistical significance: *P < 0.005 compared with muscle blood flow. Since the densities of muscle, skin and adipose tissue are about 1.05 [47], 1.10 [52] and 0.92 [53] g/ml, the experimentally observed values of blood flow through these tissues (ml min⁻¹ 100 g⁻¹ tissue, first column) are converted to ml min⁻¹ 100 ml⁻¹ tissue (second column) by multiplying the values in the first column by the density of the tissue. This procedure allows a direct comparison with the plethysmographic results of limb blood flows which are measured in ml min⁻¹ 100 ml⁻¹ limb.

<table>
<thead>
<tr>
<th>Blood flow</th>
<th>ml min⁻¹ 100 g⁻¹ tissue</th>
<th>ml min⁻¹ 100 ml⁻¹ tissue</th>
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<tbody>
<tr>
<td><strong>Limb</strong></td>
<td></td>
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</tr>
<tr>
<td>Forearm</td>
<td>2.7 ± 0.3*</td>
<td></td>
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<tr>
<td>Calf</td>
<td>3.0 ± 0.7</td>
<td></td>
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<tr>
<td><strong>Muscle</strong></td>
<td></td>
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<tr>
<td>Brachioradialis</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>Flexor digitorum</td>
<td>1.8 ± 0.7</td>
<td>1.9 ± 0.7</td>
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<tr>
<td>Upper arm</td>
<td></td>
<td></td>
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<tr>
<td>Bicep</td>
<td>1.5 ± 0.6</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>Tricep</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.4</td>
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<tr>
<td>Calf</td>
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<tr>
<td>Tibialis</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.6</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>1.4 ± 0.4</td>
<td>1.5 ± 0.4</td>
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<tr>
<td>Thigh</td>
<td>1.6 ± 0.6</td>
<td>1.7 ± 0.6</td>
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<tr>
<td>Quadriceps</td>
<td>1.6 ± 0.6</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>Forearm skin (by ¹³³Xe)</td>
<td>9.1 ± 2.6</td>
<td>10.9 ± 2.9*</td>
</tr>
<tr>
<td>Forearm adipose tissue (by ¹³³Xe)</td>
<td>3.8 ± 1.1</td>
<td>3.5 ± 1.0*</td>
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</table>

separate studies on human subcutaneous adipose tissue sampled from normal subjects [40, 41]).

**Statistics**

Statistical analysis was undertaken using Student's t-test which was applied to paired data where appropriate. Results are expressed as means ± SD. The study was approved by the Local Ethics Committee.

**RESULTS**

The subjects were estimated to have 18 ± 2% body fat by anthropometry [31] and 24 ± 3% fat by bioimpedance. Skin and subcutaneous adipose tissue were estimated to account for 13.5% of the mid-forearm cross-sectional area and 7% of the mid-calf cross-sectional area (intermuscular adipose tissue was not included in this estimate).

The results of this study demonstrate a striking difference in the values obtained for forearm blood flow and forearm muscle blood flow (Table 1). In addition, although there was some variation in the blood flow to different muscles as measured by the ¹³³Xe technique, the results were not significantly different from each other (Table 1). The average mean values of individual muscles ranged from 1.4 to 1.8 ml min⁻¹ 100 g⁻¹ in the upper limb, but there was no significant difference between them. Whole segment blood flows (forearm and calf; ml min⁻¹ 100 ml⁻¹) measured by strain gauge plethysmography, were found to be 1.5–2-fold greater (P < 0.025) than the blood flows (ml min⁻¹ 100 g⁻¹) to the forearm and calf muscles, which were measured simultaneously by the ¹³³Xe technique. The blood flows to the adipose tissue and skin of the forearm (also measured by ¹³³Xe) were found to be 3.8 ± 1.1 and 9.1 ± 2.6 ml min⁻¹ 100 g⁻¹ tissue, respectively (Table 1; not significant and P < 0.01 compared with forearm blood flow, respectively). At this time forearm blood flow was found to be 2.8 ± 0.4 ml min⁻¹ 100 ml⁻¹ forearm.

**DISCUSSION**

This study in a small number of subjects demonstrates that under the same conditions there is no significant difference in the blood flow to several human muscles at rest as measured by the ¹³³Xe clearance technique. It also confirms the results of two previous studies in normal subjects [28, 29], which showed a major discrepancy between the blood flow (ml min⁻¹ 100 g⁻¹) to calf muscles as measured by ¹³³Xe, and blood flow to all the calf tissues (ml min⁻¹ 100 g⁻¹) as measured by plethysmography. This study demonstrates a similar discrepancy in the forearm and provides more detailed information about the distribution of blood flow in the forearm. The results have important implications about the use of the forearm catheterization technique to assess the rate of exchange of metabolites across muscle.

