Does oxygen delivery explain interindividual variation in forearm critical impulse?

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Abstract
Within individuals, critical power appears sensitive to manipulations in O₂ delivery. We asked whether interindividual differences in forearm O₂ delivery might account for a majority of the interindividual differences in forearm critical force impulse (critical impulse), the force analog of critical power. Ten healthy men (24.6 ± 7.10 years) completed a maximal effort rhythmic hand-grip exercise test (1 sec contraction-2 sec relaxation) for 10 min. The average of contraction impulses over the last 30 sec quantified critical impulse. Forearm brachial artery blood flow (FBF; echo and Doppler ultrasound) and mean arterial pressure (MAP; finger photoplethysmography) were measured continuously. O₂ delivery (FBF arterial oxygen content [venous blood [hemoglobin] and oxygen saturation from pulse oximetry]) and forearm vascular conductance (FVC; FBF/MAP⁻¹) were calculated. There was a wide range in O₂ delivery (59.98–121.15 O₂ mL⁻¹min⁻¹) and critical impulse (381.5–584.8 N) across subjects. During maximal effort exercise, O₂ delivery increased rapidly, plateauing well before the declining forearm impulse and explained most of the interindividual differences in critical impulse (r² = 0.85, P < 0.01). Both vasodilation (r² = 0.64, P < 0.001) and the exercise pressor response (r² = 0.33, P < 0.001) independently contributed to interindividual differences in FBF. In conclusion, interindividual differences in forearm O₂ delivery account for most of the interindividual variation in critical impulse. Furthermore, individual differences in pressor response play an important role in determining differences in O₂ delivery in addition to vasodilation. The mechanistic origins of this vasodilatory and pressor response heterogeneity across individuals remain to be determined.

Introduction
Critical power is the maximal power output at which a metabolic steady state characterized by a plateau in VO₂, stable intracellular levels of Pi, PCr, ADP, ATP, H⁺, and stable blood lactate is reached (Poole et al. 1988; Jones et al. 2008, 2010). Exercising above critical power is limited by factors determining the fixed supracritical power work capacity, termed W', and results in progressively increasing VO₂, intracellular [Pi] and blood lactate until exhaustion at which point VO₂ is at maximum (Jones et al. 2008).

Traditionally, critical power is identified within an individual by determining the asymptote of their power-duration relationship from 3 to 4 constant load tests to

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exhaustion. Recently, critical power obtained in this manner has been found to be sensitive to manipulations in O2 delivery. For example, Vanhatalo et al. (2010) found that the power–duration curve asymptote was shifted upwards when exercise was performed while breathing hypoxic air, while Dekkerle et al. (2012) demonstrated that it was shifted downwards when exercise was performed while breathing hypoxic air. These findings support the contention that critical power represents the maximal power output at which aerobic ATP production can meet ATP demand without requiring additional substrate level phosphorylation (Dekerle et al. 2012), and that this aerobic ATP production rate is sensitive to manipulation of O2 delivery to the exercising muscle within an individual.

Critical power can also be determined using a single bout, maximal effort exercise protocol, validated for upright cycling (Burnley et al. 2006), knee extension (Burnley 2009) and most recently forearm handgrip exercise (Kellawan and Tschakovsky 2014). In this type of critical power identification test, subjects are required to produce maximal effort exercise that results in an exponential decay in power output to a plateau which represents critical power. It has been demonstrated that this method provides valid estimates of critical power (Burnley et al. 2006; Vanhatalo et al. 2007; Kellawan and Tschakovsky 2014). As critical power represents the upper limit of sustainable work rates, interindividual differences in critical power reflect interindividual differences in the range of tolerable exercise work rates. In this context, identifying factors that contribute to interindividual differences in critical power has important implications for understanding exercise (in)tolerance at the level of the individual.

Studies employing within-subject manipulation of O2 delivery, while providing evidence in support of an O2 delivery sensitivity of critical power (Vanhatalo et al. 2010; Dekkerle et al. 2012), cannot address the question of whether interindividual differences in O2 delivery contribute to interindividual differences in critical power. Instead, we reasoned that if the answer to this question was “yes”, then under the conditions of a single–bout maximal effort exercise test, whether O2 delivery stabilizes before power output, and finally to what extent any such interindividual differences in O2 delivery are due to differences in vasodilatory versus pressor responses.

