Metabolic Signatures of Human Adipose Tissue Hypoxia in Obesity

Leanne Hodson,1 Sandy M. Humphreys,1 Fredrik Karpe,1,2 and Keith N. Frayn1

Adipose tissue (AT) hypoxia has been proposed as the cause of obesity-related AT dysfunction, moving the tissue toward a proinflammatory phenotype. In humans, AT oxygenation has been assessed by expression of hypoxia-sensitive genes or direct assessment of O2 tension; the obvious read out of hypoxia, effects on intermediary metabolism, has not been investigated. We used tissue-specific venous catheterization of subcutaneous abdominal AT in humans to investigate oxygen-related metabolic processes, searching for metabolic signatures relating to hypoxia in obesity. O2 delivery to AT was reduced in obesity (P < 0.05). However, O2 consumption was low (<30% of resting forearm skeletal muscle [SM], P < 0.001); this was not related to obesity. AT primarily oxidized glucose, as demonstrated by a respiratory quotient close to 1.0 (higher than SM, P < 0.05). AT was a net producer of lactate, but there was an inverse relationship between lactate-to-pyruvate ratio (a marker of cytosolic redox state) and BMI, suggesting that AT is glycolytic but obese AT is not hypoxic. Although delivery of O2 to the obes AT is reduced, O2 consumption is low, and metabolic signatures of human AT do not support the notion of a hypoxic state in obesity.

Subcutaneous adipose tissue (SCAT) is a complex metabolic organ that responds dynamically to alterations in nutritional state. As the tissue expands, macrophages infiltrate and orchestrate inflammatory responses via molecules such as tumor necrosis factor-α, interleukin-6, and monocyte chemotactic protein-1, all of which have been implicated in pathological changes in AT physiology (1,2). Hypoxia within the tissue has been proposed as an underlying cause of AT dysfunction, moving the tissue toward a proinflammatory phenotype (3–5).

Tissue O2 partial pressure (pO2) reflects the balance between O2 delivery and consumption. AT blood flow (ATBF) plays an integral role in oxygen supply. It is markedly lower in obese than in nonobese subjects in both the fasted (6–9) and postprandial (6,8) states. Thus, in obese individuals it could be anticipated that oxygen delivery to the tissue is compromised. Beyond this, it is also well established that expansion of fat tissue often leads to larger cells (6), increasing the diffusion distance for O2.

The level of oxygen deficiency within human AT that defines hypoxia remains unclear. Direct measurements of AT pO2 have been made in murine and human models. Ye et al. (4) reported a 70% lower interstitial pO2 within epididymal fat pads of ob/ob compared with lean mice (4). The pO2 of obese AT is reported to be significantly lower than nonobese AT in most (10–12) but not all studies. Recently, Goossens et al. (6) noted a markedly higher AT pO2 in obese compared with lean individuals. The authors suggested that "hyperoxia" in the obese AT could be explained by lower AT O2 consumption (6). This would fit with increasing evidence of a downregulation of expression of metabolic pathways in AT in obesity, including mitochondrial oxidative pathways (8,13). Thus, the influence of adiposity on arterial O2 content, O2 delivery to AT, or AT O2 consumption remains unclear.

AT is not a large consumer of O2. It accounts for ~5% of whole-body O2 consumption in normal-weight individuals (14). Little is known about the processes that require O2 in human AT or how they are altered in obesity. Measurements of the respiratory quotient (RQ) of AT in vitro suggest that glucose is the major metabolic fuel (15,16). Glucose taken up into AT can be partitioned between conversion to lactate; conversion to glycerol-3-phosphate, which is used for fatty acid (FA) reesterification; oxidation; or storage as glycogen and possibly lipid. It could therefore be that in obese AT, with low oxygenation, there would be a repartitioning of glucose toward lactate rather than glycerol-3-phosphate production. A possible consequence could be less FA reesterification within the tissue and, hence, increased FA release.

At a cellular level, a pivotal signal of low oxygenation is hypoxia-inducible factor (HIF)-1α, which acts as a central controller of oxygen-related gene expression (5). In human obesity, it remains unclear whether the genetic hallmarks of hypoxia (i.e., HIF-1α or HIF-1α target gene expression) are reflected in AT (6,12).

It seems, therefore, that the question of AT hypoxia in obesity would be best addressed by looking at functional consequences in terms of a "metabolic signature" of hypoxia. An initial cellular response to low O2 results in the cell switching to anaerobic glycolysis and increasing lactate production, which has to be exported from the cell (3). Lactate is released by human AT in vivo in the fasting (17–19) and postprandial (18–20) states. An even more specific marker of cellular redox state may be the blood lactate-to-pyruvate ratio (21).

