Am J Physiol Heart Circ Physiol 314: H853–H862, 2018.
First published December 29, 2017; doi:10.1152/ajpheart.00435.2017.

RESEARCH ARTICLE | *Integrative Cardiovascular Physiology and Pathophysiology*

Maximal strength training-induced improvements in forearm work efficiency are associated with reduced blood flow

Ole Kristian Berg,[1] Stian Kwak Nyberg,[2] Tobias Midtvedt Windedal,[2] and Eivind Wang[1,2,3]

[1]*Faculty of Health and Social Sciences, Molde University College, Molde, Norway;* [2]*Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; and* [3]*Department of Internal Medicine, University of Utah, Salt Lake City, Utah*

Submitted 13 July 2017; accepted in final form 28 December 2017

Berg OK, Nyberg SK, Windedal TM, Wang E. Maximal strength training-induced improvements in forearm work efficiency are associated with reduced blood flow. *Am J Physiol Heart Circ Physiol* 314: H853–H862, 2018. First published December 29, 2017; doi:10.1152/ajpheart.00435.2017.—Maximal strength training (MST) improves work efficiency. However, since blood flow is greatly dictated by muscle contractions in arms during exercise and vascular conductance is lower, it has been indicated that arms rely more upon adapting oxygen extraction than legs in response to the enhanced work efficiency. Thus, to investigate if metabolic and vascular responses are arm specific, we used Doppler-ultrasound and a catheter placed in the subclavian vein to measure blood flow and the arteriovenous oxygen difference during steady-state work in seven young men [24 ± 3 (SD) yr] following 6 wk of handgrip MST. As expected, MST improved maximal strength (49 ± 9 to 62 ± 10 kg) and the rate of force development (923 ± 224 to 1,086 ± 238 N/s), resulting in a reduced submaximal oxygen uptake (30 ± 9 to 24 ± 10 ml/min) and concomitantly increased work efficiency (9.3 ± 2.5 to 12.4 ± 3.9%) (all $P < 0.05$). In turn, the work efficiency improvement was associated with reduced blood flow (486 ± 102 to 395 ± 114 ml/min), mediated by a lower blood velocity (43 ± 8 to 32 ± 6 cm/s) (all $P < 0.05$). Conduit artery diameter and the arteriovenous oxygen difference remained unaltered. The maximal work test revealed an increased time to exhaustion (949 ± 239 to 1,102 ± 292 s) and maximal work rate (both $P < 0.05$) but no change in peak oxygen uptake. In conclusion, despite prior indications of metabolic and vascular limb-specific differences, these results reveal that improved work efficiency after small muscle mass strength training in the upper extremities is accompanied by a blood flow reduction and coheres with what has been documented for lower extremities.

NEW & NOTEWORTHY Maximal strength training increases skeletal muscle work efficiency. Oxygen extraction has been indicated to be the adapting component with this increased work efficiency in arms. However, we document that decreased blood flow, achieved by blood velocity reduction, is the adapting mechanism responding to the improved aerobic metabolism in the forearm musculature.

handgrip; mechanical efficiency; oxygen extraction; small muscle mass; work economy

INTRODUCTION

Maximal strength training (MST), performed at ~90% of one repetition maximum (1RM) intensity, has been well documented to yield large improvements in maximal muscle strength and rate of force development (RFD) and, in turn, reduce oxygen uptake ($\dot{V}O_2$) during submaximal exercise (21, 22, 31, 53, 60). If $\dot{V}O_2$ is seen in relation to the energy cost of the work performed, it is commonly referred to as work efficiency (3). The majority of the studies that have investigated MST-induced effects on work efficiency have measured pulmonary $\dot{V}O_2$ during steady-state whole body work (22, 24, 61). However, a recent investigation (3) identified the improved work efficiency to be of peripheral origin. Using a thermodilution technique, this study also documented that the submaximal cycling work efficiency improvement led to a reduced blood flow to the exercising limb, whereas the arteriovenous oxygen difference (a-vO_{2diff}) remained unaltered (3).

MST-induced effects may differ between the lower and upper extremity musculature. The only study to date to investigate this in arms, to our best knowledge, observed blood flow to be unchanged after training (27). Rather, the reduction in $\dot{V}O_2$ in this study was attributed to the other component in the Fick equation: a-vO_{2diff}. Although a-vO_{2diff} was calculated indirectly from pulmonary $\dot{V}O_2$, the proposal may be reasonable as several differences in vascular and metabolic responses exist between arm and leg exercise (8, 9, 35). A pivotal impediment in arms (36, 44) compared with legs is the larger influence from muscle contractions, resulting in a substantial hindrance to blood flow. This may be decisive for blood flow as an adapting mechanism in arms, and a-vO_{2diff} may thus be the regulated component in the oxygen supply and demand interplay after arm MST. Notably, arms are also shown to exhibit ~25% lower work efficiency compared with the lower extremities (26, 32), and such a divergence in physiological premises or/and fitness status may shift the oxygen transport chain toward a demand limitation (13). However, there are also arguments that speak against the proposal of a-vO_{2diff} as the mechanism accompanying submaximal work efficiency improvements in arms. First, oxygen extraction is substantially lower in the arms compared with legs (9), and it seems somehow counterintuitive that a factor that is already compromised would be further reduced after training. Second, the vascular strain is high during arm exercise compared with legs (8), and it could be argued that a reduction in blood flow after

Address for reprint requests and other correspondence: O. K. Berg, Faculty of Health and Social Sciences, Molde University College, Britvegen 2, Molde 6410, Norway (e-mail: olbe@himolde.no).

training would be even more favorable in the arms compared with legs and thus be the likely adapting mechanism in response to reduced oxygen demand.

MST has typically been shown to reduce submaximal pulmonary $\dot{V}O_2$, but although studies that investigated both large and small muscle mass in the lower and upper extremities have appeared to arrive at the same doorstep, previous observations suggest that this advantageous training response may be achieved by different mechanisms in arms (27) compared with legs (3). Thus, since it is an intriguing question if MST-induced aerobic endurance limb-specific differences exist, but direct assessment of skeletal muscle arm $\dot{V}O_2$, to our best knowledge, is lacking, the aim of the present study was to investigate the work efficiency of the forearm flexors in response to MST. By experimental design, we sought to determine skeletal muscle adaptations in a-vO_{2diff} and blood flow components using a catheter-based approach in conjunction with Doppler-ultrasound at steady-state submaximal exercise. Specifically, in accordance with prior results obtained through direct assessment of $\dot{V}O_2$ after half-squat MST, we hypothesized that 6 wk of dynamic handgrip MST would result in improved work efficiency and, in turn, result in a reduced blood flow but unaltered a-vO_{2diff}.

METHODS

Subjects. Seven healthy, nonsmoking, moderately trained men (age: 24 ± 3 yr, height: 178 ± 8 cm, and body weight: 77 ± 8 kg) volunteered to participate in the study. The included number of subjects was based on previous results (3) and a prestudy power analysis of the main outcome variables. Subjects were recruited among students at the Norwegian University of Science and Technology (Trondheim, Norway), and their reported general fitness level was confirmed by a treadmill maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$) test, revealing an aerobic power of 58 ± 5 ml·kg^{-1}·min^{-1}. However, participants were excluded if they had a history of sport-specific training of the forearm. Other exclusion criteria were any medical illness that would affect the muscular or vascular system, regular use of medications, having been through any form of surgery the last year, and previous history of deep venous thrombosis. The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics. Each subject gave written informed consent before participating in the study. All parts of the study were performed according to the Declaration of Helsinki.

Study design and timeline. All subjects completed an identical 2-day test procedure before and after 6 wk of MST (Fig. 1). The first test day started with assessment of forearm volume and muscle mass followed by an incremental forearm maximal work rate (WR_{max}) test, forearm strength tests, and finally a treadmill $\dot{V}O_{2max}$ test. After 1 day of rest, the subjects returned to the laboratory for catheter-insertion followed by a forearm work efficiency test as well as a WR_{max} test with blood gas measurements. As previous studies have documented that work efficiency is not altered by time and testing procedures (20, 53), we considered that repetitive insertions of catheters in the basilic vein, advanced to the positioning in the subclavian vein, could not be warranted by incorporation of a control group.

