

Effects of forearm bier block with bretylium on the hemodynamic and metabolic responses to handgrip

FRANK LEE,¹ J. KEVIN SHOEMAKER,⁶ PATRICK M. McQUILLAN,³
ALLEN R. KUNSELMAN,² MICHAEL B. SMITH,⁴ QING X. YANG,⁴
HARVEY SMITH,⁴ KRISTEN GRAY,^{1,5} AND LAWRENCE I. SINOWAY^{1,5}
Sections of ¹Cardiology, ²Biostatistics, and ³Anesthesiology and ⁴Department of Radiology, Center for Nuclear Magnetic Resonance Research, The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, Hershey 17033; ⁵Lebanon Veterans Affairs Medical Center, Lebanon, Pennsylvania 17042; and ⁶School of Kinesiology, University of Western Ontario, London, Ontario, Canada N2L 3G1

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Lee, Frank, J. Kevin Shoemaker, Patrick M. McQuillan, Allen R. Kunselman, Michael B. Smith, Qing X. Yang, Harvey Smith, Kristen Gray, and Lawrence I. Sinoway. Effects of forearm bier block with bretylium on the hemodynamic and metabolic responses to handgrip. *Am J Physiol Heart Circ Physiol* 279: H586–H593, 2000.—We tested the hypothesis that a reduction in sympathetic tone to exercising forearm muscle would increase blood flow, reduce muscle acidosis, and attenuate reflex responses. Subjects performed a progressive, four-stage rhythmic handgrip protocol before and after forearm bier block with bretylium as forearm blood flow (Doppler) and metabolic (venous effluent metabolite concentration and ³¹P-NMR indexes) and autonomic reflex responses (heart rate, blood pressure, and sympathetic nerve traffic) were measured. Bretylium inhibits the release of norepinephrine at the neurovascular junction. Bier block increased blood flow as well as oxygen consumption in the exercising forearm ($P < 0.03$ and $P < 0.02$, respectively). However, despite this increase in flow, venous K⁺ release and H⁺ release were both increased during exercise ($P < 0.002$ for both indexes). Additionally, minimal muscle pH measured during the first minute of recovery with NMR was lower after bier block (6.41 ± 0.08 vs. 6.20 ± 0.06 ; $P < 0.036$, simple effects). Meanwhile, reflex effects were unaffected by the bretylium bier block. The results support the conclusion that sympathetic stimulation to muscle during exercise not only limits muscle blood flow but also appears to limit anaerobiosis and H⁺ release, presumably through a preferential recruitment of oxidative fibers.

blood flow; autonomic nervous system

DURING EXERCISE THE SYMPATHETIC nervous system is activated. The neural systems responsible for sympathetic activation are unclear, although it is widely believed that engagement of the muscle reflex plays an important role (18, 22). Once the sympathetic nervous system is engaged, there is an increase in blood pressure and vasoconstrictor tone to inactive skeletal muscle beds (31, 32, 37). The effect of sympathetic

activation on flow in exercising muscle remains an area of considerable study. Work from a number of laboratories has focused on the concept that sympathetic tone to exercising muscle is “lysed” by some substance released or present during muscle exercise (15, 29). Other groups, including our own, have emphasized the role the sympathetic nervous system plays in restraining flow to exercising muscle (7, 26, 35).

In this study, we were interested in determining whether the sympathetic nervous system restrains limb blood flow and oxygen consumption in human subjects during exercise. To examine this issue, we utilized a recently described bretylium bier block technique (15). The bier block method allows investigators to isolate the pharmacological effects of infused substances to a single upper extremity of human subjects. Bretylium inhibits norepinephrine release at the neurovascular junction and in the process causes a “pharmacologically induced sympatholysis.”

We also examined the impact of the bretylium bier block on muscle metabolism and the reflex responses to forearm exercise. To examine muscle metabolism, we measured venous effluent metabolites and obtained ³¹P-NMR spectra during forearm exercise. To examine the effects of sympathetic stimulation on muscle reflex activation, we measured the blood pressure, heart rate, and peroneal nerve muscle sympathetic nerve activity (MSNA; microneurography). Our hypotheses were that after bier block with bretylium 1) forearm exercise flow would increase, 2) forearm oxygen consumption would remain constant, 3) muscle acidosis would be reduced, and 4) reflex responses to handgrip would be attenuated. Our results suggest that the bier block increased both flow and forearm oxygen consumption. Despite this, we observed an increase in muscle acidosis and no change in muscle reflex engagement.

