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Human skeletal muscle feed arteries: evidence of regulatory potential

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Abstract

Aim: Recently, it has been recognized that human skeletal muscle feed arteries can be harvested during exploratory surgery for melanoma. This approach provides vessels for *in vitro* study from a wide spectrum of relatively healthy humans.

Although, the regulatory role of skeletal muscle feed arteries in rodent models has been documented, whether such vessels in humans possess this functionality is unknown.

Methods: Therefore, skeletal muscle feed arteries (~950 μ m OD) from 10 humans (48 ± 4 , 27–64 years) were studied using pressure myography. Vessel function was assessed using potassium chloride (KCl), phenylephrine (PE), acetylcholine (ACh) and sodium nitroprusside (SNP) concentration–response curves (CRCs) to characterize non-receptor and receptor-mediated vasoconstriction as well as endothelium-dependent and independent vasodilation respectively. To understand the physiological relevance of the diameter changes as a result of pharmacological stimulation, the estimated conductance ratio (CR) was calculated.

Results: Vessel function protocols revealed significant vasoconstriction in response to PE and KCl (35 ± 6 ; $43 \pm 9\%$ vasoconstriction, respectively) and significant vasodilation with ACh and SNP (85 ± 7 ; $121 \pm 17\%$ vasodilation, respectively). Both PE and KCl significantly reduced the CR (0.26 ± 0.05 and 0.23 ± 0.07 , respectively), whereas ACh and SNP increased the CR (2.56 ± 0.10 and 5.32 ± 1.3 , respectively).

Conclusion: These novel findings provide evidence that human skeletal muscle feed arteries are capable of generating significant diameter changes that would translate into significant changes in vascular conductance. Thus, human skeletal muscle feed arteries likely play a significant role in regulating vascular conductance and subsequently blood flow *in vivo*.

Keywords conductance, feed artery, muscle blood flow, resistor.

Traditionally, pre-capillary sphincters in the microvasculature have been thought of as the sole site regulating vascular resistance and functional hyperaemia during exercise (Calbet & Joyner 2010, Sarelius & Pohl 2010). However, relatively recently, using animal models, researchers have determined that feed arteries produce resistance to blood flow as pressure in these vessels is lower than systemic pressure (Williams & Segal 1993, Segal 2005), but greater than downstream 1A arterioles (Schrage *et al.* 2000), indicating that the feed artery is a resistor (Williams & Segal 1993). The notion that the skeletal muscle feed artery is a key point of skeletal muscle blood flow regulation has gained credence over the last 20 years (Segal & Duling 1986, Williams & Segal 1993, Lash 1994, Segal 2000, Van Teeffelen & Segal 2003, Van Teeffelen & Segal 2006), although it should be noted that Schretzenmayr (1933) may actually have been the first to recognize that contraction-induced vasodilation was possible in arteries upstream of the muscle bed in 1933. Indeed, there is now evidence from rodent models that feed arteries are not only capable of producing vascular resistance (Van Teeffelen & Segal 2003, Van Teeffelen & Segal 2006), but can also elicit significant vasodilation in response to muscle contraction, ischaemia or pharmacological stimuli (Segal & Duling 1986, Williams & Segal 1993, Van Teeffelen & Segal 2006). In fact, back in 1986, Segal and Duling (Segal & Duling 1986) suggested that feed arteries be recognized as 'resistance vessels'. However, despite this designation and the highlighting of the potential importance of these vessels, there is a dearth of information characterizing the role of skeletal muscle feed arteries

in humans.

Investigators have obtained human arteries for *in vitro* study, however it is important to note the different sources of these arteries, such as subcutaneous arteries from aged (Coats *et al.* 2001) or obese (Grassi *et al.* 2009, De Ciuceis *et al.* 2011) subjects, ciliary arteries (Nyborg & Nielsen 1990) and arterioles from skeletal muscle during amputation procedures (Jarajapu *et al.* 2001). Of additional note, the majority of these studies were performed using wire myography. Utilizing the same methodology, but in combination with the novel approach of obtaining human skeletal muscle feed arteries during axillary and inguinal sentinel lymph node biopsy or dissection, and with an interest in translating prior work from the animal model, we have successfully studied the functional characteristics of these vessels. With this method, we have begun to investigate potential factors, such as temperature, that could alter skeletal muscle feed artery function (Ives *et al.* 2011). Unlike pressure myography, which assesses vessel diameter change, wire myography measures force generation. Therefore, wire myography does not answer the questions as to whether these arteries are, indeed, capable of altering vascular resistance and thus truly involved in the regulation of skeletal muscle blood flow.