Treadmill $\dot{V}O_{2max}$. At baseline, as a measure of the subjects' general fitness level, a $\dot{V}O_{2max}$ test was included in this study. $\dot{V}O_{2max}$ data were collected with a Metamax II gas analyzer (Cortex Biophysik) during an incremental treadmill (Woodway PPS Med, Woodway) protocol where inclination was kept at 5% and speed was increased with 1 km·h^{-1}·min^{-1} until exhaustion in accordance with previous literature (62).

Forearm WR_{max}. WR_{max} was tested using a modified cable pulley machine with a custom-made handgrip-device, on which the subjects performed rhythmic dynamic contractions of the forearm flexor muscles while lying in the supine position with their hand fully extended at the level of their heart. The range of motion of the contraction was 5 cm, with a duty cycle of 1-s contraction and 1-s extension (0.5 Hz) with no rest between contractions. Subjects received audio stimuli from a metronome to indicate when to contract. WR_{max} was determined using an incremental protocol where the weight opposing the movement was increased 1 kg (0.49 W) after every 3 min of work until failure to complete the standardized contractions. The workload at failure was recorded as the subjects' WR_{max}, and time to exhaustion was noted based on the absolute time of the incremental test.

Forearm maximal strength and RFD. Maximal handgrip strength was determined as 1RM during a 5-cm range of motion from an extended to a contracted position. After two light-moderate warmup sets with five repetitions, the weight was gradually increased by increments of 2.5–5 kg depending on the relative ease the subject felt the contraction could be completed with. When subjects were incapable of completing the contraction, the previous weight that could be lifted successfully was noted as the 1RM. 1RM was achieved within six to eight lifts, and less than four lifts were carried out at weights of >80% of 1RM. Subsequent to the 1RM test, subjects carried out a RFD test using the same setup as for the maximal test. The weight was corresponding to 70% of the subjects 1RM, and force measurements were obtained from a force cell (model 620-1000M-F, Vishay Tedea-Huntleigh load cell) attached between the weights and the handgrip. Data collected at 2,000 Hz were analyzed using a ME6000-biomonitor and MegaWin-software (Mega Electronics, Kuopio, Finland). Subjects were instructed to perform this contraction as forcefully and quickly as possible. Emphasis was made in instructing the subjects not to use any other muscle groups than the forearm flexors to assist the lift. The best of three successful lifts were analyzed for RFD, in accordance with established procedure (54). RFD timeframes of 0–30 and 0–50 ms into the concentric muscle action, respectively, were calculated as Δforce/Δtime from a starting point 3% above baseline. The short movement and speed of the contraction resulted in several subjects reaching peak force within 100 ms. Consequently, RFD values over 0–50 ms were not analyzed. The highest force attained during RFD muscle contractions was noted as peak force.

Forearm anthropometry measurement. Forearm volume, fat content, and lean muscle mass was assessed by fluid displacement plethysmography (4) in combination with a skinfold caliper (Baty International). Muscle volume estimation from anthropometric mea-

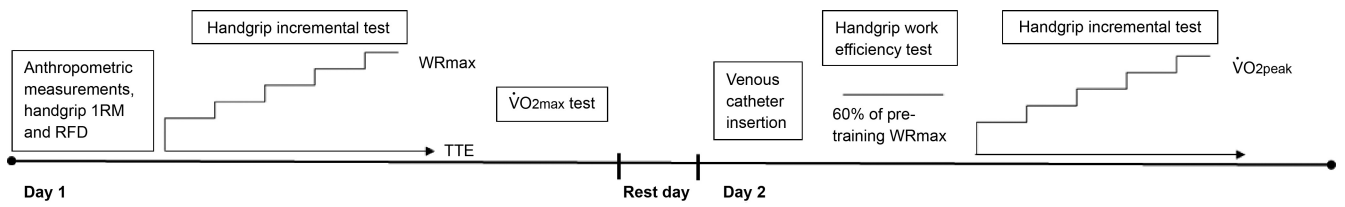

Fig. 1. Timeline for test days before and after 6 wk of maximal strength training (MST). 1RM, handgrip one repetition maximum; RFD, rate of force development; WR_{max}, maximal work rate; TTE, time to exhaustion; $\dot{V}O_{2max}$, whole body maximal oxygen consumption; $\dot{V}O_{2peak}$, peak oxygen consumption during forearm exercise.

surements has been compared with proton magnetic resonance imaging (^{1}H-MRI) and found to be a valid approach (30) and was calculated using the following equation in this study:

$$\text{muscle volume} = \text{forearm volume} \times 0.871 - (S - 0.04) \times 2^{-1} \times \text{length} \times (O_1 + O_2 + O_3) \times 3^{-1}$$

where 0.871 is to a factor for exclusion of bone tissue (33), S is skinfold thickness, and O is forearm circumference. Muscle mass was calculated assuming a muscle tissue density of 1.049 g/cm^3 (42). Additionally, forearm flexor muscle mass during isolated forearm handgrip exercise may be assumed to be ~53% of the total forearm muscle volume (48).

Subject preparation and blood gas measurements. When subjects returned to the laboratory for *day 2* of testing, a catheter was placed in the subclavian vein for blood gas measurements (10). A subclavian placement was considered preferable to control for all venous outflow from exercising muscle, especially important when aiming to detect training-induced differences from pretest to posttest. The insertion of the catheter was made in the basilic vein using the Seldinger technique (50) with a catheterization kit (Turbo-Ject PICC set power injectable, Cook Medical). Simultaneously, a B-mode ultrasound (M-Turbo; SonoSite) was used to verify the position of the basilic vein before and during insertion. Ultrasound was also used to verify guidewire advancement to and positioning in the subclavian vein and localization of confluence with the jugular veins. In addition, placement was controlled by X-ray imaging of the thorax (Oec fluorostar, GE Medical Systems, Salt Lake City, UT). Criteria for placement of the catheter lumen were distal to the inlet from the jugular veins and proximal enough to represent venous drainage from the whole arm. At the end of the pretest catheterization, the length of the catheter that was inside the vein was noted, from lumen to the insertion point. This length was used in conjunction with the imaging techniques to assure the same placement at posttest. Given the reasonable assumption of constant arterial oxygen content during small muscle mass work for healthy young individuals at sea level, 97% saturation was assumed for calculations of arterial oxygen content (Ca_{O_2}) (7, 14, 23, 52).

Blood flow measurements. Blood flow was measured in the proximal part of arteria brachialis using a Vivid E9 ultrasound scanner (GE Healthcare, Little Chalfont, UK) with a linear 4- to 12-MHz probe (GE 11L). A three-lead ECG was attached for the sake of time tracking. Simultaneous measurement of arterial diameter and blood velocity was enabled by the triplex functionality of the Vivid E9 system. Each recording was set to a timeframe of 16 s. Vessel diameter was calculated from the B-mode recording based on four frames with good image quality from each recording: two frames from the concentric contraction phase and two frames from the eccentric phase. In each of the four frames, the respective diameter was an average of four diameter measures. Diameter measurements from every frame were then averaged and used as brachial artery diameter for that 16-s recording. A pilot study revealed a low test-retest variability using this analyzing technique, with a Bland-Altman plot returning a 0.00-cm test-retest difference, upper and lower 2SD of ± 0.02 cm, and variation coefficients between 1% and 2% from rest to maximal exercise. In parallel with the B-mode recording, pulsed-wave Doppler was measured and used to calculate blood velocity. Retrograde blood velocity was shown as negative values, and time of retrograde velocity was measured from spectral Doppler intersection of the abscissa to the intersection where the value became positive again. The sample volume was fitted within the borders of the intimal layer of the vessel. The insonation angle of the Doppler beam was kept ≤60° to the direction of the vessel, and aliasing of blood velocity was avoided by sufficient adjustment of the scale of the spectral Doppler output. Time-averaged blood velocity (V_b) integrated from the spectral Doppler velocity time output was used in conjunction with average diameter to calculate blood flow as follows: blood flow = $[(\pi \times r^2) \times V_b] \times 60$ s/min.

From the venous catheter, during steady-state work, a blood sample was drawn in parallel to each ultrasound recording. Blood samples were drawn in dry lithium heparinized syringes (Line Draw, Smiths Medical) and immediately put on ice to conserve samples for analysis. All samples were analyzed within 30 min of collection using a blood gas analyzer (RapidLab 1265, Siemens Healthcare Diagnostics, Tarrytown, NY). Venous oxygen content (Cv_{O_2}) and Ca_{O_2} (in ml/dl) were calculated as follows: Cv_{O_2} and Ca_{O_2} = 1.34(Hb) × (So_2/100) + 0.003 × Po_2, where Hb is hemoglobin and So_2 is oxygen saturation. a-vO_{2diff} was further given as $Ca_{O_2} - Cv_{O_2}$. With the use of the Fick equation, $\dot{V}o_2$ was computed as the product of blood flow and a-vO_{2diff}. Lactate concentration was also analyzed from whole blood in the same blood gas samples.