Address for reprint requests and other correspondence: L. I. Sinoway, Sect. of Cardiology, MC H047, The Pennsylvania State Univ., The Milton S. Hershey Medical Center, PO Box 850, Hershey, PA 17033 (E-mail:lsinoway@psu.edu).

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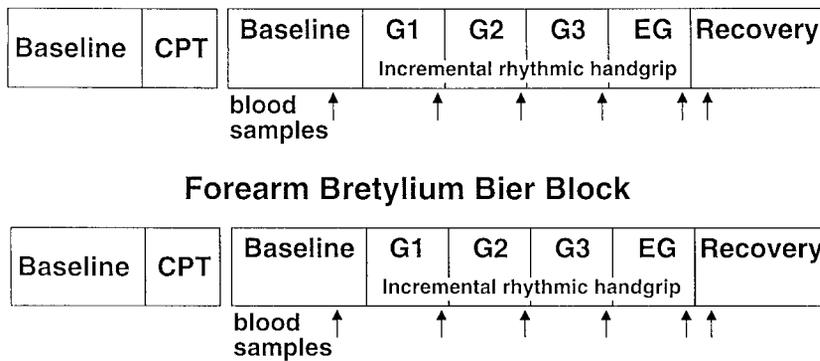


Fig. 1. Schematic representation of the experimental protocol. CPT, cold pressor test; G1, G2, G3, minutes 1–3 of incremental handgrip, respectively; EG, end grip.

METHODS

Subjects

Fifteen healthy subjects (male) volunteered for this study. The subjects were 27 ± 2 (SE) yr of age (range 20–40 yr) and weighed 78 ± 2 kg. All subjects provided informed written consent to the experimental protocol, which was approved by the Institutional Review Board of The Milton S. Hershey Medical Center. All subjects were in good health.

Protocols

The exercise protocols to be described are similar to those previously reported by our group (35). Two separate sets of experiments were performed. The first set was performed in the General Clinical Research Center of the Hershey Medical Center (*study A*). The second group was performed in the NMR facilities of the medical center (*study B*). In *study A* ($n = 8$), we measured forearm blood flow (Doppler method; model 500 M, Multigon, Yonkers, NY), skin blood flow (SBF; laser-Doppler technique; Laserflo BPM², Vasomedics, St. Paul, MN), MSNA, heart rate (electrocardiogram), blood pressure (Finapres, Ohmeda, Madison, WI; and Dinamap, Critikon, Tampa, FL), venous concentrations of lactate (Stat-Plus 2300, Yellow Springs Instrument, Yellow Springs OH), lactate release (index of flow \times venous lactate concentration), venous K⁺ concentration (ion-selective electrode, Roche Diagnostics, Indianapolis, IN), and venous K⁺ release. In addition, venous blood gases were analyzed (model ABL 510, Radiometer, Copenhagen, Denmark) to calculate venous H⁺ concentration and release and venous oxygen saturation and forearm oxygen consumption (index of flow \times oxygen extraction). The saturation values obtained were corrected for the effects of pH on an oxygen-hemoglobin dissociation. From the venous oxygen saturation and the measured hemoglobin concentration, venous oxygen content was determined.

Study A. On arrival at the General Clinical Research Center, each subject read and signed the informed consent and underwent a routine history and physical examination. A Doppler probe was placed over the brachial artery. The laser-Doppler diode was placed on the forearm skin, and an intravenous catheter was placed in a retrograde fashion into an antecubital vein in the exercising forearm. A second intravenous catheter was placed in a forearm vein of the opposite arm for the purpose of providing systemic intravenous access. Microneurography electrodes were placed in the peroneal nerve and in the adjacent subcutaneous tissue.

After at least 5 min of rest, each subject performed 1 min of rhythmic isometric handgrip exercise at each of four increasing workloads. Each subject performed rhythmic handgrip for 1 min at workloads of 11, 21, 31, and 41 lbs.,

respectively. The contractions at each workload were performed with the nondominant forearm in a work-rest schedule of 1 s: 1 s. There were no rest periods between the workloads. Subjects exercised using a handgrip dynamometer, which was electronically linked to an analog meter. This meter provided visual feedback to the subjects, enabling them to maintain the prescribed tension. Exercise was followed by a 5-min recovery period. On the basis of prior experiments, we believed that this paradigm would lead to a high level of perceived effort by the end of the fourth workload (35).

