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M. L. Armstrong, A. K. Dua and C. L. Murrant

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L. F. Ferreira, A. J. Harper and T. J. Barstow

J Appl Physiol, March 1, 2006; 100 (3): 817-825.

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J. W. G. E. VanTeeffelen and S. S. Segal

Am J Physiol Heart Circ Physiol, January 1, 2006; 290 (1): H119-H127.

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Muscle blood flow at onset of dynamic exercise in humans

G. RÅDEGRAN AND B. SALTIN

Copenhagen Muscle Research Centre, Rigshospitalet, DK-2200 Copenhagen N, Denmark

Rådegran, G., and B. Saltin. Muscle blood flow at onset of dynamic exercise in humans. *Am. J. Physiol.* 274 (*Heart Circ. Physiol.* 43): H314–H322, 1998.—To evaluate the temporal relationship between blood flow, blood pressure, and muscle contractions, we continuously measured femoral arterial inflow with ultrasound Doppler at onset of passive exercise and voluntary, one-legged, dynamic knee-extensor exercise in humans. Blood velocity and inflow increased ($P < 0.006$) with the first relaxation of passive and voluntary exercise, whereas the arterial-venous pressure difference was unaltered [$P =$ not significant (NS)]. During steady-state exercise, and with arterial pressure as a superimposed influence, blood velocity was affected by the muscle pump, peaking ($P < 0.001$) at $\sim 2.5 \pm 0.3$ m/s as the relaxation coincided with peak systolic arterial blood pressure; blood velocity decreased ($P < 0.001$) to 44.2 ± 8.6 and $28.5 \pm 5.5\%$ of peak velocity at the second dirotic and diastolic blood pressure notches, respectively. Mechanical hindrance occurred ($P < 0.001$) during the contraction phase at blood pressures less than or equal to that at the second dirotic notch. The increase in blood flow (Q) was characterized by a one-component ($\sim 15\%$ of peak power output), two-component ($\sim 40\text{--}70\%$ of peak power output), or three-component exponential model ($\geq 75\%$ of peak power output), where $Q(t) = Q_{\text{passive}} + \Delta Q_1 \cdot [1 - e^{-(t - TD_1/\tau_1)}] + \Delta Q_2 \cdot [1 - e^{-(t - TD_2/\tau_2)}] + \Delta Q_3 \cdot [1 - e^{-(t - TD_3/\tau_3)}]$; Q_{passive} , the blood flow during passive leg movement, equals 1.17 ± 0.11 l/min; TD is the onset latency; τ is the time constant; ΔQ is the magnitude of blood flow rise; and subscripts 1–3 refer to the first, second, and third components of the exponential model, respectively. The time to reach 50% of the difference between passive and voluntary asymptotic blood flow was $\sim 2.2\text{--}8.9$ s. The blood flow leveled off after $\sim 10\text{--}150$ s, related to the power outputs. It is concluded that the elevation in blood flow with the first duty cycle(s) is due to muscle mechanical factors, but vasodilators initiate a more potent amplification within the second to fourth contraction.

blood pressure; muscle pump; intramuscular pressure; vasodilatation

SKELETAL MUSCLE BLOOD FLOW increases markedly at initiation of voluntary contractions to make the oxygen delivery meet the regionally elevated metabolic demands (17, 22, 28, 29). However, despite more than a century of research, the exact time course of the increase in muscle blood flow at onset of intense dynamic exercise in humans is still unknown, as the techniques for measuring blood flow have either had unsatisfactory temporal resolution or have at best been semiquantitative (2, 4, 5, 8, 11, 27). An ultrasound Doppler has previously been utilized at the onset of, and during, intermittent static contractions of the quadriceps muscle to detect, on a beat-by-beat basis, a rapid increase in blood velocity (22, 28, 29). However, the inherent variability of this sampling procedure, due

to the temporal dissociation between the kicking duty cycle (muscular contraction-relaxation phases) and the cardiac cycle (28, 29), limits the possibility of following the precise transitional changes in blood velocity and flow. In addition, these studies were not designed to investigate the exact time course and the magnitude of increase in blood flow in relation to the intensity of dynamic work. Such data are of value not only to examine how quickly regional blood flow and thus oxygen delivery matches the energy demand after onset of exercise but also to identify the factors that may induce the hyperemia, and especially their time restraints. This is now possible by sampling the blood velocity continuously with an ultrasound Doppler and estimating the blood flow in relation to each kicking duty cycle (16).

It has been suggested that the muscle pump during muscular contractions promotes muscle blood flow by squeezing the blood out of the venous capacitance vessels (15), thereby inducing a lowering of the venous pressure (P_v) and a gain in the pressure gradient ($\Delta P = P_a - P_v$, where P_a is the arterial pressure) across the vascular bed (6), a pressure gradient that, in this context, along with the vascular conductance (VC), determines the arterial inflow ($Q_a = \Delta P \times VC$). This pressure gradient has furthermore been suggested to be enhanced by a negative venular pressure, induced on muscle relaxation by the pulling open of the veins attached to the surrounding tissue (13). Thus, indirectly, the muscle pump also enhances the venous return by promoting the propulsion of blood out of the muscle (3, 4, 6, 7, 13, 15, 21, 24, 26). Moreover, the extent of the effect of the muscle pump depends on the force, frequency, and duration of the muscle contractions. The force determines the compression of the vasculature and degree of venous emptying, whereas the frequency and duration determine the extent of venous refilling (13). However, in this context it should be noted that the muscle contractions may also impose a significant mechanical hindrance to the arterial inflow, where the intramuscular pressure may rise to a level at which the resistance vessels collapse. Recently, it was also proposed that the muscle pump may promote a part of the sudden initial rise in blood flow at onset of exercise, before a further metabolic vasodilatation (21, 26). However, the precise temporal relationship between the arterial blood velocity (inflow) and the variations in intramuscular, arterial, and venous blood pressure has not been described.

To explore these questions, two different experiments were performed. In the first, the temporal course of the initial rise in blood flow was characterized at onset of dynamic muscle contractions at different intensities. In the second, the role and potency of the muscle mechani-

cal factors were studied at onset of exercise at one of these intensities by investigating the temporal relationship between the arterial blood velocity and the fluctuations in intramuscular, arterial, and venous pressure.