Work efficiency. Work efficiency was assessed by setting a submaximal weight corresponding to 60% of the subjects WR_{max} at pretest in the modified handgrip pulley setup. The subject then performed rhythmic work for 6 min, and work efficiency data were collected within the final minute of this exercise period. In combination, a prior study (36) and a pilot study showed that blood gas and forearm blood flow measurements reached a plateau, defined as no change in $\dot{V}o_2$ over time (3), the final 2–3 min of the test. Position, contraction range of motion, and frequency were identical to that of the WR_{max} test. Between 5 and 6 min of work, two blood samples and two 16-s ultrasound recordings were made and averaged for the analysis. Simultaneously mean arterial blood pressure (MAP) was measured with beat-by-beat photoplethysmography on the fingers (Finapres Medical Systems, Amsterdam, The Netherlands) at the nonexercising hand, also placed at the level of the heart, while heart rate was measured with three-lead ECG. Exercise was terminated after 6 min of work. Work efficiency $\dot{V}o_2$ was averaged from the time points where blood flow and a-vO_{2diff} were measured. Importantly, the same absolute load that corresponded to 60% of pretraining WR_{max} was used to assess work efficiency also at posttest. Work efficiency was computed as follows: (external work accomplished/local energy expenditure) × 100. External work was given by the exercise load in kilograms, the range of motion, and the frequency. The local energy expenditure was given by the calculated forearm $\dot{V}o_2$ at steady state. In accordance with previous literature (24), external work and forearm energy expenditure were converted to kilocalories using a fixed conversion rate (49) before the calculation of work efficiency and expressed as a percentage. Forearm vascular conductance (FVC) was calculated based on the average of ultrasound recordings, and the average of blood pressure, in the last minute of the submaximal exercise test, and was computed as blood flow/MAP.

Also on the second test day, with the catheter in place, a second identical WR_{max} protocol was included in this study for determination of peak $\dot{V}o_2$ ($\dot{V}o_{2peak}$). During this test, Doppler-ultrasound recordings and blood samples were obtained at the end of each of the incremental 3-min steps. Approaching exhaustion, guided by information of time to exhaustion from the first WR_{max} test, in combination with feedback from subjects and visual signs of fatigue, a final set of recordings and samples were taken within the final 15 s of the test. $\dot{V}o_{2peak}$ was recorded as the highest measured $\dot{V}o_2$, and the protocol provided recordings for all increments. Mean capillary Po_2 and the corresponding muscle oxygen diffusing capacity at $\dot{V}o_{2peak}$ was calculated as previously described by Bohr integration and Fick's law of diffusion (43, 45).

Maximal strength training intervention. Subjects performed 6 wk of supervised training with 4 sessions/wk for an aimed target of 24 sessions in total during the intervention period. Training sessions consisted of strength training with four repetitions and four sets with focus on maximal mobilization of force in the concentric phase. Training was performed standing with the arm vertically positioned parallel to the body. The weights were attached to the mobile custom-made handgrip device that was used for the testing. The range of motion was 5 cm also for the strength training. Contractions were

Table 1. *Maximal forearm strength and rate of force development before and after 6 wk of maximal strength training*

	Pretest	Posttest
One repetition maximum, kg	49 ± 9	62 ± 10*
Rate of force development, N/s		
0−30 ms	957 ± 285	1,038 ± 329
0−50 ms	923 ± 224	1,086 ± 238*
Peak force, N	447 ± 75	471 ± 81
Time to peak force, s	0.095 ± 0.021	0.100 ± 0.015
Forearm muscle mass, g	833 ± 167	856 ± 181

Data are means ± SD; $n = 7$. *$P < 0.05$ vs. pretraining.

performed under the same criteria as for the 1RM and RFD tests. Training load corresponded to ~90% of the subjects' respective 1RM, and between sets there were 3 min of recovery. Load was increased if subjects were able to perform more than four correctly executed repetitions in their sets. All training sessions were monitored in the laboratory. Throughout the study period, subjects were encouraged to keep other physical activity routines constant.

Statistical analyses. IBM SPSS statistics software (version 21) was used for statistical analyses, and GraphPad Prism software (version 7.0) was used for graphic illustrations. Data were tested for normality by the Shapiro-Wilk test and visually by Q-Q plots. Changes from pretest to posttest were assessed by paired-sample *t*-tests. For all analyses, the level of significance was set as $P < 0.05$. For descriptive purposes, data are presented as means ± SD in text and tables, whereas figures depict means ± SE.

RESULTS

All subjects successfully completed all tests pretraining and posttraining. Participants performed 20 ± 1 of the planned 24 sessions over the 6-wk MST intervention period (83 ± 4% compliance). No difference in body weight, estimated forearm volume, or forearm muscle mass was observed from pre-MST to post-MST.

Forearm maximal strength and rate for force development. After MST, subjects improved their 1RM ($P = 0.001$) and RFD 30 ms ($P = 0.051$) and 50 ms ($P = 0.035$) into the contraction. During the RFD performance, no changes in peak force or time to reach peak force were observed after MST (Table 1).

Steady-state submaximal endurance performance. At the workload corresponding to 60% of the pretest WR_{max}, $\dot{V}O_2$ was (22 ± 19%) lower after MST ($P = 0.014$; Fig. 2*A*). In turn, work efficiency on this load exhibited a concomitant 35 ± 34% increase ($P = 0.048$; Fig. 2*B*). In relation to estimated forearm flexor muscle mass, $\dot{V}O_2$ was 7.2 ± 1.9 ml·100 g^{-1}·min^{-1} (pre) and 5.4 ± 1.5 ml·100 g^{-1}·min^{-1} (post), respectively. The reduction in submaximal $\dot{V}O_2$ was accompanied by a 19 ± 12% reduction in blood flow to the exercising muscle ($P = 0.004$; Fig. 2*C*), whereas no changes in a-vO_{2diff} (Fig. 2*D*), fractional O_2 extraction, lactate concentration in blood, or venous PO_2 were observed. The blood flow reduction was mediated by a reduced blood velocity ($P < 0.001$; Fig. 3*A*) while brachial artery diameter remained unchanged (Fig. 3*B*). The change in brachial artery blood velocity dynamics for a representative subject after MST is shown in Fig. 4. Retrograde blood flow remained unchanged after MST. However, the time when retrograde blood flow occurred, per recording, decreased ($P = 0.021$; Table 2). Moreover, FVC exhibited a MST-induced tendency to decrease (4.9 ± 0.8 to 4.2 ± 0.9 ml·min^{-1}·$mmHg^{-1}$, $P = 0.066$). No changes were observed for blood flow or FVC normalized to $\dot{V}O_2$. Central hemodynamics revealed that heart rate exhibited a reduction from 66 ± 4 to 59 ± 7 beats/min after MST ($P = 0.036$), whereas MAP remained unchanged from pre-MST (99 ± 7 mmHg) to post-MST (95 ± 12 mmHg). The MST-induced reduction in $\dot{V}O_2$ during submaximal work was also supported by data from the WR_{max} test, at least in part, on test *day 1*. The submaximal increments (*steps 1* and *2*) during this test resulted in a MST-induced reduction (2-kg increment: −2.78 ± 2.39