As a first step, we pursued this objective at the level of isolated small muscle mass exercise, where determinants of exercising muscle O2 delivery are dependent on local vasoregulatory and systemic pressor responses, using our recently validated single–bout maximal effort forearm isometric handgrip exercise test (Kellawan and Tschakovsky 2014). In this type of exercise the contraction impulse represents the force analog of power output, and forearm critical force impulse (critical impulse) represents the force analog of critical power. We hypothesized that interindividual differences in O2 delivery would account for a majority of the interindividual variation in critical impulse, and a plateau in O2 delivery would clearly precede that for contraction impulse. Further to this we hypothesized that interindividual differences in vasodilatory response would account for the majority of interindividual variation in O2 delivery.

Materials and Methods

Subjects

Ten healthy men (age 24.6 ± 7.10 years) volunteered to participate in the study. The participants were recreationally active (268.15 ± 25.68 metabolic equivalents/week; most of the activity was from participation in team sports that involved the whole body and running, but did not participate in forearm exercise training). Participant’s characteristics are outlined in Table 1. After receiving a complete verbal and written description of the experimental protocol and potential risks, each subject provided signed consent to the experimental procedures that were approved by the Queen’s University Health Sciences Research Ethics Board (QUHSREB) in accordance with the terms of the Declaration of Helsinki on research ethics.

Experimental design

Maximal effort forearm critical force impulse test

All experimental sessions were conducted in a temperature-controlled laboratory (20–22°C) after a minimum 2 h fast and 12 h without exercise and caffeine. The
subjects lay supine with the experimental arm (left) extended 90° at heart level. After 2 min of quiet rest, subjects completed 10 min of rhythmic, maximal effort isometric handgrip contractions (1 sec contraction to 2 sec relaxation). This type of exercise results in a roughly exponential decay in contraction impulse (the area under the contraction force tracing) to an eventual plateau, the magnitude of which represents critical impulse (Kellawan and Tschakovsky 2014). Subjects received continuous, strong verbal encouragement, and coaching of contraction performance throughout the test to ensure that they gave a maximal effort during each contraction and to maintain the work-to-rest duty cycle.

**Measurements**

**Mean arterial blood pressure (MAP) and heart rate (HR)**

Beat by beat MAP (mmHg) was measured by finger photoplethysmography (Finometer MIDI, Finapres Medical Systems BV, Amsterdam, the Netherlands) on the middle finger of the control arm resting at heart level during all trials. HR was acquired using a three-lead ECG (Meditrace 535; Tyco HealthCare Group, Pointe Claire, Quebec, Canada).

**Forearm blood flow (FBF) and vascular conductance (FVC)**

Mean blood velocity (MBV, cm·sec⁻¹) was measured in the brachial artery with a 4-MHz pulsed Doppler probe (model 500V TCD; Multigon Industries, Mt. Vernon, NY) secured to the skin over the brachial artery. To maximize the between-subject comparability of our forearm blood flow measures, we have calibrated our Doppler ultrasound probe with known flow velocities, and we measure the angle of the brachial artery relative to the skin surface (i.e., relative to the probe insonation angle). This allows us to correct for differences in insonation angle that may exist between subjects. This has been previously described in detail (Tschakovsky et al. 2011). Brachial artery diameter was measured just proximal to the Doppler probe placement (10-MHz linear echo Doppler ultrasound probe operating in B-mode, Vingmed System Five, GE Medical, Mississauga, Ontario, Canada). FBF (mL·min⁻¹) was calculated from MBV and artery diameter (FBF = \( \frac{\text{MBV}}{\text{diameter}^2} \)). Forearm vascular conductance (FVC; mL·min⁻¹·mmHg⁻¹) was calculated from FBF and MAP (FBF·MAP⁻¹).

**Hemoglobin concentration ([Hb]), % saturation (\( S_\text{O}_2 \)), arterial oxygen content (\( C_\text{O}_2 \)), and oxygen delivery**

A venous blood sample was taken from the antecubital vein and analyzed for Hb content by an automated blood gas analyzer (Stat Profile M, Nova Biomedical, Waltham, MA). Arterial oxygen saturation (\( S_\text{O}_2 \)) was measured from the index finger of the control arm using pulse oximetry (Nellcor, the Netherlands). Oxygen content of arterial blood (\( C_\text{O}_2 \)) was calculated: 1.34 mL O₂·g Hb⁻¹·g Hb·mL of blood⁻¹·% \( S_\text{O}_2 \) + 0.003 mL O₂·mL of blood⁻¹. O₂ delivery (mL O₂·min⁻¹) was calculated by multiplying \( C_\text{O}_2 \) and FBF.