METHODS

Subjects

Fourteen healthy male volunteers with a mean age of 26.4 ± 1.0 (SE) yr (range 21–31 yr), height of 182.2 ± 1.4 cm (range 174.3–192.5 cm), and body weight of 80.2 ± 2.0 kg (range 71.0–98.1 kg) were divided into two homogeneous groups that participated in the two different experimental protocols. The mean quadriceps muscle mass, as estimated from anthropometric estimates (2, 10) with muscle insertion points measured from patella to os pubis, was 3.15 ± 0.18 kg (range 2.68–3.99 kg) for the seven subjects in *protocol I* and 2.98 ± 0.07 kg (range 2.77–3.27 kg) for the seven subjects in *protocol II*. The subjects who volunteered to participate in this study were informed about the experimental procedure and its potential risks and discomfort and were told that they could withdraw at any time without any consequences. They were allowed to participate after signed informed consent was received. The experiments were carried out with the approval of the Ethical Committees of Copenhagen and Fredriksberg (KF-01–013/96).

Experimental Design

Before the experiments all subjects were familiarized with the one-legged, dynamic knee-extensor exercise model (1) by training at 60 contractions/min (cpm) until they were comfortable and could fully relax the hamstring muscles, so that the work was performed solely by the knee extensors (1). Their mean peak power output with the one-legged, dynamic knee-extensor exercise, which they could sustain for 3 min at 60 cpm, was 74.3 ± 6.4 W (range 55–100 W) for the subjects in *protocol I* and 77.8 ± 4.1 W (range 70–100 W) for the subjects in *protocol II*.

Protocol I: Temporal course of changes in blood flow at onset of dynamic exercise. In the sitting position the subjects ($n = 7$) performed repeated 3-min bouts of one-legged, dynamic knee-extensor exercise (60 cpm) at 10 W ($n = 7$), 30 W ($n = 7$), 50 W ($n = 5$), and 70 W ($n = 2$), corresponding to 14.1 ± 3.1 , 42.2 ± 9.4 , 66.9 ± 15.6 , and $74.0 \pm 5.5\%$ of peak power output. The blood velocity was continuously measured at rest, at onset of passive leg movement, and in the transition to, as well as during, voluntary exercise at each workload. Passive leg movement was included to study the muscle mechanical factors alone, compared with additional metabolic components during voluntary exercise, as well as to control an instantaneous and reproducible start at a fixed contraction rhythm of 60 cpm at onset of the voluntary contractions. This was done by attaching the subject's leg to the knee-extensor lever arm and moving it up to 60 revolutions/min. Each work bout was separated by at least 30 min of rest until the blood velocity spectra and flow had normalized to resting control level. The work bouts were performed in incremental order to avoid a sustained effect of the highest on the lowest bouts. The subjects had before the first incremental exercise bout 1 min of passive leg movement and a warmup for 15–20 min in the knee-extensor ergometer, followed by >30 min of rest. Thus all bouts were preceded by another exercise bout.

Protocol II: Temporal relationship between blood velocity and intramuscular, arterial, and venous pressure at onset of dynamic exercise. Intramuscular pressure was measured with a Millar Micro-Tip catheter transducer (2-Fr, diffused

semiconductor, model SPC-320, Millar Instruments, Houston, TX) inserted under sterile conditions via a venflon in the quadriceps muscle of the subjects ($n = 7$), about one-half the distance between the pubic bone and patella. The insertion was performed at an angle of ~ 30 – 45° with respect to the skin and with a length giving a location and fixed depth approximately central in the muscle. The signal was amplified by a Millar transducer control unit (Millar Instruments). The intramuscular pressure transducer was specifically calibrated in relation to a water column of different heights, and the measured pressure related to this external pressure. Intra-arterial and venous blood pressure (Dialogue 2000, Danica Elektronik, Copenhagen, Denmark) were measured via catheters (20G, Ohmeda, Wiltshire, UK) placed in the proximal direction in the femoral artery and vein, 2–5 cm below the inguinal ligament. The knee-extensor force (strain gauge) and the femoral arterial blood velocity determined by the ultrasound Doppler (model CFM 800, Vingmed Sound, Horten, Norway) were measured simultaneously and continuously. The subjects performed the exercise with their thighs in the horizontal position and their upper body slightly bent upward (160°). The exercise began by five to seven passive leg movements at 60 revolutions/min. They thereafter started the voluntary exercise at a workload of 47.1 ± 1.8 W ($65.4 \pm 3.6\%$ of peak power output), at which they exercised for 5–8 min. The load was thereafter increased with 5- to 10-W increments every 30 s up to their maximum workload of 72.8 ± 3.8 W.

Instrumentation and Methodological Considerations

The equipment and procedures of measurements have previously been reported (16). The instrument used was an ultrasound Doppler (model CFM 800, Vingmed Sound) equipped with an annular phased array transducer (APAT, Vingmed Sound) probe (11.5 mm in diameter), operating at an imaging frequency of 7.5 MHz, and variable Doppler frequencies of 4.0–6.0 MHz, in high-pulsed repetition frequency mode (4–36 kHz). The site for vessel diameter (cross-sectional area) determination and blood velocity measurements in the common femoral artery was distal to the inguinal ligament but above the bifurcation into the superficial and profundus femoral branch. The position was chosen to minimize turbulence and interference of blood flow to the inguinal region, as well as because the artery is easily accessible and well insonated in this region. The ultrasound image of the arterial diameter is also unaffected by distortions from contractions and relaxations at this site proximal to the muscle. The ultrasound Doppler equipment was connected via a switch-box to an eight-channel analog-to-digital converter in a personal computer (IBM compatible, Pentium based), in which a data-acquisition program (obtained from the Institute of Physiology, Oslo, Norway) had been installed. This allowed continuous data transfer of the blood velocity and all other measured parameters (heart rate, arterial and venous blood pressure, and intramuscular pressure) with a sampling frequency of 100 Hz.

The femoral artery was insonated (direction of the ultrasound waves at the site of measurement) at a fixed perpendicular angle. Two-dimensional longitudinal images were captured and stored, with 25 frames/s in the image buffer and on magneto-optical discs. The diameter was subsequently determined along the central path of the ultrasound beam where the best spatial resolution is achieved. The systolic and diastolic diameters were separately measured over the cardiac cycle guided by the electrocardiogram (ECG). A diameter [$D_{(1/3\text{systole}+2/3\text{diastole})}$] based on the relative time periods of the systolic (one-third) and diastolic (two-thirds) blood-pressure

phases was assumed to be the most representative diameter size and was utilized to determine the cross-sectional area, $A = \pi r^2$, where r is the radius of the vessel (16).

The blood velocity was measured with the Doppler probe stabilized in a fixed position at an insonation angle as low as possible, during simultaneous vessel visualization. This procedure allows centering and size adjustment of the sample volume in relation to the vessel diameter, so that the sample volume covers the width of the vessel and the parabolic velocity profile, and also allows direct correction for the angle of insonation by positioning the rotatable axis of the sample volume parallel with the direction of the flow and vascular walls. It also enables optimization of the Doppler velocity recording on the basis of a direct feedback from the sample volume size and positioning in the vessel as well as the Doppler signal intensity (16). Slight turbulence and velocity irregularities occurring at the pulsating vascular walls were reduced by low-velocity rejection filtration.