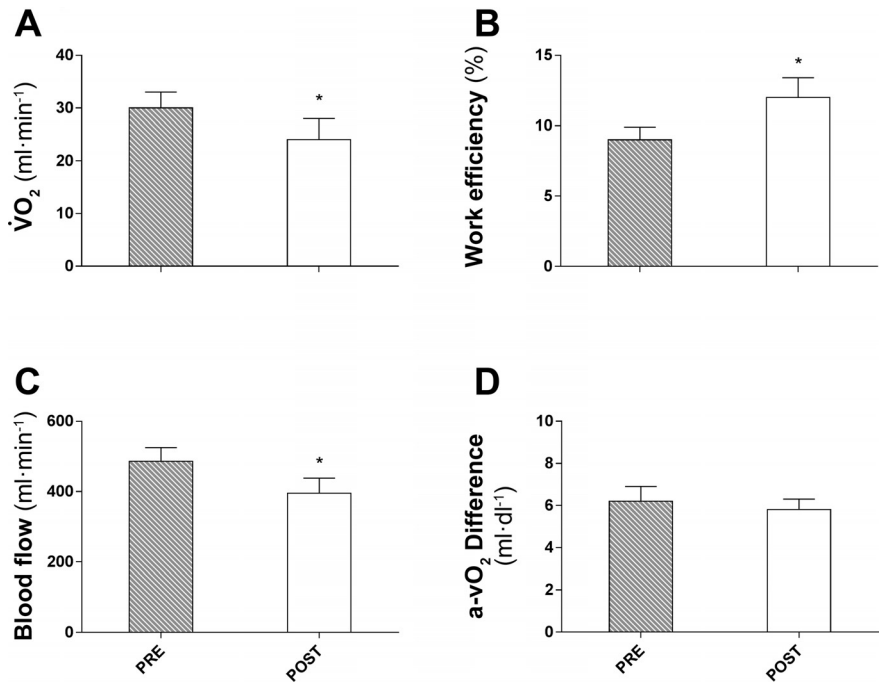

Fig. 2. Forearm oxygen consumption ($\dot{V}O_2$; *A*), work efficiency (*B*), brachial artery blood flow (*C*), and arteriovenous oxygen difference (a-vO_{2diff}; *D*) during dynamic handgrip exercise at fixed submaximal load, corresponding to 60% of pretest maximal work rate (WR_{max}), before and after 6 wk of maximal strength training (MST). Values are means ± SE; $n = 7$. *$P <$ 0.05 vs. pretraining.

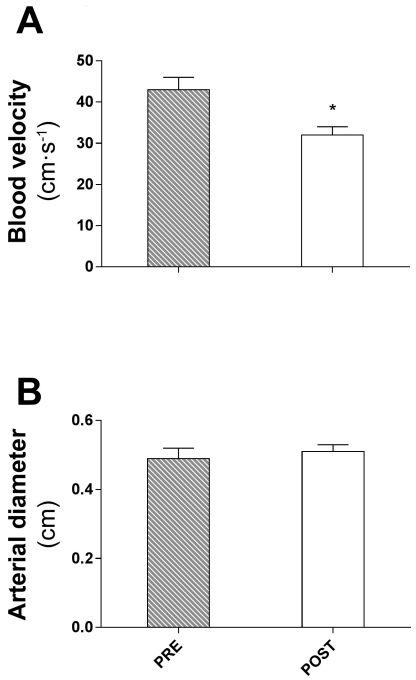

Fig. 3. Brachial artery blood flow derivates during 60% of maximal work rate (WR_{max}) before and after 6 wk of maximal strength training (MST). *A*: mean blood velocity. *B*: brachial artery diameter. Values are means ± SE; $n = 7$. *$P < 0.05$ vs. pretraining.

ml/min, $P = 0.022$) and tendency to reduction (3-kg increment: −4.94 ± 7.47 ml/min, $P = 0.131$) in $\dot{V}O_2$. No significant differences were seen for the associated blood flow and a-vO_{2diff}.

Table 2. *Alterations in peripheral hemodynamics and venous blood gas variables during submaximal exercise (60% of maximal work rate) before and after 6 wk of maximal strength training*

	Pretest	Posttest
Blood flow		
Antegrade, ml/min	458 ± 113	375 ± 123*
Retrograde, ml/min	27 ± 16	20 ± 16
Time with retrograde, ms	1,737 ± 615	1,238 ± 732*
Blood gas		
pH	7.37 ± 0.02	7.36 ± 0.01
Lactate concentration, mmol/l	1.7 ± 0.8	1.4 ± 0.4
P_{CO_2}, kPa	6.56 ± 0.45	6.71 ± 0.28
P_{O_2}, kPa	5.13 ± 0.74	5.13 ± 0.51
Hemoglobin, g/dl	14.9 ± 0.9	15.0 ± 0.9
Calculated arterial O_2 content, ml/dl	20.4 ± 1.2	20.5 ± 1.3
Calculated venous O_2 content, ml/dl	14.2 ± 2.8	14.3 ± 2.0

Data are means ± SD; $n = 7$. Time with retrograde, sum of time during 16 s of recording when spectral Doppler displayed negative velocity. *$P < 0.05$ vs. pretraining.

Maximal handgrip endurance performance. After MST, subjects exhibited an increase ($P = 0.018$) in time to exhaustion (17 ± 13%), and this was accompanied by an improved WR_{max} performance (3.3 ± 0.6 to 3.7 ± 0.8 W, $P = 0.045$). In contrast, $\dot{V}O_{2peak}$ did not increase from pretest to posttest. Albeit, at $\dot{V}O_{2peak}$ after MST, a-vO_{2diff} was lower (6.1 ± 1.7 to 4.8 ± 1.7 ml/dl, $P = 0.008$) and blood flow tended to increase (664 ± 300 to 765 ± 261 ml/min, $P = 0.100$). Venous blood gas also revealed an increased P_{O_2} (5.19 ± 0.57 to 5.69 ± 0.68 kPa, $P = 0.045$). Similarly, calculated mean capillary P_{O_2} tended to be higher at posttest (5.80 ± 0.62 to 6.25 ± 0.64 kPa, $P = 0.053$). However, muscle diffusive capacity and

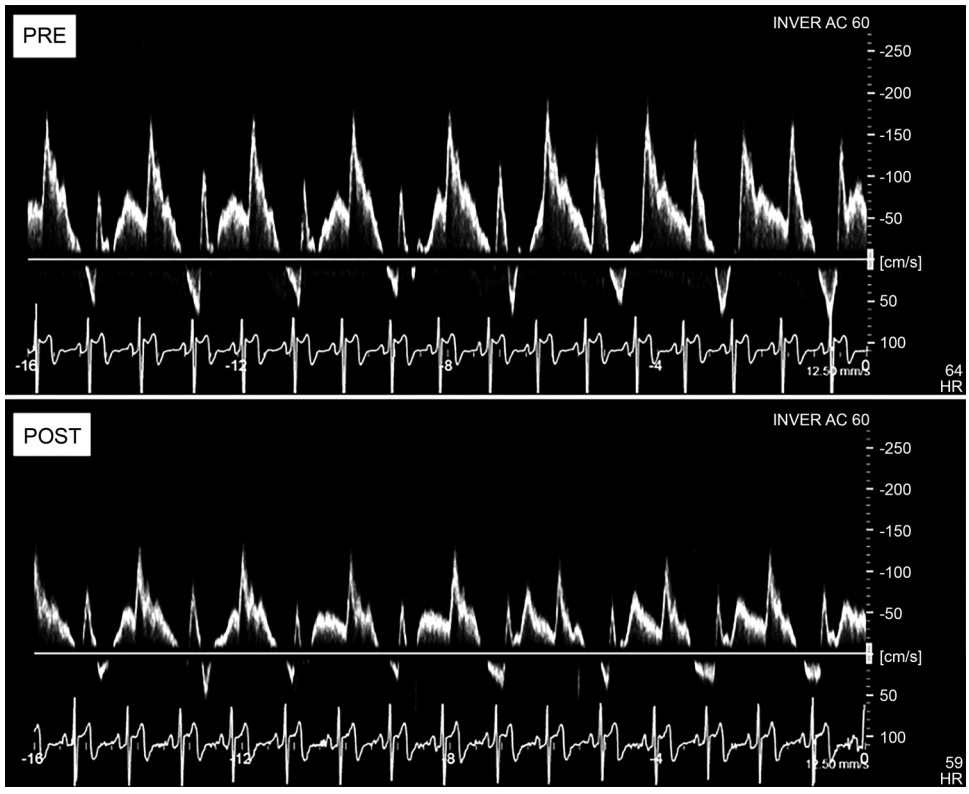

Fig. 4. Brachial artery blood velocity dynamics for a representative subject before and after 6 wk of maximal strength training (MST). Shown are two 16-s pulsed wave Doppler recordings during steady-state dynamic handgrip exercise corresponding to 60% of pretest maximal work rate (WR_{max}).

lactate concentration in blood sampled at $\dot{V}O_{2peak}$ were both unchanged after MST.

DISCUSSION

The main finding in the present study was that MST improved forearm muscle work efficiency at submaximal intensity, causing brachial artery blood flow to be reduced, whereas arm a-vO_{2diff} remained unaltered. In turn, the reduced conduit artery blood flow was achieved by a reduction in blood velocity, whereas the diameter remained unaltered. These findings indicate a similar regulation of limb blood flow and a-vO_{2diff}, in response to MST-induced work efficiency improvement, in upper extremities as that previously documented for lower extremities (3).

