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The role of perfusion in the oxygen extraction capability of skin and skeletal muscle

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Submitted 15 January 2016; accepted in final form 22 March 2016

Thorn CE, Shore AC. The role of perfusion in the oxygen extraction capability of skin and skeletal muscle. Am J Physiol Heart Circ Physiol 310: H1277–H1284, 2016. First published March 25, 2016; doi:10.1152/ajpheart.00047.2016.—Oxygen extraction (OE) by all cells is dependent on an adequate supply of oxygen in proximal blood vessels and the cell’s need and ability to uptake that oxygen. Here the role of blood flow in regulating OE in skin and skeletal muscle was investigated in lean and obese men. OE was derived by two optical reflectance spectroscopy techniques: 1) from the rate of fall in mean blood saturation during a 4 min below knee arterial occlusion, and thus no blood flow, in calf skin and skeletal muscle and 2) in perfused, unperturbed skin, using the spontaneous falls in mean blood saturation induced by vasomotion in calf and forearm skin of 24 subjects, 12 lean and 12 obese. OE in perfused skin was significantly higher in lean compared with obese subjects in forearm (Mann-Whitney, P < 0.004) and calf (P < 0.001) and did not correlate with OE in unperfused skin (ρ = −0.01, P = 0.48). With arterial occlusion and thus no blood flow, skin OE in lean and obese subjects no longer differed (P = 0.23, not significant). In contrast in skeletal muscle with arterial occlusion and no blood flow, the difference in OE between lean and obese subjects occurred, with obese subjects exhibiting significantly higher OE (P < 0.012). The classic model of metabolic blood flow regulation to support oxygen extraction is evident in perfused skin; OE is perturbed without blood flow and reduced in obesity. In resting skeletal muscle other mechanism(s), independent of blood flow, are implicated in oxygen extraction.

NEW & NOTEWORTHY

A novel noninvasive optical technique has uniquely demonstrated that oxygen extraction in skin is dependent on blood flow, whereas in resting skeletal muscle other mechanisms independent of perfusion are implicated. Obesity is associated with lower oxygen extraction in skin independent of temperature and higher oxygen extraction in resting skeletal muscle.

THE VIABILITY OF ALL HUMAN cells is dependent on two separate fundamental processes: the ability of the cardiovascular system to supply nutrients in close proximity to the cell via the microcirculation and the ability of the cell to uptake and metabolize these products. Crucial to all tissue health is the ability to couple together these two processes and match local blood flow with changing metabolic demands. The classic model of the metabolic regulation of blood flow is thought to be driven by either the accumulation of vasodilator metabolites such as CO₂, lactate, H⁺, K⁺, and adenosine related to the local level of hypoxia or the existence of oxygen sensors such as the release of ATP from red blood cells (10, 11, 18) that respond to local changes in tissue PO₂. The metabolites may act alone as vascular smooth muscle relaxants or stimulate nitric oxide or prostacyclin release from the vascular endothelium (21). Key to this classic theory of matching local blood flow with metabolic demand is that as a feedback system by definition, regulation will only occur when homeostasis is perturbed. This leads to a cyclical behavior fluctuating between normoxic and hypoxic states. There is increasing agreement that there can be no single signaling molecule that drives this process (38) and that alternative models of the regulation of blood flow to match supply and demand in different tissues are required (17, 24, 32).