**Data acquisition and analysis**

MAP, HR, and MBV data were collected at 200 Hz with a data acquisition system (Powerlab, ADInstruments,
Colorado Springs, CO) and recording computer. Brachial artery images were recorded in Digital Imaging and Communications in Medicine (DICOM) format for offline measurement of brachial artery diameter using custom automated edge-detection software (Woodman et al. 2001). Baseline and hyperemic values of MAP, HR, FBF, and calculated FVC were obtained on a beat-by-beat basis. These values were averaged over 3 sec (contraction/relaxation duty cycle duration) time bins. Brachial artery images were recorded continuously and diameter measurements performed on clear images during relaxation selected at 30 sec intervals. Each individual’s diameter data were then curve fit using an exponential rise to maximum nonlinear regression. One, two, or three component models were used depending on which model fit of an individual’s data resulted in the residuals being equally distributed and of the smallest magnitude possible using custom software as previously described in Pyke and Tschakovsky (2007). O2 delivery area under the curve calculations was derived from every individual’s 3 sec avg profile during exercise.

Contraction impulse for each duty cycle was calculated as the area under the force displacement curve for each contraction. The critical impulse was calculated from the average of the contraction impulses generated during the last 30 sec (~10 contractions) of the exercise test. To compare time to plateau of contraction impulse and O2 delivery responses, a low-pass filter was applied to each subject’s contraction impulse and O2 delivery profiles as outlined by Ferreira et al. (2005). The Δcontraction impulse and ΔO2 delivery values were then averaged over 3 sec time bins and normalized for each subject from 0%, corresponding to rest for O2 delivery and the first contraction for contraction impulse to 100% reflecting the stable plateau values (values averaged over the last 30 sec of the test). The average of five 3 sec time bins every 30 sec was used for statistical analysis to identify when a stable plateau was reached.

Statistical analysis

Two-way repeated measures ANOVA was performed on the % of stable plateau in contraction impulse and O2 delivery responses in order to identify time points where these variables differed as well as when within a variable the response was no longer different from the stable plateau.

Pearson moment correlation and forward stepwise linear regression was used to determine how much interindividual variation in critical impulse, O2 delivery and FBF was accounted for by interindividual differences in variables of interest. For critical impulse the variables included in the forward stepwise regression were forearm characteristics (volume and girth), maximal voluntary contraction and O2 delivery. For O2 delivery these variables were FBF and Cao2. For ΔFBF these variables were ΔFVC and ΔMAP. All analyses were performed using Sigmaplot 11, Systat Software, Chicago, IL. Significance was set a priori at P ≤ 0.05.

Results

Baseline characteristics

Subject characteristics can be viewed in Table 1.

Interindividual variation in critical impulse: which variables account for this?

O2 delivery during the maximal effort test varied substantially between subjects (O2 delivery AUC range 533–1231 mL O2, plateau in O2 delivery 73.59–154.10 mL O2 min⁻¹) as did critical impulse (381.5–584.8 N). Forward stepwise regression of O2 delivery plateau and forearm characteristics against critical impulse identified O2 delivery as a strong predictor of critical impulse (O2 delivery r = 0.92, r² = 0.85, P < 0.001), whereas forearm characteristics fell out of the model as they had no relationship with critical impulse (MVC r = 0.969, forearm volume r = 0.639, forearm girth r = 0.381). The O2 delivery AUC was also a strong predictor, explaining 77% of the variance in critical impulse when regressed separately (O2 delivery AUC r = 0.88, r² = 0.77, P < 0.01) (Fig. 1A and B). In contrast, the ΔO2 delivery from baseline accounted for only 66% of the variance in critical impulse. Furthermore, while forearm volume was significantly correlated with MVC (r² = 0.42, P = 0.04) forearm girth was not (r² = 0.06, P = 0.48). However, addition of subjects from previously published studies (Moynes et al. 2013; Kellawan and Tschakovsky 2014) as well as unpublished data from ongoing investigations increasing the total n to 47 identified a weak, albeit statistically significant, relationship between critical impulse and MVC (Fig. 2; r² = 0.125, P = 0.015).