Consequently, utilizing the pressure myography technique, the purpose of this study was to determine if human skeletal muscle feed arteries are capable of significant vasodilation and vasoconstriction which will alter the estimated conductance ratio (CR) of these vessels (Segal & Duling 1986, Williams & Segal 1993). Specifically, we hypothesized that human feed arteries will be capable of producing significant changes in estimated conductance through non-receptor and receptor-mediated pathways. The implications of which would be, a role for human feed arteries in the regulation of skeletal muscle blood flow.

Methods

Subjects and general procedures

A heterogeneous group of subjects agreed to have their vessels harvested during surgery and used in this study (Table 1). Although medical conditions and

medications were noted, by means of medical records, there were no exclusions based on this information. All subjects included in this study had not received chemotherapy, as this was a contraindication for surgery. This study conforms with good publishing practice in physiology (Persson & Henriksson 2011).

Table 1. Subject characteristics ($n = 10$)

	Mean±SE	Normal Range
Age (year)	48 ± 4	–
	(27-64)	
Males/females (n)	4/6	
Height (cm)	169±9	–
Body mass (kg)	93±10	–
BMI (kg m ⁻²)	33±3	<30
Systolic blood pressure (mmHg)	133±5*	≤120
Diastolic blood pressure (mmHg)	82±3*	≤80
MAP (mmHg)	99±4	–
Glucose (mg dL ⁻¹)	100±8	65-100
Blood urea nitrogen (mg dL ⁻¹)	15.7±1.2	6-21
Creatinine (mg dL ⁻¹)	0.8±0.1	0.52-0.99
Albumin (g dL ⁻¹)	3.9±0.1	3.3-4.8
Bilirubin (mg dL ⁻¹)	0.4±0.1	0.2-1.3
Lactate dehydrogenase (U L ⁻¹)	458±39	300-600
WBC (K μL ⁻¹)	6.3±1.1	3.2-10.6
Platelets (K μL ⁻¹)	230±18	150-400
RBC (M μL ⁻¹)	4.9±0.1	4-5.2
Haemoglobin (g dL ⁻¹)	14.2±0.4	12-16
Medications (users/ n)	42.3±0.8	36-46
Cardiovascular		
Statin	6/10	
Ca ⁺⁺ Channel Blocker	1/10	
Beta Blocker	1/10	
ACE inhibitor	2/10	
Diuretic	2/10	
Other		
Insulin	0/10	
Metformin	2/10	
Hypothyroid	2/10	
*Data obtained during preoperative examination		

Vessel harvest

Human skeletal muscle feed arteries from the axillary and inguinal regions were obtained during melanoma-related node dissection surgeries at the Huntsman Cancer Hospital, University of Utah. Patients were anaesthetized using a standard protocol including: propofol, fentanyl, benzodiazepines and succinylcholine. After the removal of sentinel lymph nodes or lymph node dissection, skeletal muscle feed arteries in the axillary (e.g. serratus anterior or latissimus dorsi) (Fig. 1) or inguinal (e.g. hip adductors or quadriceps femoris) regions were identified and classified as feed arteries based on entry into a muscle bed, structure, colouration and pulsatile bleed pattern. The vessels were ligated, excised and immediately placed in iced normal physiological saline solution (PSS) and brought to the laboratory within 15 min of harvesting.