Using arterio-venous difference methodology, with selective venous catheterization of abdominal SCAT, we recently described the metabolic characteristics of human AT after an overnight fast in a large cohort of healthy individuals (22). However, no information was available on O2 delivery or consumption or its metabolic use, and studies were not made in the fed state either. We have therefore now examined gas exchange and substrate use...
in the fasting and postprandial state over 24 h in abdominal SCAT (22,23) and skeletal muscle (SM) (24) in human volunteers across a range of adiposity. The aim of the study was to investigate whether an expansion of fat mass alters oxygen-related metabolic processes in SCAT in humans in the fasting and postprandial state and to seek a metabolic signature of AT hypoxia in order to test the hypothesis of AT hypoxia in obesity as a potential driver of dysfunction.

RESEARCH DESIGN AND METHODS

Samples were taken during the course of several published (8,24–27) and unpublished studies. Volunteers were recruited by advertisement and from the Oxford BioBank (28). All were metabolically healthy, not taking medication affecting lipid or glucose metabolism, and gave signed, informed consent.

However, based on fasting plasma glucose concentrations, three volunteers had impaired fasting glucose (>6.1 mmol/L), but none were diabetic (29).

Volunteers attended our Clinical Research Unit having fasted from 10:00 P.M. the previous night. They were asked to refrain from strenuous exercise and alcohol for 24 h before the study. We measured arterio-venous differences across SCAT and forearm SM in the fasting state in 52 healthy subjects (42 males and 10 females) (Table 1). Of the 52 subjects, 40 had data for arterial and SCAT and 22 had complete data for arterial and forearm muscle. In a subgroup of 30 subjects (27 males and 3 females) (Table 1), we studied these processes in the postprandial state after subjects were fed three sequential meals over 24 h (8,24). Of these 30 subjects, 29 had complete arterial and SCAT data and 21 had data for arterial and forearm SM.

For studying tissue-specific metabolism, the superficial epigastric vein was cannulated as previously described (22,23) to sample the venous effluent of SCAT. Venous blood from forearm muscle was obtained from a cannula placed retrogradely in a deep antecubital vein (24,25). Arterial blood was sampled from a catheter in a femoral or radial artery. Blood sampling was performed simultaneously from all three sites. Abdominal subcutaneous ATBF was measured by the washout of $^{133}$Xe (24).

**Analytical methods.** Blood samples were drawn into heparinized syringes (Sarstedt, Leicester, U.K.), and plasma was prepared rapidly at 4°C. Glucose concentrations were measured immediately and remaining samples frozen before analysis. Plasma triacylglycerol, nonesterified FA, and glucose were analyzed enzymatically using commercially available kits. A sample of whole blood was added to perchloric acid for analysis of lactate, pyruvate, 3-hydroxybutyrate, and acetoacetate as previously described (30). Insulin was measured by radioimmunoassay (Millipore, Watford, U.K.).

**Blood gas measurement.** O$_2$ saturation in arterial and adipose venous blood was measured in all subjects, and 53 subjects had blood O$_2$ saturation measured additionally in muscle venous blood. In fasting-only studies, O$_2$ saturation and hemoglobin concentration were measured with a Corning 2500 coximeter (Ciba-Corning Diagnostics, Halstead, U.K.). In the postprandial studies, an OPL GEM coximeter was used (Instrumentation Laboratory, Warrington, U.K.) at times −30, 0, 150, 480, 840, and 1,440 min, where 0 is the time breakfast was given. In 19 subjects (17 males and 2 females) fasting and in 11 subjects (all male) postprandial, O$_2$, pCO$_2$, and pH were measured in arterial and venous blood using either a GEM Premier 3000 blood gas analyzer (Instrumentation Laboratory) or a Radiometer ABL 700 Series (Radiometer, West Sussex, U.K.). All blood gas measurements were made in triplicate to reduce measurement variability. We attempted to use a Corning 985 Total CO$_2$ analyzer (Ciba-Corning Diagnostics) to measure whole-blood CO$_2$ content, but as reported also by Simonsen et al. (31) it found it unreliable for measurement of the very small difference in CO$_2$ content between arterial and AT venous blood.