MST and work efficiency. As expected, in accordance with previous literature (17, 20, 37, 53), MST improved the muscle force-generating capacity in the present study. As a consequence, the $\dot{V}O_2$ cost during submaximal workloads was reduced and, concomitantly, work efficiency increased. Results of heretofore studies have typically documented a larger work efficiency effect size in upper (20, 21, 27, 56) compared with lower extremities (3, 53, 55), with the former ranging between 15% and 30% and the latter hovering at ~5%. Our data were in accordance with this, showing a reduced forearm flexor $\dot{V}O_2$ cost of ~20% after 6 wk of MST. The distinct limb-specific difference may, besides mathematically larger effects from small numbers, be explained by differences in training status between the upper and lower limbs. As the arms are typically more untrained and have also been documented to have a poor efficiency, even in healthy young individuals (26, 32), they are likely more susceptible for an improvement. Indeed, also after other training modalities, e.g., sprint interval training, work efficiency was observed to increase in arms but not legs (65).

Also in accordance with previous studies (20, 53, 55), our data showed that time to exhaustion increased, whereas $\dot{V}O_{2peak}$ remained unchanged, after MST. Although there is a close relationship between small muscle mass power output and $\dot{V}O_2$ (16, 36, 51), a mismatch has recently been demonstrated when approaching maximal intensity (36). This likely explains why, despite improvements in force-generating capacity and attenuated blood flow hindrance from muscle contractions, a greater $\dot{V}O_{2peak}$ was not evident after MST. Of note, however, is that the $\dot{V}O_{2peak}$ data should be interpreted with caution since only single blood draws were made and measurements near maximal effort were challenging.

Work efficiency, blood flow, and a-vO_{2diff}. Our data revealed that the increased skeletal muscle efficiency after MST led to a reduction in conduit artery blood flow, whereas a-vO_{2diff} remained unchanged. This is in contrast to a prior MST study (27) of the arms that concluded that the work efficiency improvements were independent of blood flow. However, by experimental design, arm $\dot{V}O_2$ was not directly measured in the study of Kemi et al. (27), limiting a direct comparison with our results. As pulmonary $\dot{V}O_2$ was observed to increase nonlinearly to arm blood flow, involvement of other muscles than the exercising biceps brachialis may have occurred in the study by Kemi et al. (27). On the contrary, the present study is in agreement with what appears to be the only other catheter-based study that has investigated MST and aerobic endurance (3). Although the study of Barrett-O'Keefe et al. (3) investigated the quadriceps of trained cyclists, the blood flow reduction was similar to what we observed in the forearm in the present study. This implies that the behavior of MST-induced effects on work efficiency may be limb and muscle mass independent. Although several metabolic and vascular differences exist between arms and legs, this may be unsurprising as the study of Barrett-O'Keefe et al. (3) documented that the reduction in pulmonary $\dot{V}O_2$ originated solely in the trained muscle bed. Thus, MST-induced improvements in work efficiency could cause similar alterations in, e.g., mechanic and metabolic afferent feedback from arm and leg skeletal muscle. The similar responses in the untrained forearm and trained quadriceps in these two studies also indicate that the matching of oxygen delivery with demand may be minimally affected by training status. Although it was recently shown that arm and untrained muscle is limited by the capacity of the mitochondria to consume oxygen (6, 13), a reduction in the demand for oxygen at submaximal intensities, as seen after MST, appears to be associated with oxygen delivery.

Recently, another study from our research group documented that blood flow was the regulating mechanism for acute $\dot{V}O_2$ increases in the forearm at moderate and high intensities (36). In fact, the oxygen extraction was similar for the different workloads. The present study is in accordance with the concept of blood flow as the key component responding to meet various oxygen demands in the forearm and expands the observations to include submaximal responses to meet MST-induced improvements in intramuscular efficiency. Considering the poor oxygen extraction in the arms (<70%) (5, 9), it may be unsurprising that the oxygen extraction is kept constant when the $\dot{V}O_2$ demand is reduced, as it seems somehow of an oxymoron to expect that the oxygen extraction would decline to an even lower level after training. Fractional oxygen extraction was even lower in the present study, likely due to mixing of blood from inactive muscle mass at the subclavian site of measurement. While this site of single outflow measurement may be well suited to detect training-induced differences, it may yield a poorer measure for absolute oxygen extraction in the forearm flexors. Indeed, measurements made in one of the outflow veins adjacent to the exercising forearm have documented an O_2 extraction of ~50–60% during handgrip exercise at 60% of WR_{max} (36). However, both the present study and the study of Nyberg et al. (36) revealed that oxygen extraction was similar in the transition from submaximal to maximal exercise. Proposed mechanisms for the poor oxygen extraction in arms have been inappropriate blood flow distribution, differences in capillary-to-fiber ratios, diffusion limitations, and mixing with blood from inactive regions (23). However, again, given the already very poor oxygen extraction, it seems counterintuitive that a reduced $\dot{V}O_2$ demand would lead to a further worsening of these factors. Rather, the blood flow appears to reflect alterations in the $\dot{V}O_2$ demand from the onset of exercise and with increasing intensity and would thus be expected to decrease in response to a lower relative intensity posttraining (36). Although the blood flow hindrance from muscle contractions is substantial in the forearm, perfusion in the relaxation periods between 60% WR_{max} muscle contractions is high. In fact, a threefold higher blood flow has been shown in the relaxation phase compared with mean blood flow from contraction-relaxation phases combined (36). As MST enhanced the muscle force-generating capacity in the present study,

shortening the time to develop the necessary force for muscle contractions and reducing the relative load (37), it led to a condition after training where the hindrance to forearm blood flow was reduced. Indeed, this was also evident at submaximal exercise as shorter periods of retrograde blood flow, which may have facilitated an oxygen delivery/$\dot{V}O_2$ relationship that benefited energy production from more efficient and fatigue resistant muscle fibers (18, 28).

The blood flow changes were achieved solely by blood velocity alterations in the present study. As a reduction of the conduit artery diameter would be disadvantageous for a realization of the blood flow potential between muscle contraction and lead to a reduced mean transit time, blood velocity may be the most appropriate component to respond to a lower metabolic demand. In addition, since MST minimally taxes the oxygen transporting organs, it is unlikely that the conduit artery diameter was directly influenced by the training. It is uncertain if this vascular MST-induced response was reflected further downstream from the conduit artery. However, blood lactate concentration, which may be interpreted as a local metabolite vasodilator, was unchanged, indicating that the more peripheral vessel responses were similar. Since lactate release was not directly measured in the present study, the contribution from glycolytic energy production cannot be excluded, but our data are in accordance with the observations in the quadriceps in the study of Barrett-O'Keefe et al. (3). Moreover, vascular conductance tended to decline and MAP remained unchanged, indicating higher vascular resistance after MST. This may, at least in part, be explained by less muscle mass being activated for work, possibly reducing vasodilatation in less active regions (29). Our observation of an unchanged MAP with training is in accordance with the study of Barrett-O'Keefe et al. (3), which also observed leg blood pressure to be unchanged after MST. Despite a lower maximal muscle mass-normalized vascular conductance in the arms compared with legs (8), the relative load was lower after MST in the present study. Since the vascular conductance decreases with relative intensity, the possible reduction during submaximal exercise falls into place.

Skeletal muscle adaptations. Strength training with maximal mobilization of force in the concentric phase is shown to enhance efferent neural drive to contracting muscle (57) and improve the force-velocity characteristics throughout the entire muscle recruitment spectrum (37). Although MST aims to target neural adaptations and does typically not alter body mass (3, 17, 21), it was recently documented that the training has the potential to increase the size and percentage of type II muscle fibers (61). However, in the study of Wang et al. (61), the size of type I fibers and the capillary-to-fiber ratio remained unchanged. Thus, during the submaximal forearm work in the present study, the required force for the standard submaximal work may have been shifted lower in the recruitment hierarchy, using a larger proportion of the more efficient type I fibers (11). Another previously suggested explanation (3) for the enhanced work efficiency may be the faster RFD after MST since this may have led to relatively shorter time in the less efficient force development phase compared with the more efficient force maintenance phase (46). Moreover, after MST, the involved muscle mass, including cocontraction from antagonists, may have been reduced and contributed to the improved work efficiency (38).