Pressure myography

Human skeletal muscle feed arteries were dissected free of perivascular adipose or connective tissue under a dissecting microscope (SZX10; Olympus, Center Valley, PA, USA) in cold (4 °C) physiological saline (PSS) containing (mM): 145.0 NaCl, 4.7 KCl, 2.0CaCl₂, 1.17 MgSO₄, 1.2 NaH₂PO₄, 5.0 glucose, 2.0 pyruvate, 0.02 EDTA, 3.0 MOPS buffer and 1 g (100 mL)⁻¹ BSA at pH 7.4. The arteries were carefully placed in the pressure myograph chamber (DMT 110P; Aarhus, Denmark) containing MOPS-buffered PSS equilibrated to room air. The arteries were cannulated at both ends with micropipette tips and secured with nylon monofilament suture (Alcon 11-0). After cannulation, the myograph chamber was transferred to the stage of an inverted microscope (TS100; Nikon Eclipse, Melville, NY, USA), equipped with a video camera, streamed in real time to edge detection software (DMT VAS v.2.0; Aarhus) to record luminal diameter. Intraluminal pressures were set to 60 mmHg (Lash 1994). Leaks were detected by pressurizing the vessel, closing the cannulas to the fluid reservoirs and assessing the capacity to maintain vessel diameter. Arteries, free from leaks, were then warmed to 37 °C and allowed to develop spontaneous tone during a 30 min equilibration period. The arteries were allowed to equilibrate and were discarded

unless at least 20% baseline tone was achieved prior to addition of vasoactive agents. Once equilibrated, arteries were studied using the pressure myography technique, an approach employed previously by our group (Donato *et al.* 2007, Lesniewski *et al.* 2008, Durrant *et al.* 2009).

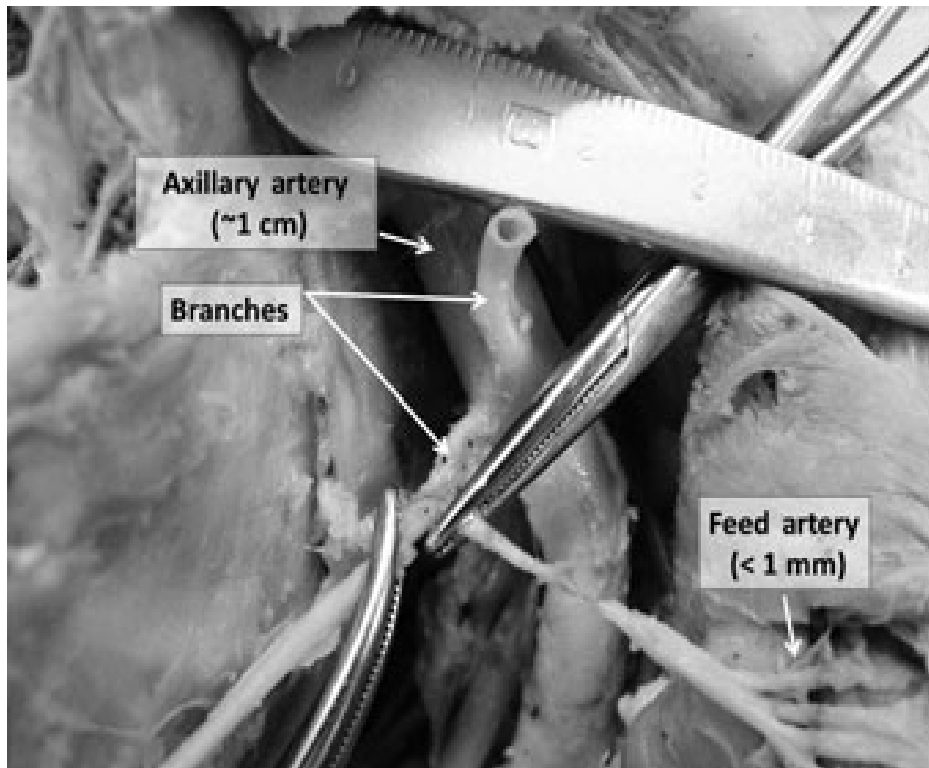


Figure 1 Dissection of the axilla in a post-mortem human cadaver, illustrating the relative size of the feed artery in comparison to larger, more proximal, conduit arteries. (Note: not actual surgery, for illustrative purposes only).

To determine non-receptor- and receptor-mediated vasoconstriction and vasodilation, concentration– response curves (CRC) for KCl (10–100 mM), PE (10^{-9} – 10^{-3} log M), sodium nitroprusside (SNP; 10^{-9} – 10^{-4} log M), and acetylcholine (ACh; 10^{-7} – 10^{-3} log M) were performed on each vessel and the order was balanced. PE and KCl data are presented as % vasoconstriction (%vasoconstriction = $\frac{\text{diameter} - \text{baseline diameter}}{\text{baseline diameter}} \times 100$) (Donato *et al.* 2007). ACh and SNP are presented as % vasodilation (%vasodilation = $\frac{[\text{diameter} - \text{baseline diameter}]}{[\text{maximal diameter} - \text{baseline diameter}]} \times 100$) (Donato *et al.* 2007). To understand the physiological relevance of these diameter changes, in terms of skeletal muscle blood flow *in vivo*, the estimated CR was

