

Rapid onset vasodilatation is blunted in obese humans

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Abstract

Aim: Conduit artery function in obese humans is frequently assessed at rest, but very little is known about resistance artery function in response to muscle contraction. We tested the hypothesis that obese adults will exhibit reduced contraction-induced rapid onset vasodilatation. Single and brief forearm contractions were used to isolate the local effects of muscle contraction on the forearm vasodilatory response, independent of systemic haemodynamic and sympathetic neural influence.

Methods: We measured forearm blood flow (Doppler ultrasound), blood pressure (finger photoplethysmography) and heart rate (electrocardiogram) on a beat-by-beat basis in 14 obese (body mass index = $36.2 \pm 1.7 \text{ kg m}^{-2}$) and 14 lean (body mass index = $21.6 \pm 0.7 \text{ kg m}^{-2}$) young (18–40 years) adults. Percent changes from baseline in forearm vascular conductance (FVC%) were calculated in response to single, brief forearm contractions performed in random order at 15, 20, 25, 30, 40 and 50% of maximal voluntary contraction (MVC).

Results: In both groups, each single contraction evoked a significant ($P < 0.05$), immediate (within one cardiac cycle) and graded FVC% increase from one up to six cardiac cycles post-contraction. Immediate (20–50% MVC), peak (15–50% MVC) and total (area under the curve, 20–50% MVC) vasodilatory responses were reduced with obesity. The degree of impaired vasodilatation increased with increasing workloads.

Conclusions: These novel findings demonstrate a blunted contraction-induced rapid onset vasodilatation with obesity that is exercise intensity dependent. Impaired rapid onset vasodilatation may negatively impact haemodynamic responses to everyday intermittent activities performed by obese humans.

Keywords exercise, hyperaemia, muscle contraction, obesity, vascular conductance.

Obesity is a major risk factor for a variety of cardiovascular diseases associated with low levels of physical activity and reduced cardiorespiratory fitness (Vanhecke *et al.* 2009). Whereas exercise is recommended as a common non-pharmacological treatment option for obese patients (Weinstock *et al.* 1998, Mcinnis 2000), any impairment in vasodilatory responses could potentially impair exercise tolerance. As such, exploration

into the mechanisms of any altered functional vasodilatation in obesity is an important research area.

Only a few studies have examined vasodilatory responses to exercise in obesity and results are conflicting. Throughout three min of static forearm exercise, Negro *et al.* (2001) demonstrated greater vascular resistance but maintained blood flow in the non-exercising forearm of obese adults. In contrast, during

dynamic steady-state forearm exercise, Limberg *et al.* (2010a,b) showed obese otherwise healthy subjects exhibited preserved blood flow and vascular conductance. These results conflict animal models of obesity demonstrating impaired vasodilatation in response to *in situ* contractions (Xiang *et al.* 2005). Previous studies in humans focused on vasodilatory responses at steady state; however, activities of daily living are predominately brief, frequent transitions between rest and movement (i.e. household chores, moving from seated to standing, climbing a flight of stairs). In the context of short bursts in activity, mechanical factors associated with contraction may play a predominate role in regulating flow at the onset of movement (Clifford *et al.* 2006).

In healthy adults, mechanical effects evoke an immediate and significant increase in blood flow after the release of the first muscle contraction (Sheriff *et al.* 1993, Naik *et al.* 1999, Tschakovsky & Sheriff 2004, Kirby *et al.* 2007, Carlson *et al.* 2008). This rapid onset vasodilatation peaks within approx. 4–6 cardiac cycles and its magnitude is proportional to the intensity of contraction (Tschakovsky & Sheriff 2004, Kirby *et al.* 2007, Carlson *et al.* 2008). Growing experimental evidence clearly demonstrates rapid onset vasodilatation as obligatory for this hyperaemic response (Naik *et al.* 1999, Hamann *et al.* 2004, Tschakovsky *et al.* 2004, Kirby *et al.* 2007); classical metabolic dilators cannot account for the rapid response (Wunsch *et al.* 2000).

Whereas mechanical influences are thought to play an important role in blood flow responses to brief muscle contractions in healthy humans, the impact of obesity on rapid onset vasodilatation remains unknown. Notably, resistance arteries from skeletal muscles of obese rats exhibit altered myogenic responses (Frisbee *et al.* 2002) – suggesting mechanical factors associated with contraction may negatively impact vasodilatation in human obesity. From a mechanistic perspective, rapid onset vasodilatation is dependent upon potassium channel opening (Armstrong *et al.* 2007), and obese animals exhibit impaired potassium channel-mediated vasodilatation (Hodnett *et al.* 2008).

With this background in mind, we tested the hypothesis that obese, otherwise healthy adults, would exhibit reduced muscle rapid onset vasodilatation in response to a brief, single forearm contraction compared with healthy lean controls.