The $\dot{V}O_2$ slow component may also have been a potential contributor to the observed MST-induced $\dot{V}O_2$ reduction. Although $\dot{V}O_2$ appears to reach a plateau at 60% WR_{max} forearm exercise (36) and be below critical power if seen in relation to previous literature (25), a potential delay of steady state up to >15 min has been documented (41). Thus, the potential impact of the $\dot{V}O_2$ slow component on the improved work efficiency in the present study should not be excluded. Diminished perturbations to blood flow due to a lower relative load, evident by less time of retrograde blood velocity, may have generated conditions where the $\dot{V}O_2$ slow component was abated (41). Furthermore, the increase in WR_{max} and time to exhaustion suggests that the gradual development of fatigue due to loss of force-generating capacity during repeated submaximal contractions was deferred, blunting the slow increase in $\dot{V}O_2$ (59).

Both the contractile (conversion of ATP into mechanical work) and mitochondrial (conversion of chemical energy into ATP) efficiency (63) could have contributed to the increased work efficiency observed in the present study. Although no measurement conducted in the present investigation can detect alterations of these ATP-consuming processes, some speculations can be made. For instance, Ca^{2+} handling has been observed to account for as much as 30–40% of the total cost of muscle contraction (2). Recognizing that Ca^{2+} handling may be optimized in trained muscle (12, 15, 64), reduced Ca^{2+} leak, enhanced myofilament sensitivity to Ca^{2+}, and more efficient Ca^{2+} pumping may all have contributed to increased work efficiency after training. In addition, a tighter coupling of mitochondrial respiration has been reported in strength-trained muscle (47) and could thus be a contributing factor to the improved work efficiency after MST.

Handgrip peak aerobic capacity. In line with previous MST studies (3, 17, 53), $\dot{V}O_{2peak}$ in the preent study remained unchanged. However, also in accordance with previous literature (20, 31), WR_{max} and the time to exhaustion increased. A likely explanation for this finding is a shift in the power-duration relationship, allowing for an increased time to exhaustion (39). The two components of the Fick equation appeared, however, to counteract each other at $\dot{V}O_{2peak}$. Whereas a-vO_{2diff} decreased, blood flow tended to increase. The latter may have been caused by increased skin blood flow or by increased muscle blood flow in response to a higher workload. A higher blood flow to the exercising muscle may, in turn, possibly reduce capillary mean transit time and consequently a-vO_{2diff}. Albeit, MST did not change muscle diffusion capacity. However, this may be unsurprising as MST has been documented to not alter the capillary bed or increase the size of type I fibers (61). In contrast to MST, endurance training is well documented to improve arm $\dot{V}O_{2peak}$ and oxygen extraction (5).

Practical implications. MST has the potential to simultaneously improve muscle force-generating capacity and aerobic endurance and may be especially beneficial in the arms because of the relatively large hindrance of blood flow from muscle contractions (44). The MST-induced enhancement in maximal strength and ability to develop force rapidly can counteract this impact by reducing the relative load and thus mechanical blockade of muscle perfusion. The faster force development may also shorten the necessary time to develop a given contraction force and, as a consequence, lengthen periods with muscle perfusion between muscle contractions (37). In combi-

nation, the MST-induced enhancement in strength and endurance may yield a large potential for performance improvement in sports where arms are greatly involved, such as rowing, cross-country skiing, rock climbing, and swimming. Moreover, it may also have clinical value for individuals with small muscle mass limitations to oxygen transport or disabilities that require them to rely on their arms to generate propulsion during daily locomotion. Strength training with high intensity, as carried out during MST, has also been documented to have a protective effect against loss of neural function (58) and type II fibers (1, 61). Of note, MST has previously also been safely administered in frail patient populations (19, 22, 34, 60). Ultimately, MST may be used in a concurrent training intervention in combination with aerobic endurance training.

Study limitations. A direct measurement of arterial blood gas may have been used to calculate Ca_{O_2} in the present study. However, given that it was unlikely that arterial oxygen saturation would fall during small muscle mass handgrip exercise in normoxia (7), we felt that this additional invasive procedure was not warranted. Yet, a simple, noninvasive method (e.g., oximeter) may have strengthened this assumption. The study would likely also have benefited from more frequent $\dot{V}O_2$ measurements with regard to information of how $\dot{V}O_2$sc may have influenced the work efficiency improvement. Although the sample size was sufficient to detect differences for the main variables of our hypothesis, some of the secondary outcome measures (e.g., vascular conductance) seem to be slightly underpowered. Finally, the $\dot{V}O_{2max}$ protocol, used to determine the general fitness level of the participants, would have benefitted from a verification phase in accordance with the latest American Physiological Society standards (40).

Conclusions. The present study revealed that MST-induced improvements in work efficiency in the forearm lead to reductions in blood flow and not a-vO_{2diff}. This is consistent with the concept of forearm blood flow as the component adapting to meet exercise-induced changes in $\dot{V}O_2$ demand. The results imply that MST may be particularly relevant in arms for performance or therapeutic purposes, not only because it has the potential to improve work efficiency but also because the improved force-generating capacity can attenuate the substantial blood flow hindrance from muscle contractions during exercise.

GRANTS

This work was funded by the Norwegian University of Science and Technology as well as Molde University College.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

O.K.B. and E.W. conceived and designed research; O.K.B., S.K.N., T.M.W., and E.W. performed experiments; O.K.B., S.K.N., T.M.W., and E.W. analyzed data; O.K.B., S.K.N., and E.W. interpreted results of experiments; O.K.B. and E.W. prepared figures; O.K.B. drafted manuscript; O.K.B., S.K.N., and E.W. edited and revised manuscript; O.K.B., S.K.N., T.M.W., and E.W. approved final version of manuscript.

