

Pulse transit time measured by photoplethysmography improves the accuracy of heart rate as a surrogate measure of cardiac output, stroke volume and oxygen uptake in response to graded exercise

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Introduction

Controlling exercise intensity using heart rate monitors (HRMs) has long been a centerpiece of training for professional athletes as well as for sports enthusiasts. Heart rate (HR) measured by electrocardiography (ECG or EKG), i.e. the electrical activity of the heart, provides the individual with an immediate feedback on the cardiac response to exercise, and therefore represents a valuable and easily accessible tool for training programs aimed at improving conditioning [1-31]. HRMs, employing short-range telemetry, are used ubiquitously among all levels of exercisers because they are un-cumbersome, relatively simple to operate, economical and portable. Their popularity has increased tremendously over the last decade due to their seamless integration with mobile phones and other sensing technologies such as global positioning systems (GPS) that allow improved computing capabilities and user-friendly data exporting and visualization.

Heart rate has also been proposed as a surrogate of other physiological measurements relevant to exercise training. For instance, numerous studies have indicated that HR represents a valid proxy measure of oxygen uptake and energy expenditure at the individual level in healthy subjects tested under laboratory-controlled conditions [13, 32-42]. While such correlations have been shown to weaken among different age groups [27, 43-49], genders [48, 50-55], sporting disciplines [56-58] and under uncontrolled experimental conditions such as field training or competitive racing [27, 59], other studies have found stronger estimations of $\dot{V}O_2$ and energy expenditure when adjunct physiological parameters

such as rate of perceived exertion (RPE) [32, 60-68] and biomechanical measures (i.e., stride frequency via accelerometers output) [69-83] are included in prediction algorithms alongside HR. Thus, novel exercise measures that can be paired with HR have the potential to maximally exploit the mass adoption of HRMs by providing a more accurate prediction of the level of conditioning of exercising individuals. To be adopted by trainers, self-training individuals and exercise physiologists, such measures should be easily accessible and should integrate with existing HRM equipment without requiring additional actions that increase the burden on the exerciser and discourage adherence, such as requiring frequent data input by the user.

Photoplethysmography (PPG) is an optical method for detecting blood volume changes in microvasculature sites. Since measurements can be performed at easily accessible body sites such as the fingertip, toe tip or earlobe [84] using small and unobtrusive sensors, PPG is a good candidate technique for measuring exercise-related physiological parameters ubiquitously. The technique relies on the partial optical transparency of human tissues to near-infrared light, and it quantifies the changes in blood perfusion in the catchment volume. When paired with ECG, PPG allows the measurement of time-related cardiovascular parameters such as pulse transit time (PTT) and pulse wave velocity (PWV) [85]. PTT is defined physiologically as the time interval between the ventricular contraction and the appearance of the arterial blood wave at the periphery, and it is practically measured as the time interval between the peak of the ECG R-wave and the peak of the synchronized PPG waveform. Additional definitions of PTT are formulated in relation to other PPG waveform features, such as the foot or the maximum slope (first derivative) of the PPG signal [86]. PPG is consensually accepted as a surrogate of arterial compliance, as arterial stiffness increases PWV and decreases PTT [87-95]. In the past few years, PTT has also been shown to be linearly correlated with blood pressure [88, 96-105], but without the level of accuracy needed to represent beat-to-beat blood pressure [106, 107]. Pulse arrival time (PAT), defined as the sum of PTT and pre-ejection period, has also been proposed as an alternative measure of blood pressure without sphygmomanometric cuffs [108-110], although recent literature has questioned the reliability of this method [107].

In this work, we tested the ability of PTT to represent a valuable pairing to heart rate for estimating cardiovascular parameters during exercise. HR and PTT were correlated with cardiac output, stroke volume and oxygen uptake measured in a group of healthy young subjects during a graded incremental cycling protocol. Although the accuracy of clinically-accepted measurements of cardiac output (i.e., Fick equation, dye or thermo-dilution, Doppler echocardiography) is currently unsurpassed, these methods are either invasive or unusable for use outside of clinical or laboratory settings. Similarly,

portable metabolic carts for measurement of human performance parameters ($\dot{V}O_{2max}$, ventilatory threshold and cardiac output by Wassermann method [111]) are impractical due to being cumbersome, expensive and requiring periodic calibration. Therefore, non-invasive surrogate methods for indirect assessment of cardiac output, stroke volume, or oxygen uptake would represent valuable tools in both research and clinical settings and eventually in field conditions. We found that the addition of PTT improved the modeling of cardiac output, oxygen uptake and stroke volume at individual level compared to predicting models based solely on HR.

Materials and methods

Subjects

Fifteen volunteers (10 males, 5 females, age 25.7 ± 4.5 years, $\dot{V}O_{2peak} = 33 \pm 4.7$ ml/kg/min) were recruited from the student and staff population of the University of Houston for performing a maximal cycling test. All subjects received an explanation of the experimental tasks and were asked to sign an informed consent form before testing. All subjects certified that they were healthy, had no contraindications for performing vigorous exercise, and were not taking any medication within 6-weeks prior to enrolling in the study. No alcohol or caffeine was consumed by the subjects for at least 12 hours before the experiment, and no strenuous exercise was performed for at least 48 hours prior to the experiment. All procedures were approved by the Committee for the Protection of Human Subjects at the University of Houston.