Several possibilities could explain the higher blood flow to 100 g of forearm (or calf) than to 100 g of muscle. One of these concerns the assumption that the muscle/blood partition coefficient for ¹³³Xe is 0.7. If the partition coefficient was higher, the calculated blood flow to muscle would also be higher. However, the partition coefficient for a variety of tissues (e.g. muscle, kidney, liver, skin) is close to 0.7 and the value for a variety of muscles (in dogs, rats and rabbits) is also close to 0.7 with a range 0.53–0.75. For example in dogs, Conn [42] gives a value of 0.73g of muscle/g of blood at a haemoglobin concentration of 15 g/100 ml of blood (or 0.7 g of muscle/ml of blood), assuming that the density of blood is about 1.05 [43], and Chen et al. [44] give a value of 0.69 (g/ml). In the rat, Andersen and Ladefoged [45] give a value of 0.58 (g/g) for thigh muscle and 0.78 for abdominal muscle (-0.74 g/ml), and using the data of Yeh and Peterson [46] the value for rabbit muscle can be calculated to be 0.61 (g/ml) [42]. Therefore, there seems to be a general consensus that the value of the muscle/blood partition coefficient for ¹³³Xe is close to 0.7; and although this value may be affected to some extent by the lipid content of muscle and the blood packed cell volume [40], this is not considered a likely explanation for the large differ-
ence between blood flow to 100 g of muscle (calf or forearm muscle) measured by $^{133}$Xe, and 100 g of mixed forearm or calf tissues measured by plethysmography. Similarly, although the blood flow to 100 g of muscle is about 5% lower than the blood flow/100 ml of muscle (in males muscle has a density of about 1.05 g/ml [47]), this can only explain a small proportion of the difference between the two blood flow measurements.

Another possible explanation for the apparent difference between blood flow to 100 g of muscle and 100 g of forearm or calf is that there are two distinct blood flows within muscle, nutritive (capillary flow) and non-nutritive (shunt) blood flow, so that $^{133}$Xe injected into muscle is cleared by capillary blood but not necessarily by blood that is shunted in muscle some distance from the site of $^{133}$Xe injection. Although there has been long-standing controversy about the existence of such vascular shunts in muscle [48], recent evidence suggests that there is little or no shunting of blood through muscle (see [49] for evidence, and for other references to support this view).

Another possible explanation for the observations is that the blood flow to the muscles injected with $^{133}$Xe does not reflect the blood flow of other muscles in the limb. Although this remains a possibility, a remarkably small difference was found between the blood flow of the two forearm muscles injected with $^{133}$Xe (forearm flexor and extensor) and, indeed, between these and many of the other muscles injected with $^{133}$Xe.

Finally, it is possible that previous workers have underestimated the contribution of non-muscular tissues to the blood flow of the forearm (or calf). The anatomical dissection studies of Cooper et al. [16] suggest that muscle accounts for about 65% of the forearm tissue, tendon accounts for 5%, adipose tissue 8%, bone 18.5% and skin 8.5%. Similar values have been obtained using scanning techniques (e.g. [18]) in subjects with a similar body composition to those used in this study. The calculated cross-sectional area of the skin and subcutaneous adipose tissue in the forearms of our subjects is consistent with these observations.

Using the values given by Cooper et al. [16] and the values of blood flow to muscle, adipose tissue and skin obtained in this study (and a value of 1 ml min$^{-1}$ 100 g$^{-1}$ [50] for normal human bone, and a similar value for tendon), it can be calculated that the blood flow to the forearm is (0.65 x 1.7 + (0.05 x 1) + (0.08 x 3.8) + (0.085 x 9.1) + (0.135 x 1) = (2.4 ml min$^{-1}$ 100 g$^{-1}$ or 2.5 ml min$^{-1}$ 100 ml$^{-1}$ forearm assuming the density of muscle to be 1.05 g/ml. This value corresponds closely to the value (2.7 ml min$^{-1}$ 100 ml$^{-1}$ forearm) estimated by plethysmography. Studies in dogs [51] suggest that blood flow to bone is variable and depends on the type of bone (e.g. 1.6 ml min$^{-1}$ 100 g$^{-1}$ cancellous bone). However, if the blood flow to the forearm bone in our subjects was as high as 2 ml min$^{-1}$ 100 g$^{-1}$, this would only increase total forearm flow by 0.135 ml min$^{-1}$ 100 g$^{-1}$. In contrast, it is possible that skin blood flow may have been overestimated due to the difficulties in assessing the confounding effects of possible reactive hyperaemia in a tissue which shows a rapid loss of $^{133}$Xe. Using measurements of blood flow to muscle ($^{133}$Xe) and forearm (plethysmography) we calculate that less than half of the total blood flow to the forearm is directed towards muscle, and similar conclusions can be made for the calf. In contrast, measurements of blood flow to the forearm before and after iontophoresis [16, 21, 22] with adrenaline suggest that 55–80% of the total blood flow to the forearm is directed towards muscle. However, the assumptions underlying the iontophoresis technique are open to criticism (see the Introduction). Differences in forearm composition and the variable blood flow to individual forearm tissues is expected to account for substantial inter-individual variability. This study was carried out at an environmental temperature of $25 \pm 0.5^\circ$C. It would be interesting to undertake similar studies between 20 and $27^\circ$C, which covers the range of most metabolic studies in the literature, in order to assess the extent to which the variability in skin blood flow alters the relationship between muscle and forearm blood flows.

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