The purpose of this study is to use noninvasive optical techniques to examine the relationship between local blood flow regulation and oxygen extraction in two different tissue types: skin and skeletal muscle, in resting lean and obese humans. The established techniques of white light optical reflectance spectroscopy (ORS) and near infrared spectroscopy (NIRS) noninvasively assess the oxygenation status and hemodynamics of the microcirculation and provide a measure of the supply and uptake of oxygen in the tissue. The most established method of deriving a measure of oxygen extraction using these techniques requires the forced induction of hypoxemia using either an arterial occlusion (12, 20) or venous occlusion (4, 22) or both (44). Oxygen extraction estimations have also been derived with NIRS from the gradual decrease in muscle oxygenation during exercise (5, 8, 13, 19, 39). This oxygen extraction is derived from the rate at which HbO₂ is converted into Hb, assuming a closed system where the total hemoglobin or blood volume remains constant during the measurement and there is no blood flow. We previously described an alternative novel technique for the measurement of oxygen extraction in tissue with normal perfusion and without the need for forced hypoxia in unperturbed tissue (41). Instead of deriving oxygen extraction from a sustained fall in [HbO₂] and increase in [Hb] induced by a cuff (i.e., induced hypox-
emia), oxygen extraction is derived in a similar manner but on this occasion from the spontaneous falls in [HbO₂] and rises in [Hb] observed as a consequence of vasomotion in the skin microcirculation. Vasomotion is the spontaneous rhythmic vasodilation and vasoconstriction of blood vessels thought to play a role in the delivery of oxygen to tissue (16, 29, 35, 36, 43). It has been shown that in unperturbed conditions in the skin, vasomotion with a period of around one minute induces rhythmic oscillations in the mean blood oxygen saturation (S_mabO₂) in the skin microcirculation (42). There are periods where both blood flux and blood volume remain constant in the microcirculation but there is a steady decrease in oxyhemoglobin [HbO₂] and equal and opposite increase in deoxyhemoglobin [Hb] that might reasonably be assumed to be a consequence of oxygen extraction alone (41). This research suggests that conforming to the classic model of the metabolic theory of local blood flow regulation (17) these spontaneous rhythmic falls in blood oxygenation in skin subsequently induce hypoxic vasodilation and induce a surge in blood flow to the tissue (41). This particular form of vasomotion is less evident in skeletal muscle and therefore precludes this noninvasive measurement of oxygen extraction in perfused muscle. Therefore the aim of this study is to investigate the effect of blood flow occlusion on the regulation of oxygen extraction in skin and then to compare the oxygen extract in skin and skeletal muscle during an arterial occlusion. To extend the range of resting oxygen extraction a cohort of both lean and obese subjects was studied.

MATERIALS AND METHODS

Optical reflectance spectroscopy. The ORS instrumentation used in this study was the O2C (Lea Medizintechnik, Giessen, Germany) with an LF-2 surface probe. Continuous white light (500–850 nm) is guided to the skin via an optical fiber, and backscattered light is collected by a detector fiber encapsulated in the same probe at a distance of 2 mm from the light source. The sampled volume of tissue is considered to be to a depth of approximately half the probe spacing: therefore, a total skin thickness of 1 mm is considered to be sampled (2). This has been established both by direct measurement (9) and Monte Carlo modeling (30). The collected light is spectrally analyzed in steps of 1 nm (500–620 nm) to derive relative concentrations of oxy- and deoxyhemoglobin. The derived concentration parameters [HbO₂] and [Hb] can also provide a measure of changes in blood volume in the skin obtained from the concentration of total hemoglobin [rHb], being the sum of [HbO₂] and [Hb]. Similarly, the mean blood oxygen saturation defined by S_mabO₂ = [HbO₂] × 100/([HbO₂] + [Hb]) can be determined. However, it is important to recognize that ORS calculates the mean values of [HbO₂] and [Hb] across all vessels in the microcirculation of the skin. Therefore, the derived S_mabO₂ is a measure of mean blood oxygen saturation across arterioles, capillaries, and venules.

Near infrared spectroscopy. Instead of a broadband light source, the Hamamatsu NIRO 200 uses four pulsed-laser diodes at wavelengths of 775, 825, 850, and 905 nm. The light source and detector are spaced 4 cm apart, giving a tissue sample volume to a depth of ~2 cm. This spectrometer has the capacity to determine absolute values of the concentrations of oxy- and deoxyhemoglobin in tissue by spatially resolved spectroscopy (SRS) (28). SRS calculates a normalized tissue hemoglobin index (nTHI) and tissue oxygen index (TOI) without the necessity for absolute reflectance measurements. The parameter nTHI is set to a value of 1 at the start of the study such that a subsequent nTHI of 1.1 defines a blood volume increase of 10% since measurement commenced. The parameter TOI has the same dimensions as S_mabO₂ being the percentage of total hemoglobin bound to oxygen in the microcirculation of the volume of tissue being studied. In this article, the terms nTHI, TOI, and [Hb] will be used to denote generic parameters that include both hemoglobin and myoglobin. The absorption spectrum for myoglobin is almost indistinguishable from hemoglobin; however, the oxygen-myoglobin dissociation curve is a rectangular hyperbola, where myoglobin only releases O₂ at low PO₂ < 20 mmHg or around 25% oxygen saturation. In this study oxygen extraction in muscle is derived during the linear part of the oxygen dissociation curve from ~70 to 35% where there should be no change in the oxygenation status of myoglobin.