Cardiovascular measures

Three-lead electrocardiographic and photoplethysmographic signals were collected using OEM sensors (respectively EG01010 and EG00532, Medlab, Germany) embedded in a custom-designed wearable system [112]. Analog outputs from the sensors were simultaneously acquired and digitized by a microcontroller to maximize the accuracy of timing computations between their significant features. Adhesive stress ECG electrodes (Blue Sensor SP, Ambu A/P, Denmark) were placed across the chest in a conventional 3-lead layout (left and right shoulders, left hip) to optimize the quality of the ECG readings. The PPG probe consisted of a sensor that was clipped on the right thumb, i.e. the location least sensitive to reduced blood perfusion in the fingertips caused by grasping the handlebars on the cycle ergometer. ECG and PPG analog signals were sampled synchronously every 20ms and transmitted wirelessly to a

remote receiver (i.e., laptop) for further processing. To minimize the error on the calculated PTT, ECG's QRS complexes and PPG pulses affected by excessive noise or movement artifacts were removed from processing. All significant features (maxima, minima, maximum slopes) of ECG and PPG signals were automatically identified by peak-detection algorithms applied after noise-reduction filtering (low-pass Butterworth filter, 3rd order, cut-off frequency 40Hz). Beat-to-beat heart rate (HR) was calculated as a reciprocal of ECG's R-R interval. Pulse transit times were calculated as the time interval between the electrocardiographic R-wave peak and the maximum amplitude (peak, PTT_p), minimum amplitude (foot, PTT_f) and maximum first derivative of the rising slope (PTT_s) of the photoplethysmographic waveform. We also calculated the beat-to-beat ratio between PTT_p and R-R interval (hereby specified as PTT_p/RR) as an indicator of the balance between the expected decreases of RR and PTT during graded exercise. Moving averaging (20-sample window) was applied to all beat-to-beat recordings to reduce short-time variability and instrumental noise. During the experiment, oxygen uptake ($\dot{V}O_2$) was measured by respiratory gas analysis using a metabolic cart (Quark, Cosmed Inc., Italy). Cardiac output (Q) and stroke volume (SV=Q/HR) were estimated by the cart's software with the Wassermann method [111]. All signal processing steps on ECG and PPG waveforms were performed in MATLAB (The MathWorks, Natick, MA).

Experimental protocol

All subjects performed a cycling exercise protocol consisting of a 5-minute warm-up at a 50W workload, followed by a graded increment of 15W/minute until volitional exhaustion or task failure occurred following the protocol described by Storer et al. [113]. The task failure was determined by the inability of the subject to maintain a set cadence of 60 ± 5 rpm throughout each 1-minute exercise stage. The exercise workload was controlled by an electromechanical resistance (CompuTrainer Lab, RacerMate Inc., Seattle, WA) applied to the rear wheel of a stationary road bicycle previously calibrated to the body mass of each individual.

Statistical analysis

We evaluated statistically significant relationships between independent variables (HR, PTT_p, PTT_f, PTT_s, PTT_p/RR) and dependent variables (Q, SV) using linear regression models and linear mixed models. Linear regression was used to model the variability of group-averaged outcomes, while mixed models were used to provide a more complete description that included within-subject and between-subject

variability. The type I error rate used to determine the significance of the model terms was set at 5%. Akaike Information Criterion (AIC) was used for selection among competing linear mixed models [114]. To standardize the workload (WL) across subjects, WL was normalized to the maximum workload WL_{max} that each individual was able to exert. All statistical computations were computed in *R* using the package *lme4* for linear mixed modeling [115, 116].

Results

Heart rate

The increase in heart rate (HR) as a function of exercise workload at individual and group level is reported in Fig. 1. The basal HR at the start of the exercise (0%WL) was recorded at the end of the 5-minute warm-up period. When individual variability was retained, the data were best fit by a mixed model with fixed effects represented by a second-order polynomial increase with both intercept and growth rate (slope) allowed to vary randomly across subjects. The group-averaged heart rate also grew as a quadratic polynomial (adjusted $R^2=0.995$). Both growth curves were modeled by the equation $p_2WL^2+p_1WL+p_0$ ($p_2=-0.29$, $p_1=10.99$, and $p_0=105.2$), where *WL* denotes the normalized workload.

Pulse Transit Times

During exercise, the flow-mediated dilation of the arteries increased the velocity of the blood wave travelling from the heart to the periphery as a result of workload increase, thus causing the pulse transit times to decrease. The transit time PTT_p from the ECG R-wave to the peak amplitude of the PPG signal is reported in Fig. 2a at both the individual and group level. PTT_p was notably affected by a substantial variance at the individual level across the workload stages, which is mainly explained by movement artifacts and by poor time resolution of the PTT sensor compared to the average change of PTT_p induced by each workload increment. Specifically, since PTT_p was calculated as the time difference between two waveform features (i.e., peak of ECG and PPG signals) each identified with an uncertainty of ± 10 ms, the resulting variance of PTT_p was ± 20 ms (with triangular distribution). The decay of PTT_p as a function of workload was best fit by a quadratic mixed model with random intercept and slope. The group average equally exhibited a quadratic decay with coefficients $p_2=0.34$, $p_1=-14.68$, and $p_0=424.1$ (adjusted $R^2=0.9848$).