Materials and methods

Subjects

A total of 14 obese [body mass index (BMI) = $36.2 \pm 1.7 \text{ kg m}^{-2}$] and 14 lean (BMI = $21.6 \pm 0.7 \text{ kg m}^{-2}$)

adults (half men, half women for each group), whose characteristics are displayed in Table 1, participated in the present study. All subjects completed a screening process in which physical activity and personal health history, including history of medications and family history of cardiovascular disease, were assessed. Except for obesity, all subjects were healthy and free from overt cardiovascular disease, as judged from self-reported medical history and fasting blood lipid and glucose levels. All subjects were non-smokers and were not taking any medications. Female subjects were excluded if pregnant and hormonal contraception was allowed (lean $n = 3$, obese $n = 2$). All women were studied during the early follicular/placebo phase (days 1–5) of the menstrual cycle. All subjects led a sedentary lifestyle and did not participate in regular aerobic exercise for the prior 6 months (current aerobic exercise was $<60 \text{ min week}^{-1}$ and included jogging, biking, tennis and soccer). Subjects were instructed to refrain from exercise, alcohol NSAIDs and caffeine for 24 h before the study day. Written informed consent was obtained from all subjects. All procedures were approved by the Institutional Review Board at the University of Wisconsin–Madison and conformed to the standards set by the Declaration of Helsinki.

Measurements

Body composition. Weight and height measurements were performed, and BMI (body mass index) was calculated as weight in kilograms divided by height in

Table 1 Subject characteristics

	Lean	Obese
Male/female	7/7	7/7
Age (year)	24.3 ± 1.6	29.5 ± 2.5
Height (cm)	176 ± 2	174 ± 3
Weight (kg)	$66.6 \pm 2.0^*$	110.7 ± 7.7
BMI (kg m^{-2})	$21.6 \pm 0.7^*$	36.2 ± 1.7
Body fat (%)	$17 \pm 3^*$	27 ± 2
Waist circ. (cm)	$76 \pm 2^*$	113 ± 6
Hip circ. (cm)	$97 \pm 1^*$	123 ± 3
Waist/hip ratio	$0.78 \pm 0.02^*$	0.91 ± 0.03
Forearm vol. (mL)	$968 \pm 48^*$	1430 ± 107
Glucose (mg dL^{-1})	85 ± 3	89 ± 3
HDL (mg dL^{-1})	46 ± 5	50 ± 7
LDL (mg dL^{-1})	$90 \pm 8^*$	129 ± 9
Cholesterol (mg dL^{-1})	152 ± 10	194 ± 19
Triglyceride (mg dL^{-1})	87 ± 11	131 ± 20
MVC (kg)	35.0 ± 2.0	42.4 ± 3.5

Values are mean \pm SE.

* $P < 0.05$ vs. obese adults.

BMI, body mass index; Circ., circumference; Vol., volume; MVC, maximal voluntary contraction.

squared metres (kg m^{-2}). A three-site skinfold assessment (Jackson & Pollock 1978, Jackson *et al.* 1980), a waist circumference and a waist-to-hip ratio were collected and used for the analysis of body fatness. Forearm volume was determined using water displacement (Wilkins *et al.* 2006). Fasting plasma levels of LDL, HDL, total cholesterol, triglycerides and glucose were measured using venous blood.

Arterial blood pressure and heart rate. All data were collected with subjects supine. Baseline mean arterial pressure (MAP) in the resting limb was measured once at the beginning of each workload (approximately every 6 min) by an electronic sphygmomanometer (Datex-Ohmeda Helsinki, Finland) on the upper arm at rest. In addition, beat-to-beat changes in blood pressure were continuously measured for all trials at the heart level using finger photoplethysmography (Finometer, Finapres, the Netherlands) on the middle finger of the resting hand. Beat-by-beat heart rate was monitored continuously and recorded from a three-lead ECG (Datex-Ohmeda).

Forearm blood flow. Blood velocity and artery diameter were measured as described previously (Limberg *et al.* 2010a,b) using Doppler ultrasound with a 12-MHz linear array probe (Vivid 7; General Electric, Milwaukee, WI, USA). The probe insonation angle was $<60^\circ$, and the sample volume was adjusted to cover the width of the artery using identical methods as described previously (Schrage *et al.* 2004, 2007, Wilkins *et al.* 2006). The probe was placed approximately midway between the antecubital and axillary regions, medial to the *biceps brachii* muscle. The ultrasound probe operator continuously adjusted the probe position to maintain a fixed insonation angle, compensating for subjects' movements because of forearm contraction. Forearm blood flow (FBF) was determined as the product of mean blood velocity (cm s^{-1}) and vessel cross-sectional area (radius in cm^2) and was reported in mL min^{-1} . Except during intermittent artery diameter measurements, arterial blood velocity was continuously assessed throughout the experiment. Diameter measurements taken at rest, prior to contraction, typically resulted in loss of pulse wave signal for 15 s. To determine vessel cross-sectional area, artery diameter was taken offline for each workload as an average of five measurements in late diastole at rest. Arterial diameter was measured on B-mode images in the part of the artery running perpendicular to the ultrasound beam and was identified by strong wall signals and longitudinal section of the artery in each image (measuring the distance between proximal and distal wall intima-media interface) (Limberg *et al.* 2010a,b).