Laser-Doppler fluximetry. Incorporated within the O2C probe is an optical fiber that guides the output from 830 nm (30 mW) laser diode to the surface of the skin, adjacent to the ORS white light source. The moving red blood cells in the microcirculation of the skin Doppler shift the laser light, which returns to a detector 2 mm from the laser source. This probe separation is the same as for optical reflectance spectroscopy, and therefore the area of tissue sampled by laser-Doppler flowmetry overlaps that studied by ORS. The only role of laser-Doppler flowmetry in this study is to ensure that blood flux remains constant for the derivation of oxygen extraction in perfused, unperturbed conditions.

Experimental protocols. The investigation was carried out with the approval of the Devon and Torbay Research Ethics Committee (09/ Q2102/99) and in accordance with the Declaration of Helsinki. Twenty-four healthy, nondiabetic, normotensive, male volunteers took part in the study; their clinical characteristics are in Table 1. Twelve obese subjects [body mass index (BMI) > 30 kg/m²] were age matched with twelve lean subjects (BMI < 26 kg/m²). All volunteers gave written, informed consent and were studied in the morning having fasted and refrained from caffeine, alcohol, and smoking from 22.00 h the previous evening. Participants were not taking any vasoactive medication. Subjects lay supine and were acclimatized for 30 min in a thermostatically controlled room at a temperature of 22.0 ± 0.5°C. Skin temperature was continuously monitored in the lateral calf and forearm to ensure it remained constant for the duration of the study. A below knee cuff was placed around the right leg to provide a 4-min arterial occlusion at 200 mmHg. The O2C probe was placed on the lower lateral right calf, distal from the cuff, and the NIRS probe was placed over the lateral aspect of the planter flexor muscles of right calf. Upon acclimatization and stabilization of skin temperature, baseline data were collected for 30 min in unperturbed skin for the derivation of OE with flow. The below knee arterial cuff was then rapidly inflated to 200 mmHg for the derivation of skin and skeletal muscle OE with no flow. Data were simultaneously collected from a second O2C probe placed ~10 cm distally to the lateral epicondyle of Table 1. Comparison of clinical characteristics of 24 healthy male subjects, 12 lean and 12 obese

<table>
<thead>
<tr>
<th>Subject Details of 24 Healthy Male Subjects</th>
<th>Normal</th>
<th>Obese</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56 (38–67)</td>
<td>52 (35–61)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mmHg</td>
<td>120 (116–132)</td>
<td>133 (122–137)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mmHg</td>
<td>76 (72–77)</td>
<td>76 (74–82)</td>
<td>ns</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.2 (4.8–5.4)</td>
<td>5.4 (5.1–5.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Fasting cholesterol, mmol/l</td>
<td>5.4 (4.8–5.7)</td>
<td>5.8 (4.7–6.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/l</td>
<td>0.82 (0.74–0.90)</td>
<td>1.59 (1.22–2.58)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.1 (23.2–25.1)</td>
<td>32.1 (30.7–36.5)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Forearm skin temperature, °C</td>
<td>29.3 (28.2–31.0)</td>
<td>30.5 (30.2–31.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Calf skin temperature, °C</td>
<td>28.3 (26.5–29.2)</td>
<td>29.2 (28.2–30.3)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are medians (interquartile range). ns, Not significant.
the humerus over the extensor muscles of the right forearm. The definition of oxygen extraction in this article is taken to be the rate of decoupling of oxygen bound to hemoglobin and is derived from the equal and opposite reduction in oxyhemoglobin concentration [HbO₂] and accumulation of deoxyhemoglobin [Hb]. This may also be termed oxygen consumption or oxygen uptake and is in contrast to the Fick definition of oxygen extraction, which has units of milliliter O₂ per liter blood (OEFick). The definition of hypoxemia is taken to be a lower than normal oxygen tension in the blood, therefore a lower than normal saturation of hemoglobin and oxygen content per unit volume (37).