**Calculations.** We had fasting blood gas data and hemoglobin measurements in 37 of 41 subjects and full postprandial data (from 30 subjects) for 10 subjects, with the remainder of subjects missing either one time point (n = 2) or more time points (n = 10). We calculated the dissolved O$_2$, O$_2$ content, and tissue O$_2$ consumption for the individuals with complete data and found it to be stable over time; therefore, we interpolated missing data using time points before and after. If a baseline time point was missing and we had an end-of-study (24 h) time point, we used that and vice versa. We calculated O$_2$ content, O$_2$ delivery, tissue O$_2$ consumption, CO$_2$ delivery, CO$_2$ content of blood, tissue CO$_2$ production, tissue-specific RQ, and SCAT FA reesterification as described in more detail in Supplementary Data.

**Statistics.** Data were analyzed using IBM SPSS Statistics, version 18 (IBM SPSS Products, Chertsey, U.K.). All data are presented as means ± SEM unless otherwise stated. All datasets were tested for normality with the Shapiro-Wilk test. Comparisons were made between AT and SM or within sites at different time points using a paired t test. Repeated-measures ANOVA, with time and site as factors, were used to investigate the change between sites over time with feeding. Where statistical significance was found, we did post hoc analysis with Bonferroni corrections. Correlations were assessed using the non-parametric Spearman rank correlation coefficient, $r_{SC}$. To assess trends across BMI groups, we used polynomial contrasts across the groups that tested for a linear trend in the data.

**RESULTS**

**Tissue O$_2$ delivery and consumption.** O$_2$ saturation for arterial and venous blood draining SM and SCAT were significantly (P < 0.001) different from each other, with arterial being the most O$_2$-enriched compared with the venous blood from SM and SCAT at 97.2 ± 0.2, 56.1 ± 1.6, and 86.6 ± 0.5%, respectively (Fig. 1A). This was also true for the O$_2$ content (millimoles per liter), both fasting and postprandially, with the artery being significantly higher (P < 0.001) than the venous blood draining SCAT and SM (Fig. 1B). There was no change in O$_2$ content with feeding in the artery or venous blood draining SCAT, but there was an increase (P = 0.029) in O$_2$ content in SM venous blood (Fig. 1B). O$_2$ consumption was 3.7-fold greater in SM than in AT (P < 0.001). This marked difference highlights that SCAT is not a large consumer of O$_2$ compared with SM.

**Tissue CO$_2$ release and RQ.** The CO$_2$ content (millimoles per liter) of venous blood draining SM was significantly

**TABLE 1**

Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Fasting data</th>
<th>Postprandial data</th>
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</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>42/10</td>
<td>27/3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 (22–58)</td>
<td>42 (22–58)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25.5 (19.5–54.1)</td>
<td>25.5 (19.5–37.1)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>26 (8–48)</td>
<td>26 (8–33)</td>
</tr>
</tbody>
</table>

**Fasting biochemical parameters**

<table>
<thead>
<tr>
<th></th>
<th>Fasting data</th>
<th>Postprandial data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood O$_2$ saturation (%)</td>
<td>98 (95.3–99.9)</td>
<td>97.7 (95.3–99.9)</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>5.0 (4.3–6.8)</td>
<td>4.9 (4.3–5.4)</td>
</tr>
<tr>
<td>Plasma insulin (mU/L)</td>
<td>11.8 (0.8–76.4)</td>
<td>10.8 (2.5–25.2)</td>
</tr>
<tr>
<td>Plasma triacylglycerol (μmol/L)</td>
<td>973 (428–2702)</td>
<td>904 (448–1792)</td>
</tr>
<tr>
<td>Plasma NEFA (μmol/L)</td>
<td>551 (173–859)</td>
<td>505 (188–844)</td>
</tr>
<tr>
<td>Whole-blood 3-hydroxybutyrate (μmol/L)</td>
<td>105 (13–373)</td>
<td>113 (15–373)</td>
</tr>
<tr>
<td>ATBF (mL · 100 g$^{-1}$ · min$^{-1}$)</td>
<td>2.6 (0.3–11.3)</td>
<td>3.2 (1.2–11.30)</td>
</tr>
<tr>
<td>SM blood flow (mL · 100 mL$^{-1}$ · min$^{-1}$)</td>
<td>1.9 (1.0–3.4)</td>
<td>2.0 (1.1–3.4)</td>
</tr>
</tbody>
</table>

Data are median (range). NEFA, nonesterified FAs.
higher, both fasting and postprandially, than arterial and venous blood draining SCAT (Fig. 1C). The CO₂ content of arterial blood was significantly ($P < 0.05$) lower than that of venous blood draining SCAT (Fig. 1C). Blood CO₂ content increased ($P < 0.05$) over the postprandial period in all three sites ($P < 0.05$) (Fig. 1C). CO₂ production was significantly greater ($P < 0.001$) in SM than SCAT both fasting and postprandially, highlighting the oxidative metabolic activity of SM compared with SCAT.