calculated using the formula developed by Segal & Duling (Segal & Duling 1986, Williams & Segal 1993), ($CR = Diameter_{response}^4 / Diameter_{baseline}^4$), which assumes that vascular conductance is proportional to the fourth power of the diameter. Estimated CRs of <1 imply reductions in vascular conductance, whereas those >1 imply an increase in vascular conductance.

Statistical analyses

As there are no data on the sensitivity of human skeletal muscle feed arteries, the logEC₅₀ was individually calculated using a sigmoidal parameter $[(a + (b - a) / (1 + 10^{(x - c)}))]$ to estimate vascular sensitivity to each agonist (biodatafit v.1.02; Castro Valley, CA, USA). One-way repeated measures ANOVA were used to determine significant responses in vessel diameter for each CRC (SPSS v.16; Chicago, IL, USA). Where significant main effects of concentration were found, Tukeys HSD *post hoc* tests were utilized to determine which doses were different from pre-drug baseline ($\alpha = 0.05$). Paired *t*-tests were used to determine if each drug altered the CR from baseline to maximal response ($\alpha = 0.05$). All data are expressed as mean \pm SE.

Results

Skeletal muscle feed arteries were harvested from 10 volunteers (48 ± 4 years, four men, six women) (Table 1). None of these subjects had overt coronary artery disease, peripheral vascular disease or cerebrovascular disease, or a history of MI/stenting/angioplasty. Because of inadequate statistical power to detect differences in vascular function between sex, age, vessel location, medication use, complete blood count and blood chemistry on any of the outcome variables, all data were combined. The average pressurized basal external diameter for these feed arteries prior to the PE and KCl concentration responses was 952 ± 96 μ m and 956 ± 112 μ m respectively. The maximal diameter for these vessels was 1100 ± 152 μ m. Vessel function protocols revealed significant vasoconstriction in response to the maximal dose of PE and KCl [$35 \pm 6\%$ (657 ± 104 μ m); $43 \pm 9\%$ vasoconstriction ($527 \pm$

105 /m)], respectively; Fig. 2a,b; $P < 0.05$ vs. baseline). The $\log EC_{50}$ for PE and KCl was -5.47 ± 0.25 and 43 ± 6.6 respectively.

The feed arteries achieved significant vasodilation ($P < 0.05$ vs. baseline) in response to the maximal dose of the endothelium-dependent agonist ACh, or the endothelium-independent agonist SNP (85 ± 7 ; $99 \pm 7\%$ vasodilation, respectively) (Fig. 2c,d). The $\log EC_{50}$ for ACh and SNP was -5.28 ± 0.45 and -5.72 ± 0.37 respectively. Taken together, these results document that these human feed arteries had functional smooth muscle, α_1 -adrenergic receptors and an intact endothelium.

Using the estimated CR to understand the potential *in vivo* relevance of the aforementioned feed artery diameter changes with pharmacologic stimulation, assuming all other variables constant, PE yielded a CR of 0.26 ± 0.05 ($P < 0.05$ vs. baseline; Fig. 3a), or conversely an approximate 75% increase in resistance. Similarly, KCl induced a CR of 0.23 ± 0.07 ($P < 0.05$ vs. baseline; Fig. 3a), again this would yield nearly an 80% increase in resistance. Endothelium-dependent vasodilation using ACh significantly increased the CR to 2.56 ± 0.10 ($P < 0.05$ vs. baseline; Fig. 3b), whereas the endothelium-independent vasodilator SNP increased the CR to 5.32 ± 1.34 ($P < 0.05$ vs. baseline; Fig. 3b). These results are not likely due to a time effect, as baseline diameters, and thus estimated vascular conductance, were unchanged across the study; this stability across time was most likely due to the experimental design in which the order of CRCs was balanced.