Data analysis. The derivation of a measure of oxygen extraction during an arterial occlusion in this study is made only when 1) the blood volume [rHb] remains constant, 2) there is an equal and opposite change in [HbO₂] and [Hb], and 3) SmbO₂ in skin or TOI in muscle falls linearly with time. Under these specific conditions, oxygen extraction was derived in Excel (Microsoft) from the gradient of a simple linear regression performed on the first 60 s of data after cuff inflation for SmbO₂ in skin (Fig. 1) and TOI in muscle (not shown). Linearity in all analysis was confirmed by tight linear correlation with all Pearson’s correlation coefficient $r^2 > 0.90, P < 0.001$. A positive measure of oxygen extraction was obtained by taking the negative of the gradient of the appropriate parameter during arterial occlusion. The oxygen extraction is a measure of the rate of oxygen uptake as a proportion of the blood concentration in tissue under investigation and is not a measure of oxygen consumption.

The full description of the derivation of oxygen extraction in perfused, unperturbed skin has been previously described (41). In brief, each subject’s raw ORS baseline data were manually examined to identify patterns in fluctuation in [HbO₂], [Hb], [rHb], and hence SmbO₂ spontaneously induced by vasomotion. Data were defined as suitable for the measurement of oxygen extraction if 1) the frequency of oscillation was <0.02 Hz related to endothelial activity, 2) there was an antiphase change in [HbO₂] and [Hb] with minimal changes in total blood volume [rHb] synchronized predominantly with changes in [HbO₂], and 3) the rise in SmbO₂ was synchronized with a short surge in flux. Examples of this data are highlighted in Fig. 2.

During this period, the steady decrease in [HbO₂] and rise in [Hb] was assumed to be a consequence of oxygen extraction alone. The fall in SmbO₂ induced by the vasomotion is nonlinear, and a measure of this oxygen extraction has been approximated to the reciprocal of the
time for the mean blood oxygen saturation to fall by half during this period ($t_{0.5}$).

Statistics. Data presented in the text are medians and interquartile ranges unless specified as means ± SD. Statistical analysis was performed by IBM Statistics 22 (SPSS, Chicago, IL) with data sets tested for normality using the Kolmogorov-Smirnov test. For normally distributed data, group comparisons were made by parametric unpaired t-test. For nonnormally distributed data, nonparametric statistics were applied. Spearman’s correlation coefficient ($\rho$) is applied where data sets are not normally distributed. The study was powered on previously published data of forearm skin oxygen extraction in lean and obese subjects (41). A sample size of $N = 12$ in each group provided a power of 0.99 at a significance level of 5% to detect a difference of 2 SD.

RESULTS

Skin oxygen extraction, without intervention and with blood flow, was uniquely derived in the calf and forearm of lean and obese subjects from the spontaneous oscillations in $S_{\text{mO}_2}$, [HbO$_2$], [Hb], [rHb], and flux induced by vasomotion in the skin microcirculation. There is good correlation between this calf skin OE and forearm skin OE ($\rho = 0.51$, $P < 0.018$, Fig. 3) in 17 subjects, the transient nature of vasomotion precluding data from all subjects (41). The repeatability of this novel technique had an intrasubject coefficient of variation of 12% (7–16%) for all lean and obese subjects, 14% (8–18%) for lean subjects, and 10% (7–15%) for obese subjects in the forearm. There was no significant difference in repeatability between the lean and obese groups (Mann-Whitney, $P = 0.55$).

If oxygen extraction in the skin is regulated by the metabolic regulation of blood flow, then this would be perturbed by an arterial cuff. Indeed, calf skin oxygen extraction derived in all 24 subjects through the established technique requiring an arterial occlusion, and thus no blood flow, did not correlate with the oxygen extraction derived in the same tissue in physiologically unperturbed conditions [$\rho = -0.01$, not significant (ns), Fig. 4] (with blood flow).

We have previously demonstrated that in unperturbed forearm skin, oxygen extraction is significantly greater in lean compared with obese subjects (41). In this study we confirm this finding on a different site by demonstrating that oxygen extraction in perfused calf skin is significantly greater in 11 lean subjects compared with 10 obese subjects (0.077 vs. 0.050 s$^{-1}$, $P < 0.001$, Fig. 5). The difference in skin oxygen extraction between lean and obese individuals was lost when blood flow was occluded by an arterial cuff (Fig. 6, Mann-Whitney, 0.32 ± 0.11 vs. 0.36 ± 0.11%/s, $P = 0.23$, ns).