Study B. In this study, ³¹P-NMR spectra were obtained from the flexor digitorum superficialis muscle of the exercising forearm. We examined muscle metabolism during forearm exercise in one group before and after bretlyium ($n = 9$) and in a second group in whom forearm handgrip was performed after receiving an infusion of saline (no bretlyium) before the second trial ($n = 7$). Four subjects performed both *study A* and *B*, and two subjects performed *study A* and were a control in *study B*. Three subjects in *study B* received bretlyium and also served as controls (received saline). The protocols for *study A* and *B* are shown in Fig. 1.

Bretlyium Bier Block (Performed in Both Study A and B)

Inhibition of norepinephrine release was accomplished by infusing bretlyium tosylate (1 mg/kg; bier block) into the antecubital vein of the exercising forearm after sequential exsanguination of forearm blood volume [compression bandage placed on the forearm and circulatory arrest (15, 33)]. Circulatory arrest was applied by using a compression cuff around the upper arm inflated to 250–300 mmHg. The circulatory arrest was maintained for 20 min. After a 60-min rest period, testing was resumed. The efficacy of sympathetic blockade was determined by measuring the forearm flow during a 90-s cold pressor test. For this test, the foot without the peroneal nerve electrode was placed in iced saline.

NMR Studies (Performed in Study B)

Muscle metabolism during forearm skeletal muscle exercise was assessed by using ³¹P-NMR spectroscopy. This method allows for the noninvasive repetitive assessment of muscle phosphocreatine (PCr), P_i, and pH. The high-energy phosphate measurements were obtained with a 1.9-T 26 cm-bore superconducting magnet (Oxford Instruments, Abington, UK) interfaced with a radio frequency transmitter and receiver (Nicolet Instrument, Madison, WI). A coil 2.5 cm in diameter was placed over the flexor digitorum superficialis muscle. The obtained spectra were collected at 32.5 MHz and represented the Fourier transformation of 32 transients averaged over 60 s during rest, during each exercise workload,

and during each minute of recovery. The relative concentrations of PCr were calculated from the area under the resonance curve and are expressed in arbitrary units. Intracellular pH was calculated from the shift of the P_i resonance relative to PCr. The NMR technique has been described previously (3).

Measurements of MSNA (Performed in Study A)

Multiunit recordings of postganglionic MSNA were obtained from the peroneal nerve with an insulated 200- μ m-diameter tungsten electrode with a tapered uninsulated 1- to 5- μ m diameter tip. A microelectrode was inserted transcutaneously into the peroneal nerve (just posterior to the fibular head), and a reference electrode was positioned subcutaneously 1–3 cm from the recording site. Neuronal activity was amplified ($\times 50,000$ – $100,000$), the signal was filtered (bandwidth of 700–2,000 Hz), rectified, and integrated, yielding a mean voltage neurogram. MSNA data were analyzed according to the burst frequency (11). Resting burst frequency has been shown to be reproducible (8, 39) when readings are performed on different days. Complete sets of the MSNA data were collected in six of the eight subjects studied.

Forearm Flow Measurements (Performed in Study A)

Brachial artery limb blood flow was determined by combined pulsed and echo Doppler ultrasound. A 4- or 5-MHz flat probe was used to measure blood flow velocity. The probe was positioned over the brachial artery in the antecubital fossa. In each case, the probe was fixed to the skin with hypoallergenic tape. During measurements, small adjustments of the probe were necessary to maintain the optimal signal. Signal strength was optimized by using both visual and auditory feedback of the Doppler shift frequencies. The depth and gate size of the ultrasound beam were adjusted to insonate the entire vessel lumen.

The Doppler shift signal was demodulated to provide instantaneous mean blood velocity (MBV) data in real time. The signal was calibrated by an electronically generated phase shift of 1 mV, allowing conversion of the demodulated data to MBV values calculated and stored on a computer-based system at 100 Hz.