The Doppler blood velocity spectra and the strain-gauge kicking-force tracings were continuously sampled and transferred with a frequency of 100 Hz via the analog-to-digital converter to the PC. This continuous sampling procedure allows a direct quality control of each velocity spectra after the experiments, where insonation failures can be detected and excluded from the flow analysis (16). It also eliminates the possible interference in the size of the averaged mean blood velocity and corresponding flow value that may occur when the blood flow velocity is averaged for each cardiac cycle triggered by the ECG (22, 28, 29). The blood velocity and flow were analyzed in relation to the muscle contraction force (strain-gauge) profile (16). A cuff below the knee around the calf muscles was temporarily inflated to a suprasystolic (>240 mmHg) blood pressure before the flow measurements to eliminate blood flow contributions to the lower leg. The volume of blood flow (in l/min) ($\dot{Q} = 6 \times 10^4 \times v_{\text{mean}} \times \pi r^2$) was calculated over the parabolic velocity profile by multiplying the cross-sectional area [$A = \pi r^2$ (in m^2)] of the artery with the angle-corrected, time- and space-averaged, and amplitude (signal intensity)-weighted mean blood velocity (v_{mean} , in m/s). The constant 6×10^4 is the conversion factor from meters per second to liters per minute.

Statistical Analysis

Parametric statistics (multiple analyses of variance for repeated measures and Tukey's honestly significant difference post hoc tests when more than two groups were compared over time, and paired t -test when only two groups were compared) were used for data analysis. Nonlinear regression (SPSS) was used for mathematical curve fitting describing the exponential rise in blood flow at onset of exercise. A P value <0.05 was considered statistically significant, and $P = \text{NS}$ indicates that the comparison was not statistically significant. The values are means \pm SE unless otherwise indicated.

RESULTS

Temporal Changes

Blood velocity and flow. Femoral artery blood velocity and flow were not different ($P = \text{NS}$) before the start of the different exercise interventions, with mean values of 0.062 ± 0.0046 m/s and 0.35 ± 0.028 l/min (~ 3.5 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$), respectively. With passive leg movements, both increased ($P < 0.008$) with the very first passive relaxation, reaching a plateau ($P = \text{NS}$) within four to five passive duty cycles at a 3.3-fold higher level

compared with rest and with a mean blood flow of 1.17 ± 0.11 l/min (~ 37 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$). The level of blood flow was similar ($P = \text{NS}$) regardless of the following exercise intensity, as well as during the full minute of passive leg movement during the warmup session.

With the very first voluntary contraction, the arterial inflow was either blocked (zero), or, in some cases, there was a tendency ($P = \text{NS}$) for blood velocity and blood flow to be in the retrograde direction, with an increased nadir velocity amplitude of $-45.2 \pm 6.7\%$. During the very first relaxation after the first voluntary contraction there was an immediate increase ($P < 0.005$) in the velocity amplitude with as much as $62.6 \pm 6.7\%$. The mean blood velocity and flow thereafter successively increased ($P < 0.005$) for each full kicking duty cycle during the first 0.5- to 5-s period to a level at the fifth second (duty cycle) of 1.89 ± 0.14 (~ 60 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$), 2.59 ± 0.42 (~ 82 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$), and 2.61 ± 0.20 l/min (~ 83 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$) at 10, 30, and 50 W, respectively, with an equally apparent increase to 4.40 ± 0.26 l/min (~ 140 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$) for the two subjects who sustained 70 W (Fig. 1).

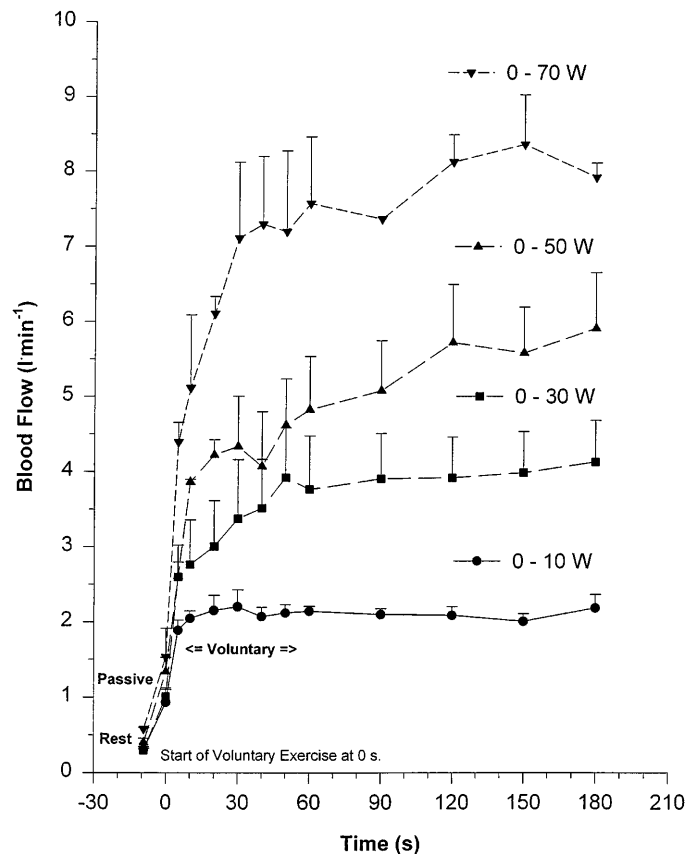


Fig. 1. Blood flow (mean \pm SE) in the femoral artery in the transition from rest to passive exercise and to voluntary, 1-legged, dynamic knee-extensor exercise at 10 W ($n = 7$), 30 W ($n = 7$), 50 W ($n = 5$), and 70 W ($n = 2$). Voluntary exercise was initiated at time 0. Increase in blood flow was significant ($P < 0.05$) at all time points from rest to passive and voluntary exercise, as well as from passive to voluntary exercise, at 10, 30, and 50 W, and there was an equally apparent further elevation in blood flow for the 2 subjects at 70 W.