We determined the RQ of SM and SCAT in the fasting and postprandial states. The fasting RQ of SM was 0.78 ± 0.03 ($n = 29$); for SCAT, it was 0.93 ± 0.06 ($n = 26$) ($P < 0.05$) (Fig. 1D). For SM, this value was significantly <1.0 ($P < 0.001$), but for SCAT this was not so. The RQ in both tissues increased significantly ($P < 0.01$) in the postprandial state (1.06 ± 0.09 and 1.22 ± 0.10 for SM [$n = 11$] and SCAT [$n = 9$], respectively) (Fig. 1D). For SM, this value was not significantly >1.0, but for SCAT it was ($P = 0.044$).
Tissue oxygenation in obesity. It has been proposed that hypoxia may occur with an expansion of AT mass. We found a significant inverse correlation (\( r_s = -0.43, P = 0.002, n = 49 \)) between BMI and arterial blood \( O_2 \) saturation (Fig. 2A).

We investigated the influence of adiposity on fasting AT \( O_2 \) delivery and consumption in lean (BMI < 25 kg/m²), overweight (BMI > 25 and < 30 kg/m²), and obese (BMI > 30 kg/m²) individuals. Their characteristics are reported in Supplementary Table 1. There was an inverse correlation between BMI and ATBF (\( r_s = -0.40, P = 0.004, n = 50 \)). We found an inverse linear trend (\( P = 0.05 \)) across the BMI groups for \( O_2 \) delivery to SCAT, indicating that with an increasing BMI (fat mass) there is a decrease in the amount of \( O_2 \) being consumed by SCAT across the BMI groups was less clear (\( P = 0.099 \)) (Fig. 2C). ATBF increased after the meal (\( P = 0.008 \), repeated measures over time), whereas SM blood flow did not change as observed previously (24, 32) (Supplementary Fig. 1).

Tissue glucose metabolism. We compared the uptake of glucose into SM and SCAT in fasting and across postprandial periods. In the fasting state, the arterio-venous difference for glucose uptake was greater in SM than in SCAT (0.37 ± 0.06 vs. 0.20 ± 0.02 mmol/L, respectively, \( P = 0.006 \)) (Fig. 3A). In the postprandial state, the uptake of glucose into SM was greater and displayed a very different pattern compared with SCAT (\( P < 0.001, \text{time} \times \text{site interaction} \)) (Fig. 3A). Plasma insulin concentrations increased in the postprandial state (\( P < 0.001, \text{change over time} \)) (Fig. 3A). The higher uptake of glucose into SM in the early (1–2 h) postprandial period was maintained in the late (3–5 h) postprandial period (Fig. 3A).

FAs that are taken up into SCAT require the provision of glycerol-3-phosphate for reesterification to triacylglycerol. Assuming that this glycerol-3-phosphate is derived from glucose, we calculated the proportion of measured glucose uptake for reesterification. In the fasting state (time 0 and 24 h), FA reesterification as a percent of glucose uptake was between 3 and 7% (Fig. 3B). With feeding, FA reesterification as a percent of glucose uptake significantly increased (\( P < 0.001 \)), and over the postprandial periods this was on average 9% (Fig. 3B) (\( P < 0.001, \text{change over time} \)).

We calculated the proportion of glucose taken up by the SM and SCAT that was released as lactate and pyruvate (Fig. 3C). At baseline and 24 h, ~35% of glucose taken up by SCAT was released as lactate and pyruvate (Fig. 3C). The proportion of glucose taken up and released as lactate and pyruvate at baseline in SM was significantly lower (\( P < 0.001 \)) than for SCAT, at ~10%, and was negligible at 24 h (Fig. 3C). The release of lactate and pyruvate in the postprandial period was greater for AT (~23% of glucose taken up) than SM (~5%) (Fig. 3C). There was an effect of site (\( P < 0.001 \)) and time (\( P < 0.001 \)) but no time × site interaction for the proportion of glucose taken up and released as lactate and pyruvate from SCAT and SM (Fig. 3C). We did not find an association between BMI and fasting glucose uptake and release as lactate and pyruvate from SCAT.

