ACTA PHYSIOLOGICA

Acta Physiol 2012, **204**, 362–370

Attenuated relationship between cardiac output and oxygen uptake during high-intensity exercise

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Received 30 March 2011, revision requested 30 April 2011, final revision revised 27 June 2011, accepted 12 July 2011

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Abstract

Aim: Recent findings have challenged the belief that the cardiac output (CO) and oxygen consumption (VO_2) relationship is linear from rest to maximal exercise. The purpose of this study was to determine the CO and stroke volume (SV) response to a range of exercise intensities, 40–100% of VO_{2max}, during cycling.

Methods: Ten well-trained cyclists performed a series of discontinuous exercise bouts to determine the CO and SV vs. VO_2 responses.

Results: The rate of increase in CO, relative to VO_2, during exercise from 40 to 70% of VO_{2max} was 4.4 ± 1.4 L L^{-1}. During exercise at 70–100% of VO_{2max}, the rate of increase in CO was reduced to 2.1 ± 0.9 L L^{-1} (P = 0.01). Stroke volume during exercise at 80–100% of VO_{2max} was reduced by 7% when compared to exercise at 50–70% of VO_{2max} (134 ± 5 vs. 143 ± 5 mL per beat, P = 0.02). Whole body arterial-venous O_2 difference increased significantly as intensity increased.

Conclusion: The observation that the rate of increase in CO is reduced as exercise intensity increases suggests that cardiovascular performance displays signs of compromised function before maximal VO_2 is reached.

Keywords maximal exercise, oxygen uptake, stroke volume.

A tenet of exercise physiology is that cardiac output (CO) increases linearly from rest to maximal exercise with CO increasing 4–6 L min^{-1} for every 1 L min^{-1} increase in oxygen uptake (VO_2; Rowell 1986, Gledhill *et al.* 1994, Proctor *et al.* 1998, Wiebe *et al.* 1998, 1999, Barker *et al.* 1999, Warburton *et al.* 1999, 2000, 2004, Ferguson *et al.* 2001, McArdle *et al.* 2001, Zhou *et al.* 2001). While this relationship may hold true for low (<50% VO_{2max}) and moderate-intensity exercise (50–70% VO_{2max}), some investigations utilizing continuous exercise protocols (Stringer *et al.* 1997, 2005, Mortensen *et al.* 2005, Beck *et al.* 2006, Calbet *et al.* 2007) raise doubt as to whether the same relationship can be applied to high-intensity exercise (70–100% VO_{2max}). The concept that CO continues to increase in a linear manner and with the same slope (4–6 L L^{-1}) during exercise of high to maximal intensity implies that cardiovascular function does not show signs of strain even when functioning at VO_{2max}. However, empirical evidence suggests that stroke volume (SV) plateaus during moderate-intensity exercise and may decline at maximal exercise intensities (Bevegard *et al.* 1963, Astrand *et al.* 1964, Higginbotham *et al.* 1986, Flamm *et al.* 1990, Seals *et al.* 1994, Stringer *et al.* 1997, 2005, McCole *et al.* 1999, Gonzalez-Alonso & Calbet 2003, Gonzalez-Alonso *et al.* 2004), indicating a cardiovascular limitation to maximal exercise.

The CO vs. VO_2 relationship has been examined using discontinuous exercise bouts lasting 3–8 min with periods of rest between each bout (Bevegard *et al.* 1963, Astrand *et al.* 1964, Grimby *et al.* 1966, Ekblom & Hermansen 1968, Ekblom *et al.* 1968, Hermansen *et al.* 1970) and by continuous/incremental exercise tests during which intensity was increased every 2–4 min (Higginbotham *et al.* 1986, Gledhill *et al.* 1994, Stringer *et al.* 1997, 2005, Proctor *et al.* 1998, Wiebe *et al.*