Which of O2 delivery and critical impulse achieves a stable plateau first?

Figure 3 illustrates the time course of changes in O2 delivery and contraction impulse over the course of a 10 min, maximal effort handgrip exercise test. O2 delivery increased to a stable plateau, whereas maximal effort contraction impulse declined to a stable plateau (Fig. 3A). The magnitude of change from onset to plateau is expressed as % of change from onset to plateau in Fig. 3B in order to facilitate comparison of the time to plateau in
O₂ delivery versus contraction impulse. The increase in O₂ delivery to stable plateau is no longer statistically significantly different from stable plateau by 90 sec (\(P = 0.48\)), whereas the contraction impulse remains statistically significantly below steady state and lower than the change in O₂ delivery up to 210 sec (\(P = 0.03\) and \(P = 0.02\), respectively, at 210 sec), confirming that O₂ delivery stabilizes well before contraction impulse during this type of exercise.

How much interindividual variation in O₂ delivery is accounted for by interindividual differences in FBF and arterial oxygen content (CaO₂)?

Forward stepwise linear regression analysis identified that both FBF and CaO₂ contributed independently to interindividual differences in steady-state O₂ delivery, but FBF was by far the stronger determinant accounting for ~94% of interindividual differences in our study sample (Table 2).

How much interindividual variation in FBF is accounted for by FVC and MAP?

When assessed separately with simple linear regression, correlation of ΔFBF with ΔFVC from baseline was statistically significant (\(r = 0.80, r^2 = 0.64, P = 0.006\) but not with ΔMAP (\(r = 0.49, r^2 = 0.235, P = 0.15\)). However, forward stepwise linear regression analysis revealed that the addition of ΔMAP to ΔFVC substantially improved the model’s ability to account for interindividual variation in FBF (Table 3 and Fig. 4).

Discussion

In support of the construct that critical power represents the highest power output that can be sustained via oxidative phosphorylation such that \(\dot{V}O_2\), PCr and pH stabilize, investigators have provided indirect evidence for its oxygen dependence (Vanhatalo et al. 2010; Dekerle et al. 2012). These experiments involved the within-subject manipulation of arterial oxygen content via hypoxic and hyperoxic inspired gas, inferring altered O₂ delivery to exercising muscle. They demonstrated that critical power was increased with hyperoxia and decreased with hypoxia.

However, these studies were not intended to answer the question of whether and to what degree interindividual differences in O₂ delivery can account for interindivid-
ual variation in critical power. By its very nature, this question cannot be answered by manipulation of \( O_2 \) delivery within subjects. Instead, evidence has to come from the strength of association of interindividual variation in \( O_2 \) delivery and critical power and the relative timing of a stable plateau in \( O_2 \) delivery versus critical power. Therefore, we tested the hypothesis that interindividual differences in \( O_2 \) delivery would account for a majority of the interindividual variation in critical impulse, the force analog of critical power, and that a plateau in \( O_2 \) delivery would precede a plateau in contraction impulse. Further to this, we tested the hypothesis that interindividual differences in vasodilatory response would account for the majority of interindividual variation in \( O_2 \) delivery.

The novel findings of this investigation were as follows. First, interindividual differences in \( O_2 \) delivery, which were predominantly due to FBF with only a small contribution from \( C_4O_2 \), explained 85% of the interindividual variation in critical impulse. Second, the increase in \( O_2 \) delivery at a given time point. All \( P < 0.05 \).

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**Table 2.** Forward stepwise linear regression quantifying the independent contribution of forearm blood flow (FBF) and arterial oxygen content \( (C_4O_2) \) to interindividual differences in \( O_2 \) delivery.

| Dependent variable | Independent variable | \( \Delta \rho^2 \) by addition to model | \( \rho^2 \) | \( P \) value |
|--------------------|----------------------|----------------------------------------|----------|------------|
| \( O_2 \) delivery | FBF                  | 0.944                                  | 0.944    | <0.001     |
|                    | \( C_4O_2 \)         | 0.0515                                 | 0.996    | <0.001     |
| Total regression   |                      |                                        | 0.996    | <0.001     |