Discussion

The main finding of this study is that human skeletal muscle feed arteries are capable of eliciting significant alterations in vessel diameter which, *in vivo*, would result in significant changes in vascular conductance. While previously documented in animal models, these data are the first to translate this recognized ability of skeletal muscle feed arteries to have such vasomotion and assumed changes in conductance. This observation confirms prior studies in animals, translates this prior work into humans and has significant implications for our understanding of blood

flow regulation, in terms of both local and systemically governed vasoreactivity, as well as the role of autonomic control. Indeed, each of these factors may impact human feed artery conductance and therefore play a role in the distribution of blood from inactive to active muscle beds.

The regulatory nature of the feed artery

Anatomically, the feed artery is well positioned to be a control point in determining skeletal muscle blood flow, acting as the main inlet to the muscle (Fig. 1). Functionally, it appears, at least in animals (Segal & Duling 1986, Hester & Duling 1988, Williams & Segal 1993, Lash 1994), that skeletal muscle feed arteries are capable of altering muscle blood flow by increasing or decreasing vascular conductance to skeletal muscle depending upon metabolic activity. Prior animal studies have documented that the feed artery is capable of significant vasoconstriction *in vitro* (Jasperse & Laughlin 1999), which translates into significant basal vascular resistance *in vivo* (Segal & Duling 1986, Hester & Duling 1988, Williams & Segal 1993, Lash 1994). The significant vasoconstriction observed in the current study with human arteries, using either PE or KCl (Figs 2 and 3), was less than the rat feed artery (~40 vs. 65% vasoconstriction, respectively) (Jasperse & Laughlin 1999); however, it is important to recognize that the larger human feed arteries are mathematically disadvantaged in this comparison by a larger baseline diameter. This size issue should not be misinterpreted as a similarity between human feed arteries and rodent conduit vessels, as these feed arteries, by human standards, are still very small compared to conduit level vessels (Fig. 1). In terms of vasodilation, comparing the results of the current study to the *in situ* work of Segal and colleagues (Segal & Duling 1986, Williams & Segal 1993), administration of ACh or SNP (Fig. 3) resulted in similar increases in the estimated CR previously observed in the feed arteries of the extensor digitorum longus of the rat (Williams & Segal 1993). Irrespective of magnitude, the ability to generate significant alterations in vascular conductance would certainly serve to redirect cardiac output from metabolically inactive to active skeletal muscle *in vivo*.