1998, 1999, Warburton *et al.* 1999, 2000, 2004, Ferguson *et al.* 2001, Zhou *et al.* 2001, Mortensen *et al.* 2005, Beck *et al.* 2006, Calbet *et al.* 2007). To our knowledge, a classic study by Astrand *et al.* (1964) is the only study of at least six (Bevegard *et al.* 1963, Grimby *et al.* 1966, Ekblom & Hermansen 1968, Ekblom *et al.* 1968, Hermansen *et al.* 1970) to report an attenuated CO vs. VO_2 relationship during high-intensity exercise using a discontinuous exercise protocol. The findings from continuous incremental are equivocal as some report a linear increase in CO vs. VO_2 accompanied by a progressive increase in SV (Wiebe *et al.* 1998, 1999, Warburton *et al.* 1999, 2000, 2004, Ferguson *et al.* 2001), while others demonstrate an attenuated increase in CO driven primarily by a plateau or even reduction in SV (Stringer *et al.* 1997, 2005, Mortensen *et al.* 2005, Beck *et al.* 2006, Calbet *et al.* 2007). The reason for such discrepancies is not entirely clear but may be due to differences in the exercise modality (cycling vs. running), training status, duration of the exercise bout, method for the determination of CO, timing of the CO and VO_2 measurements and manner in which exercise intensity was matched between subjects [VO_2, workload, heart rate (HR)].

Given the equivocal findings of the available research and the importance of the CO vs. VO_2 relationship in understanding limitations to exercise, a well-controlled examination of the CO vs. VO_2 relationship in highly trained individuals was undertaken. Establishing an attenuated increase in CO as VO_2 and exercise intensity increases may provide support for the idea that cardiac function is limiting maximal exercise. We hypothesized that as exercise intensity progressed the increase in CO relative to VO_2 is attenuated.

Methods

Subjects

Ten healthy, well-trained male cyclists (31 ± 8 years of age, range 18–45) provided written informed consent to participate in this study. The protocol, experimental design and informed consent were approved by the Institutional Review Board at the University of Texas at Austin. The subjects' stature, body mass and VO_{2max} (means ± SD) were as follows: 1.79 ± 0.07 m, 74.9 ± 7.9 kg and 4.70 ± 0.33 L min^{-1} (63.1 ± 4.4 mL kg^{-1} per min), respectively.

Experimental design and protocol

The experimental protocol was completed over four visits to the laboratory. The first visit served to establish the submaximal VO_2 vs. work rate relationship and VO_{2max}. The second visit further familiarized the subject with the techniques to be used during the experimental trials and to verify that the work rates for the high-intensity exercise bouts were appropriate. Visits three and four served as the main experimental data collection visits and were separated by 1 week. All experimental testing was performed at the same time of day.

Experimental procedures

The submaximal VO_2 vs. work rate relationship was determined during a continuous incremental protocol on a cycle ergometer (Excalibur Sport, Lode, the Netherlands), and gas analysis was determined breath by breath using a mass spectrometer (Perkin-Elmer MGA 1100, St. Louis, MO, USA). The submaximal test included five stages, each lasting 5 min. Work rate was progressively increased by 20–40 W, and VO_2 and HR were collected continuously. Oxygen uptake was averaged over the final minute of each stage. Following a 10-min period of rest, subjects performed an incremental VO_{2max} test lasting 8–12 min in which work rate was increased by 25–40 W every 2 min. To verify a plateau in VO_2, subjects rested again for 10 min before performing a constant load exercise bout at either the work rate they fatigued at during the incremental protocol or 25 W higher than that work rate. The criteria for determining the work rate during this VO_{2max} verification trial depended on the duration of the final stage of the incremental test (Taylor *et al.* 1955, Lafrenz *et al.* 2008). If subjects lasted less than 1 min during the final stage of the incremental test, the same work rate at which they fatigued at was used for the VO_2 verification trial, if the subject lasted longer than 1 min during the final stage 25 W was added to this work rate.

One week following the preliminary tests, subjects returned to the laboratory for a second day of VO_{2max} verification trials. This second day of testing was performed to determine whether a plateau in VO_2 was achieved during the first visit. Based on the submaximal VO_2 vs. work rate relationship, linear regression was used to determine the minimal work rate needed to elicit VO_{2max}. This work rate was then used for the 100% of VO_{2max} interval. Following a 20-min warm-up (5 min at 40, 50, 60, 70% of VO_{2max}), subjects performed three high-intensity exercise bouts at 100% VO_{2max}, 100% minus 25 W and 100% plus 25 W. Each interval was performed for 4 min or until exhaustion. Five minutes of passive recovery followed by 5 min of active recovery (30 W) separated the intervals. The order of the intervals was randomized. This method in combination with the incremental exercise test and constant load verification trials from all subjects exhibited a clear levelling off of VO_2 and thus a valid VO_{2max}.

