Arteriolar reactivity and capillarization in chronically stimulated rat limb skeletal muscle post-MI

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Thomas, D. Paul, and Olga Hudlická. Arteriolar reactivity and capillarization in chronically stimulated rat limb skeletal muscle post-MI. J. Appl. Physiol. 87(6): 2259–2265, 1999.—The purpose of this study was to assess whether electrical stimulation-induced increases in muscular activity could improve capillary supply and correct previously documented abnormal vasodilator and vasoconstrictor responses of arterioles in limb skeletal muscle post-myocardial infarction (MI). Extensor digitorum longus (EDL) muscle from rats with surgically induced MI (≈30% of the left ventricle) was chronically stimulated (Stim) 8 h/day for 6 ± 1 days, at 11 wk post-MI. Third- (3A) and fourth-order (4A) arterioles in EDL from nine MI rats and four MI + Stim rats were compared with those of 11 controls (Con). Compared with Con rats, MI alone caused a reduction in the resting diameter of 3A and 4A arterioles, which was completely reversed by MI + Stim. However, Stim did not correct the attenuated vasodilator response to 10−4 M adenosine seen in 4A arterioles from MI rats compared with Con. The constrictor response of both 3A and 4A vessels in Con rats to low doses of acetylcholine (10−9 M, 10−8 M) and norepinephrine (10−9 M) was accentuated in MI + Stim. The proportion of oxidative fibers in EDL was accentuated in MI or MI + Stim combination. However, Stim significantly increased (P < 0.05) the capillary-to-fiber ratio in this muscle compared with Con. Thus, although the increase in muscle activity induced by chronic electrical stimulation normalized the reduction in resting vessel diameter seen after MI, it failed to correct the abnormalities in vasoreactivity of these same vessels.

endothelium; skeletal muscle activity; nitric oxide; heart failure

It is now recognized that myocardial infarction (MI) not only affects central hemodynamics and ventricular function but also results in decrements in limb blood flow and muscle performance. The exertional fatigue commonly seen in heart failure patients may thus be caused by perfusion deficits (13, 19) as well as by abnormalities in muscle per se (9). Changes in the vasculature of both the large conduit arteries and smaller resistance vessels in both heart patients and animal models of MI and chronic heart failure have also been described (6, 7, 39, 42). At the arteriolar level, abnormalities include increases in resting tone (42) as well as diminished vasodilator capacity and exaggerated vasoconstrictor sensitivity (6, 7, 42). The findings from these and other studies highlight the role that changes in vascular endothelium as opposed to smooth muscle play in the observed perfusion deficits and implicate a defect in the nitric oxide (NO) synthesis and/or release pathways (11, 12, 22, 31).

In contrast, increasing muscle blood flow by exercise training has been shown to elevate mRNA levels for NO synthase in canine aortic extracts (34) and the production of NO from coronary arteries and skeletal muscle arterioles in dogs and rats, respectively (34, 40). It also enhanced the endothelium-dependent (ACh) but not endothelium-independent (sodium nitroprusside) relaxation in abdominal aortic rings (5) and in gracilis muscle arterioles from the rat (40). These alterations in endothelial function have been postulated as one mechanism to explain the improved muscle perfusion and performance seen with exercise training (20, 35). Similarly, daily handgrip exercise in heart-failure patients resulted in significant improvements in ACh- and occlusion-mediated increases in forearm blood flow (13, 19). However, exercise training had no effect on the relaxation response of aortic strips to ACh in infarcted rats (26).

Whether hyperemia induced by muscle contractions via chronic electrical stimulation alters vasoreactivity of the supplying blood vessels has not been investigated, although it is recognized that there are some similarities in adaptation of skeletal muscle to these two interventions such as increased capillary supply (17, 32). In addition, electrical stimulation (Stim) normalized terminal arteriole resting diameters and their response to adenosine (Ado) in animals treated with NOS-nitro-L-arginine (L-NNNA) (36). Electrical stimulation of calf and quadriceps muscles in heart failure and cardiac transplant patients for 5 and 8 wk, respectively, also resulted in an improvement in peak O2 consumption and exercise performance (26, 44). However, these studies did not evaluate whether enhanced muscle perfusion resulting from improvements in vascular smooth muscle or endothelial function contributed to the overall increase in functional capacity.