Mathematical modeling. Curve fitting of the increase in blood velocity and flow for the full-kicking duty cycles at onset of the voluntary dynamic contractions was best described by a one-, two-, or three-component exponential model. In the transition from passive leg movement to voluntary exercise, blood flow increased according to the equation $\dot{Q}(t) = \dot{Q}_{\text{passive}} + \Delta\dot{Q}_1 \cdot [1 - e^{-(t - TD_1/\tau_1)}] + \Delta\dot{Q}_2 \cdot [1 - e^{-(t - TD_2/\tau_2)}] + \Delta\dot{Q}_3 \cdot [1 - e^{-(t - TD_3/\tau_3)}]$. In this equation, \dot{Q}_{passive} represents the blood flow during passive leg movement; $\Delta\dot{Q}_1$, $\Delta\dot{Q}_2$, and $\Delta\dot{Q}_3$ represent the magnitude of response for each component toward the stable steady-state asymptotic blood flow, leveling off at $\dot{Q}_{\text{passive}} + \Delta\dot{Q}_1 + \Delta\dot{Q}_2 + \Delta\dot{Q}_3$; the time constants τ_1 , τ_2 , and τ_3 reflect the rapidity of the rise for each exponential component, where smaller time constants correspond to faster rises, and TD_1 , TD_2 , and TD_3 represent the onset latency time of each component, respectively.

The hyperemia at 10-W exercise was represented by a one-component model ($r = 0.99$), whereas a two-component model best described the response at 30 W ($r = 0.99$) and 50 W ($r = 0.97$) and a three-component model best described the response at the highest workload of 70 W ($r = 0.99$). The onset latency of the respective components was $TD_1 \approx 0.3\text{--}0.5$ s (i.e., approximately the time to the first relaxation), $TD_2 \approx 4\text{--}5$ s, and $TD_3 \approx 30$ s. The rate and magnitude of rise, as well as the time point for leveling in the response, were related to the exercise intensity. In general, higher workloads corresponded to a faster initial rate of rise and a greater magnitude of increase to asymptotic leveling off ($P = \text{NS}$), which occurred at 2.18 l/min (~ 69 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$), 4.04 l/min (~ 128 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$), and 5.92 l/min (~ 188 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$) at 10, 30, and 50 W, respectively, and at ~ 8.53 l/min (~ 270 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$) at 70 W (Fig. 1, Table 1). As workload decreased, leveling off occurred more quickly ($P = \text{NS}$) after 10 s at 10 W, after 50–60 s at 30 W, after 90–150 s at 50 W, and after ~ 150 s at 70 W (Fig. 1). The time to reach 50% of the difference between passive and voluntary asymptotic blood flow leveling increased with exercise intensity and was in the range of 2.2–8.9 s (Table 1).

Temporal Relationship

Rest and passive movement. The intramuscular pressure at rest was stable at $\sim 25.8 \pm 5.3$ mmHg and changed for all subjects at the start of passive leg

movement as a function of the force; it was highest (68.6 ± 15.7 mmHg) during passive pulling (muscle elongation) and lowest (6.4 ± 8.6 mmHg) during passive pushing (muscle shortening) of the leg ($P < 0.002$). Analogous with *protocol I*, femoral arterial mean blood velocity and flow increased ($P < 0.05$) with $52.5 \pm 22.2\%$ in the first pushing phase of the first duty cycle of the passive leg movements and increased ($P < 0.05$) further successively for each subsequent duty cycle to level off ($P = \text{NS}$) at a 4.4-fold higher magnitude (compared with rest) between the fourth and fifth passive leg movement at a blood flow of 1.01 ± 0.092 l/min (~ 34 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$).

Voluntary contraction. At the onset of the voluntary contractions (47.1 ± 1.8 W), the amplitude of the oscillations in intramuscular pressure increased ($P < 0.004$) further compared with rest and during the passive leg movements (Figs. 2 and 3) in relation to the knee-extensor force over the contraction-relaxation cycle. The mean blood velocity and flow peaked with an amplitude increase ($P < 0.006$) of $28.1 \pm 6.6\%$ with the first relaxation, analogous with *protocol I*, giving a $TD_1 \approx 0.3\text{--}0.5$ s. The blood flow furthermore increased ($P < 0.05$) for the consecutive kicking duty cycles to a mean value of 1.65 ± 0.24 l/min (~ 55 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$), 2.0 ± 0.4 l/min (~ 67 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$), and 2.2 ± 0.32 l/min (~ 74 ml \cdot min $^{-1} \cdot 100$ g $^{-1}$) after 1, 3, and 5 s (duty cycles), respectively.

Arterial pressure. Mean arterial blood pressure increased ($P < 0.05$) initially within the time frame of the first to third contraction by 8.9 ± 1.9 and 6.4 ± 2.3 mmHg compared with rest and passive leg movements, respectively. This was followed by a temporary decrease ($P < 0.002$) of 8.1 ± 1.0 mmHg compared with during the first three contractions and a tendency ($P = \text{NS}$) to decrease by 2.0 ± 2.0 and 4.2 ± 2.1 mmHg below the mean arterial pressure level at rest and during passive leg movements, respectively. The decrease in the arterial blood pressure was observed ($P < 0.002$) with a time delay of 4.2 ± 0.5 s after the onset of voluntary exercise and reached its nadir and turning point within 6.5 ± 0.6 s, indicating a period of vasodilatation, and analogous with *protocol I*, an observable onset latency time point (TD_2) for the start of *phase 2*. At steady-state voluntary exercise, mean arterial pressure increased ($P < 0.02$) compared with rest and passive leg movements, whereas it was unaltered ($P =$

Table 1. Variables for the one-, two-, and three-component exponential model of increase in femoral artery blood flow in transition from passive leg movement to voluntary, one-legged, dynamic knee-extensor exercise

Load, W	\dot{Q}_{passive} , l/min	$\Delta\dot{Q}_1$, l/min	τ_1 , $10^{-3} \times$ min	$\Delta\dot{Q}_2$, l/min	τ_2 , min	$\Delta\dot{Q}_3$, l/min	τ_3 , min	t_{50} , s	\dot{Q}_{asympt} , l/min
10	0.94	1.24	59					2.2	2.18
30	1.01	1.28	1.7	1.76	0.52			4.5	4.04
50	1.34	1.61	1	2.97	0.98			8.5	5.92
70	1.54	1.56	0.5	3.87	0.23	1.56	2.12	8.9	8.53

Equation for exponential model for increase in femoral artery blood flow (in l/min) is $\dot{Q}(t) = \dot{Q}_{\text{passive}} + \Delta\dot{Q}_1 \cdot [1 - e^{-(t - TD_1/\tau_1)}] + \Delta\dot{Q}_2 \cdot [1 - e^{-(t - TD_2/\tau_2)}] + \Delta\dot{Q}_3 \cdot [1 - e^{-(t - TD_3/\tau_3)}]$ for n subjects at 10 W ($n = 7$), 30 W ($n = 7$), 50 W ($n = 5$), and 70 W ($n = 2$) with onset latencies for each of the 3 components of $TD_1 \approx 0.3\text{--}0.5$ s, $TD_2 \approx 5$ s, and $TD_3 \approx 30$ s, respectively. \dot{Q}_{passive} , blood flow during passive leg movement; $\Delta\dot{Q}_1$, $\Delta\dot{Q}_2$, and $\Delta\dot{Q}_3$, magnitudes of response for each component toward stable steady-state asymptotic blood flow leveling off (\dot{Q}_{asympt}); τ_1 , τ_2 , and τ_3 , time constants for 3 exponential components, respectively; and t_{50} , time to reach 50% of difference between passive and voluntary \dot{Q}_{asympt} .