Visits three and four consisted of discontinuous cycling at 40, 50, 60, 70, 80, 90 and 100% of VO_{2max}. The 40–70% VO_{2max} bouts lasted 5 min and were separated by 6 min of cycling at 30 W. The high-intensity bouts (i.e. 80–100% of VO_{2max}) were performed for 4 min and separated by 6 min of cycling at 30 W. The duration of these high-intensity bouts was reduced to 4 min to ensure that subjects were able to complete all the exercise bouts without fatigue. The 80, 90 and 100% bouts were performed twice per visit, and the order of these bouts was randomized. Breath-by-breath VO_2 measurements began at least 2 min prior to each interval. Cardiac output was measured at min 3 and 4.5 of each moderate-intensity bout and at min 2 and 3.5 of each high-intensity bout. The 1.5-min time period between CO measurements was selected based on pilot data that showed adequate washout of acetylene.

On arrival, subjects dressed in cycling shorts and shoes. Approximately 30 min prior to exercise, subjects consumed 400 mL of water, while during exercise, a 6% CHO/electrolyte beverage (Powerbar Endurance Formula; Powerbar, Glendale, CA, USA) was consumed. Subjects were allowed to drink *ad libitum* during visit 3. The volume and timing of fluid ingestion were recorded and matched during visit 4. On average, 1.2 ± 0.3 L of fluid was consumed. The overall change in bodyweight from pre- to post-exercise was <0.25 kg, indicating that hydration was maintained.

Respiratory and cardiovascular measurements

Oxygen uptake was measured breath by breath using open-circuit spirometry according to the calculations described by Beaver *et al.* (1981). Subjects breathed through a two-way non-rebreathing valve connected to a pneumotachometer (Hans Rudolph, Kansas City, MO, USA). Oxygen and carbon dioxide concentrations of inspired and expired gases were determined by a mass spectrometer. Gas samples were collected at the mouthpiece via a 2-m capillary tube connected to the mass spectrometer.

Cardiac output was determined by open-circuit acetylene washin as described by Johnson *et al.* (2000). Briefly, at the end of normal expiration, the participants breathed for a minimum of 8 breaths through a mouthpiece connected to a bag filled with mixed gases, including 0.7% acetylene, 9.0% helium, 21% oxygen and balance nitrogen. The concentrations of acetylene and helium were monitored by continuous sampling at the mouthpiece, and data were viewed on a personal computer. Cardiac output was calculated from the washin curve of the acetylene according to a single alveolar one-compartment lung model. The iterative method as described by Johnson *et al.* (2000) was used for the calculation of CO.

The open-circuit acetylene washin method for determining CO has been compared and validated against thermodilution in anesthetized and ventilated dogs, the acetylene rebreathing technique in humans and the direct Fick method in humans during both submaximal and maximal exercises (Stout *et al.* 1975, Gan *et al.* 1993, Nielsen *et al.* 1994, Johnson *et al.* 2000). Most relevant to the current study, Johnson *et al.* (2000) determined that the open-circuit technique was both valid and reliable in the measurement of CO from rest to maximal exercise when compared to direct Fick technique. As addressed by Johnson *et al.* (2000), ventilation inhomogeneity and ventilation-to-perfusion mismatching will cause CO and lung volumes to be underestimated when using the open-circuit washin technique or any rebreathing technique. When examining the difference in CO between the Fick and open-circuit techniques and correlating this difference with the alveolar-to-arterial oxygen tension difference ($A\text{-}aDO_2$), there was no significant correlation when using the iterative calculation of CO. This suggests that ventilation-to-perfusion mismatching did not contribute to the observed difference in CO between the two methods (Johnson *et al.* 2000). Based on the finding that ventilation-to-perfusion mismatching increases slightly yet significantly in healthy individuals during exercise (Hopkins *et al.* 1998), one caveat of the open-circuit technique is that it may underestimate CO especially during high-intensity exercise. Based on pilot data (unpublished) performed by Beck and colleagues on six healthy individuals using inert gas washin of dimethyl ether to estimate the bias or decrement in CO because of ventilation-perfusion mismatch, it is estimated that the ventilation-to-perfusion mismatch may account for a 0.5 to 1.1 L min^{-1} underestimation in CO at rest and moderate-intensity exercise, respectively. According to Hopkins *et al.* (1998), the ventilation-to-perfusion mismatch as measured by the multiple inert gas washin technique remains relatively constant from 65 to 90% of VO_{2max} ($logSD_Q = 0.65$). Assuming that this degree of mismatch remains constant from moderate- to high-intensity exercise, we estimate that the open-circuit acetylene washin technique may underestimate CO by approx. 1 L min^{-1} from 60 to 100% of VO_{2max}. Because the underestimation of CO is likely constant above 60% VO_{2max}, it would not substantially affect curvature estimates in this study. Another factor that could potentially contribute to an underestimation of CO when using the open-circuit acetylene method or any ventilatory-dependent method for assessing CO is the presence of anatomical shunts. However, studies (Hopkins *et al.* 1998, 2008) using the multiple inert gas technique have consistently demonstrated that such an intrapulmonary shunt is always <1% of CO. The role of anatomical shunts is controversial; however, gas