Higher skin oxygen extraction in lean subjects may reasonably arise from either a higher resting tissue blood flow or a higher skin temperature (and thus metabolic demand). There was no statistical difference between the average resting blood flux in the lean and obese subjects in the forearm or calf skin (Mann-Whitney, $P = 0.79$ and $P = 0.27$, respectively) to account for the difference in oxygen extraction observed. There was also no significant difference between the lean and obese groups in skin temperature in either the forearm or calf skin (Table 1).
Perfused skin oxygen extraction increased with skin temperature in the lean subjects in the calf (Pearson’s correlation coefficient \( r = 0.86, P < 0.015 \)) and forearm (\( r = 0.81, P < 0.020 \)) but not in obese subjects (\( P = 0.27 \) and \( P = 0.67 \), respectively, Fig. 7). No correlation was demonstrated across the 24 subjects between their individual skin temperature and their mean blood flux in the calf skin (\( P = 0.98 \) and \( P = 0.54 \), respectively) or in the forearm (\( P = 0.43 \) and \( P = 0.19 \), respectively, data not shown).

Oxygen extraction in resting skeletal muscle during an arterial occlusion, and thus no blood flow, was significantly lower in lean subjects compared with obese subjects (0.062 vs. 0.083%/s, \( P = 0.012 \), Fig. 8). Across our whole study group of lean and obese subjects, oxygen extraction in perfused skin is associated with unperfused skeletal muscle oxygen extraction (\( r = 0.70, P < 0.005 \), Fig. 9). Within the lean subjects alone, this correlation is evident (\( r = 0.59, P < 0.05 \)) though for the obese subjects their constrained oxygen extraction in both skin and skeletal muscle precludes this association (\( r = 0.14 \), ns).

A schematic diagram summarizing our data is shown in Fig. 10. In both lean and obese subjects, the mean blood saturation of the calf skeletal muscle was 10% higher than in the skin. In lean subjects, the forearm and calf \( S_{\text{mbO}_2} \) were 47.1 ± 9.5 and 45.5 ± 11.1% compared with a muscle TOI of 57.2 ± 10.6%, whereas in the obese subjects, the forearm and calf \( S_{\text{mbO}_2} \) were 46.6 ± 12.7 and 47.1 ± 12.0% compared with a muscle TOI of 57.2 ± 10.6%. Oxygen extraction with no flow is derived during the first minute of an arterial occlusion in skin and muscle from the gradient of the fall in mean tissue oxygen saturation \( S_{\text{mbO}_2} \). The oxygen extraction is a measure of the rate of oxygen uptake as a proportion of the concentration of available blood in the tissue, and therefore there is no direct comparison between different tissue types. As an approximation, the capillary density of postural skeletal muscle is approximately eightfold higher than skin (313 and 317 vs. 38 number/mm²) (1, 6, 33), each capillary in muscle supplying oxygen to a smaller volume of tissue compared with skin. From our oxygen extraction gradient measurements in skin and muscle, we would therefore predict that skeletal muscle oxygen consumption to be (8 × 0.06)/0.3 = 1.5 times higher than skin consumption, which is consistent with the literature [0.43 ml·min⁻¹·100 g tissue muscle⁻¹ vs. 0.21 ml·min⁻¹·100 g tissue skin⁻¹ (23, 45)]. Oxygen extraction with flow is derived from the spontaneous fluctuations in calf skin \( S_{\text{mbO}_2} \) induced by vasomotion falling by 7.6 ± 3.5% in lean subjects and 7.5 ± 3.9% in obese subjects before triggering a hypoxic vasodilation. Similar oscillations of amplitude of 8.9 ± 3.7 and 9.2 ± 4.6% were observed in lean and obese forearm skin, respectively.

**DISCUSSION**

Our novel, noninvasive, optical technique measures oxygen extraction in unperturbed skin and has demonstrated that lean subjects exhibit a wide range of oxygen extraction which is significantly higher than that of obese subjects. This was demonstrated in both forearm and calf skin. This oxygen
This is a single document page containing text related to the oxygen dissociation curve and muscle oxygen extraction. The page discusses the relationship between skin oxygen saturation and blood flow, highlighting that oxygen extraction was higher in lean subjects with higher skin temperatures but not in the obese.