REFERENCES

1. **Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjaer M.** Role of the nervous system in sarcopenia and muscle atrophy with aging: strength training as a countermeasure. *Scand J Med Sci Sports* 20: 49–64, 2010. doi:10.1111/j.1600-0838.2009.01084.x.
2. **Barclay CJ, Woledge RC, Curtin NA.** Energy turnover for Ca^{2+} cycling in skeletal muscle. *J Muscle Res Cell Motil* 28: 259–274, 2007. doi:10.1007/s10974-007-9116-7.
3. **Barrett-O'Keefe Z, Helgerud J, Wagner PD, Richardson RS.** Maximal strength training and increased work efficiency: contribution from the trained muscle bed. *J Appl Physiol* 113: 1846–1851, 2012. doi:10.1152/japplphysiol.00761.2012.
4. **Boland R, Adams R.** Development and evaluation of a precision forearm and hand volumeter and measuring cylinder. *J Hand Ther* 9: 349–358, 1996.
5. **Boushel R, Ara I, Gnaiger E, Helge JW, González-Alonso J, Munck-Andersen T, Sondergaard H, Damsgaard R, van Hall G, Saltin B, Calbet JA.** Low-intensity training increases peak arm $\dot{V}O_2$ by enhancing both convective and diffusive O_2 delivery. *Acta Physiol (Oxf)* 211: 122–134, 2014. doi:10.1111/apha.12258.
6. **Boushel R, Gnaiger E, Calbet JA, Gonzalez-Alonso J, Wright-Paradis C, Sondergaard H, Ara I, Helge JW, Saltin B.** Muscle mitochondrial capacity exceeds maximal oxygen delivery in humans. *Mitochondrion* 11: 303–307, 2011. doi:10.1016/j.mito.2010.12.006.
7. **Boushel R, Pott F, Madsen P, Rådegran G, Nowak M, Quistorff B, Secher N.** Muscle metabolism from near infrared spectroscopy during rhythmic handgrip in humans. *Eur J Appl Physiol Occup Physiol* 79: 41–48, 1998. doi:10.1007/s004210050471.
8. **Calbet JA, González-Alonso J, Helge JW, Søndergaard H, Munch-Andersen T, Saltin B, Boushel R.** Central and peripheral hemodynamics in exercising humans: leg vs arm exercise. *Scand J Med Sci Sports* 25, *Suppl* 4: 144–157, 2015. doi:10.1111/sms.12604.
9. **Calbet JA, Holmberg HC, Rosdahl H, van Hall G, Jensen-Urstad M, Saltin B.** Why do arms extract less oxygen than legs during exercise? *Am J Physiol Regul Integr Comp Physiol* 289: R1448–R1458, 2005. doi:10.1152/ajpregu.00824.2004.
10. **Calbet JA, Jensen-Urstad M, van Hall G, Holmberg HC, Rosdahl H, Saltin B.** Maximal muscular vascular conductances during whole body upright exercise in humans. *J Physiol* 558: 319–331, 2004. doi:10.1113/jphysiol.2003.059287.
11. **Coyle EF, Sidossis LS, Horowitz JF, Beltz JD.** Cycling efficiency is related to the percentage of type I muscle fibers. *Med Sci Sports Exerc* 24: 782–788, 1992. doi:10.1249/00005768-199207000-00008.
12. **Ferreira JC, Bacurau AV, Bueno CR Jr, Cunha TC, Tanaka LY, Jardim MA, Ramires PR, Brum PC.** Aerobic exercise training improves Ca^{2+} handling and redox status of skeletal muscle in mice. *Exp Biol Med (Maywood)* 235: 497–505, 2010. doi:10.1258/ebm.2009.009165.
13. **Gifford JR, Garten RS, Nelson AD, Trinity JD, Layec G, Witman MA, Weavil JC, Mangum T, Hart C, Etheredge C, Jessop J, Bledsoe A, Morgan DE, Wray DW, Rossman MJ, Richardson RS.** Symmorphosis and skeletal muscle $\dot{V}O_{2max}$: in vivo and in vitro measures reveal differing constraints in the exercise-trained and untrained human. *J Physiol* 594: 1741–1751, 2016. doi:10.1113/JP271229.
14. **Goldberg S, Buhbut E, Mimouni FB, Joseph L, Picard E.** Effect of moderate elevation above sea level on blood oxygen saturation in healthy young adults. *Respiration* 84: 207–211, 2012. doi:10.1159/000336554.
15. **Haram PM, Kemi OJ, Lee SJ, Bendheim MO, Al-Share QY, Waldum HL, Gilligan LJ, Koch LG, Britton SL, Najjar SM, Wisløff U.** Aerobic interval training vs. continuous moderate exercise in the metabolic syndrome of rats artificially selected for low aerobic capacity. *Cardiovasc Res* 81: 723–732, 2009. doi:10.1093/cvr/cvn332.
16. **Hartling OJ, Kelbaek H, Gjørup T, Schibye B, Klausen K, Trap-Jensen J.** Forearm oxygen uptake during maximal forearm dynamic exercise. *Eur J Appl Physiol Occup Physiol* 58: 466–470, 1989. doi:10.1007/BF02330698.
17. **Heggelund J, Fimland MS, Helgerud J, Hoff J.** Maximal strength training improves work economy, rate of force development and maximal strength more than conventional strength training. *Eur J Appl Physiol* 113: 1565–1573, 2013. doi:10.1007/s00421-013-2586-y.
18. **Heinonen I, Koga S, Kalliokoski KK, Musch TI, Poole DC.** Heterogeneity of muscle blood flow and metabolism: influence of exercise, aging, and disease states. *Exerc Sport Sci Rev* 43: 117–124, 2015. doi:10.1249/JES.0000000000000044.
19. **Hill TR, Gjellesvik TI, Moen PM, Tørhaug T, Fimland MS, Helgerud J, Hoff J.** Maximal strength training enhances strength and functional performance in chronic stroke survivors. *Am J Phys Med Rehabil* 91: 393–400, 2012. doi:10.1097/PHM.0b013e31824ad5b8.