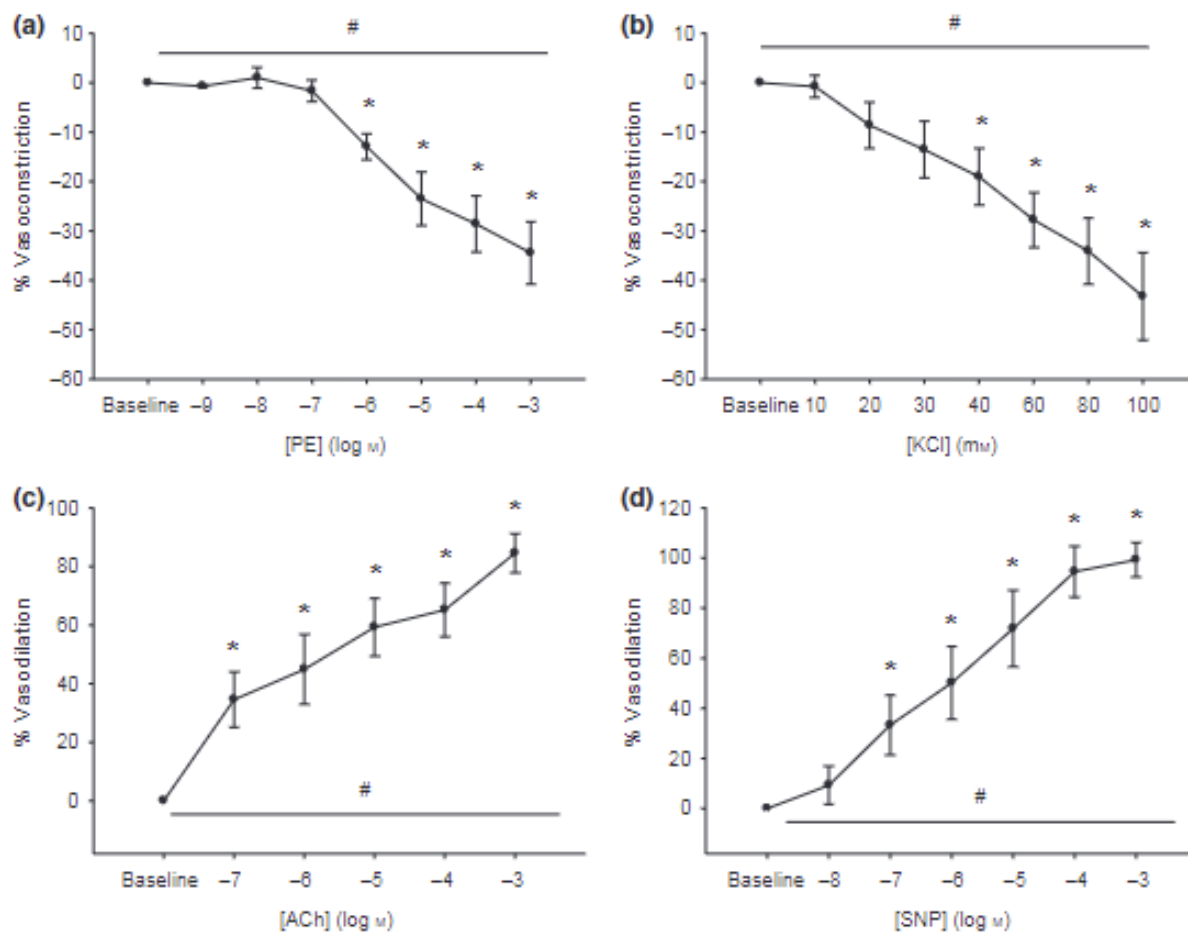


Figure 2 Human skeletal muscle feed artery functional characteristics. (a) Phenylephrine (PE) concentration response for α_1 -adrenergic mediated vasoconstriction (% change in diameter), (b) KCl concentration response for non-receptor mediated vasoconstriction (% change in diameter), (c) Acetylcholine (ACh) concentration response (% vasodilation), for endothelium dependent vasodilation, (d) Sodium Nitroprusside (SNP) concentration response (% vasodilation) for endothelium-independent vasodilation. ($n = 10$) # $P < 0.05$ main effect of concentration, * $P < 0.05$ vs. baseline. Data are presented as mean \pm SE.

Additionally, prior research has recognized that muscular contractions, *per se*, were capable of increasing conductance in feed arteries as well as in the distal microvasculature of skeletal muscle (Segal & Duling 1986, Bjornberg *et al.* 1989, Lash 1994). Specifically, observations made in the rodent model indicate that the feed artery is capable of flow-mediated dilation (Jasperse & Laughlin 1997), mechanically induced vasodilation (Clifford *et al.* 2006), pharmacologically induced

vasodilation (Segal & Duling 1986, Williams & Segal 1993) and may even be susceptible to conducted vasodilation (Bagher & Segal 2011) and venous-arterial feedback (Segal 2005), a form of counter-current exchange. Collectively, with these resistor characteristics, combined with the high potential for local regulation, the feed artery is poised to be a significant locus of control in determining skeletal muscle blood flow at rest and during challenges to homeostasis (e.g. exercise and orthostasis), and this is supported by the current data.

The role of feed arteries in humans

The ability to regulate blood flow and oxygen delivery at rest and during physiological challenges such as exercise and orthostasis is of clear importance in terms of homeostasis (Calbet & Joyner 2010, Sarelius & Pohl 2010). Recently using a novel approach to obtain human skeletal muscle feed arteries during node dissection surgeries (Fig. 1), our group has begun to study the factors regulating skeletal muscle blood flow in these vessels. Thus far, we have documented that heat exerts a 'sympatholytic' effect upon α_1 -adrenergic receptor responsiveness; however, as these measurements were taken by wire myography, the question remained as to whether the arteries used in such studies were indeed regulatory in nature. While further research is needed to delineate the role and regulation of the human skeletal muscle feed artery, the findings from this study strongly suggest a regulatory role, as documented by the significant changes in estimated conductance with pharmacological stimulation (Fig. 3). This coupled with the possibility for inhibition because of metabolic heat production (Ives *et al.* 2011) implicates the feed artery in the regulation of muscle blood flow during exercise. Certainly, however, far more work is needed to determine whether our understanding of the feed artery, its governance and role in the regulation of muscle blood flow in the animal model does, in fact, translate completely to human physiology. Given the potentially significant role of the feed artery in determining skeletal muscle blood flow, understanding the function and dysfunction of these vessels may be paramount in determining factors that undermine muscle perfusion in ageing (Lawrenson *et al.* 2003) or diseased populations, such as

heart failure (Wilson *et al.* 1984), or hypertension (Vongpatanasin *et al.* 2011).