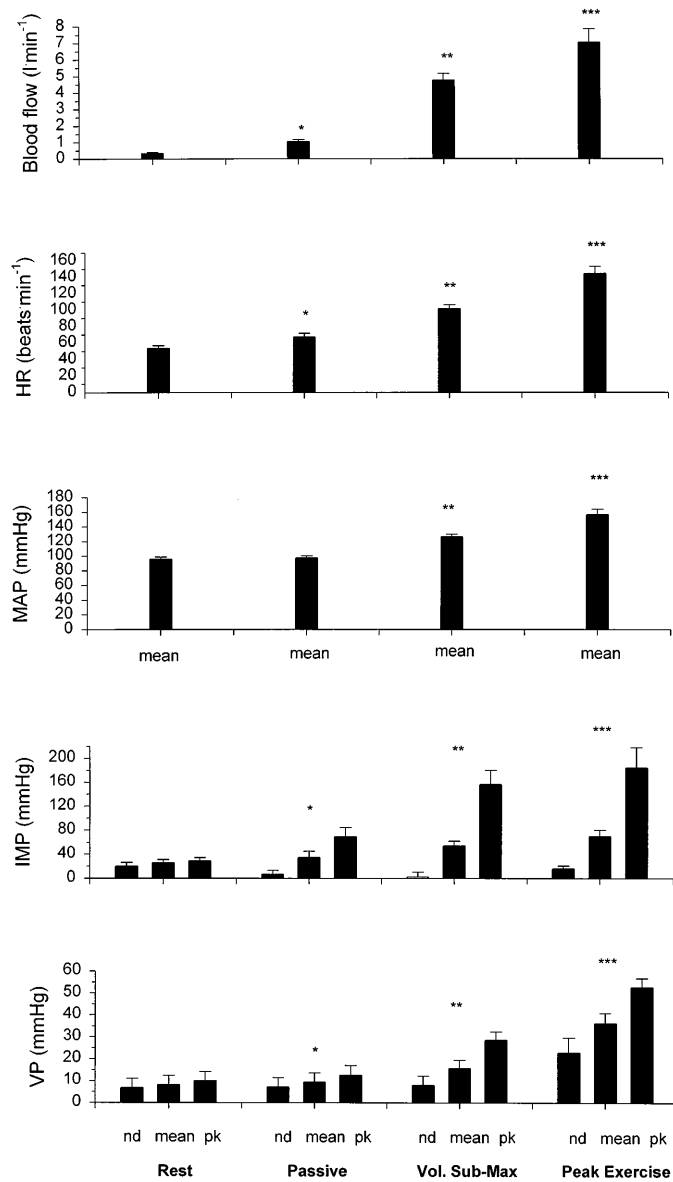


Fig. 2. Mean blood flow, heart rate (HR), and mean arterial blood pressure (MAP), as well as nadir (nd)-to-peak (pk) variations and mean values of intramuscular (IMP) and venous pressure (VP) at rest; during passive exercise; during voluntary, 1-legged, dynamic knee-extensor exercise at 47.1 ± 1.8 W [$65.4 \pm 3.6\%$ of maximum work rate; i.e., submaximal voluntary exercise (Vol. Sub-Max)]; and at peak exercise effort of 72.8 ± 3.8 W. Significant differences ($P < 0.05$): * from rest, ** from rest and passive, and *** from rest, passive, and submaximal voluntary exercise, respectively.

NS), with only a slight tendency to increase, with passive leg movement compared with rest (Fig. 2).

Venous pressure. The oscillations in venous pressure on the femoral level, which increased ($P < 0.001$) with the onset of passive leg movements, giving an elevation of mean venous pressure with 1.3 ± 0.1 mmHg compared with rest, were further potentiated ($P < 0.025$) at the onset of the voluntary contractions in phase with the intramuscular pressure variations (see below). The mean venous pressure increased ($P < 0.025$) by 7.6 ± 1.7 and 6.4 ± 1.6 mmHg compared with rest and passive leg movement, respectively (Fig. 2). The arterial-

venous pressure difference on the femoral level was, however, unaltered ($P = \text{NS}$) with the first contractions of *phase 1*.

Temporal variation. The blood velocity altered from being three phasic and dependent on the cardiac cycle and pulse pressure at rest (Fig. 3) to being directly related to the elongation and shortening of the muscle during the passive leg movements and voluntary contractions (Figs. 3 and 4). The arterial pulse pressure had a superimposed influence on the primary effects of the variations in intramuscular pressure during the contraction and relaxation phases, respectively (Fig. 4). When a series of (≥ 12) kicking duty cycles for each subject were studied, the intramuscular and venous pressures were significantly greater ($P < 0.001$, $P < 0.04$) during the contraction phase than during the relaxation phase, respectively, but were unaffected ($P = \text{NS}$) by the arterial pulse pressure during each condition (Table 2). The arterial pressure was furthermore increased ($P < 0.03$) during the contraction phase compared with the relaxation phase at the second diastolic notch and at diastole, both by approximately 6–7 mmHg. The peak systolic blood pressure was similar ($P = \text{NS}$) under both conditions (Table 2).

The mean arterial blood velocity was found to be highest ($P < 0.001$) and peaked at $\sim 2.5 \pm 0.3$ m/s (v_1) during the relaxation phase, when minimum intramuscular pressure coincided with peak arterial pulse pressure (Table 2). The blood velocity thereafter successively decreased ($P < 0.001$) with decreasing arterial pulse pressure during the relaxation phase, exhibiting minimum intramuscular pressure, giving an intermediate velocity value of 1.01 ± 0.14 m/s (v_2 , $44.2 \pm 8.6\%$ of peak velocity) at the second diastolic blood pressure notch and the lowest velocity of 0.65 ± 0.09 m/s (v_3 , $28.5 \pm 5.5\%$ of peak velocity) at the lowest arterial pulse pressure (Table 2).