Study protocol

Maximal voluntary contraction (MVC) of the experimental (non-dominant) arm was determined as the highest measurement from five consistent trials using a hand dynamometer (LaFayette Instruments, LaFayette, IN, USA). Handgrip exercise was then randomly completed at relative workloads: 15, 20, 25, 30, 40 and 50% of forearm MVC. A total of three trials were performed at each workload to calculate an average response for each subject at each workload. Subjects laid supine with non-dominant arm extended to the side (approx. 90°) and placed above heart level to minimize the muscle pump contribution to any blood flow increase by eliminating the venous hydrostatic column (Shiotani *et al.* 2002, Laughlin & Joyner 2003). Dynamic, brief, non-dominant forearm exercise required participants to squeeze and release two handles together 4–5 cm to raise and lower a weight over a pulley within 1 s. Subjects were instructed to contract and relax on verbal command from the operator. Only contractions performed on proper timing were analysed. Two minutes of relaxation were given between each contraction to allow ample time for haemodynamic variables to return to baseline value (Tschakovsky *et al.* 2004, Kirby *et al.* 2007). Single and brief forearm contractions, involving a small muscle mass, were used to isolate the local effects of muscle contraction on the forearm vasodilatory response, by limiting the contribution of any cardiac output change to the forearm vasodilatory response (Kirby *et al.* 2007) and by eliminating any neural mechanisms including any reflex activation of the sympathetic nervous system (Corcondilas *et al.* 1964, Dyke *et al.* 1998, Buckwalter & Clifford 1999, Naik *et al.* 1999).

Data acquisition and analysis

A commercial interface unit (Multigon Industries, Yonkers, NY, USA) processed the angle-corrected, intensity-weighted Doppler audio information from the ultrasound system into a flow velocity signal that was sampled in real time with signal-processing software (PowerLab, ADInstruments, Colorado Springs, CO, USA). All haemodynamic data were digitized, stored on a personal computer at 400 Hz and analysed offline using PowerLab; post-processing using PowerLab's Chart application package yielded mean blood velocities.

The primary analysis tested whether the vasodilatory response to single contraction was impaired in obese adults when compared to results from lean controls. Because there was a tendency for higher MAP in the obese group (Table 2), the main dependent variable was forearm vascular conductance (FVC). To determine vascular conductance, FBF measurements were

Table 2 Baseline haemodynamics

	15%	20%	25%	30%	40%	50%
Mean arterial pressure (mmHg)						
Lean	88 ± 2	90 ± 2	89 ± 2	89 ± 2	87 ± 2	88 ± 2
Obese	96 ± 3	94 ± 2	94 ± 3	94 ± 2	93 ± 2	95 ± 2
Heart rate (bpm)						
Lean	66 ± 2	67 ± 3	67 ± 2	67 ± 3	67 ± 2	68 ± 3
Obese	63 ± 2	65 ± 3	66 ± 3	64 ± 2	65 ± 3	66 ± 3
Brachial artery diameter (mm)						
Lean	4.2 ± 0.2	4.1 ± 0.2	4.2 ± 0.2	4.2 ± 0.2	4.2 ± 0.2	4.1 ± 0.2
Obese	4.1 ± 0.2	4.2 ± 0.2	4.1 ± 0.2	4.2 ± 0.2	4.2 ± 0.2	4.2 ± 0.2
Forearm blood flow (mL min ⁻¹)						
Lean	55 ± 7*	53 ± 7*	57 ± 8*	54 ± 7*	52 ± 6*	58 ± 8*
Obese	87 ± 8	105 ± 16	101 ± 12	98 ± 13	98 ± 14	111 ± 16
Forearm vascular conductance (mL min ⁻¹ per 100 mmHg)						
Lean	63 ± 8*	60 ± 7*	64 ± 9*	60 ± 7*	60 ± 7*	67 ± 10*
Obese	92 ± 9	110 ± 16	112 ± 16	102 ± 12	104 ± 13	116 ± 15

Values are mean ± SE.

* $P < 0.05$ vs. obese adults.

normalized for beat-by-beat MAP. Dynamic FVC was calculated as FBF_n/MAP_n , where n corresponds to the cardiac cycle number with reference to contraction. Baseline FVC, FBF, MAP and heart rate represent an average of the last 30 s of the resting time period before any muscle contraction.