The purpose of this study was therefore to examine whether electrical stimulation could correct the previously documented abnormal vasoreactive responses in limb muscle arterioles and increase capillary supply in an infarct model of depressed left ventricular (LV) function without overt failure (42). In this manner we sought to evaluate whether electrical stimulation could provide an alternative means of correcting the defect in vascular endothelial function seen in both human heart patients and animal models of MI and CHF.
METHODS

Animal selection and infarct surgery preparation. Experiments were performed on young adult female Wistar rats in accordance with the United Kingdom Animals (Scientific Procedures) Act of 1986. All surgical procedures were performed under aseptic conditions. Rats to receive infarct surgery were anesthetized with a medetomidine (0.25 mg/kg)-ketamine (60 mg/kg) combination administered intraperitoneally, intubated, and placed on a rodent respirator (model 683, Harvard). A chronic MI was then surgically produced as described in detail previously (42). After thoracotomy and pericardectomy, medium-sized infarcts were produced in the left ventricle free wall by passing a 6-0 Cardiopoint suture under the left anterior descending coronary artery 3–4 mm caudal to the left atrium. Once successful production of an infarct had been verified by tissue blanching and/or electrocardiogram changes, the chest was closed and the lungs fully expanded. Muscle and skin incisions were immediately closed with separate sutures. All surviving rats received a broad-spectrum antibiotic (enrofloxacin, 2.5 mg/1 ml) for 4 days postsurgery, and every attempt was made to minimize discomfort (buprenorphine, 2.5 µg/0.1 ml twice daily) during this period.

Electrical stimulation. In five previously infarcted rats, a second surgical procedure was performed ~11 wk later in which multistranded stainless-steel, tetrafluoroethylene-insulated electrodes were implanted unilaterally in the vicinity of the peroneal nerve under anesthesia. The wires were tunneled under the skin to the interscapular region, where they were exteriorized and attached to the skin with a piece of Velcro. They were connected to an external stimulator (Neurotech, Shannon, Ireland) by lightweight leads and were covered with another piece of Velcro when the animal was not being stimulated. Stimulation commenced the day after electrode implantation and was performed up to 7 days [6 ± 1 (SE) days]. Rats were stimulated for 8 h/day at 10 Hz, pulse width 0.3 ms, and at sufficient voltage (3–5 V) to produce maximal contraction on palpation without causing the animal any apparent discomfort. Results from one of the stimulated rats were excluded from the myocardial infarction + electrical stimulation (MI + Stim) data set because the coronary ligature came undone and no evidence of infarction was present.

Intravital preparation and observation of muscle microcirculation. Eleven to twelve weeks after MI surgery, control (Con; n = 11), MI (n = 9), and MI + Stim (n = 4) rats were anesthetized with the medetomidine-ketamine combination before surgical preparation of EDL as performed previously (16). In brief, the right jugular vein and carotid artery were cannulated for administration of additional anesthetic whenever necessary (pentobarbitral sodium, bolus 5 mg/kg) and recording of arterial blood pressure, respectively, and the right hindlimb was prepared for exposure of the EDL muscle (42). The foot was partially rotated, which permitted evaluation of the arteriolar supply to this muscle. Throughout these surgical procedures, and during the subsequent observation period, the surface of the exposed muscle was continuously superfused with a warmed deoxygenated Krebs-Henseleit solution (131.9 mM NaCl, 4.7 mM KCl, 1.17 mM MgSO₄ · 7H₂O, 2.0 mM CaCl₂ · 2H₂O and 22.0 mM NaHCO₃, pH 7.35–7.45) at a temperature of 32–34°C at 5 ml/min (16).