exchange deficits have not been demonstrated in studies using intravenously injected microbubbles to identify an intrapulmonary shunt (Hopkins *et al.* 2008).

The overall coefficient of variation for the measurement of CO for the present investigation was 4.8 ± 2.7%. Custom software (Beck Integrated Physiological Systems, St. Paul, MN, USA) was used to determine breath-by-breath VO_2 and to calculate CO. The mass spectrometer was calibrated prior to each experimental trial using gases of known concentration. Volume was calibrated using a 3-L syringe (Hans Rudolph) at low, moderate and high flow rates. HR was measured via a 3-lead ECG, and the average HR corresponding to the period of time in which the CO measurement was made was used for the calculation of SV (SV = CO/HR). Arterial-venous oxygen difference (a-vO_{2diff}) was calculated by dividing VO_2 by CO.

Statistics

All statistical analyses were performed using SPSS version 14.0 (IBM, Armonk, New York, USA). Data are presented as mean ± standard deviation of the mean. Selected figures are presented as mean ± standard error for the purpose of clarity. Data were separated into two categories to directly compare the slope from 40 to 70% vs. 70 to 100% of VO_{2max}. A paired samples *t*-test was used to determine significant differences between slopes for HR, CO and a-vO_{2diff} from 40 to 70% vs. 70 to 100% of VO_{2max}. A one-way repeated measures ANOVA was used to test for significant differences between exercise intensities. When appropriate, an *a priori* analysis of sequential exercise intensities (40–50, 50–60, 60–70, 80–90 or 90–100% of VO_{2max}) was employed following a significant main effect of condition. The number of *a priori* comparisons was limited to $k - 1$ for the selected variable, where k is equal to the number of means compared. If Mauchly's test of sphericity was violated, the Greenhouse–Geisser correction was used to correct for this violation and to ensure that the main effect was significant. All non-sequential pairwise comparisons were corrected using the Sidak correction for multiple comparisons (i.e. 40–60 or 80–100% of VO_{2max}). Significance was accepted at the $P < 0.05$ level.

Results

Work rate, exercise intensity and ventilation

Exercise was performed at work rates eliciting 42, 51, 60, 70, 83, 91 and 99% of VO_{2max}. For the purpose of clarity, further discussion of the aforementioned intervals will be referred to as 40, 50, 60, 70, 80, 90 and 100% of VO_{2max}. Absolute VO_2, VE and corresponding work rates are reported in Table 1.

Cardiovascular responses

Each increase in work rate was accompanied by a significant increase in HR with one exception (Table 1). The random order of the high-intensity intervals elevated HR at 80%, thereby making the difference between 80 and 90% not significant ($P = 0.87$). Overall, the slope of the increase in HR from 40 to 70% (24.8 ± 4.8 bpm L^{-1} per min) of VO_{2max} was not significantly different than the slope from 70 to 100% (23.9 ± 7.1 bpm L^{-1} per min; $P = 0.75$).

Table 1 Exercise intensity, respiratory, and cardiovascular responses to exercise