20. **Hoff J, Gran A, Helgerud J.** Maximal strength training improves aerobic endurance performance. *Scand J Med Sci Sports* 12: 288–295, 2002. doi:10.1034/j.1600-0838.2002.01140.x.
21. **Hoff J, Helgerud J, Wisløff U.** Maximal strength training improves work economy in trained female cross-country skiers. *Med Sci Sports Exerc* 31: 870–877, 1999. doi:10.1097/00005768-199906000-00016.
22. **Hoff J, Tjønna AE, Steinshamn S, Høydal M, Richardson RS, Helgerud J.** Maximal strength training of the legs in COPD: a therapy for mechanical inefficiency. *Med Sci Sports Exerc* 39: 220–226, 2007. doi:10.1249/01.mss.0000246989.48729.39.
23. **Hughson RL, Shoemaker JK, Tschakovsky ME, Kowalchuk JM.** Dependence of muscle $\dot{V}O_2$ on blood flow dynamics at onset of forearm exercise. *J Appl Physiol* 81: 1619–1626, 1996. doi:10.1152/jappl.1996.81.4.1619.
24. **Husby VS, Helgerud J, Bjørgen S, Husby OS, Benum P, Hoff J.** Early postoperative maximal strength training improves work efficiency 6-12 months after osteoarthritis-induced total hip arthroplasty in patients younger than 60 years. *Am J Phys Med Rehabil* 89: 304–314, 2010. doi:10.1097/PHM.0b013e3181cf5623.
25. **Jones AM, Vanhatalo A, Burnley M, Morton RH, Poole DC.** Critical power: implications for determination of V̇O2max and exercise tolerance. *Med Sci Sports Exerc* 42: 1876–1890, 2010. doi:10.1249/MSS.0b013e3181d9cf7f.
26. **Kang J, Robertson RJ, Goss FL, Dasilva SG, Suminski RR, Utter AC, Zoeller RF, Metz KF.** Metabolic efficiency during arm and leg exercise at the same relative intensities. *Med Sci Sports Exerc* 29: 377–382, 1997. doi:10.1097/00005768-199703000-00013.
27. **Kemi OJ, Rognmo O, Amundsen BH, Stordahl S, Richardson RS, Helgerud J, Hoff J.** One-arm maximal strength training improves work economy and endurance capacity but not skeletal muscle blood flow. *J Sports Sci* 29: 161–170, 2011. doi:10.1080/02640414.2010.529454.
28. **Koga S, Rossiter HB, Heinonen I, Musch TI, Poole DC.** Dynamic heterogeneity of exercising muscle blood flow and O_2 utilization. *Med Sci Sports Exerc* 46: 860–876, 2014. doi:10.1249/MSS.0000000000000178.
29. **Laaksonen MS, Kalliokoski KK, Kyröläinen H, Kemppainen J, Teräs M, Sipilä H, Nuutila P, Knuuti J.** Skeletal muscle blood flow and flow heterogeneity during dynamic and isometric exercise in humans. *Am J Physiol Heart Circ Physiol* 284: H979–H986, 2003. doi:10.1152/ajpheart.00714.2002.
30. **Layec G, Venturelli M, Jeong EK, Richardson RS.** The validity of anthropometric leg muscle volume estimation across a wide spectrum: from able-bodied adults to individuals with a spinal cord injury. *J Appl Physiol* 116: 1142–1147, 2014. doi:10.1152/japplphysiol.01120.2013.
31. **Loveless DJ, Weber CL, Haseler LJ, Schneider DA.** Maximal leg-strength training improves cycling economy in previously untrained men. *Med Sci Sports Exerc* 37: 1231–1236, 2005. doi:10.1249/01.mss.0000170071.33880.f8.
32. **Marais G, Dupont L, Maillet M, Weissland T, Vanvelcenaher J, Pelayo P.** Cardiorespiratory and efficiency responses during arm and leg exercises with spontaneously chosen crank and pedal rates. *Ergonomics* 45: 631–639, 2002. doi:10.1080/00140130210151821.
33. **Maughan RJ, Watson JS, Weir J.** The relative proportions of fat, muscle and bone in the normal human forearm as determined by computed tomography. *Clin Sci* 66: 683–689, 1984.
34. **Mosti MP, Kaehler N, Stunes AK, Hoff J, Syversen U.** Maximal strength training in postmenopausal women with osteoporosis or osteopenia. *J Strength Cond Res* 27: 2879–2886, 2013. doi:10.1519/JSC.0b013e318280d4e2.
35. **Nishiyama SK, Walter Wray D, Berkstresser K, Ramaswamy M, Richardson RS.** Limb-specific differences in flow-mediated dilation: the role of shear rate. *J Appl Physiol* 103: 843–851, 2007. doi:10.1152/japplphysiol.00273.2007.
36. **Nyberg SK, Berg OK, Helgerud J, Wang E.** Blood flow regulation and oxygen uptake during high intensity forearm exercise. *J Appl Physiol* 122: 907−917, 2017. doi:10.1152/japplphysiol.00983.2016.
37. **Østerås H, Helgerud J, Hoff J.** Maximal strength-training effects on force-velocity and force-power relationships explain increases in aerobic performance in humans. *Eur J Appl Physiol* 88: 255–263, 2002. doi:10.1007/s00421-002-0717-y.
38. **Ploutz LL, Tesch PA, Biro RL, Dudley GA.** Effect of resistance training on muscle use during exercise. *J Appl Physiol* 76: 1675–1681, 1994. doi:10.1152/jappl.1994.76.4.1675.
39. **Poole DC, Burnley M, Vanhatalo A, Rossiter HB, Jones AM.** Critical power: an important fatigue threshold in exercise physiology. *Med Sci Sports Exerc* 48: 2320–2334, 2016. doi:10.1249/MSS.0000000000000939.
40. **Poole DC, Jones AM.** Measurement of the maximum oxygen uptake $\dot{V}O_{2max}$:$\dot{V}O_{2peak}$ is no longer acceptable. *J Appl Physiol* 122: 997–1002, 2017. doi:10.1152/japplphysiol.01063.2016.
41. **Poole DC, Jones AM.** Oxygen uptake kinetics. *Compr Physiol* 2: 933–996, 2012.10.1002/cphy.c100072.
42. **Radegran G, Blomstrand E, Saltin B.** Peak muscle perfusion and oxygen uptake in humans: importance of precise estimates of muscle mass. *J Appl Physiol* 87: 2375–2380, 1999. doi:10.1152/jappl.1999.87.6.2375.
43. **Richardson RS, Knight DR, Poole DC, Kurdak SS, Hogan MC, Grassi B, Wagner PD.** Determinants of maximal exercise $\dot{V}O_2$ during single leg knee-extensor exercise in humans. *Am J Physiol Heart Circ Physiol* 268: H1453–H1461, 1995. doi:10.1152/ajpheart.1995.268.4.H1453.
44. **Robergs RA, Icenogle MV, Hudson TL, Greene ER.** Temporal inhomogeneity in brachial artery blood flow during forearm exercise. *Med Sci Sports Exerc* 29: 1021–1027, 1997. doi:10.1097/00005768-199708000-00006.
45. **Roca J, Hogan MC, Story D, Bebout DE, Haab P, Gonzalez R, Ueno O, Wagner PD.** Evidence for tissue diffusion limitation of $\dot{V}O_{2max}$ in normal humans. *J Appl Physiol* 67: 291–299, 1989. doi:10.1152/jappl.1989.67.1.291.
46. **Russ DW, Elliott MA, Vandenborne K, Walter GA, Binder-Macleod SA.** Metabolic costs of isometric force generation and maintenance of human skeletal muscle. *Am J Physiol Endocrinol Metab* 282: E448–E457, 2002. doi:10.1152/ajpendo.00285.2001.
47. **Salvadego D, Domenis R, Lazzer S, Porcelli S, Rittweger J, Rizzo G, Mavelli I, Simunic B, Pisot R, Grassi B.** Skeletal muscle oxidative function in vivo and ex vivo in athletes with marked hypertrophy from resistance training. *J Appl Physiol* 114: 1527–1535, 2013. doi:10.1152/japplphysiol.00883.2012.
48. **Sanchís-Moysi J, Idoate F, Olmedillas H, Guadalupe-Grau A, Alayón S, Carreras A, Dorado C, Calbet JA.** The upper extremity of the professional tennis player: muscle volumes, fiber-type distribution and muscle strength. *Scand J Med Sci Sports* 20: 524–534, 2010. doi:10.1111/j.1600-0838.2009.00969.x.
49. **Scott C.** Misconceptions about aerobic and anaerobic energy expenditure. *J Int Soc Sports Nutr* 2: 32–37, 2005. doi:10.1186/1550-2783-2-2-32.
50. **Seldinger SI.** Catheter replacement of the needle in percutaneous arteriography; a new technique. *Acta Radiol* 39: 368–376, 1953. doi:10.3109/00016925309136722.
51. **Shephard RJ, Bouhlel E, Vandewalle H, Monod H.** Muscle mass as a factor limiting physical work. *J Appl Physiol* 64: 1472–1479, 1988. doi:10.1152/jappl.1988.64.4.1472.
52. **Siggaard-Andersen O, Wimberley PD, Fogh-Andersen N, Gøthgen IH.** Arterial oxygen status determined with routine pH/blood gas equipment and multi-wavelength hemoximetry: reference values, precision, and accuracy. *Scand J Clin Lab Invest Suppl* 203: 57–66, 1990. doi:10.3109/00365519009087492.
53. **Støren O, Helgerud J, Støa EM, Hoff J.** Maximal strength training improves running economy in distance runners. *Med Sci Sports Exerc* 40: 1087–1092, 2008. doi:10.1249/MSS.0b013e318168da2f.
54. **Suetta C, Aagaard P, Magnusson SP, Andersen LL, Sipila S, Rosted A, Jakobsen AK, Duus B, Kjaer M.** Muscle size, neuromuscular activation, and rapid force characteristics in elderly men and women: effects of unilateral long-term disuse due to hip-osteoarthritis. *J Appl Physiol* 102: 942–948, 2007. doi:10.1152/japplphysiol.00067.2006.
55. **Sunde A, Støren O, Bjerkaas M, Larsen MH, Hoff J, Helgerud J.** Maximal strength training improves cycling economy in competitive cyclists. *J Strength Cond Res* 24: 2157–2165, 2010. doi:10.1519/JSC.0b013e3181aeb16a.
56. **Tørhaug T, Brurok B, Hoff J, Helgerud J, Leivseth G.** The effect from maximal bench press strength training on work economy during wheelchair propulsion in men with spinal cord injury. *Spinal Cord* 54: 838–842, 2016. doi:10.1038/sc.2016.27.
57. **Unhjem R, Lundestad R, Fimland MS, Mosti MP, Wang E.** Strength training-induced responses in older adults: attenuation of descending neural drive with age. *Age (Dordr)* 37: 9784, 2015. doi:10.1007/s11357-015-9784-y.
58. **Unhjem R, Nygard M, van den Hoven LT, Sidhu SK, Hoff J, Wang E.** Lifelong strength training mitigates the age-related decline in efferent drive. *J Appl Physiol* 121: 415–423, 2016. doi:10.1152/japplphysiol.00117.2016.

59. **Vollestad NK, Wesche J, Sejersted OM.** Gradual increase in leg oxygen uptake during repeated submaximal contractions in humans. *J Appl Physiol* 68: 1150–1156, 1990. doi:10.1152/jappl.1990.68.3.1150.
60. **Wang E, Helgerud J, Loe H, Indseth K, Kaehler N, Hoff J.** Maximal strength training improves walking performance in peripheral arterial disease patients. *Scand J Med Sci Sports* 20: 764–770, 2010. doi:10.1111/j.1600-0838.2009.01014.x.
61. **Wang E, Nyberg SK, Hoff J, Zhao J, Leivseth G, Tørhaug T, Husby OS, Helgerud J, Richardson RS.** Impact of maximal strength training on work efficiency and muscle fiber type in the elderly: Implications for physical function and fall prevention. *Exp Gerontol* 91: 64–71, 2017. doi:10.1016/j.exger.2017.02.071.
62. **Wang E, Solli GS, Nyberg SK, Hoff J, Helgerud J.** Stroke volume does not plateau in female endurance athletes. *Int J Sports Med* 33: 734–739, 2012. doi:10.1055/s-0031-1301315.
63. **Whipp BJ, Wasserman K.** Efficiency of muscular work. *J Appl Physiol* 26: 644–648, 1969. doi:10.1152/jappl.1969.26.5.644.
64. **Zampieri S, Pietrangelo L, Loefler S, Fruhmann H, Vogelauer M, Burggraf S, Pond A, Grim-Stieger M, Cvecka J, Sedliak M, Tirpáková V, Mayr W, Sarabon N, Rossini K, Barberi L, De Rossi M, Romanello V, Boncompagni S, Musarò A, Sandri M, Protasi F, Carraro U, Kern H.** Lifelong physical exercise delays age-associated skeletal muscle decline. *J Gerontol A Biol Sci Med Sci* 70: 163–173, 2015. doi:10.1093/gerona/glu006.
65. **Zinner C, Morales-Alamo D, Ørtenblad N, Larsen FJ, Schiffer TA, Willis SJ, Gelabert-Rebato M, Perez-Valera M, Boushel R, Calbet JA, Holmberg HC.** The physiological mechanisms of performance enhancement with sprint interval training differ between the upper and lower extremities in humans. *Front Physiol* 7: 426, 2016. doi:10.3389/fphys.2016.00426.