The animal was next placed under an intravital microscope fitted with a television camera connected to a video recorder, and arterioles identified by means of an immersion objective (×25/0.6 numerical aperture) by using fiber-optic epillumination. Images were recorded on the video recorder and displayed on a television monitor giving a final magnification of approximately ×1,000 with resolution of 0.45 µm/pixel on the monitor. The ability of the eye to perceive changes in location is far better than its ability to resolve two objects. Hence, actual errors are considered to be less than this value, with visual interpolation giving an effective resolution of <0.4 µm/pixel. Both precapillary [fourth-order (4A)] and the next highest order of arterioles [third-order (3A)] were identified by their location within the branching microvascular network. Arteriolar luminal diameters (µm) were measured by aligning vessel images on the television screen in the vertical plane and superimposing a previously calibrated video reticle generator. Repeated measurements of the same vessel at various intervals gave virtually the same values. All reticle measurements were displayed on a chart recorder and saved on videocassette, which also recorded time and frame counts (14). A total of 30, 29, and 16 (3A) and 40, 32, and 29 (4A) EDL arterioles were measured from 11 Con, 9 MI, and 4 MI + Stim rats and were treated as independent observations.

Luminal diameters were obtained both at rest, and after randomized topical administration of 1 ml of 10⁻³ and 10⁻⁴ M Ado, 10⁻⁹, 10⁻⁸ and 10⁻⁷ ACh, and 10⁻⁸, 10⁻⁷ and 10⁻⁶ M norepinephrine (NE) in superfusion buffer administered via syringes to the muscle surface under the objectives. Care was taken to keep the solutions without access to air as much as possible and to keep the temperature similar to that of the superfusion fluid. The drugs were administered over a 5- to 10-s period so that the actual concentration was lower because of dilution by the superfusate. Several minutes were allowed to elapse before administration of each subsequent dose/drug so that diameter of the arteriole being evaluated had returned to resting values. Total duration of observation did not exceed 2 h, by which time there were no signs of deterioration of the preparation as judged by white blood cell adhesion to postcapillary venules.

Hemodynamic measurements. Immediately after the intravital studies a Millar 3-Fr microtip transducer catheter was advanced down the right carotid artery into the left ventricle to continuously record LV end-diastolic pressure and the peak positive derivative of LV pressure (LV +dP/dtmax). The LV pressure trace was temporarily switched to high gain (+10×), to record end-diastolic pressure, which was measured as the inflection point in the diastolic pressure trace. LV +dP/dtmax, was derived from the LV pressure trace by using an Electromed differentiator channel. After completion of all functional measurements, euthanasia was achieved by anesthetic overdose.

Skeletal muscle characteristics. The EDL was rapidly excised and weighed before histochemical analysis of succinic dehydrogenase (SDH) activity and capillarity. The muscle was sectioned in midbelly, rapidly frozen in liquid nitrogen-cooled isopentane, and subsequently sectioned in a cryostat. Sections (12 µm thick) were stained for SDH to demonstrate oxidative activity (42), and adjacent sections were processed to demonstrate all anatomically present capillaries, which were stained for alkaline phosphatase by using 5-bromo-4-chloro-3-indoxyl phosphate toluidine salt as substrate and tetrazolium as chromagen (14). Capillary supply was expressed as the capillary-to-fiber (C/F) ratio from counts made in 20 fascicles of 5 (Con), 5 (MI) and 4 (MI + Stim) muscles from the three groups (14).