Mechanical hindrance to blood flow was found with a minimum ($P < 0.001$) and retrograde blood velocity of -0.36 ± 0.085 m/s (v_6 , $-15.8 \pm 3.9\%$ of peak velocity) during the muscle contraction phase, as peak intramuscular pressure coincided with minimum arterial pulse pressure, and was furthermore also retrograde or zero when the second diastolic blood pressure notch occurred simultaneously with maximum intramuscular pressure during the contraction phase, giving a retrograde ($P < 0.001$) blood velocity of -0.11 ± 0.047 m/s (v_5 , $-4.9 \pm 2.0\%$ of peak velocity) (Table 2). However, the perfusion pressure was large enough to overcome ($P < 0.001$) the mechanical hindrance, as peak arterial blood pressure occurred during the contraction phase with peak intramuscular pressure, giving a mean blood velocity of 0.57 ± 0.079 m/s (v_4 , $25.9 \pm 4.4\%$ of the peak velocity), that is, at a blood flow level of the same magnitude ($P = \text{NS}$) as when minimum arterial blood pressure coincided with minimum intramuscular pressure during the relaxation phase (Table 2).

In general, with the elevation of the workload up to peak power output, blood flow at the termination of exercise, as well as the mean values and the nadir-to-peak variation (mean \pm SE) of intramuscular, arterial,

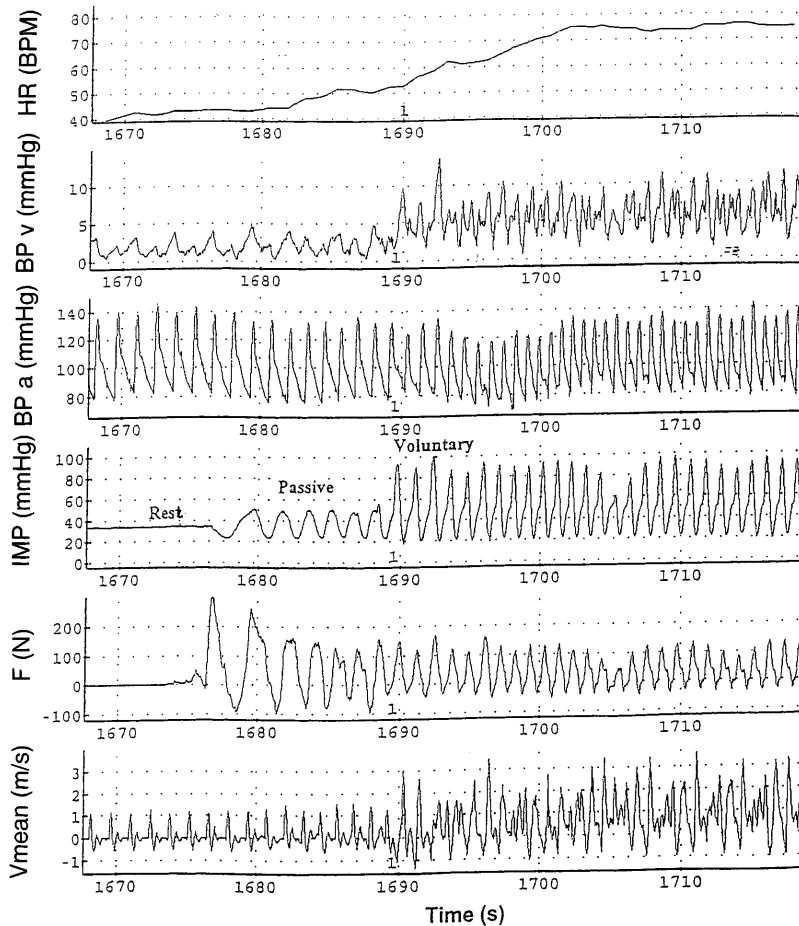


Fig. 3. Femoral arterial blood velocity (v_{mean}), knee-extensor force (F), IMP, arterial (BP_a) and venous (BP_v) blood pressure, and HR in the transition from rest to passive exercise to voluntary, 1-legged, dynamic knee extensor exercise at 50 W from 1 representative subject. Onset of voluntary exercise is marked by a "1." BPM, beats/min.

and venous pressures further increased ($P < 0.025$) compared with rest and during passive as well as submaximal exercise (Fig. 2). Thus blood flow, heart rate, mean arterial pressure, intramuscular pressure, and venous pressure all increased ($P < 0.05$) between each condition; the only exception was that mean arterial pressure was similar ($P = \text{NS}$) at rest and during passive exercise (Fig. 2).

DISCUSSION

This study demonstrates that it is possible in humans to continuously measure the arterial inflow to dynamically contracting muscle in the transition from rest to exercise at different intensities up to levels approaching peak power output. Moreover, the temporal resolution of the ultrasound Doppler technique makes it possible to follow each phase of a duty cycle, demonstrating a very close temporal relationship between the changes in arterial blood velocity, and thus inflow, to the contraction- and relaxation-induced variations in intramuscular, arterial, and venous pressures.

The arterial blood velocity and inflow are significantly elevated already at the first relaxation phase of a passive leg movement, plateauing at a 3.3- to 4.4-fold higher level compared with rest within four to five passive duty cycles, i.e., an elevation due purely to muscle mechanical factors. On initiation of voluntary exercise, arterial blood velocity and inflow may be

either blocked (zero) or retrograde with the first contraction. A marked elevation in blood flow follows with the first relaxation phase, due to refilling of the vascular bed, a process just as apparent as for the purely passive leg movements. Furthermore, the mean arterial blood velocity in the femoral artery (internal diameter of ~ 10 mm) increased by $\sim 50\%$ by the end of the first passive or voluntary duty cycle compared with a rest velocity of ~ 0.06 m/s. Thus this arterial inflow corresponds well with the ~ 50 -ml volume of blood contained in the knee-extensor muscles, with a muscle volume of $\sim 3,000$ ml, and assuming a capillarization of $\sim 1.5\%$, along with the volume contributions in venules and small arteries (18). Moreover, the squeezing of the blood volume out of the muscle during the contraction and the refilling of the vasculature during the relaxation seem sufficient to induce the initial elevation in blood flow during the first relaxation phase. Depending on power output, this process contributes to the elevation in blood flow during the first seconds of work with a 5.5- to 12.5-fold elevation compared with rest. The mean arterial-venous pressure gradient on the femoral level was unaltered with the first three contractions, as the mean pressures of both were slightly elevated. It must be emphasized, however, that these pressures are valid for the level of measurement in the vascular tree and may not represent the absolute true values in the microvasculature. However, their changes may respec-