The average pulse transit time PTT_f between the R-wave of the ECG signal and the foot of the PPG signal is shown in Fig. 2b. In the same chart, we reported also the average R-R interval and pulse

transit times PTT_p and PTT_s for comparison. For improved readability of the charts, individual growth curves for these measures are not reported. In contrast to PTT_p , the decay of PTT_f flattened after 50% workload, thus indicating a profile change of the PPG waveform along the exercise. The span of the group-averaged PTT_f (i.e., $PTT_p(100\%WL) - PTT_p(0\%WL)$) was 56ms, which was substantially lower than the corresponding span of PTT_p (108ms). Similarly, the time interval PTT_s between the peak of R-wave and the maximum rising slope of PPG spanned 69ms at group level (Fig. 2a). Since the overall changes of PTT_f and PTT_s were modest compared to the noise level induced by motion artifacts and inherent resolution of the sensor, we chose to exclude these two PTT measures from statistical models.

The percent ratio between PTT_p and R-R interval calculated at the individual and group levels are shown in Fig. 2c. This measure exhibited a substantial degree of variability across subjects. The best fitting model across individuals was a quadratic fixed effect with random intercept and slope, whereas the group-averaged data were best fit by a quadratic polynomial growth with parameters $p_2=-0.23$, $p_1=4.48$, and $p_0=74.59$ (adjusted $R^2=0.9648$).

Oxygen Uptake ($\dot{V}O_2$), cardiac output and stroke volume

Oxygen uptake ($\dot{V}O_2$) measured by respiratory gas analysis at the individual and group levels are shown in Fig. 3. The $\dot{V}O_2$ growth was best fit by a model with quadratic dependence on workload and random intercept and slope ($p_2=-0.11$, $p_1=26.5$, and $p_0=946$ (adjusted $R^2=0.988$)).

Cardiac output (Q) measured by respiratory gas analysis [111] and calculated stroke volume ($SV=Q/HR$) are shown in Fig. 4 and Fig. 6, respectively. The increase in Q at the individual level is best fitted with a quadratic model for both fixed and random effects; the same model also best fit the group-averaged Q (adjusted $R^2=0.9981$). Similarly to Q, the increase in SV is best fitted with a quadratic function for both random and mixed effects (adjusted $R^2=0.8547$).

Models of Cardiac Output, Stroke Volume, and Oxygen Uptake

Since the main goal of this study was to assess if pairing PTT to HR improved the indirect estimation of cardiovascular parameters of interest to exercise monitoring such as cardiac output, stroke volume and oxygen uptake, we sought to find statistically significant models of these physiological measures using both HR and PTT as independent variables.

Prior to modeling, we normalized HR and PTT_p to their resting value (denoted as HR_n , PTT_{pn}) and applied logarithmic transformation to all variables to improve handling of their nonlinear relationships.

The dependent variables Q , SV , $\dot{V}O_2$ were modeled with linear mixed models using main effects and interactions of the log-transformed variables, including resting values (HR_0 , PTT_{p0}) and normalized values (HR_n , PTT_{pn}). The within-subject correlation and inter-subject variance were taken into account simultaneously by inclusion of random intercept and slope that varied per subject. Since we sought to compare models of the outcomes Q , SV , $\dot{V}O_2$ built using both HR and PTT to models built with just HR, the random slope of the mixed models was kept simple and corresponded to the HR_n term.

We found that the mixed models that best fitted each of the three outcomes Q , SV , $\dot{V}O_2$ used similar terms, i.e. $\log(HR_0)$, $\log(HR_n)$, $\log(PTT_{pn})$, $\log(HR_n)*\log(PTT_{pn})$ (Table 1). Specifically, PTT_{pn} contributed significantly to all models, whereas resting heart rate HR_0 was a significant predictor for stroke volume only. The reason for this was the existence of a linear inverse relationship between HR and SV in resting conditions (Fig. 6, $p=0.013$), which implied that some of the between-subject variability was not random. A measure of the goodness of fit of linear mixed models, denoted R_1^2 and analogous to the Pearson's coefficient R^2 for regression models [117], was found to be greater in all models including PTT_p (0.419 for SV, 0.548 for Q , and 0.771 for $\dot{V}O_2$) than in the best models based on HR alone (0.379 for SV, 0.503 for Q , and 0.745 for $\dot{V}O_2$).