The vasodilatory response to contraction was calculated starting with the first unimpeded brachial velocity waveform post-contraction and for each cardiac cycle thereafter for 30 cycles. The reported values represent the average of 3 trials for all subjects. As presented by Buckwalter and Clifford (see Table 1, p. 162 in (Buckwalter & Clifford 2001)), to determine the vasodilatory response magnitude across different baseline flow (as is the case in this study when obese and lean adults data are compared; see Table 2), it is most appropriate to express vascular conductance as a percent change from baseline. For each workload, contraction-induced vasodilatation was thus calculated as follows: [(FVC post-contraction – FVC baseline) ÷ FVC baseline × 100], and termed FVC%. The immediate (defined as FVC% at the first cardiac cycle post-contraction) and peak (defined as the mean of the three consecutive greatest FVC%) vasodilatory responses were determined. The total contraction-induced vasodilatation was calculated as the area under dynamic response curve (sum) of FVC% post-contraction. These different indices were compared at absolute and relative (percent of MVC) workloads.

Statistics

Normality of the data and homogeneity of the variances of the distributions (equal variance) were tested using

the Shapiro–Wilk test and the Levene test respectively. If test was passed, differences between groups for subjects' characteristics and baseline data were determined by means of unpaired t -tests. If test failed, group differences were determined by means of Mann–Whitney tests. The time-dependent effect (expressed as cardiac cycles post-contraction) of obesity on FVC% was tested using a two-way repeated-measures ANOVA with Holm–Sidak post hoc test (performed when appropriate). To characterize the relationship between FVC% indices and workload, a linear regression analysis was also performed on individual slopes to determine significance between lean and obese adults. All data are presented as mean ± standard error. Differences were considered significant if $P < 0.05$. Statistical analysis was performed using SigmaPlot software 11.0 (Systat Software, Tulsa, OK, USA).

Results

Subjects' characteristics and baseline haemodynamics

Fourteen lean and 14 obese adults completed the present study. Subject characteristics are summarized for each group in Table 1. There were no significant group difference in age, height, MVC, glucose and HDL cholesterol concentration. In contrast, obese subjects had significantly ($P < 0.05$) greater values for body weight, body fat, BMI, waist-to-hip ratio, forearm volume and LDL cholesterol.

Table 2 summarizes the mean baseline haemodynamic values for each group and for each trial. There were no significant differences for each variable between trials, demonstrating a constant haemodynamic

baseline over the entire experiment. There were also no significant group differences in baseline brachial artery diameter, HR and MAP. In contrast, baseline FBF and FVC were greater ($P < 0.05$) in obese subjects compared to lean subjects.

Heart rate and blood pressure responses to single forearm contraction

Figure 1 shows a representative example of the blood pressure response to a single handgrip contraction at 50% MVC in a lean subject. For all trials, and consistent with previous studies (Tschakovsky & Sheriff 2004, Kirby *et al.* 2007, Carlson *et al.* 2008), there were no significant contraction-induced changes in MAP and HR compared to baseline (data not shown). Therefore, any changes in FVC_% observed in our study were attributed to mechanisms from local microvascular origin.

Forearm vasodilatory responses to single forearm contraction

The FVC_% dynamic response following a single handgrip contraction for each group and for each workload is shown in Figure 2. For all trials, brief single forearm contraction evoked a significant ($P < 0.05$), immediate (within one cardiac cycle) and graded rapid onset vasodilatation from one to up to six cardiac cycles post-contraction. Thereafter, FVC_% returned toward resting value. From the rapid onset vasodilatory response to contraction, we determined the following key indices.

Immediate vasodilatory response

At the lowest workload (15% MVC), the immediate (first cardiac cycle post-contraction) vasodilatory response was not significantly different between groups ($66 \pm 11\%$ vs. $49 \pm 8\%$, lean vs. obese respectively) (Fig. 2). In contrast, it was significantly ($P < 0.05$)

lower in obese adults at all subsequent workloads. As shown in Figure 3a, this reduction was exaggerated with increased workloads as obese adults showed a significant ($P < 0.05$) and marked reduction in the slope of the immediate FVC_% response to workload increases. Response slopes in obese adults averaged 28 and 32% of the lean adults' response slopes, for absolute and normalized workloads respectively (Fig. 3a).

Peak vasodilatory response

Both groups reached a peak vasodilatory response between the fourth and the sixth cardiac cycle post-contraction, with time-to-peak FVC_% increasing with increasing workloads (Figs 2 and 3b). As shown in Figure 3b, we observed a gradual increase in the peak vascular conductance with workload increase in both groups. However, this peak vasodilatory response was significantly ($P < 0.05$) reduced in obese adults. As shown in Figure 3b, this reduction was greater with increased workloads as obese adults showed a significant ($P < 0.05$) and marked reduction in the slope of the peak FVC_% response to workload increases. Response slopes in obese adults averaged 42 and 48% of the lean adults' response slopes, for absolute and relative workloads respectively (Fig. 3b).