We determined the maximal contribution that tissue glucose uptake could make to tissue \( O_2 \) consumption if all the glucose were oxidized. We did this after correction of glucose uptake for lactate and pyruvate release as previously described (33). In SCAT, we additionally corrected glucose uptake for that consumed in glycerol-3-phosphate production, calculated from the reesterification rate. In the fasting state, the potential maximal contribution of complete glucose oxidation to \( O_2 \) consumption was significantly higher for SCAT compared with SM (73 ± 5 vs. 58 ± 9% for SCAT [\( n = 37 \)] and SM [\( n = 21 \)], respectively; \( P = 0.045 \)) (Fig. 3D). Transiting to the postprandial state resulted in a >1.5-fold increase (\( P < 0.001 \)) in both tissues in the maximal contribution that glucose could make to \( O_2 \) consumption (Fig. 3D). For SM and SCAT, the postprandial value was significantly >100% (\( P < 0.001 \) SM and \( P = 0.045 \) SCAT), implying glucose storage.

Are there metabolic signatures of AT hypoxia? A possible consequence of hypoxia is that cellular metabolism may switch to anaerobic glycolysis and this would lead to an increase in lactate production. We measured the concentrations of lactate and pyruvate in arterial and venous blood samples. In fasting, there was a net release of lactate from SM and SCAT (Fig. 4A). Blood lactate concentrations increased with feeding in all three sites (\( P < 0.001, \text{time} \times \text{site interaction} \)) and tended to remain highest in the venous blood from SCAT (Fig. 4B). We found an
association between arterial lactate concentration and BMI ($r_s = 0.28, P = 0.046$) but not with percentage body fat.

In fasting, there was net uptake of pyruvate from the blood into SM, while there was a net release of pyruvate from AT (Fig. 4C). Blood pyruvate concentrations increased after the consumption of a meal, and the increment was greatest in arterial blood and venous blood from SCAT ($P < 0.001$, for all three sites a site × time interaction). Fasting arterial blood pyruvate concentrations were positively associated with BMI ($r_s = 0.60, P < 0.001$) and percentage body fat ($r_s = -0.41, P = 0.025$). This inverse correlation was driven by the positive relationship between BMI and arterial pyruvate concentration. We calculated the change across SCAT in lactate-to-pyruvate ratio as a measure of tissue-specific hypoxia as follows: (veno–arterio difference lactate)/(veno–arterio difference pyruvate). We found no association between this tissue-specific change in lactate-to-pyruvate ratio and BMI ($r_s = 0.11$) (Fig. 4E). However, the proportion of glucose released as lactate and pyruvate in SCAT was strongly negatively correlated with BMI (Fig. 4F). A lactate-to-pyruvate ratio of 10:1 or below is considered normal (21). The lactate-to-pyruvate ratio in arterial and SCAT venous blood was not significantly different from 10, suggesting adequate systemic and cellular oxygenation.
FIG. 4. A–F: Fasting (A and C) and postprandial (B and D) concentrations of lactate and pyruvate in arterial (ART), SM venous (SM_V), and SCAT venous (SCAT_V) blood and associations with BMI (kg/m²) (E and F). A: Fasting blood lactate concentrations (µmol/L) in arterial, SM venous, and SCAT venous. *P = 0.004 arterial vs. SM venous; †P < 0.001, arterial vs. SCAT venous; ‡P = 0.004, SM venous vs. SCAT venous.

B: The postprandial concentrations (µmol/L) of lactate in arterial, SM venous, and SCAT venous blood. Meals of similar energy and macronutrient composition were fed at 0, 5, and 10 h (dotted lines); P < 0.001, repeated measures over time for all sites, and P < 0.001, time × site interaction for all sites.

C: Fasting blood pyruvate concentrations (µmol/L) in arterial, SM venous, and SCAT venous; P = NS, arterial vs. SM venous; †P = 0.01, arterial vs. SCAT venous; ‡P < 0.001, SM venous vs. SCAT venous.

D: The postprandial concentrations (µmol/L) of pyruvate in arterial, SM venous, and SCAT venous blood. Meals of similar energy and macronutrient composition were fed at 0, 5, and 10 h (dotted lines). P < 0.001, repeated measures over time for all sites, and P < 0.001, time × site interaction for all sites.

E: The correlation for the (veno–arterio difference lactate) / (veno–arterio difference pyruvate) ratio with BMI (kg/m²).