Discussion

In this study, we investigated the relationship between standard (Q , SV , $\dot{V}O_2$) and non-standard (PTT) measures of cardiovascular response to graded cycling exercise. Respiratory gas analysis was used to measure oxygen uptake and estimate cardiac output and stroke volume [111], while electrocardiography and photoplethysmography were used to measure heart rate and pulse transit times. We found that PTT_p — i.e., the time interval between the R-wave of ECG and the peak of amplitude of the PPG signal — improved the fit statistics of mixed model of Q , SV and $\dot{V}O_2$ with respect to best-fitting mixed models based on HR alone. Oxygen uptake expectedly exhibited the best fit statistics amongst all variables dependent on HR and PTT_p , as HR alone is known to be a good predictor of $\dot{V}O_2$ in healthy young adults during non-steady exercise [39]. The goodness of fit of the best-fitting model of SV was also significantly improved when the linear relationship between resting stroke volume and resting HR was accounted for. Hence, the results of this study suggest that combining HR and PTT could serve as a superior surrogate measure of established physiological responses to exercise, particularly in applications where standard measuring methods are either impractical or not accessible. Indeed, ECG and PPG sensing technologies have additional advantages in being portable, non-invasive,

economical, and not requiring calibration, thus enabling the uncomplicated assessment of cardiovascular functions when exercising under field conditions. For instance, the integration of these techniques into wearable sensors could serve as valuable accompaniments to heart rate monitors in fitness and telemedicine realms. ECG and PPG could also impact clinical applications where continuous monitoring of cardiac output is valuable yet impractical, such as home-based monitoring of congestive heart failure or in cardiac rehabilitation.

Notwithstanding, combining these sensing technologies has challenges with regards to the implementation, validation and adoption by end-users. Specifically, unlike ECG that is being used in mass-produced products like heart rate monitors, PPG has yet to find widespread applications outside of the clinical setting (e.g., pulse oximetry). Our work, although limited in scope, has confirmed some general drawbacks that adversely affected the diffusion of PPG for the assessment of fitness and human performance. Primarily, PPG has shown to be inherently sensitive to movement artifacts, which may limit widespread usability in the field. Ideally, a PPG sensor is required to maintain secure contact with a tissue where a capillary bed is optically accessible, yet without applying excessive pressure that would cause capillary occlusion. In this study, we noticed that PPG signals collected using a standard pulse oximetry probe was strongly sensitive to the placement site and to the grasping force that the subject exerted on the bike's handlebar, which occasionally caused poor blood perfusion of the fingertips. To consistently obtain PPG signals of acceptable quality during the cycling protocol, we asked the subjects to support the upper body with the palms of their hands on the handlebar and to relax the thumbs, to which we clipped the sensor. Occasionally, portions of PPG signals in some subjects were not decipherable due to movement artifacts, compromising the calculation of pulse transit times during those adverse events. Future investigations with cycling protocols should consider alternate placements for PPG, such as earlobes, that are supposedly less sensitive to posture and movement. Importantly, the physiological interpretation of PTT in relation to the measuring location for PPG has yet to be fully understood. Although vasodilation is a known systemic effect of physical exercise, differences exist between vasodilatory responses of different arteries within and across different types of exercise. For instance, recent studies showed that a marked vasodilation of the brachial artery induced by shear stress occurs during prolonged leg cycling exercise, but only following a temporary decrease of blood flow taking place immediately after the onset of exercise [118, 119]. This finding is consistent with the results of our study. In contrast, another study suggests that local dilation mechanisms may play a preponderant role in mediating shear rate and blood flow in the femoral artery during arm-crank exercise [120]. Hence, since vascular adaptation is the main determinant of changes in PTT during

exercise, its physiological meaning and its relationship with other cardiovascular measures need to be interpreted within the context of a specific exercise protocol.

An important caveat of this study was that the fitting of the models was affected by a significant variance of the PTT measurements to which several factors contributed, including the intrinsic time resolution of the sensor, physiological differences across subjects and movement artifacts. In resting conditions, i.e. discounting the effect of movement artifacts, PTT_p exhibited a standard deviation across subjects of 43.3ms, which was largely influenced by the limited time resolution (20ms) of the sensors used in this study. In addition, the variance of the training status of the individuals recruited for this study may have had a role in the overall variance of PTT_p , although mixed models were used to minimize such influence. We therefore hypothesize that a custom-designed sensor with time resolution of 5ms or better, whilst also accounting for the age and fitness status of the individual, will substantially reduce measurement error and improve statistical modeling. Ultimately, this will provide greater insight to the relationships between PTT and physiological measures such as cardiac output, stroke volume and oxygen uptake during physical exercise.