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**Figure 3.** Change in \( O_2 \) delivery and contraction impulse during maximal effort exercise. Dotted lines identify stable plateau. Panel A: absolute changes. Dashed line is contraction impulse. Solid line is \( O_2 \) delivery. Panel B: expressed as % of the change from baseline to steady state for \( O_2 \) delivery and from the first maximal effort contraction to steady state for contraction impulse. Dashed line and open squares is contraction impulse. Solid line and closed squares is \( O_2 \) delivery. *Significantly different from steady state within a variable. #Significantly different from \( O_2 \) delivery at a given time point.
delivery reached a plateau well before the decline in forearm contraction impulse. This rules out the possibility that the strength of association is simply because O₂ delivery is adjusting to meet a set metabolic demand but supports the possibility that the established O₂ delivery determines the sustainable metabolic demand. Taken together, these two findings are consistent with the hypothesis that inherent interindividual differences in O₂ delivery is an important determinant of interindividual differences in critical impulse. Third, vasodilatory response differences between individuals independently accounted for a majority of the interindividual differences in FBF during maximal effort forearm exercise. However, pressor response differences between individuals also accounted for a significant amount of interindividual FBF variation. These findings are the first to draw attention to the potential importance of interindividual differences in the maximal effort exercise pressor response as a determinant of interindividual differences in FBF. Finally, forearm critical force within the study sample was unrelated to MVC, forearm girth, or forearm volume. However, when we included data from published studies (Moynes et al. 2013; Kellawan and Tschakovsky 2014) and other ongoing unpublished work, there was a weak, albeit statistically significant, relationship between MVC and critical impulse.

**O₂ delivery explains interindividual variation in critical impulse**

The absolute O₂ delivery to the forearm was the strongest predictor of critical impulse (Table 2 and Fig. 1A and B, \( r^2 = 0.85 \)) and was considerably stronger than \( \Delta O₂ \) delivery from rest (\( r^2 = 0.66 \)). This suggests that absolute O₂ delivery is the more relevant O₂ delivery for critical impulse. The most plausible explanation is that O₂ delivery at baseline is an important part of the O₂ available to tap into by the working muscle when its demand for O₂ increases.

The strong association between O₂ delivery and the stable contraction impulse plateau (critical impulse) could be due to one of two reasons. Either the stabilized contractile work rate representing ATP demand was determining the stabilized O₂ delivery magnitude (O₂ demand

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**Table 3.** Forward stepwise linear regression quantifying the independent contribution of forearm vascular conductance (FVC) and mean arterial pressure (MAP) to interindividual differences in FBF. \( \Delta \) – change from baseline. AUC – area under the curve of the total response. test.

| Dependent variable | Independent variable | \( \Delta r^2 \) by addition to model | \( r^2 \) | P value |
|-------------------|----------------------|-------------------------------------|--------|--------|
| \( \Delta \) FBF   | \( \Delta \) FVC      | 0.63                                | 0.63   | <0.001 |
|                   | \( \Delta \) MAP      | 0.34                                | 0.97   | <0.001 |
| Total regression  |                       | 0.97                                |        |        |
| FBF AUC           | \( \Delta \) FVC AUC  | 0.51                                | 0.51   | <0.001 |
|                   | \( \Delta \) MAP AUC  | 0.39                                | 0.89   | 0.002  |
| Total regression  |                       | 0.89                                |        | <0.001 |
determining O₂ supply), or the stabilized O₂ delivery was constraining the contractile work rate that could be maintained (O₂ supply determining O₂ demand). By continuously measuring both contraction impulse and O₂ delivery throughout the maximal effort test, we were able to assess which of these two variables stabilized first. As matching of ATP demand with aerobic ATP supply is a required condition of sustainable exercise characterized by stable VO₂, PCR, Pi, ADP, and pH, the variable that plateaus first would dictate or constrain the level at which the other variable plateaus.

We therefore quantified the ΔO₂ delivery and the Δ contraction impulse over the course of the maximal effort test as a percent of their stable plateau (i.e., the plateau of these variables represented 100% of their response, and so changes from rest could be quantified as a % of the plateau (Fig. 3A and B)). Statistical analysis could then determine when a variable was no longer different from its stable plateau. This analysis identified that O₂ delivery reached a stable plateau well before contraction impulse. Stabilization of O₂ supply prior to demand could not occur if demand was determining supply, effectively ruling out this scenario. Instead, this temporal order of stabilization is consistent with the hypothesis that interindividual variation in O₂ delivery is an important determinant of interindividual variation in critical impulse.