Determination of ventricular weights and infarct size. The heart was blotted and weighed after excision and removal of both atria. Both ventricles were then individually weighed after the right ventricular wall (RV) had been dissected away from its attachment to the LV septum. The entire LV was then immersion-fixed in 10% buffered formaldehyde for a mini-
Table 1. Body weight and right and left ventricular weights in control, myocardial infarcted, and infarcted-stimulated rats

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>BW, g</th>
<th>RV Wt, mg</th>
<th>RV/BW, mg/g</th>
<th>LV Wt, mg</th>
<th>LV/BW, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td>11</td>
<td>285 ± 5</td>
<td>188 ± 8</td>
<td>0.67 ± 0.03</td>
<td>680 ± 21</td>
<td>2.39 ± 0.08</td>
</tr>
<tr>
<td>MI</td>
<td>9</td>
<td>324 ± 11*</td>
<td>235 ± 25*</td>
<td>0.73 ± 0.05</td>
<td>860 ± 28†</td>
<td>2.67 ± 0.13†</td>
</tr>
<tr>
<td>MI + Stim</td>
<td>4</td>
<td>282 ± 12</td>
<td>187 ± 8</td>
<td>0.67 ± 0.05</td>
<td>813 ± 92†</td>
<td>2.86 ± 0.19†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. BW, body weight; RV and LV Wt, right and left ventricular weights, respectively; Con, MI, and MI + Stim, control, myocardial infarcted, and infarcted-stimulated rats. *P < 0.05 vs. Con or MI + Stim. †P < 0.05 vs. Con.

Table 2. Infarct size and central hemodynamics from control, myocardial infarcted, and infarcted-stimulated rats

<table>
<thead>
<tr>
<th></th>
<th>MI size, % of LV</th>
<th>MAP, mmHg</th>
<th>LVEDP, mmHg</th>
<th>LV + dP/dtmax, mmHg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td>11</td>
<td>33 ± 4</td>
<td>3.1 ± 0.3</td>
<td>4,881 ± 286</td>
</tr>
<tr>
<td>MI</td>
<td>9</td>
<td>33 ± 3</td>
<td>5.3 ± 0.7*</td>
<td>3,807 ± 233*</td>
</tr>
<tr>
<td>MI + Stim</td>
<td>4</td>
<td>31 ± 4†</td>
<td>14.1 ± 4.2†</td>
<td>2,850 ± 817*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. MI size, infarct size; LV, left ventricle; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; LV + dP/dtmax, peak first derivative of left ventricular pressure trace. *P < 0.05 vs. Con. †P < 0.05 vs. Con or MI.

RESULTS

Body, LV, and RV weights. Rats in the MI group were significantly heavier than those in the other two groups. For this reason, all LV and RV weights were expressed in both relative and absolute units (Table 1). Even when corrected for body weight, LV weight was significantly heavier in MI and MI + Stim rats compared with that of Con animals (both P < 0.05). In this regard, there were no differences in RV mass among the three groups when normalized for body weight (Table 1).

Infarct size and LV function. Infarct size ranged from 24 to 41% in the MI group, with individual values of 38, 20, 34, and 32% for the MI + Stim group. Infarct size was not significantly different between MI and MI + Stim groups (Table 2). Mean blood pressure and LVEDP were significantly higher in the MI + Stim group compared with either MI or Con groups as illustrated in Table 2. Use of LV + dP/dtmax as an index of LV contractility also revealed a significantly depressed contractile state in both MI and MI + Stim hearts compared with Con.

Arteriolar diameters. Resting lumen diameter for both 3A and 4A arterioles in the three groups is shown in Fig. 1. Mean diameter for 3A but not 4A arterioles was significantly smaller in the MI group compared with Con. The combination of MI + Stim corrected this situation so that lumen diameters in this group were significantly larger than in MI rats and similar (3A) or larger (4A) than seen in Con.

Vasoactive responses. Dilatation in response to 10⁻⁵ and 10⁻⁴ M Ado was somewhat, albeit not significantly, attenuated in 3A arterioles in both experimental groups compared with Con (Fig. 2). In 4A arterioles, dilatation in response to 10⁻⁵ M Ado was significantly attenuated in MI rats, but stimulation restored the ability of these microvessels to dilate to a similar degree as those of Con (13, 19, and 23% for MI, MI + Stim, and Con respectively). However dilatation to a higher dose of Ado was significantly attenuated in both groups of infarcted animals. Although very little change was seen in Con 3A or 4A vessel diameter in response to 10⁻⁹ M and 10⁻⁸ M ACh, vessels from infarcted rats constricted to these same concentrations of ACh (Fig. 3). This response was even more pronounced in the group also receiving electrical stimulation so that at both 10⁻⁹ M and 10⁻⁸ M ACh vessels from MI + Stim were significantly more constricted than those from MI alone (P < 0.01 or greater).
At 10⁻⁷ M, ACh constricted both categories of vessels from all groups, but 4A arterioles from the MI Stim group were still more constricted than in either of the other two groups.