Total vasodilatory response

At the lowest workload (15% MVC), the total vasodilatory response (corresponding to the area under the curve shown in Figure 2) was not significantly different between groups ($1860 \pm 374\%$ vs. $1316 \pm 214\%$, lean vs. obese respectively) (Figs 2 and 3c). In contrast, it was significantly ($P < 0.05$) impaired in the obese adults at all subsequent workloads. As shown in Figure 3c, this impairment was greater with increased workloads as obese adults showed a significant ($P < 0.05$) and marked reduction in the slope of the total FVC_%

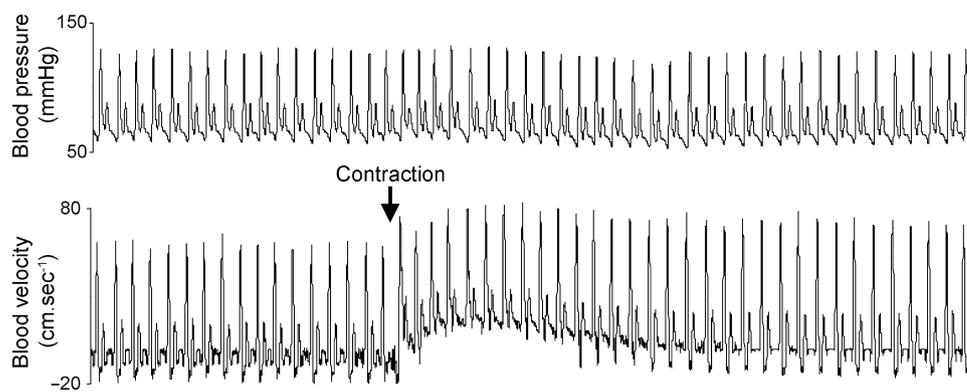


Figure 1 Representative arterial blood pressure (top) and blood velocity (bottom) pre- and post-contraction in a lean subject at 50% of maximal voluntary contraction. Note the marked response in velocity despite any change in the blood pressure time course.