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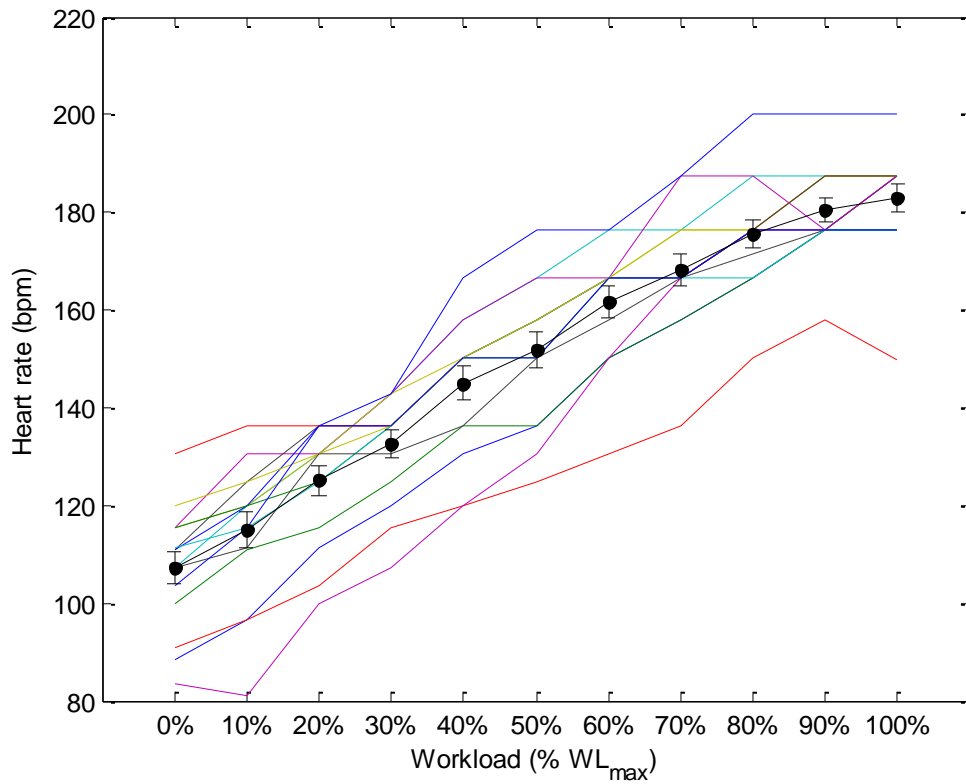
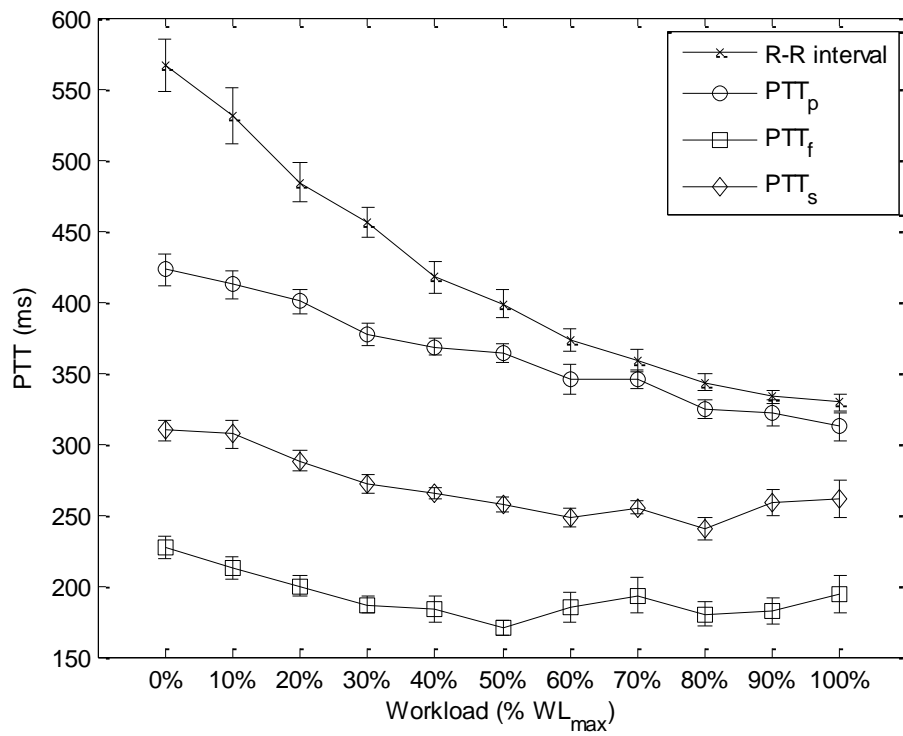
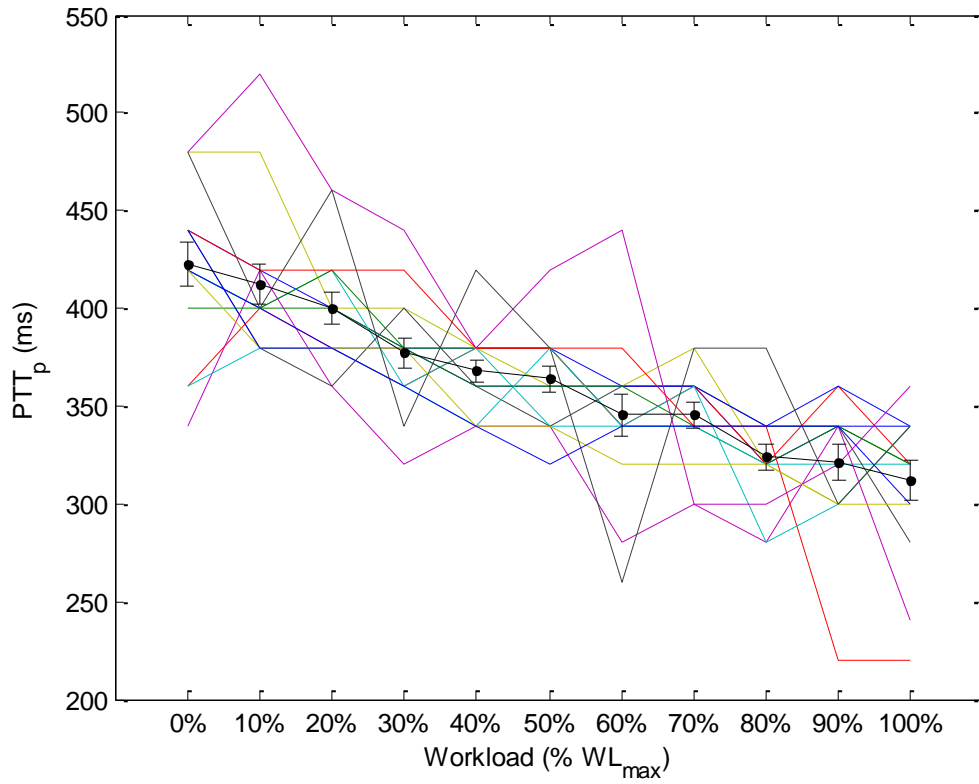