	Rest	40%	50%	60%	70%	80%	90%	100%
Workrate, W	0 ± 0	132 ± 15*	174 ± 18*	216 ± 23*	257 ± 27*	300 ± 31*	341 ± 35*	383 ± 38*
VO_2, L min^{-1}	0.4 ± 0.05	2.00 ± 0.14*	2.40 ± 0.18*	2.82 ± 0.18*	3.31 ± 0.21*	3.91 ± 0.36*	4.21 ± 0.33*	4.51 ± 0.36*
% VO_{2max}	9 ± 1	42 ± 3	51 ± 3	60 ± 2	70 ± 3	83 ± 4	91 ± 2	99 ± 1
VE, L min^{-1}	16 ± 3	49 ± 5*	59 ± 6*	70 ± 8*	86 ± 11*	115 ± 21*	129 ± 17*	148 ± 18*
HR, bpm	70 ± 13	116 ± 9*	127 ± 11*	137 ± 11*	149 ± 10*	168 ± 8*	171 ± 8	179 ± 9*
% HR_{max}	37 ± 7	62 ± 5*	68 ± 5*	73 ± 5*	80 ± 4*	90 ± 3*	92 ± 3	96 ± 3*
CO, L min^{-1}	7.6 ± 0.9	16.0 ± 16*	18.2 ± 1.8*	19.7 ± 1.7*	21.9 ± 1.8*	23.1 ± 2.2*	23.9 ± 2.2*	24.6 ± 2.6
SV, mL $beat^{-1}$	112 ± 21	139 ± 17*	145 ± 17*	145 ± 18	148 ± 16	138 ± 16†	140 ± 15	138 ± 16†
a-vO_2 diff, mL dL^{-1}	5.6 ± 0.8	12.7 ± 1.4*	13.2 ± 1.0	14.4 ± 0.9*	15.2 ± 1.1*	17.1 ± 1.6*	17.7 ± 1.2*	18.5 ± 1.3*

Values are mean ± SD of 10 subjects.

% W_{max}, Percent of work rate maximum; VO_2, oxygen uptake; % VO_{2max}, percent of maximal oxygen uptake; VE, ventilation; HR, heart rate; % HR_{max}, percent of heart rate maximum; CO, cardiac output; SV, stroke volume; a-vO_{2diff}, arterial-venous oxygen difference.

*Significant difference from previous value.

†Significant decrease from 70%, $P < 0.05$.

There was no significant difference between the duplicate measures of CO taken at the two times during each exercise bout ($P = 0.26$). Furthermore, the attenuation of the slope of the CO vs. VO_2 relationship is preserved independent of which measurement of CO (first or second) is used for the analysis. Cardiac output increased significantly from one work rate to the next until 90% of VO_{2max} (Fig. 1). The increase in CO from 90 to 100% of VO_{2max} was not significant (23.9 ± 2.2 to 24.6 ± 2.6 L min^{-1}, $P = 0.12$). From rest to 70% of VO_{2max}, the increase in CO vs. VO_2 was 5.0 ± 0.4 L L^{-1}. The slope of CO vs. VO_2 from 70 to 100% VO_{2max} was reduced when compared to the slope from 40 to 70% of VO_{2max} (2.0 ± 0.4 vs. 4.4 ± 0.3 L L^{-1}, $P = 0.03$). The reduced increase in the CO vs. VO_2 relationship at high exercise intensities coupled with the non-significant increase in CO from 90 to 100% of VO_{2max} indicates a CO limitation during high-intensity exercise.

Stroke volume increased from rest to 40% VO_{2max} (112 ± 21 to 139 ± 17 mL per beat, $P < 0.01$; Fig. 2). Stroke volume peaked at 70% of VO_{2max} (148 ± 16 mL per beat) and was reduced by approximately 7% ($P < 0.05$) at 80 and 100% of VO_{2max}. Stroke volume was not different from 50 to 70% or from 80 to 100%, and when pooled together, the SV was lower during high-intensity exercise (80, 90 and 100% of VO_{2max}) compared to moderate-intensity exercise (50, 60 and 70% of VO_{2max}; 139 ± 15 vs. 146 ± 17 mL per beat, $P = 0.02$; Table 1).

The a-vO_{2diff} increased as exercise intensity increased with the only exception being from 40 to 50% of VO_{2max} (Table 1). The slope of the a-vO_{2diff} from 70 to 100% of VO_{2max} was slightly higher than the slope from 40 to 70% of VO_{2max}; however, this difference was not statistically significant (2.9 ± 1.1 vs. 2.0 ± 1.0 mL dL^{-1} L^{-1} per min, $P = 0.14$).

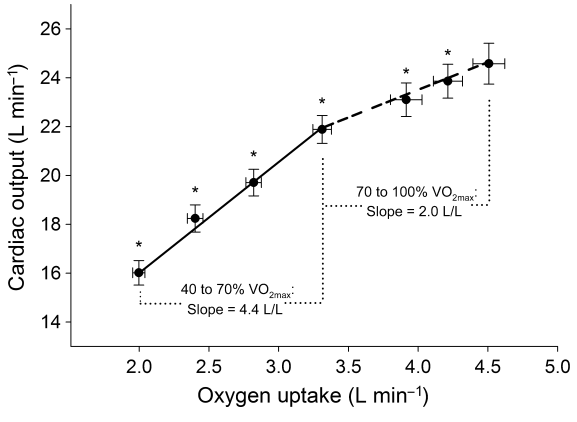

Figure 1 Cardiac output vs. oxygen uptake. Resting values of cardiac output and oxygen uptake have been omitted from the figure. *Significant difference from previous value, $P < 0.05$. Values are mean ± SE of 10 subjects.