Blood flow was determined from both the blood velocity and the vessel cross-sectional area (blood flow = $MBV \times \pi r^2$, where r is the vessel radius). Vessel dimensions were measured at each workload by using echo Doppler sonography as two-dimensional B-mode images were obtained with a 7.5-MHz transducer. Vessel dimensions were determined by three investigators, and the coefficient of variation was calculated to be $<5\%$. Vascular resistance and conductance were calculated from the mean arterial pressure and forearm blood flow. Relative changes in SBF were determined by using a laser-Doppler flow probe that was placed on the forearm, and the position was marked. During the bier block procedure, it was necessary to remove the probe. It was replaced in the marked location on the forearm.

The "release" of K^+ , H^+ , and lactate was determined by measuring the flow and multiplying this value by the concentration of the various substances in the venous effluent. In these calculations, we assumed that the increases in flow and changes in metabolite concentrations with exercise were due predominantly to increases in muscle flow. Prior literature suggests that this approach is valid (4, 34). Forearm oxygen consumption was determined by the following equation: forearm flow \times [arterial oxygen saturation – venous oxygen saturation \times hemoglobin \times 1.39]. In these studies we assumed an arterial oxygen saturation of 100%.

Statistics

The longitudinal design of this study consisted of two factors repeated for each subject: bretylium effect (pre- and postbier block) and handgrip. To assess the effects of bretylium and handgrip, as well as their possible interaction, on the blood flow, metabolism, and reflexes, doubly repeated-measures analysis of variance models were fit to the data (21). The fit of these models were assessed by using residual diagnostics. When the interaction effect was significant, simple effects were tested and adjusted for multiple comparisons via Bonferroni's procedure. Descriptive data for continuous variables (e.g., blood flow) are presented as means \pm SE. A P value ≤ 0.05 was considered statistically significant. The data were analyzed by using the MIXED procedure from the SAS statistical software (SAS Institute, Cary, NC).

For six of the eight subjects in our study, the vessel diameters were known for each phase of the exercise paradigm. For two of the eight subjects, however, only baseline vessel diameter was known. Because vessel diameter was necessary to calculate blood flow, we imputed values for the missing vessel diameters for these two subjects. On the basis of the empirical distribution of vessel diameters from the six subjects with complete data, we selected two of these subjects, whose baseline diameters closely matched the baseline diameters of the two subjects with missing data, and imputed their values for the missing vessel diameters. This method of imputation is preferable to other methods, such as imputing the mean values of nonmissing diameters, because it does not dampen the variability of the vessel diameter distribution.

RESULTS

Study A

The bier block caused a marked reduction in forearm resistance during the cold pressor maneuver (pre-bretylium 1.98 ± 0.19 resistance units, post-bretylium 0.82 ± 0.12 resistance units). The bier block procedure also attenuated the blood pressure seen during the cold pressor intervention (change pre-bretylium 19.0 ± 2.2 mmHg; change post-bretylium 10.3 ± 1.6 mmHg; $P < 0.03$). This suggested that this intervention had systemic as well as local effects.

Forearm exercise led to a large increase in forearm flow, a rise in forearm conductance, a reduction in venous oxygen saturation, and an increase in oxygen consumption (Fig. 2).

After bier block, resting flow and forearm conductance were higher (Fig. 2) than before bretylium block (flow: pre-bretylium 59.4 ± 9.0 ml/min; post-bretylium 163.5 ± 33.6 ml/min; conductance: pre-bretylium 0.623 ± 0.076 ml \cdot min $^{-1}$ \cdot mmHg $^{-1}$; post-bretylium 1.682 ± 0.336 ml \cdot min $^{-1}$ \cdot mmHg $^{-1}$). The bier block increased forearm blood flow (bretylium effect, $P < 0.03$), the flow velocity ($P < 0.0001$), and the forearm vascular conductance ($P < 0.02$) in the exercising forearm. This was associated with a greater forearm oxygen consumption (bretylium effect, $P < 0.023$; Fig. 2).