Figure 1: Individual (colored lines) and group average (black marked line) of heart rate recorded at each 10% workload increment. The error bars represent the standard error of the averaged HR values at each normalized workload increment.



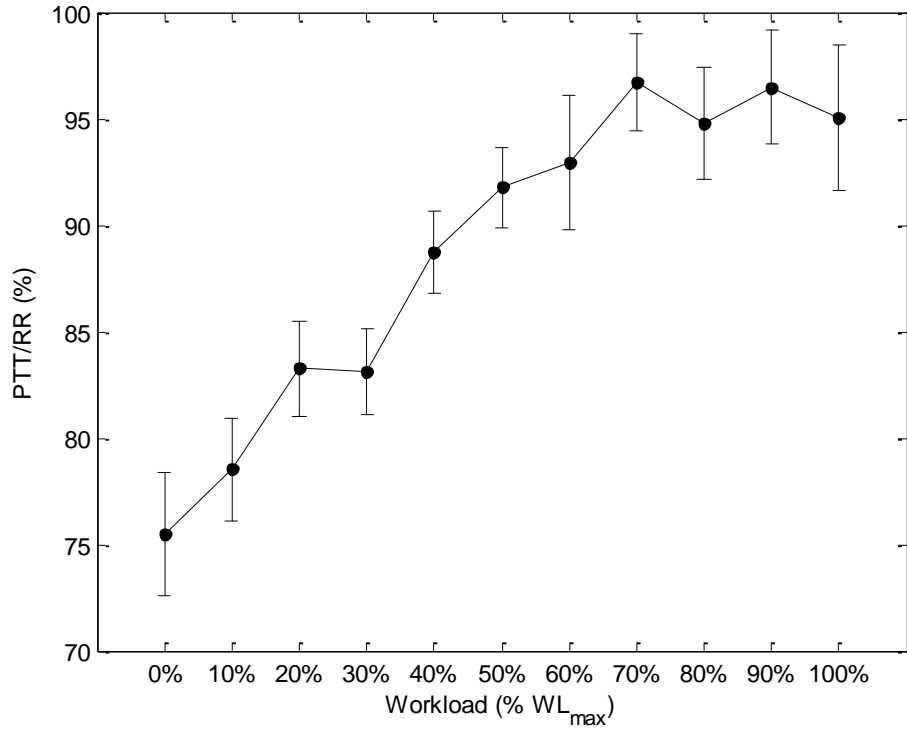


Figure 2: (a) Individual (colored lines) and group average (black marked line); (b) Group average of pulse transit times (PTT_p , PTT_f , PTT_s) and R-R interval; (c) Group average of the percent ratio between PTT_p and R-R interval. In all charts, the error bars represent the standard error of the measure at each normalized workload increment.