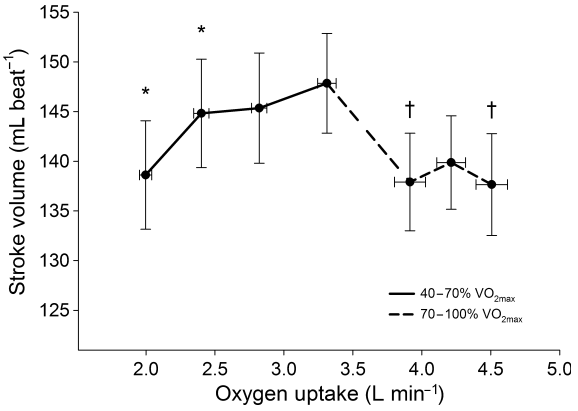

Figure 2 Stroke volume vs. oxygen uptake. Resting values of stroke volume and oxygen uptake (VO_2) have been omitted from the figure. *Significant difference from previous value, and †significant decrease from value at 70% of VO_{2max}, $P < 0.05$. Values are mean ± SE of 10 subjects.

Discussion

The main finding of the present study was that during moderate to high-intensity exercise (70 to 100% VO_{2max}) the slope of the CO vs. VO_2 relationship was attenuated when compared to the slope from low- to moderate-intensity exercise (40 to 70% VO_{2max}; 2.0 ± 0.4 vs. 4.4 ± 0.3 L L^{-1}, $P = 0.03$). In combination with this attenuated slope, CO increased by only 1.5 L min^{-1} from 80 to 100% of VO_{2max}. Furthermore, SV during exercise at 80–100% VO_{2max} was significantly lower than during 50–70% VO_{2max}. The attenuated increase in the CO vs. VO_2 relationship coupled with the decline in SV suggests that a cardiovascular limitation is experienced during high-intensity cycling in endurance-trained men.

To our knowledge, only one study by Astrand *et al.* (1964), using a discontinuous exercise protocol in a heterogeneous group of subjects including physically active ($n = 19$) and well-trained subjects ($n = 4$), suggests a reduction in the slope of the CO vs. VO_2 relationship during high-intensity exercise. This preliminary observation has been largely overlooked as the relationship between CO and VO_2 is commonly described as being linear from rest to maximal exercise (Rowell 1986, Gledhill *et al.* 1994, Proctor *et al.* 1998, Wiebe *et al.* 1998, 1999, Barker *et al.* 1999, Warburton *et al.* 1999, 2000, 2004, Ferguson *et al.* 2001, McArdle *et al.* 2001, Zhou *et al.* 2001). There are several important differences between the present study and that of Astrand *et al.* (1964). First, a systematic and consistent protocol was presently employed to determine the CO vs. VO_2 relationship from 40 to 100% VO_{2max} using equal increments in work rate (=40 W) and VO_2 (=10%) between exercise bouts. Additionally,

repeated measurements of CO were made at all intensities including VO_{2max} (4 measures of CO at each of the intensities from rest to 70% of VO_{2max} and 8 measures of CO at each of the intensities from 80 to 100% of VO_{2max}). Astrand *et al.* (1964) made only 1 to 2 measures of CO beyond 70% of VO_{2max}, and the average increment in VO_2 between successive measurements of CO was inconsistent between subjects and averaged approximately 20% of VO_{2max}. The frequent measurement of CO during high-intensity exercise allowed for improved resolution of the CO to VO_2 relationship in the current study. Second, the fitness level of our subjects was significantly greater than that of Astrand *et al.* (1964; VO_{2max}, present study; 63.1 ± 4.4 vs. Astrand *et al.*; 54.0 ± 5.4 mL kg^{-1} per min, $P < 0.01$). This increased level of fitness and homogeneity among our subjects is important as it: (i) allows for the determination of maximal exercise responses in well-trained individuals performing at or near their peak ability and (ii) extends the previous finding that the attenuation in the CO vs. VO_2 relationship may be increased as level of fitness increases (Beck *et al.* 2006). While the slope of the CO vs. VO_2 relationship was similar from rest to 70% of VO_{2max} between the present study (5 L min^{-1}) and Astrand *et al.* (1964; 6 L min^{-1}), the reduction in slope from 70 to 100% of VO_{2max} was substantially greater in the present study (2 L min^{-1}) compared to Astrand *et al.* (1964; 4.4 L min^{-1}). The greater resolution of the CO vs. VO_2 relationship coupled with the higher level of fitness and the homogeneity of the current subjects may explain the greater observed reduction in the slope of the CO vs. VO_2 relationship.