Stopping perfusion with an arterial cuff removes the differences between skin oxygen extraction in lean and obese individuals, suggesting that differences between the groups seen in skin may be related to a perfusion-dependent mechanism. The transfer of oxygen from blood to tissue is dependent on both flow-limited exchange and diffusion-limited exchange and is given by the following:

\[ \text{OE}_{\text{Fick}} = \left[ \left( \frac{P_{\text{inO}_2} - P_{\text{ISFO}_2}}{P_{\text{inO}_2}} \right) \left[ 1 - \exp \left( -\frac{\alpha DS}{Q} \right) \right] \right] \]

where \( P_{\text{inO}_2} \) and \( P_{\text{ISFO}_2} \) are the partial pressures of oxygen in incoming blood and interstitium, \( \alpha \) is solubility of oxygen, \( D \) is diffusion coefficient of oxygen, \( S \) is surface area of capillary divided by its wall thickness, \( Q \) is flow, \( \beta \) is the slope of the oxygen dissociation curve (\( dS/dP_{O_2} \) in mmHg\(^{-1}\)), and \([\text{Hb}]\) is blood hemoglobin concentration (31).

In perfused, unperturbed skin, \( \text{OE}_{\text{Fick}} \) is flow limited and is proportional to \( Q \) and is given by the following:

\[ \text{OE}_{\text{Fick}} = \left[ \left( \frac{P_{\text{inO}_2} - P_{\text{ISFO}_2}}{P_{\text{inO}_2}} \right) \left[ 1 - \exp \left( -\frac{\alpha DS}{Q} \right) \right] \right] \]

Fig. 8. Skeletal muscle oxygen extraction with no blood flow (%s\(^{-1}\)) in lean and obese subjects. TOI, tissue oxygen index.

Fig. 9. Oxygen extraction in perfused calf skin compared with oxygen extraction in calf muscle with no blood flow in 20 healthy males.

Fig. 10. Schematic diagram of the measurement of oxygen extraction from the rate of change of mean blood saturation. The fall in mean blood saturation was either induced by an arterial cuff (no flow) in calf skin and muscle or occurred spontaneously in skin with vasomotion (flow).

\[ S_{\text{mbO}_2} = \text{SaO}_2 - \left( \frac{V_v}{V_a + V_v} \right) \left( \frac{\text{CMRO}_2}{k \cdot Q \cdot [\text{Hb} \cdot 10^{-2}]} \right) \times 100\% \]

where \( \text{SaO}_2 \) is arterial saturation (in %), \( V_a \) is arterial blood volume per unit mass of tissue (in l/g), \( V_v \) is venous blood volume per unit mass of tissue (in l/g), CMRO\(_2\) is oxygen consumption (ml O\(_2\)/min); \( k \) (Hufner’s number) is oxygen binding capacity per 1 g hemoglobin (in ml); \( Q \) is blood flow (in ml/min), and \( \text{Hb} \) is the hemoglobin concentration (g Hb/dl blood) (40). The skin flow \( Q \) is insufficient to support the oxygen consumption, and \( S_{\text{mbO}_2} \) does not remain constant. \( S_{\text{mbO}_2} \) cycles over 60–100 s, decaying non-linearly by an additional ~10% and with further OE induced through mechanisms with either increased flow \( Q \) (\( P_{\text{inO}_2} - P_{\text{ISFO}_2} \)) or capillary density \( S \). This OE derived from the decay in \( S_{\text{mbO}_2} \) is greater in lean than obese subjects, while flow \( Q \) remains constant. It has been shown that capillary recruitment is four times higher in lean compared with obese subjects and that in obese subjects with metabolic syndrome, cutaneous capillaries are maximally recruited at rest (14). Other researchers have shown that BMI is inversely correlated with resting skin capillary density though the subjects were only overweight (BMI, 27.9 ± 2.7 kg/m\(^2\)) and had higher capillary recruitment compared with lean subjects (3). Our findings of significantly lower oxygen extraction in the skin of obese compared with lean subjects may therefore be a consequence of impaired functional capillary density. When OE in skin is derived in lean and obese subjects during an arterial occlusion and no flow, then OE is diffusion limited and proportional to \( \alpha DS \). As capillary recruitment is hindered in a closed system with no flow, we observe that OE in lean and obese subjects is no longer different.