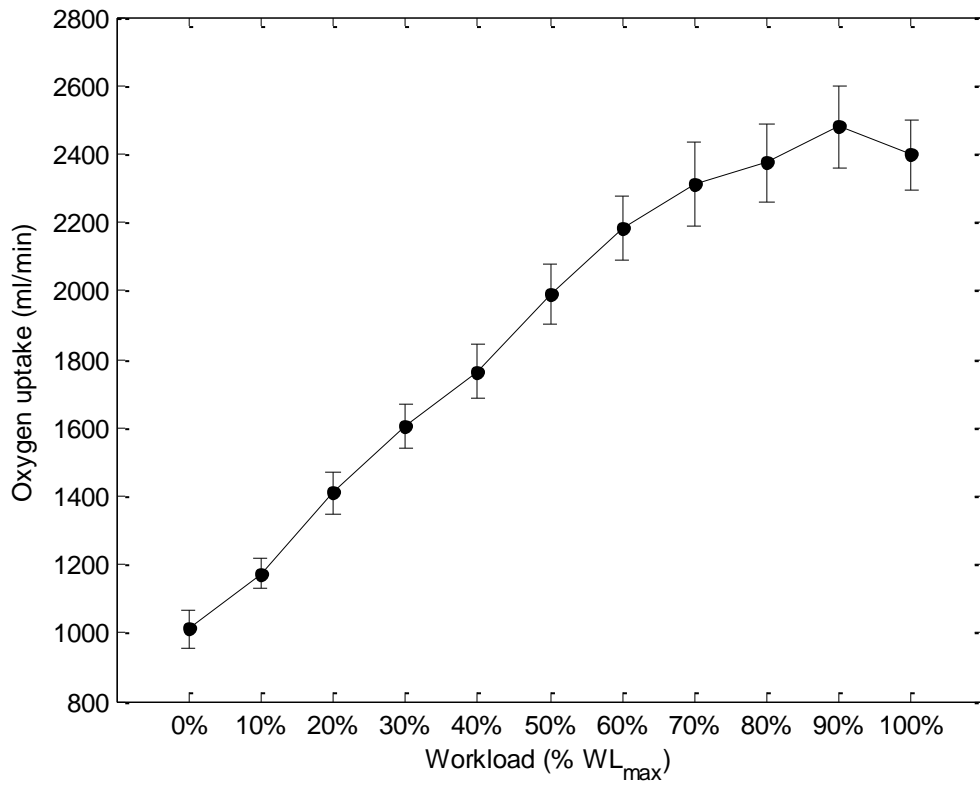


Figure 3: Group average of oxygen uptake ($\dot{V}O_2$) at group level. The error bars represent the standard error at group level evaluated at 10% workload increments.

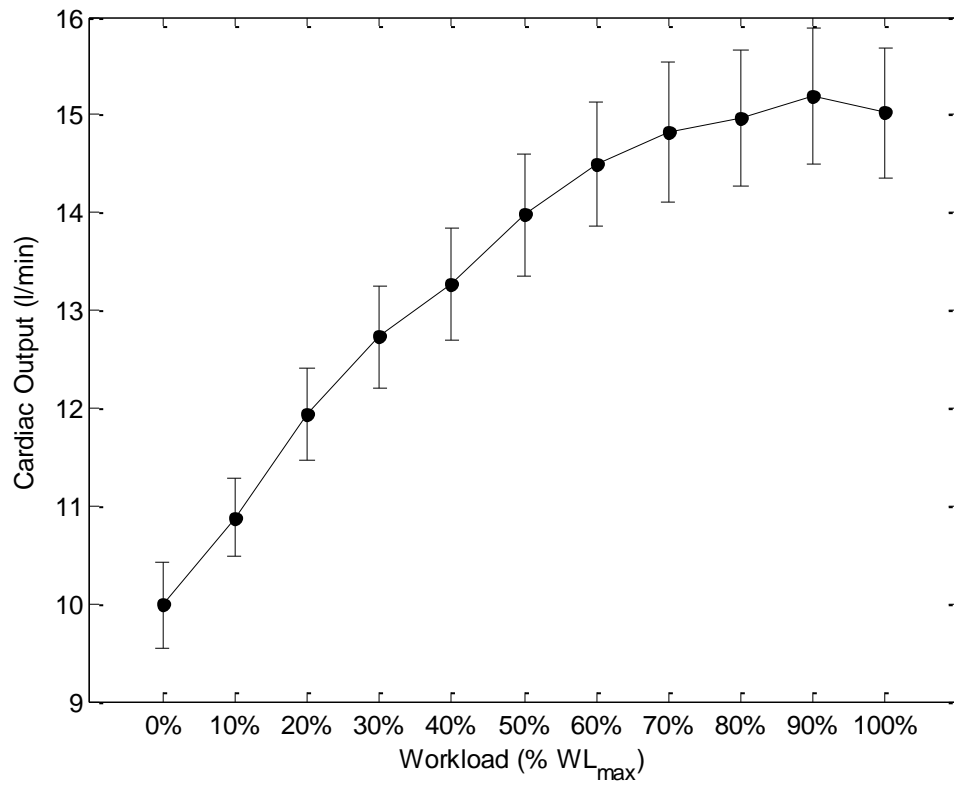


Figure 4: Group average of cardiac output (Q) as a function of workload. The error bars represent the standard error at group level evaluated at 10% workload increments.