Some evidence for an attenuated increase in CO during high-intensity exercise has been reported when using a continuous exercise protocol (Stringer *et al.* 1997, 2005, Mortensen *et al.* 2005, Beck *et al.* 2006, Calbet *et al.* 2007). However, the continuous exercise protocol may not be ideal because of carry-over effects of prior exercise and possible underestimation of CO and VO_2 as steady-state responses are likely not attained during the short 2- to 3-minute exercise stages. Stringer *et al.* (1997, 2005) used the direct Fick method to measure CO and observed a linear relationship between a-vO_{2diff} and VO_2 and an attenuated increase in CO beyond 60 to 70% of VO_{2max}. However, owing to the small number of subjects ($n = 5$), no statistical difference was found between the exponential and hyperbolic fits when compared to a linear regression. Beck *et al.* (2006) used the open-circuit acetylene washin method during continuous exercise to measure CO in a large number of subjects ($n = 72$) and showed that only 35% of these individuals displayed an attenuated increase in the CO vs. VO_2 relationship when using a quadratic fitting of the data. A positive correlation was found for fitness level and degree of curvature; however, this subset of subjects was untrained as their VO_{2max} (37.9 mL kg^{-1} per min) and maximal CO (17.1 L min^{-1}) were low compared to the present study. The present study provides novel evidence, using a discontinuous exercise protocol, of an attenuated increase in CO during high-intensity exercise in well-trained individuals.

Mechanistically, a central limitation implies that cardiovascular function shows signs of strain or limited function during high-intensity and maximal exercise. Recently, Stohr *et al.* (2011) determined that LV twist mechanics, which contribute to the LV ejection and filling, plateau during moderate-intensity exercise, indicating a true mechanical cardiac limitation in maximizing SV during high-intensity exercise. Brink-Elfegoun *et al.* (2007) used maximal and supramaximal exercise which elicited identical VO_2, CO, HR and SV responses to demonstrate that blood pressure, and thus the double product, were higher during the supramaximal exercise. Similarly, Calbet *et al.* (2007) reported a continual increase in the double product during incremental continuous exercise. As the double product is a predictor of myocardial VO_2 and coronary blood flow (Kitamura *et al.* 1972), it is evident that both the mechanical work of the heart and energetic cost of contraction can continue to increase beyond the intensity that produces maximal VO_2 and CO. These findings do not rule against a central limitation to stroke volume and possibly ventricular filling during high-intensity exercise, as suggested presently. The increase in the double product beyond maximal exercise appears solely because of the increase in systemic vascular resistance, which may reduce SV by increasing afterload. Gonzalez-Alonso & Calbet (2003) demonstrated that during maximal steady-state exercise both CO and MAP decline prior to exhaustion. Given that HR did not decline in conjunction with the reductions in CO and MAP, the double product must be reduced, indicating that the maximal pumping capacity of the heart was limited.

Another often debated topic focusing on the central limitation to exercise is the manner in which SV responds to increasing exercise intensity (Vella & Robergs 2005). Classic studies by Bevegard *et al.* (1963) and Astrand *et al.* (1964) demonstrated an initial increase in SV from rest to exercise in the upright position and then a constant SV from moderate to maximal exercise, a finding that has been repeated numerous times (Higginbotham *et al.* 1986, Flamm *et al.* 1990, Seals *et al.* 1994, Stringer *et al.* 1997, 2005, Proctor *et al.* 1998, McCole *et al.* 1999, Gonzalez-Alonso & Calbet 2003, Gonzalez-Alonso *et al.* 2004). The present study supports this finding as SV did not increase beyond 50% of VO_{2max}. Furthermore, the 10 mL per beat reduction in SV at high-intensity