Further support strengthening this interpretation comes from what is known about the VO₂ response to maximal effort exercise or fixed exercise above VO₂max. At present, data on the temporal profile of changes in power output and VO₂ relative to each other during maximal effort exercise have not been documented. However, it has been indicated by Jones et al. (2010) that in their studies employing the 3-min all-out cycle ergometer exercise test, all subjects have reached VO₂max by ~60 sec of exercise, well before the stabilization of power output near the end of such a test. The same time to peak has also been observed with constant load exercise that is 20 to 30% above VO₂max (Hughson et al. 2000; Adami et al. 2011). These are power outputs that are below those occurring during the first minute of a 3-min all-out cycling test. The point being that aerobic ATP supply appears to plateau before ATP demand in maximal effort exercise.

While the forearm exercise protocol in our study involved maximal effort contractions, the fixed 2 sec duration of relaxation between contractions meant that the plateau in contraction impulse required substantially more than 3 min, indicating that the rate of depletion of W’ was slower compared to the maximal effort cycling exercise test (Burnley et al. 2006; Vanhatalo et al. 2007). Nevertheless, the metabolic demand of maximal effort contractions during the time prior to achievement of the contraction impulse plateau would have been well above VO₂max. Thus, while we did not measure forearm VO₂ in our study, it is most likely the case that VO₂max was also reached with a similar time course to the above-mentioned supramaximal exercise protocols.

In contrast, contraction impulse continued to decline well past this time point, being greater than the critical impulse plateau until 210 sec of exercise (Fig. 3), whereas O₂ delivery was no longer different from plateau by 90 sec of exercise (Fig. 3). When taken together with observations from other studies that muscle deoxygenation plateaus rapidly during supramaximal exercise (Adami et al. 2011) stability not only in O₂ delivery but also in VO₂ would appear to occur well before the decline in contractile work stabilized in our study. This means that the stable contractile work achieved by the end of the maximal effort test would also represent a stable metabolic demand. This further supports the plausibility of the hypothesis that interindividual differences in O₂ delivery is actually a primary determinant of interindividual differences in critical impulse.

We therefore propose the following sequence of events during the maximal effort critical impulse test, based on what is known about W’ and critical power and the findings in our study. At the onset of repeated maximal effort contractions, motor unit recruitment to produce force initiates an increased ATP demand to levels well above the maximal rate of aerobic ATP supply. All three energy systems contribute to the provision of ATP, with the difference between aerobic ATP supply (which is increasing rapidly) and demand being made up by PCR hydrolysis and anaerobic glycolysis. However, force production quickly begins to decline even as O₂ delivery and aerobic ATP supply is rapidly increasing. It is not decreased motor drive as exercise continues that is responsible for the decrease in force that is observed (Bigland-Ritchie et al. 1983). Rather, accumulation of intracellular substances interfering with excitation contraction coupling ([Pᵢ] from PCR hydrolysis, [ADP] from imbalance between ATP hydrolysis and ATP regeneration, [H⁺] associated with anaerobic glycolysis) (Fitts 2008; Westerblad et al. 1991; Nelson and Fitts 2014) would be major contributors to the decrease in force.

While it is acknowledged that changes in efficiency (ATP cost per unit of power output) can occur in heavy to severe exercise domains (Poole et al. 1988, 1991, 1994; Poole 1994) and therefore contraction impulse is not perfectly representative of ATP demand, the magnitude of contraction impulse decline is so substantial that overall ATP demand is likely decreasing considerably despite any potential reductions in efficiency. Therefore, in addition to fatigue this decrease would reflect force conforming to the decline in the rate at which ATP can be supplied...
above maximal aerobic ATP supply under the rapidly changing intracellular environment. Thus, both fatigue and reductions in ATP supply rate would be contributing to declining contraction impulse until the fixed capacity for work above critical impulse ($W^*$) is completely depleted.