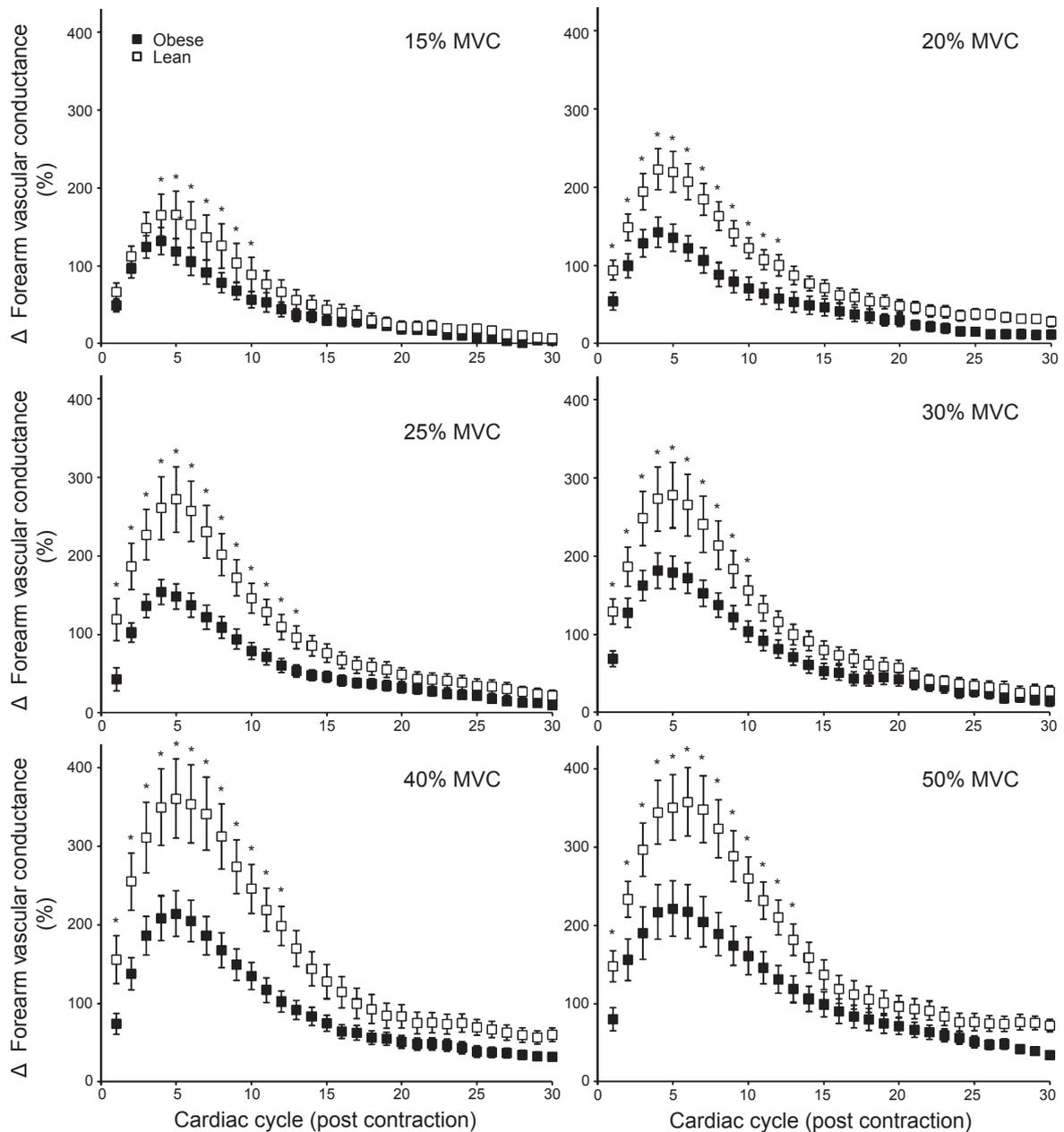


Figure 2 Time course of the vasodilatory response following single, brief forearm muscle contractions at different workloads, in lean (□) and obese (■) adults. Significant rapid vasodilatation impairments were observed in obese adults at all workloads. MVC: maximal voluntary contraction. Data are presented as mean ± SE from 14 lean and 14 obese adults. * $P < 0.05$ vs. obese adults.

response to workload increases. Response slopes in obese adults averaged 55 and 62% of the lean adults' response slopes, for absolute and normalized workloads respectively (Fig. 3c).

Return toward baseline

From the peak of the vasodilatory response, FVC% remained significantly ($P < 0.05$) greater in lean

compared to obese adults up to 13 cardiac cycles post-contraction (Fig. 2). Then, a complete return toward baseline was observed in both groups for the 15–30% MVC trials, whereas this return was still incomplete thirty cardiac cycles, after contraction for the 40 and 50% MVC trials. For these highest workloads, it was, however, confirmed that FVC% returned to baseline within the first minute post-contraction.