In Fig. 3, the change in oxygen consumption as a function of the change in flow is presented. This figure suggests that changes in flow above are not sufficient to explain the greater oxygen consumption seen after bier block. SBF during exercise was also greater after

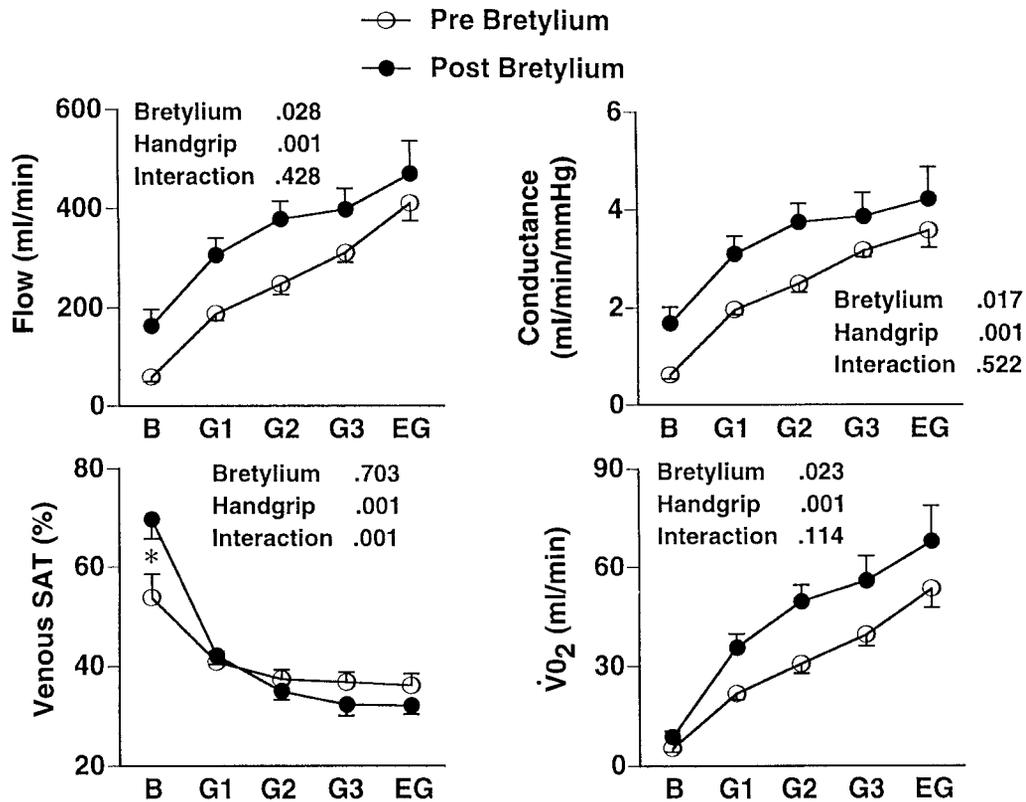


Fig. 2. Effects of bretylium bier block and handgrip exercise on flow, conductance, venous oxygen saturation (venous SAT), and oxygen consumption ($\dot{V}O_2$). B, baseline. Values are means \pm SE for 8 subjects. There was a bretylium bier block main effect for flow, conductance, and $\dot{V}O_2$. * $P \leq 0.05$ for values of B pre- and post-bretylium.

bier block (bretylium main effect $P < 0.04$; end grip values: pre-bretylium 5.6 ± 0.5 arbitrary units; post-bretylium 7.5 ± 1.3 arbitrary units).

Exercise led to an increase in the release of K^+ and H^+ but not of lactate (Fig. 4).

After bier blockade, resting MSNA was much higher, whereas heart rate and blood pressure were unchanged by the intervention (Fig. 5). Bretylium did not alter heart rate and blood pressure during exercise. Although we observed a main effect for MSNA (Fig. 5) during exercise, bretylium did not alter the change in MSNA.

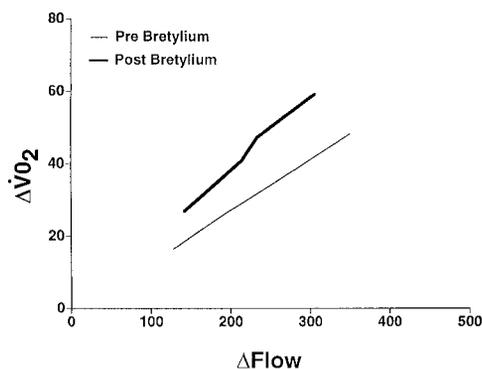


Fig. 3. Change in $\dot{V}O_2$ ($\Delta \dot{V}O_2$) vs. change in flow (Δ flow) demonstrates that the rise in $\dot{V}O_2$ was not due solely to an increase in flow, because the slope of the line was steeper post-bretylium than pre-bretylium. Units for x- and y-axis presented in the text.