Part of this fixed ATP supply in excess of critical power comes from PCr stores, and part of it would come from anaerobic glycolytic ATP production (with small initial contribution from O$_2$ stores as well). However, the PCr stores are fixed and depletion means they must eventually stabilize when contraction impulse plateaus at critical impulse, meaning that they have ceased to contribute to ATP supply. In contrast, although the rate of anaerobic glycolysis is likely declining during the course of the maximal effort exercise it must still be contributing to ATP demand as critical impulse is reached, as blood lactate and pH are known to stabilize at levels considerably different from rest (Poole et al. 1988) under conditions where mechanisms responsible for lactate and H$^+$ removal from the blood remain active (Brooks 1986, 1991; Stanley et al. 1986). Since by definition exercise at critical impulse would mean there is stability of pH and blood lactate, then this rate of anaerobic glycolysis could represent the maximal anaerobic glycolytic flux that can still be balanced by these lactate and H$^+$ removal mechanisms. At this point ATP metabolic demand (contraction impulse) that can be sustained must conform to the maximal rate of aerobic ATP production plus the sustainable anaerobic glycolytic ATP production. The maximal rate of aerobic ATP production would be dependent on the interaction of convective O$_2$ delivery, diffusive conductance of skeletal muscle, and mitochondrial content (Tschakovsky and Pyke 2008), and therefore the observed individual differences in critical impulse that were established well after stability in O$_2$ delivery would be dependent in part on O$_2$ delivery differences.

The implications of our findings are that differences between individual’s ability to supply muscle with O$_2$ during maximal effort exercise may be partly responsible for interindividual differences in critical impulse. According to the power–duration relationship, differences in critical impulse between individuals represent differences in the range of exercise intensities that would be considered sustainable (Jones et al. 2008, 2010), translating to differences in exercise tolerance.

**Vasoregulatory versus pressor mechanism contributions to forearm blood flow**

FBF accounted for virtually all of the interindividual difference in O$_2$ delivery. Thus in this group of young healthy subjects, oxygen carrying capacity plays only a very minor role in determining individual differences in O$_2$ delivery. This may reflect the relatively small range of CaO$_2$ across individuals in our sample. It would be expected that as this range increased across a sample, the potential for CaO$_2$ to explain more of the interindividual differences in O$_2$ delivery with maximal effort exercise would increase.

To quantify the magnitude of the vasodilatory and pressor response contribution to the ΔFBF response in the critical impulse test, we examined the ΔFVC and ΔMAP from baseline, as these represent the actual compensation that has to occur when metabolic demand for O$_2$ increases. Our findings indicate that it was not only the magnitude of vasodilation that determined the FBF response. Rather, interindividual differences in the magnitude of the exercise pressor response also made an important contribution (Table 3).

While changes in MAP have been shown to contribute significantly to exercising limb perfusion recovery in response to experimentally evoked ischemia (Rowell et al. 1991), to our knowledge there has been virtually no attention paid to the potential importance of the magnitude of the pressor response during exercise in determining the magnitude of exercising limb blood flow. For instance, the seminal work of Andersen and Saltin (Andersen and Saltin 1985) which identified that maximal muscle blood flow was far greater than previously thought has since been discussed from the perspective of skeletal muscle vasodilatory capacity and its implications for blood pressure regulation (Richardson et al. 2000). However, observations of vascular conductance plateauing at work rates below peak during incremental small muscle mass exercise while blood flow continues to increase (Mortensen et al. 2005; Saunders et al. 2005) suggests an important role for pressor mechanisms in determining the magnitude of the muscle blood flow response. In the case of Mortensen et al. (2005), over 30% of the maximal single-leg knee extension exercise blood flow response was due to the pressor response.

Our forward stepwise regression analysis identified how much vasodilation versus the pressor response contributed to interindividual differences in maximal effort exercise FBF. Sixty-four percent of the interindividual variation in FBF was due to vasodilation, whereas 33% was attributable to the pressor response. The findings point to the importance of considering individual differences in pressor response magnitude in addition to vasodilation as a determinant of maximal effort small muscle mass exercise blood flow.

The magnitude of elevation in MAP during maximal or near maximal effort fatiguing exercise is thought to be exercise intensity but not muscle mass dependent (Williams 1991). Contributors to the exercise pressor...
response include a resetting of the baroreflex which is mediated by central command and muscle mechano- and metabo-reflexes, as well as independent effects of the muscle metabo-reflex (Gallagher et al. 2006). Therefore, it is possible that interindividual differences in the pressor response in our study may be explained by these mechanisms. This awaits further investigation.