In contrast, in skeletal muscle the fact that the differences between oxygen extraction in lean and obese individuals are apparent during arterial occlusion provides evidence that mechanism(s) independent of blood flow may operate to explain the differences. Research has shown that even when oxygen demand is raised in skeletal muscle through maximal voluntary contractions in the forearm, oxygen consumption is independent of blood flow and unaltered by an arterial occlusion (5). Similarly, no significant change in muscle perfusion was observed in resting calf muscle in conditions of hypoxia.
while breathing 10% O₂ despite a reduction in oxygen extraction (7). Reduced blood flow heterogeneity under constant perfusion cannot, however, be discounted (25). With no flow, OE is diffusion limited and is therefore proportional to αDS(P_{inO2} - P_{isO2}). The higher oxygen extraction we observe in obese skeletal muscle compared with lean may arise from a higher (P_{inO2} - P_{isO2}) resulting from mitochondrial dysfunction with obesity. It has been shown that obese women exhibit lower mitochondrial coupling and phosphorylation efficiency in skeletal muscle compared with lean controls and that there is increased oxygen consumption not linked with phosphorylation (27). A deficiency of the electron transport chain in human skeletal muscle mitochondria has also been observed with obesity and type 2 diabetes (34), whereas electron microscopy has visualized impaired bioenergetic capacity of skeletal muscle mitochondria in type 2 diabetes and obesity (26). The literature suggests that this mitochondrial dysfunction in obesity could possibly induce the higher OE observed in the skeletal muscle of the obese subjects; however, further studies are required to validate this hypothesis. Higher oxygen extraction with obesity has been reported in resting gastrocnemius muscle of Zucker rats using a microcirculation flow probe and the Fick Principle (15).

Limitations of this study include the complications of blood flow regulation in the skin for thermoregulation. However, there was no significant difference between the lean and obese groups in skin temperature in either the calf or forearm skin, and the maximum variation of skin temperature within a study was only 0.7°C, making the confounding effects of skin thermoregulation likely to be small. There was a significant positive correlation between skin temperature and oxygen extraction in lean subjects only, again indicative of functional capillary recruitment in lean but not obese subjects.

In summary, the development of a novel noninvasive technique that can measure oxygen extraction in resting unperfused skin has uniquely demonstrated that in skin, the classic model for the metabolic regulation of blood flow is valid. Oxygen extraction is dependent on unhindered perfusion that can fluctuate as demand exceeds supply. The reduced OE observed in the skin of obese compared with lean subjects and can fluctuate as demand exceeds supply. The reduced OE is diffusion limited and is therefore proportional to αDS(P_{inO2} - P_{isO2}). The higher oxygen extraction we observe in obese skeletal muscle compared with lean may arise from a higher (P_{inO2} - P_{isO2}) resulting from mitochondrial dysfunction with obesity. It has been shown that obese women exhibit lower mitochondrial coupling and phosphorylation efficiency in skeletal muscle compared with lean controls and that there is increased oxygen consumption not linked with phosphorylation (27). A deficiency of the electron transport chain in human skeletal muscle mitochondria has also been observed with obesity and type 2 diabetes (34), whereas electron microscopy has visualized impaired bioenergetic capacity of skeletal muscle mitochondria in type 2 diabetes and obesity (26). The literature suggests that this mitochondrial dysfunction in obesity could possibly induce the higher OE observed in the skeletal muscle of the obese subjects; however, further studies are required to validate this hypothesis. Higher oxygen extraction with obesity has been reported in resting gastrocnemius muscle of Zucker rats using a microcirculation flow probe and the Fick Principle (15).

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In summary, the development of a novel noninvasive technique that can measure oxygen extraction in resting unperfused skin has uniquely demonstrated that in skin, the classic model for the metabolic regulation of blood flow is valid. Oxygen extraction is dependent on unhindered perfusion that can fluctuate as demand exceeds supply. The reduced OE observed in the skin of obese compared with lean subjects and attributed, at least in part, to impaired functional capillary density is no longer observed during an arterial occlusion. In contrast, resting muscle does not appear to exhibit these fluctuations between normoxic and hypoxic states, suggesting other nonperfusion-related regulatory mechanisms. These ensure that resting muscle is sufficiently perfused to match demand. The increased OE observed in unperfused obese muscle may be the result of mitochondrial dysfunction.

ACKNOWLEDGMENTS

We thank all the volunteers who took part in this study.

GRANTS

The work was supported by the NIHR Exeter Clinical Research Facility. The opinions given in this paper do not necessarily represent those of NIHR, the NHS or the Department of Health. This work was carried out within Peninsula College of Medicine and Dentistry before 2012 and in University of Exeter Medical School post 2012.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