Study B (Fig. 6)

In the bretylium-treated subjects we observed a lower minimum intracellular pH (simple effects during *minute 1* of recovery, $P < 0.036$). No such sequence effect was seen in the saline-treated (control) subjects. The bier block had no effect on the P_i ratio ($P_i/PCr + P_i$) in either group.

DISCUSSION

Study Findings

There are several findings in the present paper worthy of mention: 1) bier block with bretylium increased the forearm blood flow during exercise; 2) this was associated with an increase in forearm oxygen consumption during exercise; 3) despite greater levels of forearm flow after bier block, there was a greater release of H^+ and a lower minimal pH (measured during the first minute of recovery with NMR); and 4) the increase in forearm flow did not reduce the heart rate, blood pressure, or sympathetic nerve responses to forearm exercise. In the DISCUSSION, we will examine the possible mechanisms for these observations as well as their implications.

Effects of Sympathetic Tone of Forearm Blood Flow

The interrelationship between metabolic vasodilation and neurally mediated vasoconstriction has been

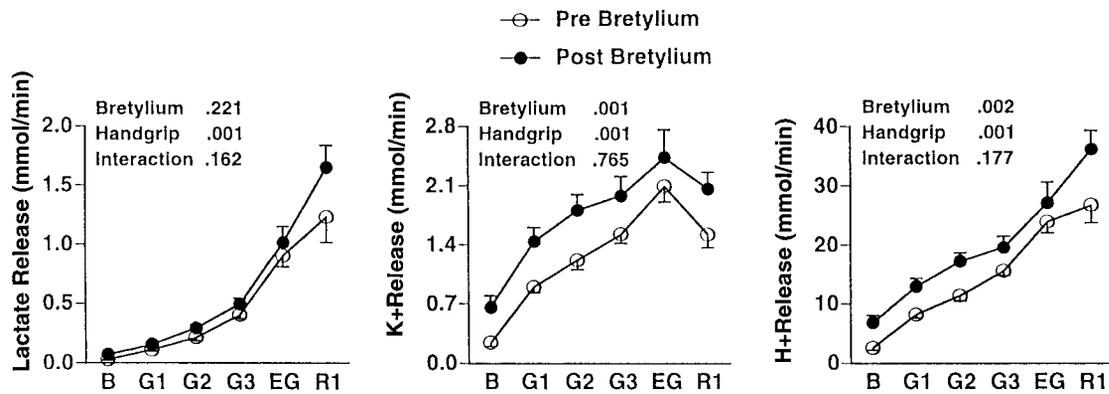


Fig. 4. Effects of bretylium bier block and handgrip exercise on lactate, K⁺, and H⁺ release. Note that bretylium bier block resulted in an increase in K⁺ and H⁺ release but not in lactate release. Values are means \pm SE for 8 subjects. R1, first minute of recovery.

an area of considerable investigation. It is interesting to note that a number of substances that may contribute to metabolic vasodilation alter norepinephrine release and reuptake (41) and in the process antagonize the effects of norepinephrine, leading to the classic concept of "functional sympatholysis" (29). Microvascular studies (20, 24) and recent near-infrared spectroscopy data in humans (15) provide further support for this concept. However, it is known that muscle blood flow capacity can greatly exceed maximal cardiac output (1, 2, 25). Given the fact that blood pressure does not fall during exercise, it must be concluded that these peak levels of muscle flow are not achieved. Rowell (30) has hypothesized that myogenic and sympathetic vasoconstrictor influences prevent muscle flow from outstripping cardiac output during maximal exercise. It must be emphasized that, in addition to this teleological approach to the problem, a number of studies using both animal and human models have shown that the sympathetic nervous system is reflexly engaged, evoking a vasoconstrictor response that actively opposes the profound local vasodilation seen within the exercising muscle (7, 12, 17, 26, 28, 35, 36, 38, 42).

We believe the findings of the present study provide evidence that sympathetic tone does restrain muscle

blood flow during exercise. After the bier block, total forearm blood flow (Doppler) as well as SBF increased. Our data do not support the notion that the increase in SBF was responsible for the majority of the increase in total forearm flow, because the skin contributes only ~11% of the vascular forearm tissue capable of vasodilation (10). Because blood pressure was similar before and after the bier block, the data suggest that the higher exercise flows postblock were not due to differences in myogenic tone but rather to "lysis" of sympathetic tone directed predominantly to skeletal muscle.