The maximal increase in vascular conductance during a maximal effort test could be constrained by the structural limitation imposed by the number and size of resistance vessels, and/or a functional vasodilatory capacity which would be dependent not only on vasodilatory mechanisms but also on the degree of sympathetic vasoconstrictor activation and its interaction with local sympatholytic factors. Understanding the factors that determine the magnitude of exercise pressor and vasodilatory responses to exercise and the mechanisms that link them to the attempt to match O₂ delivery to metabolic demand would therefore seem important in the context of understanding exercise intolerance differences between individuals. These may predispose to differences in activity levels and subsequent sedentary related disease development.

Peak force generation and critical impulse

As in our previous work (Kellawan and Tschakovsky 2014) interindividual differences in MVC (range 381.5–584.8N) were poorly correlated with critical impulse. The same was true for our indirect measures of muscle volume (forearm volume, range 780–1374 mL) and muscle cross-sectional area (forearm girth, 23–29 cm). Interestingly, while forearm volume was significantly correlated with MVC, forearm girth was not. However, when we pooled data from our laboratory that were previously published (Moynes et al. 2013; Kellawan and Tschakovsky 2014) as well as ongoing findings not yet published with a resulting n of 47, MVC accounted for a statistically significant 12.5% of the variation in critical impulse (Fig. 2). These data are consistent with the findings of Saugen et al. (1997) and Kent-Braun et al. (1993) who demonstrated that reductions in PCr and pH during exercise at the same % MVC can be drastically different between individuals. This suggests that mechanisms relating to an individual’s maximal force generating capacity are most likely minor determinants of exercising aerobic metabolic power.

Potential limitations

We were unable to measure a number of skeletal muscle specific characteristics that could potentially contribute to interindividual differences in critical impulse such as fiber type, buffering capacity, and mitochondrial content. It is quite possible that some or all of these would covary with O₂ delivery as well as have independent association with critical impulse. However, there would have to be a substantial covariation before the independent contribution of O₂ delivery would become physiologically insignificant. Finally, had these other characteristics been of a wide enough range and exerted significant independent influence on critical impulse, the variation in critical impulse that could be accounted for by O₂ delivery as observed in this study would have been lowered considerably.

Another potential issue is that, because interindividual differences in O₂ delivery were almost completely due to differences in FBF, there is the potential for an effect of blood flow-dependent removal of fatiguing substances from the skeletal muscle cytosol (Barclay 1986) on critical impulse. However, careful consideration of the determinants of W’ and critical impulse discussed previously would suggest that the magnitude of such a contribution independent of O₂ delivery support of aerobic metabolism is at best minor. For example, it remains unknown whether blood flow has an impact on intracellular levels of Pi via a “washout” effect. However, since anaerobic glycolysis must still be contributing to ATP demand as critical impulse is reached, it is conceivable that increased blood flow dependent “washout” of H⁺ could allow for a greater rate of anaerobic glycolysis to occur at the lowest tolerable cytosolic pH and thereby increase total ATP production and support a greater critical impulse. However, it seems highly unlikely that the potential impact on ATP production would be of sufficient magnitude to result in a detectable impact on differences in critical impulse between individuals. Nevertheless, it must be acknowledged as a potential mechanism.

Conclusions

In summary, we have demonstrated for the first time that O₂ delivery to the exercising forearm during a maximal effort critical impulse test varies considerably across individuals and is a strong predictor of an individual’s critical impulse. The additional finding that the increase in O₂ delivery stabilizes well before contraction impulse rules out the possibility that the association between O₂ delivery and critical impulse is simply a result of O₂ delivery adjusting to meet an established metabolic demand. Instead, it is consistent with the hypothesis that these differences in O₂ delivery between individuals causally contribute to the interindividual variation in critical impulse. This hypothesis remains to be tested. Of considerable interest was the finding that both vasodilatory and exercise pressor responses contributed to interindividual differences in FBF and subsequently O₂ delivery. This implies that small muscle mass exercise tolerance differ-
ences between individuals may be explained not only by differences in the magnitude of vasodilation response, but also by the pressor response. Understanding the underlying mechanistic basis for inherent interindividual differences in cardiovascular support of exercising muscle is an important next step in identifying contributors to exercise intolerance.

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**Conflict of Interest**

None declared.

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