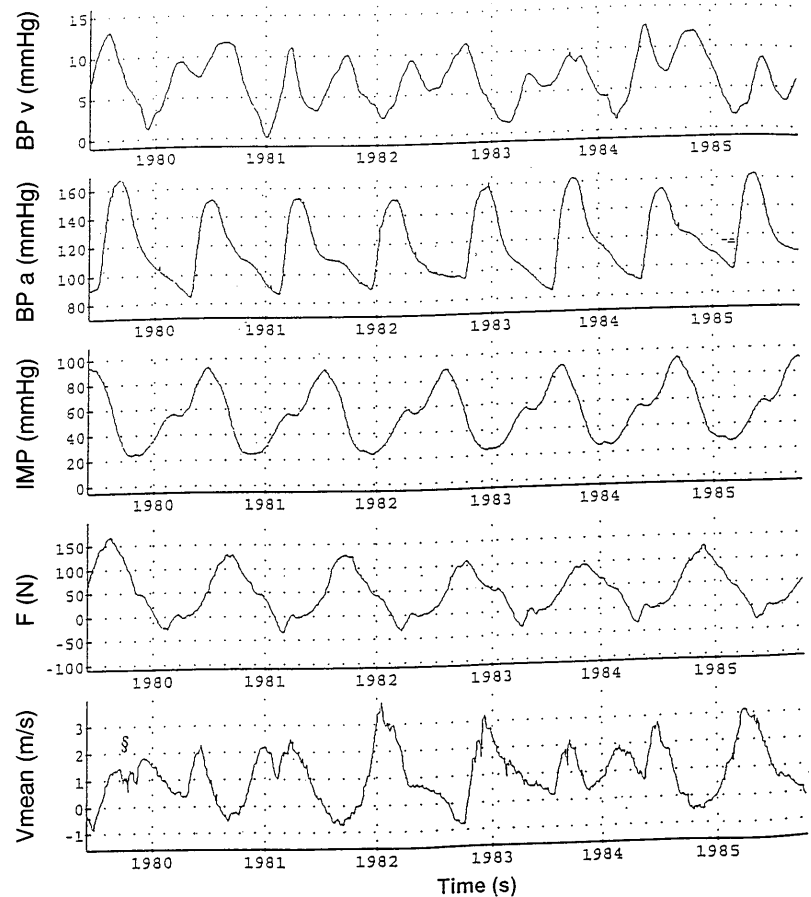


Fig. 4. Femoral arterial v_{mean} , knee-extensor F, IMP, and BP_a and BP_v during steady-state voluntary, 1-legged, dynamic knee-extensor exercise at 50 W, from 1 representative subject. Temporal variation in arterial v_{mean} and inflow for successive kicking duty cycles in relation to IMP variations is shown, along with superimposed influence of BP_a and BP_v . The § indicates an insonation failure, excluded from subsequent blood flow analysis.

tively give information about the general temporal oscillations during exercise and be used as a guideline for the events occurring. Thus, in light of the marked oscillations in venous pressure with values close to zero at a location proximal to the venous valves, there is a possibility that a small elevation in the arterial-venous pressure gradient still occurs on the microvascular level, as previously suggested (6, 13, 21). There is a

close temporal relationship between the marked oscillations in intramuscular pressure and the initial amplitude increase in arterial blood velocity already with the first relaxation(s) during passive as well as voluntary exercise. This relationship emphasizes the importance of purely muscle-mechanical factors for facilitating the first stage of the hyperemic response during the very first phase (onset latency of $\sim 0.3\text{--}0.5$ s). The arterial

Table 2. Fluctuations in femoral artery blood velocity over a series of kicking duty cycles during one-legged, dynamic knee-extensor exercise

Phase in Duty Cycle	v_{mean} , m/s	IMP, mmHg	Arterial BP, mmHg	Venous BP, mmHg
Relaxation (IMP _{min})				
At BP _{max}	$v_1 = 2.54 \pm 0.29^a$	19.7 ± 3.9	167.2 ± 3.0	8.9 ± 2.8
At 2nd dicrotic BP	$v_2 = 1.01 \pm 0.14^b$	14.6 ± 2.2	112.4 ± 2.8	11.7 ± 3.1
At BP _{min}	$v_3 = 0.65 \pm 0.09^c$	19.5 ± 3.12	99.4 ± 2.7	11.4 ± 2.7
Contraction (IMP _{max})				
At BP _{max}	$v_4 = 0.57 \pm 0.08^c$	123.8 ± 13.9^e	167.4 ± 2.5	20.6 ± 2.6^f
At 2nd dicrotic BP	$v_5 = -0.11 \pm 0.05^d$	127.8 ± 11.6^e	119.8 ± 2.5^g	18.5 ± 2.5^f
At BP _{min}	$v_6 = -0.36 \pm 0.08$	125.0 ± 12.0^e	106 ± 3.5^g	20.9 ± 2.0^f

Values are means \pm SE; $n = 7$ subjects. Data are from a series of kicking duty cycles of 1-legged, dynamic knee-extensor exercise at 47.1 ± 1.87 W ($65.4 \pm 3.6\%$ of peak power output) during relaxation and contraction phases [minimum (IMP_{min}) and maximum intramuscular pressure (IMP_{max}), respectively], as well as under superimposed influence of arterial blood pressure (BP) at peak (BP_{max}; systole), at 2nd dicrotic notch (2nd dicrotic BP), and at nadir (BP_{min}; diastole) of arterial pulse pressure. Average blood velocity (v_{mean}) was greater ($P < 0.001$) during relaxation (v_1, v_2, v_3) than during contraction (v_4, v_5, v_6) phase, respectively; v_{mean} values during relaxation phase at BP_{min} (v_3) and contraction phase at BP_{max} (v_4) were similar [$P = \text{not significant (NS)}$]. With decreasing arterial pressure, v_{mean} values decreased ($P < 0.001$) within each phase (relaxation: $v_1 > v_2 > v_3$; contraction: $v_4 > v_5 > v_6$). For v_{mean} values, superscripts indicate value significantly different from ^a v_2 – v_6 , ^b v_3 – v_6 , ^c v_5 and v_6 ; or ^d v_6 . IMP and venous pressure values were significantly greater (^e $P < 0.001$ and ^f $P < 0.04$, respectively) during contraction than during relaxation phase, respectively, but were unaffected ($P = \text{NS}$) by arterial pulse pressure during respective conditions. Arterial BP was increased (^g $P < 0.03$) during contraction compared with relaxation phase at 2nd dicrotic and diastolic points (BP_{min}) of BP curve, respectively, but was similar ($P = \text{NS}$) at peak systolic (BP_{max}) pulse pressure under both conditions.

blood velocity and inflow is increased with the successive duty cycles during the first 5 s of exercise, whereas the oscillations in intramuscular pressure variations stabilize after the first contraction at a fixed amplitude. This suggests that factors other than muscle mechanical cause the amplification of the hyperemic response.