Effects of Sympathetic Withdrawal on Oxygen Consumption

In this study, we observed that after bier block, oxygen consumption during forearm exercise was increased. This confirms prior work by Joyner et al. (17), who demonstrated that, after stellate ganglion block, exercise limb flow and oxygen consumption were greater than before block. The present report differs from the one by Joyner et al. in that we directly measured limb flow (Doppler) and the metabolic consequence of flow. Additionally, Joyner et al. used a

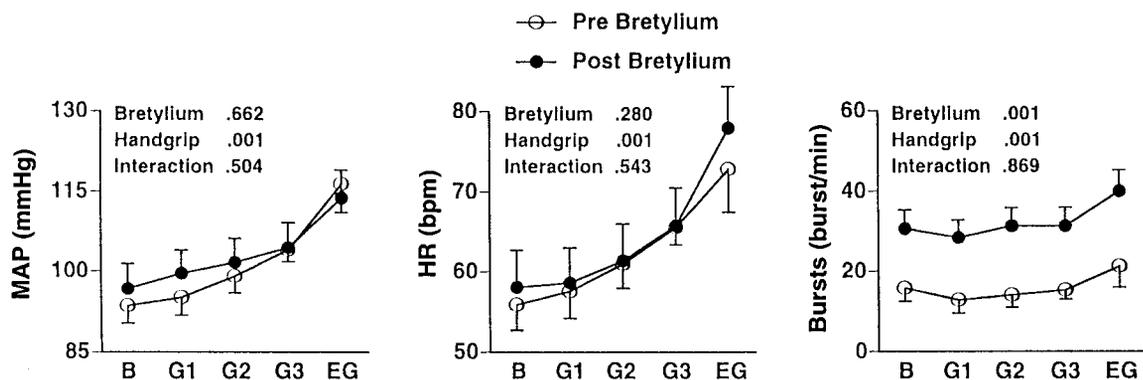


Fig. 5. Effects of bretylium bier block and handgrip exercise on mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve activity bursts. Values are means \pm SE for 8 subjects. bpm, Beats/min. Muscle sympathetic nerve activity was higher post-bretylium; however, MAP and HR were not significantly changed by the intervention.