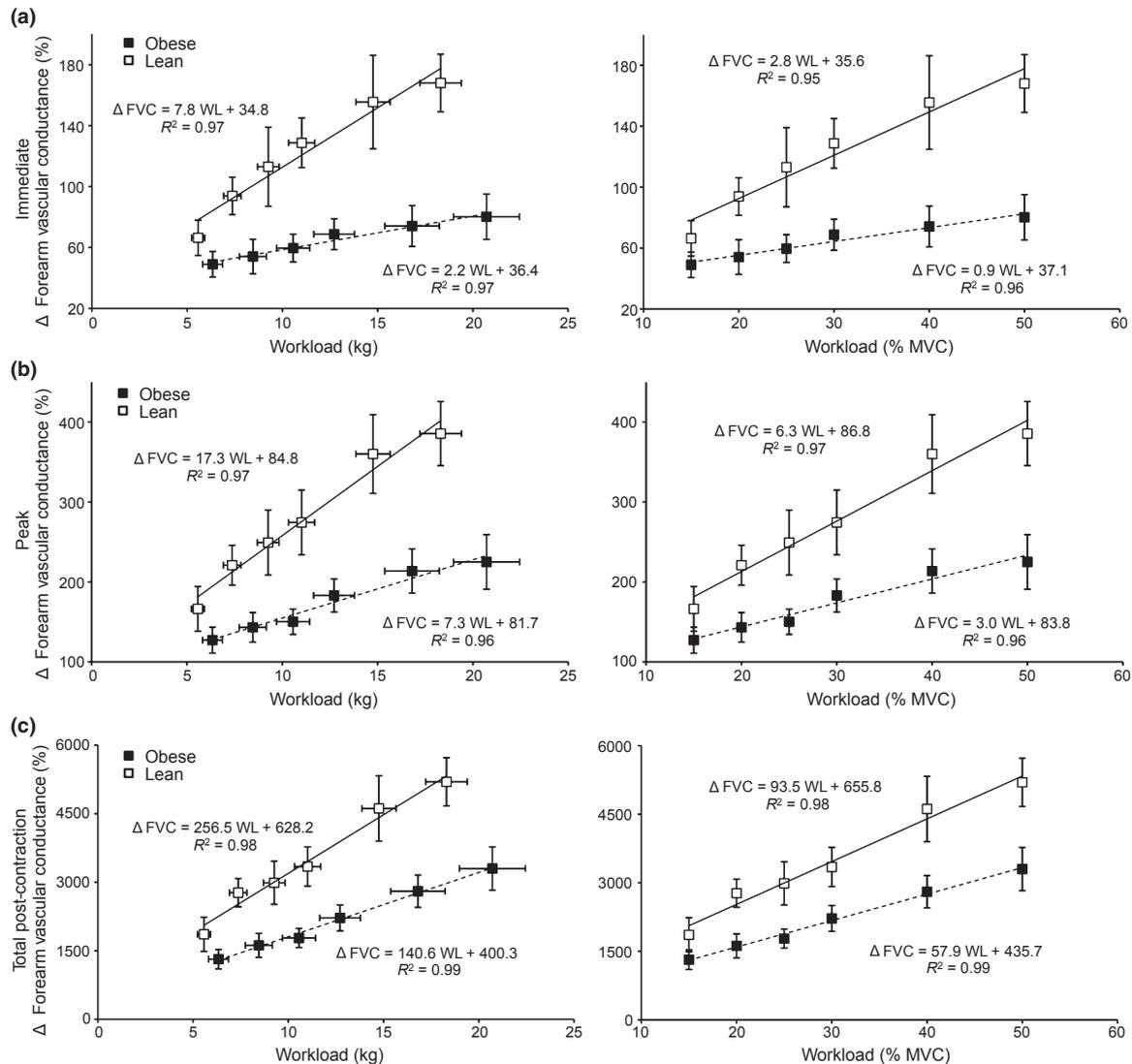


Figure 3 Responses to single, brief forearm muscle contractions at different absolute (left panel) and relative (right panel) workloads (WL) in lean (\square) and obese (\blacksquare) adults. (a) Immediate (first unimpeded cardiac cycle post-contraction) forearm vascular conductance (FVC) responses. (b) Peak (mean of the three consecutive greatest FVC%) responses. (c) Total (area under dynamic response curve of FVC% post-contraction) FVC responses. Linear regression analysis of vasodilatory responses to both absolute and relative workloads shows obese adults exhibit significantly lower slopes when compared to lean controls. MVC: maximal voluntary contraction. Data are presented as mean \pm SE from 14 lean and 14 obese adults.

Discussion

We used single brief forearm muscle contraction to examine the impact of obesity on local skeletal muscle rapid onset vasodilatation. Our data indicate with obesity (i) the peak vasodilatory response to single contraction is impaired at workloads from 15 to 50% of MVC, (ii) the immediate and total vasodilatation is impaired from 20 to 50% of MVC, and (iii) these impairments are greater with increasing workloads. These novel findings demonstrate a blunted rapid onset vasodilatation with obesity, which may negatively impact peripheral vasculature responses to brief or

intermittent bursts of activity such as those seen with activities of daily living.

Effects of obesity on the vasodilatory and hyperaemic response to exercise

To date, limited studies have evaluated the influence of obesity on exercise blood flow and vascular conductance in humans. Findings from the current study have relevant implications for the transition from rest to exercise. During dynamic steady-state forearm exercise, obese subjects exhibited preserved blood flow and vascular conductance in the exercising limb as measured

with Doppler ultrasound (Limberg *et al.* 2010a,b). We speculate mechanical factors are highly important during brief movements or at the onset of exercise and potentially play a smaller role at steady state. Alternatively, obese adults reach steady state through other mechanisms capable of compensating for the mechanical impairment observed in the current study. In this way, dynamics of blood flow may be impaired, but steady-state levels of flow maintained via compensatory mechanisms. Regardless, during the transition to moderate-intensity exercise, immediate limitations in muscle blood flow may contribute to slow VO_2 kinetics, in turn compromising exercise tolerance through an oxygen deficit. Recent work in ageing humans supports the concept of impaired rapid onset vasodilatation (Carlson *et al.* 2008) and slowed VO_2 kinetics (reviewed in Poole & Ferreira 2007) with increasing cardiovascular risk.

Potential mechanisms for impaired rapid vasodilatation with obesity

Clifford *et al.* (2006) reported the application of external pressure on isolated rat soleus feed arteries elicits a rapid vasodilatation that peaks in 4–5 s, which is similar to the peak contraction-induced vasodilatation observed in the present as well as previous studies (Corcondilas *et al.* 1964, Tschakovsky & Sheriff 2004, Kirby *et al.* 2007, Carlson *et al.* 2008). Removal of vessel endothelium (Clifford *et al.* 2006) or inhibition of nitric oxide synthase (Brock *et al.* 1998) is known to reduce this rapid vasodilatation. Thus, impairment of endothelial release of factors such as nitric oxide with obesity (Higashi *et al.* 2001, Van Guilder *et al.* 2006) could contribute to the reduced peak vasodilatory response to single contraction in our obese subjects. Additionally, increased brachial artery stiffness in obese humans (Zebekakis *et al.* 2005), as well as increased stiffness and reduction in the passive diameter of the arterioles in skeletal muscles of the obese Zucker rat (Frisbee 2003), suggests a potential structural cause of decreased vascular conductance observed in response to a single, brief forearm contraction. It remains to be determined how single or collective mechanisms contribute to the obesity-induced impaired rapid vasodilatation.

Potential candidate signals underlying the vasodilatory response to a single, brief contraction must be rapid and in proportion to workload. Findings from isolated vessel preparations (Clifford *et al.* 2006) as well as from human experiments (Kirby *et al.* 2007) show a direct local increase in interstitial pressure associated with a decrease in vessel transmural pressure (i.e. myogenic mechanism) elicits a rapid and brief (1–2 cardiac cycles) vasodilatation. Given the myogenic response is altered in the obese Zucker rat (Frisbee

et al. 2002), this mechanism could partly contribute to the blunted contraction-induced vasodilatation observed in our obese group. However, additional mechanisms are necessary to cause a reduction in vasodilatation with obesity over 4–6 cardiac cycles. Metabolites are believed to act too slowly to play a large role in rapid vasodilatation (Wunsch *et al.* 2000); a more likely candidate may be potassium channel function (Armstrong *et al.* 2007). Consistent with this concept, potassium channel-mediated vasodilatation is impaired in obese rats (Hodnett *et al.* 2008), yet this hypothesis remains untested in skeletal muscles from obese humans.