The arterial blood pressure drops after the first contractions, with an onset latency of 4.2 ± 0.5 s, reaching its nadir after 6.5 ± 0.6 s and thereafter becoming elevated again. Thus there is a distinct separate second phase in the hyperemic response, which is induced by vasodilatation. In light of the successive increases in blood flow for each duty cycle after the first contraction, and the very minor changes in blood pressure, it appears that the vasodilation is present already after the second contraction. The temporary slight drop in blood pressure before its elevation probably reflects the fact that the sympathetic drive for a brief period is lagging behind. A third phase in the elevation of blood flow was observed after ~ 30 s at the highest intensity. In previous studies with a similar exercise model, Eriksen et al. (12) have shown that there is no detectable delay between the initial increase in cardiac output and femoral arterial inflow. However, the magnitude of total increase in femoral arterial inflow may markedly exceed the increase in cardiac output (12), suggesting an immediate redistribution of blood flow from other vascular beds to ensure an adequate delivery to the contracting muscles.

The increase in arterial blood velocity and inflow at the onset of the voluntary contractions was related to the intensity and was best described by a one-component (~ 15 % of peak power output), two-component (~ 40 – 70 % of peak power output), or three-component (≥ 75 % of peak power output) exponential function. This resembles a similar mathematical model for the onset of intermittent static contractions-relaxations (each of 2-s duration) at 10% of MVC previously described by Shoemaker et al. (22). The phasic appearance of different components with different onset latencies ($TD_1 \sim 0.3$ – 0.5 s, $TD_2 \sim 4.2$ s, $TD_3 \sim 30$ s), rates of rise, and potencies further demonstrated the existence and role of several factors for elevating the blood flow during submaximal exercise. The muscle pump alone may, however, be sufficient for the initial elevation at very light workloads. The magnitude and rapidity of rise in blood flow for the first phase at onset of voluntary exercise increased with exercise intensity, where an asymptotic leveling off in blood flow was reached within 10 s for the exercise at ~ 15 % of peak power output. The slightly slower but more potent second phase induced a further elevation of the blood flow to its final level within 50–60 s and 90–150 s at ~ 40 and 70 % of peak power output, respectively. The third and slowest component induced a blood flow increase with a leveling off within ~ 150 s at ≥ 75 % of peak power output. The time for the blood flow to reach 50% of the increase in leg blood flow was in the range 2.2–8.9 s, i.e., for higher work intensity, the time was longer.

The aim of the present study was not to ascertain which substance(s) cause hyperemia in skeletal muscle but instead to give very precise information about the

time frame within which various factors may act. Even though vasodilatation may not induce the elevation in blood flow with the first duty cycle, it must be initiated during the second to fourth second to allow for the marked hyperemia that occurs. Adenosine, NO, and acetylcholine are all potent and endogenous vasodilators and candidates for this hyperemic response, but their time frame of action and source of release in relation to skeletal muscle contractions and blood flow regulation still need to be clarified *in vivo* in humans. The rapid and potent initial increase in blood flow, despite no simultaneous increase in femoral arterial diameter, stresses that its size is not the determining factor for delivery during submaximal exercise up to intensities near peak level in humans. It also emphasizes that the cause of the blood flow elevation must be attributed to the effect of the muscle mechanical factors or vasodilators on the microvasculature with its relatively larger surface area and greater vasodilatory capacity, rather than an effect on the major feeding artery. The vasodilators of interest are therefore limited to these with a short half-life, i.e., less than the time of recirculation.

The study furthermore emphasizes that the minimum and maximum intramuscular pressure variations over the relaxation and contraction cycles correspond to the highest and the lowest phase of the mean blood velocity, respectively, with the arterial pressure as a superimposed influence. Blood flow is thus promoted during the muscle relaxation phase and further enhanced by the arterial pulse pressure. At the submaximal workload studied (~ 65 % of peak power output), blood flow is impeded by mechanical hindrance during the muscle contraction phase, unless the perfusion pressure is in its peak value range, where the flow restriction may be overcome. As intramuscular pressure may vary with the tension of the muscle fibers, recording depth, and fiber geometry (9, 14, 19, 20), the intramuscular probe was inserted in the same location and muscle type in all the subjects, as well as at a fixed and specific depth approximately central in the muscle. The recorded intramuscular pressure at baseline rest was similar to previous measurements by others (14, 23, 25, 30). Even though it is beyond the focus of this study to clarify regional differences in intramuscular pressure within the muscle, it is, however, interesting to speculate that such variations may as previously has been suggested possibly be the cause of regional differences and heterogeneity in blood flow within a muscle group (23).

In addition, one could argue that the stretch of the muscle during passive leg movement could evoke a reflexive contraction via the stretch reflex, affecting the intramuscular pressure recordings. In this study we did not elucidate this phenomenon using electromyography. However, such a mechanism seems unlikely to have affected our results because the intramuscular pressure oscillations during passive exercise were extremely stable, despite the variations in the applied pulling force, which naturally was greatest in the initial acceleration phase of the ergometer lever arm during the first duty cycles from the resting condition

up to 60 revolutions/min. The oscillations in intramuscular pressure were equally stable as the applied pulling force was decreased, and started to stabilize and resemble the force during the steady-state voluntary exercise. Moreover, in a parallel study we have measured heat storage in the muscle during 60 s of passive leg movements, without any elevation in the muscle temperature. In contrast, heat is gained within the first one to three voluntary contractions. Thus the passive leg movements seem a valid comparison to the voluntary exercise, possessing the additive metabolic contributions.

In conclusion, the study demonstrates a very close temporal relationship between the arterial inflow and the variations in intramuscular, arterial, and venous pressure at onset of, and during, dynamic exercise, where the intramuscular pressure variations may promote as well as impede the muscle perfusion. The arterial blood pressure is an additional superimposed influence, although it is of less importance. The venous pressure may also still oscillate to possibly increase the pressure head and thus the driving force on the microvascular level. Blood flow to the exercising muscle is optimized when the heart beat and arterial systolic blood pressure is timed to occur during the relaxation. Depending on intensity, the initial hyperemia shows a one-, two-, or three-phasic appearance, where the arterial inflow increases with the first muscle relaxation(s) because of refilling of the arterial and the venous vasculature immediately after the emptying with the first contraction(s). The elevation of blood flow is most rapid during the first phase (0.5–5 s), initially facilitated by the muscle pump. The muscle mechanical component is followed by a second and more potent vasodilatory phase, observed with an onset latency of ~4 s but most probably initiated already during the second to fourth contraction of the muscle mechanical stage of *phase 1*. At greater intensities, a third phase is identified with an onset latency of ~30 s.

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Address for reprint requests: G. Rådegran, Copenhagen Muscle Research Centre, Rigshospitalet, Section 7652, Tagensvej 20, DK-2200 Copenhagen N, Denmark.

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