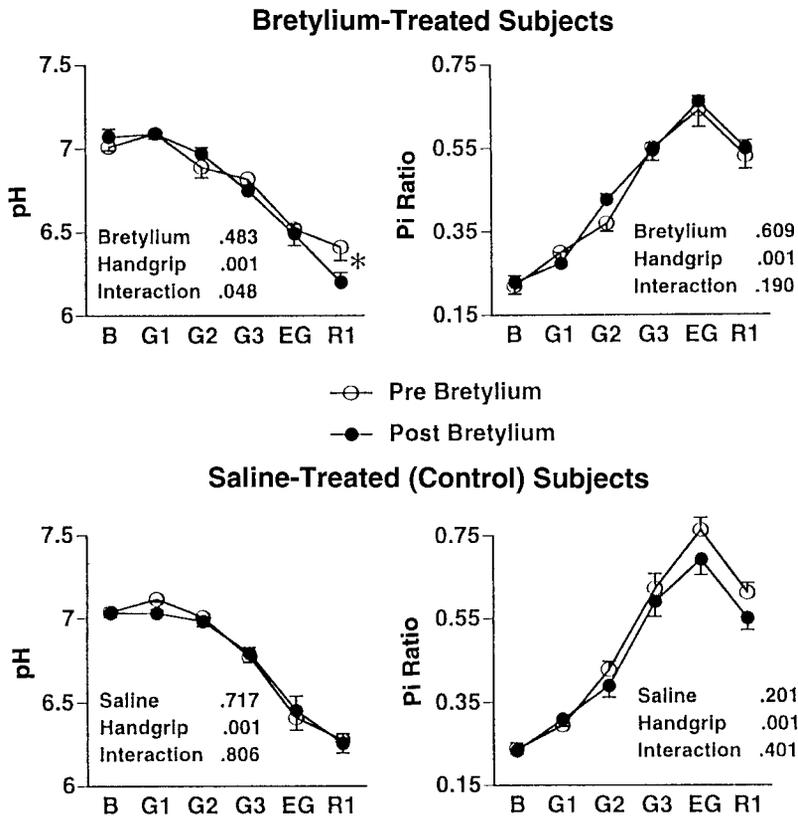


Fig. 6. NMR data for intracellular pH and P_i ratio ($P_i/PCr + P_i$) in bretylium-treated and saline-treated subjects. Values are means \pm SE for 9 for bretylium-treated subjects and 7 saline-treated subjects. In the bretylium-treated subjects, pH at R1 was lower after blockade than before. * $P < 0.05$ for pre- and post-bretylium at R1.

stellate ganglion blockade, whereas we used a bretylium bier block approach.

Additionally, we believe this finding is consistent with the concept that, under certain circumstances, oxygen delivery can play an important regulatory role in cellular respiration during muscle contraction (9); i.e., increases in oxygen delivery can lead to an increase in the amount of oxygen consumed (6, 17, 43, 44).

The increase in oxygen consumption found in our study was not solely due to the increase in oxygen delivery because the slope of line relating oxygen consumption to limb flow was greater after the bretylium block. The mechanism for this finding is not entirely clear, although we did observe a greater efflux of H^+ after bier block. This would tend to shift the partial pressure of oxygen at which 50% hemoglobin is saturated (P_{50}) for hemoglobin to the right and in the process lead to a greater release of oxygen to the exercising muscle (14).

Effects of Sympathetic Withdrawal on Cellular Metabolism

In this study, we observed that, despite higher levels of forearm blood flow, H^+ and K^+ efflux and the maximal cellular H^+ concentration (NMR) were increased after the bretylium bier block. The mechanism for these findings is not entirely clear, although we propose the following scenario. It is well known that increased sympathetic drive can increase the amount of muscle tension developed during contraction. This ef-

fect of catecholamines on muscle contractile function has been described in great detail for the heart (16) and diaphragm (13, 19). For example, it is known that increased catecholamines evoke Ca^{2+} release in the sarcoplasmic reticulum (16), a process thought to be mediated by a protein termed the dihydropyridine (DHP) receptor (5). This leads to increased contractile function.

Recently it has been shown that the cardiac isoform of the α_1 -subunit of the DHP protein is expressed in slow- but not in fast-twitch skeletal muscle (27). Accordingly, on the basis of our results, we propose the following scenario: as muscle workload increased, the muscle reflex was eventually engaged, leading to increased sympathetic tone directed to exercising muscle. This led to the release of norepinephrine, which stimulated the DHP receptors, thereby preserving slow-twitch muscle fiber contractility. The bier block reduced norepinephrine levels during handgrip and in the process reduced contractile activity by the muscle oxidative fibers. This necessitated the recruitment of more glycolytic muscle fibers to maintain muscle tension. It is known that glycolytic fibers as opposed to oxidative ones produce more lactic acid and utilize oxygen less efficiently (23, 45). We further speculate that this led to the greater oxygen consumption and the increased production of metabolic byproducts of contraction that was seen after bier block. This line of reasoning is consistent with prior rat model work demonstrating that systemic bretylium infusions lead to

the preferential utilization of glycogen from fast-twitch skeletal muscle (40).

Effects of Sympathetic Withdrawal on MSNA

In this study, we observed that, after sympathetic blockade, the MSNA response to the progressive hand-grip protocol was unchanged. We speculate that a greater flow delivery and the greater removal of interstitial metabolites would tend to reduce reflex responses. However, these effects were likely offset by the greater recruitment of muscle fibers with a more glycolytic profile that produced greater quantities of metabolites capable of stimulating muscle afferents.

Conclusion

The present study provides convincing evidence that flow to skeletal muscle is in fact restrained by sympathetic tone. We believe this ability to limit flow to exercising muscle contributes to the maintenance of blood pressure seen with vigorous exercise. The intriguing part of this study, however, is the fact that, after pharmacological sympathetic blockade, muscle acidosis and metabolite release were greater than before blockade. This suggests that the capacity of the sympathetic nervous system to influence exercise performance is multifactorial. Moreover, under the conditions of the present paradigm, we believe that the sympathetic nervous system's ability to directly alter metabolism may be more important than its ability to modulate flow.

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