It is important to note rapid onset vasodilatation does not rely on neural mechanisms (Corcondilas *et al.* 1964, Dyke *et al.* 1998, Buckwalter & Clifford 1999, Naik *et al.* 1999) nor can be attributed to the skeletal muscle pump (i.e. contraction-induced widening of the arteriovenous pressure gradient) (Hamann *et al.* 2003, 2004). For example, cervical sympathectomy in humans did not change the pattern of the single contraction-induced vasodilatation and increase in FBF, indicating the local nature of the response (Corcondilas *et al.* 1964). Moreover, the current research design ensured any muscle pump contribution to the vasodilatory response was minimized by placing the subject's arm above heart level. Taken together, our current findings cannot be explained by group differences in sympathetic activation or muscle pumping activity.

Methodological considerations and limitations

A potential limitation of the present study is our evaluation of body composition, which was limited to body mass index (BMI) and anthropometric measures rather than more advanced methods such as dual-energy X-ray absorptiometry. It has been shown that these variables correlate very well with more direct measures of obesity (Canoy 2008). Moreover, given the large and significant differences observed in BMI, body fat (via skinfold assessment) and waist/hip ratio, differences in whole body composition between our lean and obese groups were clearly identified. It does not appear blood flow to forearm adipose significantly impacted our results considering the majority of adipose tissue is subcutaneous (Hamann *et al.* 2004, Ruan *et al.* 2007), and adipose vessels are minimally affected by muscular contraction and will contribute minimally to contraction-induced vasodilatation (Heinonen *et al.* 2010).

Although maximal forearm strength was not significantly different between groups, obese subjects exhibited higher MVC on average (Table 1). Given exercise was conducted at relative intensities, and it may be possible potential differences in muscle strength influenced data interpretation. However, the slope of the

'workload vs. vasodilatory response' relationship in the current study is significantly reduced with obesity whether workload is expressed in absolute or relative (i.e. as a percent of MVC) units (see Fig. 3). Thus, for a given relative intensity, obese adults exhibit reduced dilation despite greater workloads and presumably greater vascular compression – potentially underestimating the impact of obesity on rapid vasodilatation.

To account for differences in baseline blood flow and vascular conductance between our groups, these variables were expressed as a percent change from baseline – similar to previous investigations (Kirby *et al.* 2007, Carlson *et al.* 2008). By definition, any vasodilatation corresponds to an increase in vessel radius (Buckwalter & Clifford 2001). From Poiseuille's law, we obtain that (i) large blood flow increase can result from only small changes in radius and (ii) a given percent change in radius always produces the same percent change in vascular conductance (Buckwalter & Clifford 2001). Despite different baseline blood flows, a more pronounced percent increase in vascular conductance corresponds to a predictable and more pronounced percent increase in the vessel radius (i.e. increased vasodilatory response) (Buckwalter & Clifford 2001).

When changes in FBF and FVC are expressed in absolute units, rapid onset vasodilatation appears similar between groups; however, this interpretation is not valid. Because obese subjects exhibit greater lean forearm tissue when compared to lean controls, one can conclude substantially less blood flow available per gram of muscle tissue. To test this idea, we estimated lean muscle mass (dual-energy X-ray absorptiometry) and peak vascular capacity (peak FBF in response to a 5-min circulatory occlusion of the forearm) in an additional group of subjects with similar characteristics ($n = 12$ per group). Both lean tissue (lean 961 ± 70 vs. obese 1156 ± 35 g) and peak vascular capacity (lean 612 ± 44 vs. obese 871 ± 112 mL min^{-1} 100 mmHg $^{-1}$) was greater in obese adults ($P < 0.05$). Thus, when expressed relative to lean forearm volume, results suggest a 21% greater vascular capacity in obese subjects (lean 66 ± 5 vs. obese 81 ± 12 mL min^{-1} 100 g $^{-1}$, $P < 0.05$). Taken together, to achieve a similar rise in absolute FBF (or FVC) between groups, any resistance artery in forearm muscle from obese humans dilates less than a given artery from lean subjects. Whether expressing data in relative or absolute terms, our conclusions are supported: obese humans demonstrate blunted rapid onset vasodilatation.

Conclusion

These findings demonstrate human obesity is associated with reduced contraction-induced rapid onset vasodilatation. Given our approach limits neural and cardiac

influences, our data support the concept of blunted rapid onset vasodilatation within the contracting muscle in obese, otherwise healthy young adults. This vascular dysfunction could influence hyperaemic responses to brief bouts of physical activity.

Conflict of interest

There are no potential conflicts of interest.

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