F: The proportion of glucose uptake released as lactate and pyruvate (AUC) with BMI (kg/m²).
DISCUSSION

We performed an in vivo human study to investigate whether an expansion of AT mass alters oxygen-related metabolic processes in SCAT in the fasting and post-prandial states to test the hypothesis of AT hypoxia in obesity as a potential driver of dysfunction. We did not detect a tissue-specific metabolic signature indicative of obesity-related AT hypoxia. Our data highlight the remarkably low oxygen requirement of AT to undertake its many metabolic processes compared with SM.

Angiogenesis may play a critical role in providing expanding AT with adequate oxygen (35). AT from obese individuals has lower expression of angiogenic genes and capillarization compared with lean individuals (6,12). Additionally, fasting and postprandial ATBF is decreased in obese compared with lean individuals (6–9). We found indications that with increasing obesity, arterial O₂ saturation and O₂ delivery to AT are decreased. Low oxygenation is well recognized as a mechanical effect of severe obesity (36).

Experimental data on human AT O₂ consumption are limited. We found a nonsignificant trend for O₂ consumption by AT to decrease with increasing obesity. However, the proportion of inactive triacylglycerol is greater in AT from obese subjects (37,38), so the delivery of blood and oxygen as well as oxygen consumption per unit of active cytosolic weight may not be as different as our data indicate. Goossens et al. (6) reported AT O₂ consumption to be significantly lower in obese compared with lean subjects. The AT O₂ consumption of obese individuals in the current study was 2.66 μmol · 100 g tissue⁻¹ · min⁻¹ higher than that reported by Goossens et al. (6) (0.67 μmol · 100 g tissue⁻¹ · min⁻¹). A plausible explanation for the discrepancy in findings is that Goossens et al. (6) measured pO₂ in arterialized rather than arterial blood. Arterialized blood pO₂ does not provide a valid estimation of arterial pO₂ (39). Our measurements emphasize the small O₂ requirement of AT compared with SM.

Adipocytes, like other cells, require energy for metabolic activities. In vitro work has suggested that this energy is primarily obtained by glucose catabolism (15,16). We have been able to corroborate in vivo the hypothesis that in the fasting state, human white AT oxidizes predominantly glucose. We found resting SM, in the fasting state, to have a significantly lower RQ than AT, highlighting the difference in substrate use between the tissues. SM RQ has previously been reported, and our data are in agreement with most (31,40,41) but not all (42) previous studies. The maximal contribution glucose uptake could make to O₂ consumption, if it were all oxidized, in the fasting state was ~30% of the glucose taken up was converted to lactate and pyruvate. If there were an increase in glycolysis, then production of pyruvate, the immediate precursor of lactate, would be increased. If cellular hypoxia were present, then the NADH-to-NAD⁺ ratio (cytosolic reductant state) would be increased, which would drive the equilibrium from pyruvate toward lactate, accelerating lactate production (21). If obesity-related AT hypoxia were present, it would result in a positive association between the proportion of glucose taken up released as lactate and pyruvate and BMI. However, we found a negative association. Although we found an association between BMI and arterial lactate concentrations, the difference between lean and obese groups was not statistically different, as shown previously by some (18) but not all (19).

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Whole-body lactate production is between 1–1.5 mol/24 h in healthy individuals (49). The overall contribution of SCAT to systemic lactate concentrations is minor (0.8 mmol/24 h by extrapolating our data to whole-body fat mass) such that the higher pyruvate noted with increased obesity was the result of increased production or impaired removal. Most importantly, we found no evidence that the proportion of glucose uptake released as lactate and pyruvate was increased in obesity; in fact, the opposite was true. Furthermore, the tissue-specific change in lactate-to-pyruvate ratio was unrelated to BMI. Both these observations strongly argue against functional consequences of AT hypoxia in obesity.

We report here for the first time the use of oxygen in human AT. Our data clearly demonstrate that AT is a low consumer of O2 compared with SM in lean and obese individuals. We found no evidence of a metabolic signature to support the notion of obesity-related AT hypoxia being a potential driver of dysfunction.

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L.H and S.M.H conducted experimental procedures and wrote the manuscript. F.K and K.N.F conducted experimental procedures, wrote the manuscript, and secured funding for the work. L.H. and K.N.F. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

23. McQuaid SE, Manolopoulos KN, Dennis AL, Cheeseman J, Karpe F, Frayn KN. Development of an arterio-venous difference method to study the metabolic physiology of the femoral adipose tissue depot. Obesity (Silver Spring) 2010;18:1055–1058