exercise as observed in the present study is primarily responsible for the attenuated increase in CO as HR continued to increase as intensity increased. The random order of the high-intensity exercise bouts in the current study may have lead to an elevated HR at 80% of VO_{2max}, resulting in a reduced diastolic filling time and an exaggerated decrease in SV. The reduction in SV is not without precedent as Keul *et al.* (1981) reported the first echocardiographic evidence of such a finding during upright cycling. Later, Higginbotham *et al.* (1986) determined that end-diastolic volume decreased in 17 of 24 subjects during high-intensity cycling owing to a reduction in SV. Numerous investigators (Flamm *et al.* 1990, Spina *et al.* 1992, Seals *et al.* 1994, Harper *et al.*, 2006) using a variety of techniques report an 8–11% reduction in SV during peak exercise, which closely agrees with our finding. Additionally, during high-intensity exercise, Gonzalez-Alonso & Calbet (2003; Gonzalez-Alonso *et al.* 2004) and Mortensen *et al.* (2005) have consistently found a reduction in SV.

The mechanism responsible for the attenuation in the CO vs. VO_2 relationship and the fall in SV is not entirely clear but is likely related to an interaction of factors that alter preload, afterload and left ventricular function. Direct manipulation of HR by pacing the heart in both humans and dogs demonstrates that tachycardia leads to disproportional reductions in diastolic filling time and left ventricular end-diastolic volume, which reduce preload and compromise SV and CO (Templeton *et al.* 1972, Weisfeldt *et al.* 1978, Sheriff *et al.* 1993). Using a combination of direct heart catheterization and radionuclide angiography, Higginbotham *et al.* (1986) elegantly determined that during high-intensity exercise, tachycardia is accompanied by a decrease in end-diastolic volume despite a progressive increase in filling pressure, which results in a reduction in SV. The increased ventricular filling pressure as exercise intensity increases appears to be inadequate to fully compensate for the reduction in ventricular filling time resulting in the plateau and eventual reduction in SV. Progressive increases in afterload as evidenced by the linear increase in systemic arterial pressure may also contribute to the observed plateau in SV (Calbet *et al.* 2006). The mode of exercise may also impact SV and CO as Hermansen *et al.* (1970) found that elevated blood pressure and therefore, peripheral resistance, leading to elevated afterload resulted in reductions in SV and CO during cycling compared to running.

A plateau and reduction in SV during high-intensity exercise is a finding that has not been reported by all investigators. Other investigators have found that SV in highly trained individuals continues to increase as exercise intensity increases and further report that almost all endurance athletes achieve their highest SV during maximal exercise while untrained or moderately trained individuals exhibit a plateau or drop in SV at peak exercise (Gledhill *et al.* 1994, Zhou *et al.* 2001, Vella & Robergs 2005, Warburton & Gledhill 2008a,b). The reason for the continual increase in SV in endurance-trained individuals is thought to be due to improved diastolic function as a result of chronic exercise training (Gledhill *et al.* 1994); however, these findings have been challenged (Ekblom & Ekblom 2006). Recent work by Faisal *et al.* (2009) examined the SV kinetic response to moderate- and high-intensity exercise and found that SV exhibits a substantial overshoot during the first few min of exercise and then decreases and eventually levels off as exercise duration progresses. This may explain an overestimation of SV if the measurement is made too early into the exercise bout. Therefore, the timing of the CO and SV measurement coupled with the protocol employed (continuous vs. discontinuous) may confound the SV finding and lead to an overestimation of CO and SV.

A limitation of the current investigation is the use of a non-invasive technique for the determination of CO. We were not able to directly validate the open-circuit technique against the direct Fick, a method not affected by ventilation-perfusion inhomogeneities or anatomical shunts. However, this validation was performed by Johnson *et al.* (2000), and no difference in the CO response between the open-circuit acetylene technique and the direct Fick was observed, indicating that the open-circuit technique is both valid and reliable during high-intensity exercise.

In conclusion, contrary to the commonly held belief of linearity in the CO vs. VO_2 relationship, we have documented an attenuated increase in the CO vs. VO_2 relationship in well-trained individuals when exercise becomes intense and eventually elicits VO_{2max}. This reduction in the slope of the CO vs. VO_2 relationship appears to be due to the decline in SV during high-intensity exercise as no evidence of a non-linear increase in HR was observed. Well-trained endurance athletes, when studied with longer duration exercise stages near maximal capacity, appear to be approaching a limit of their ability to pump blood to the working muscles.

Conflict of interest

The authors declare no conflict of interest.

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