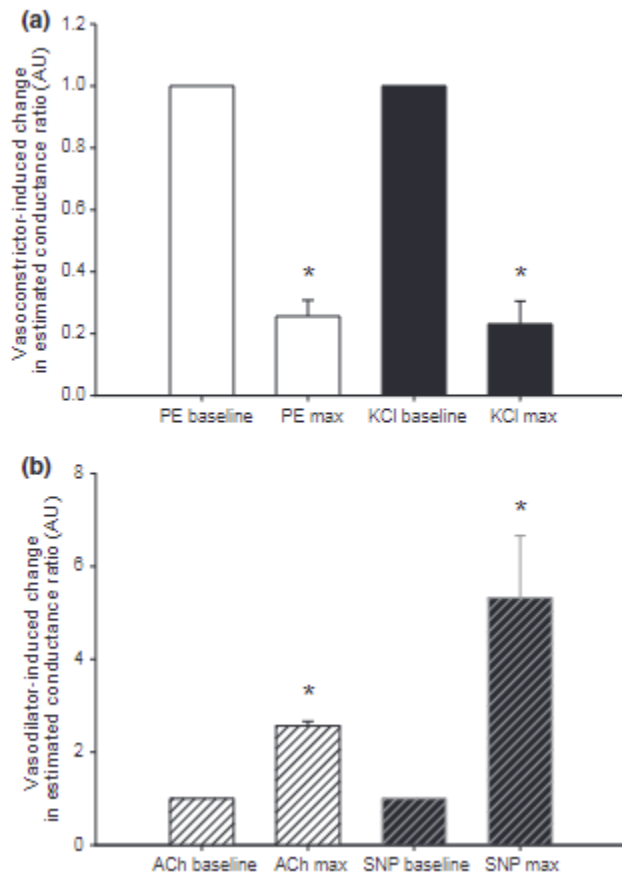


Figure 3 Baseline and maximal estimated conductance ratios in response to receptor mediated (white bars) and non-receptor (black bars) mediated vasoconstrictors (a) and vasodilators (b) in human skeletal muscle feed arteries. ($n = 10$) * $P < 0.05$ vs. baseline.

Origin of the vessel

The subjects who took part in this study were certainly heterogeneous in terms of age, gender and health, but, although exhibiting a tendency to be overweight and some evidence of systolic hypertension (although it should be noted that these measurements were obtained during preoperative examination), they were taking minimal medications and had normal blood chemistry and complete blood count data (Table 1). However, it should also be recognized that these subjects were undergoing prophylactic surgical treatment for melanoma and the majority of vessels were harvested during sentinel node biopsy, although most lymph nodes were found to be negative for melanoma metastasis via haematoxylin and eosin

staining, immunohistochemical staining and some via quantitative polymerase chain reaction analysis. In addition, it is of note that the lactate dehydrogenase values [considered to be a clinical indicator of metastasis in melanoma patients (Balch *et al.* 2009)] were within the normal range for all subjects (Table 1), and none of the subjects were undergoing chemotherapy.

Despite the rather varied origin of these vessels, the novel approach of harvesting these human arteries during surgeries yielded consistent receptor-mediated and non-receptor-mediated vasoconstriction and vasodilation characteristics (Fig. 2), suggestive of normal physiology. Therefore, despite a group of heterogeneous subjects, varied vessel harvest location (i.e. axillary and inguinal), and potential pathology, the notion that the selected agonists elicited a profound vasoreactivity speaks to the robust nature of these feed artery characteristics as they relate to blood flow regulation.

Conclusion

Utilizing a physiologically relevant *in vitro* approach to study human skeletal muscle feed artery vasomotion, we report that these arteries are, indeed, capable of significantly altering lumen diameter and therefore estimated conductance. Thus, it is highly likely that human skeletal muscle feed arteries contribute to the regulation of vascular resistance and subsequently blood flow *in vivo*.

Conflict of interest

The authors have no disclosures or conflicts of interest to report.

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