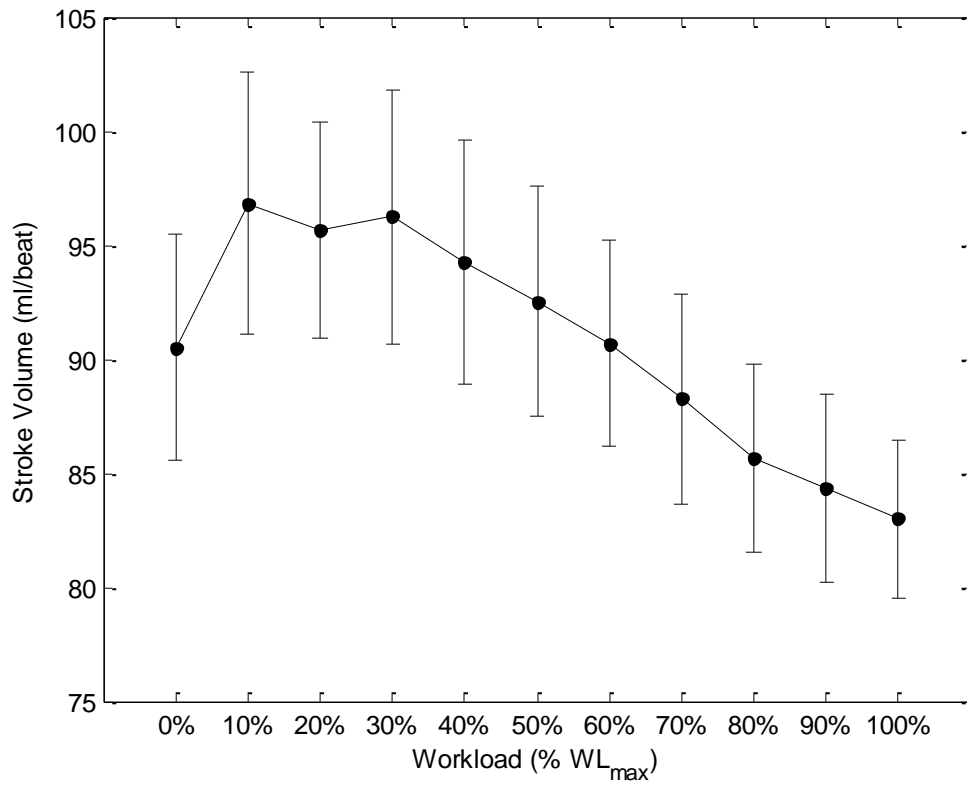


Figure 5: Group average of stroke volume (SV) as a function of workload. The error bars represent the standard error at group level evaluated at 10% workload increments.

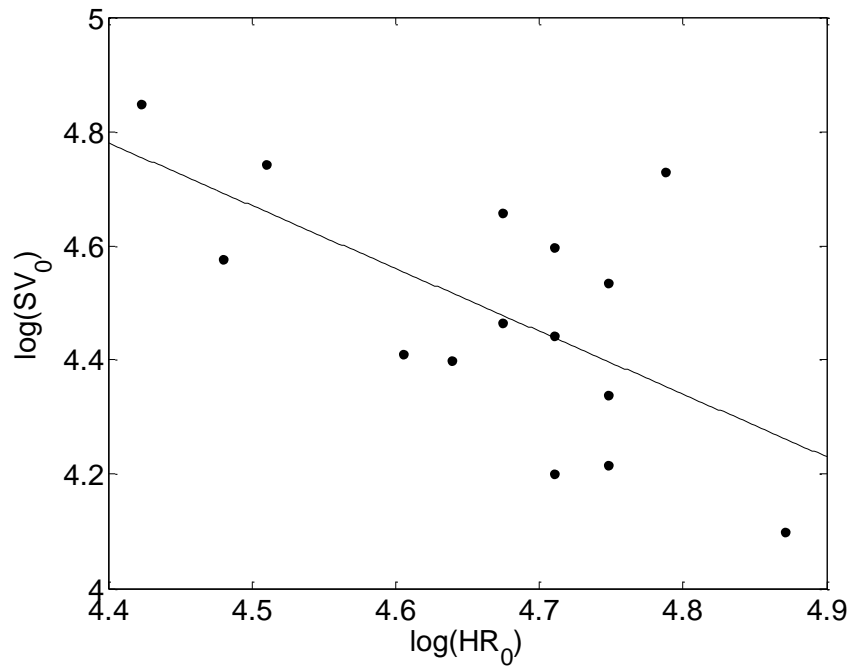


Figure 6: Stroke volume as a function of heart rate in resting condition (WL=0%), after logarithm transform.

Predictor	Stroke Volume				Cardiac Output				Oxygen Uptake			
	Estimate	95% Confidence Interval		p-value	Estimate	95% Confidence Interval		p-value	Estimate	95% Confidence Interval		p-value
		Lower	Upper			Lower	Upper			Lower	Upper	
Intercept	3.510	0.346	6.673	0.030	2.321	2.248	2.395	0.000	6.946	6.868	7.023	0.000
Log(HR ₀)	-1.260	-1.937	-0.583	0.000	-	-	-	-	-	-	-	-
Log(HR _n)	-0.112	-0.192	-0.032	0.006	0.816	0.734	0.898	0.000	1.725	1.567	1.884	0.000
Log(PTT _{pn})	-0.341	-0.502	-0.180	0.000	-0.305	-0.459	-0.151	0.000	-0.515	-0.821	-0.210	0.001
Log(HR _n) x Log(PTT _{pn})	0.950	0.612	1.288	0.000	0.867	0.544	1.190	0.000	1.355	0.708	2.002	0.000
Random intercept (Std. Dev.)	0.154				0.141				0.139			
Random slope (Std. Dev.)	0.072				0.092				0.164			
Residual (Std. Dev.)	0.047				0.044				0.088			

Table 1: Estimated coefficients, confidence intervals and p-values of best-fitting linear mixed models for cardiac output (Q), stroke volume (SV) and oxygen uptake ($\dot{V}O_2$).