NE constricted both 3A and 4A vessels from all three groups of rats in a dose-dependent manner (Fig. 4). However, at 10⁻⁹ M NE, 3A vessels in Con rats were significantly less constricted (P < 0.001) than those from MI rats, which in turn were less constricted (P < 0.001) than vessels from MI+Stim animals (−13 vs. −39 vs. −74%). A similar difference in constrictor response to the same concentration of NE was also seen in 4A arterioles from the three groups (−4 vs. −41 vs. −82%). With higher doses of NE the constriction in both infarcted groups was greater than in controls, but there were no significant differences in response between MI and MI+Stim.

EDL weight, oxidative characteristics, and capillary supply: Although EDL absolute muscle mass was significantly heavier in the MI group (P < 0.05), when corrected for body wt this significance disappeared (Table 3). Compared with Con, muscle capillarity in the MI+Stim group expressed as C/F ratio was significantly elevated (P < 0.05) after 6 days of electrical stimulation. Electrical stimulation also increased C/F ratio in the stimulated EDL compared with the value obtained on the nonstimulated contralateral side (1.59 ± 0.08 vs. 1.37 ± 0.07; P < 0.05). Percentage of oxidative fibers as assessed by SDH staining was not different among any of the three groups.

**DISCUSSION**

The present study examined the effects of chronic electrical stimulation on capillary supply and size and on vasodilator and vasoconstrictor responses in terminal (4A) and preterminal (3A) arterioles in EDL muscle from rats with medium-sized infarcts of the left ventricle with the aim of establishing whether this procedure could reverse the abnormalities in endothelial function reported previously (6, 7, 42). The major findings of this study were that 6 days of electrical stimulation reversed the luminal narrowing of terminal and preterminal arterioles that accompanied MI. Stimulation also resulted in an increased C/F ratio in EDL, but it failed to reverse the attenuated vasodilator and accentuated vasoconstrictor responses to various agonists within the microcirculatory bed of this muscle.

Fig. 2. Dilation response of 3A and 4A arterioles to adenosine (Ado; 10⁻⁵ or 10⁻⁴ M) in extensor digitorum longus muscle from Con, MI, and MI+Stim rats. *P < 0.05. **P < 0.005 vs. Con.

Fig. 3. Response (% change in diameter) of 3A and 4A arterioles to ACh (10⁻⁹, 10⁻⁸, or 10⁻⁷ M) in extensor digitorum longus muscle from Con, MI, and MI+Stim rats. **P < 0.005. ***P < 0.0001 vs. Con. †P < 0.01. ††P < 0.005 vs. MI.
Changes in microcirculation. The reduction in resting diameter of 3A and 4A arterioles in EDL muscles from MI rats compared with those from Con confirms our earlier findings (42) and those of others who showed perfusion deficits and elevated limb vascular resistance in both humans and animals postinfarction (8, 9, 30). Six days of electrical stimulation returned resting diameter to that seen for controls in these two categories of arterioles in EDL from infarcted rats. This finding is similar to preliminary results from our laboratory (36) on rats receiving L-NNA in their drinking water. L-NNA treatment resulted in a decrease in arteriolar diameter that was corrected by just 2 days of stimulation. Previously, our laboratory (31) reported that any increases in arteriolar diameter after chronic electrical stimulation in normal muscle are very transient (2 days), returning to prestimulation values by 7 days. The finding of decreased diameters in small arterioles from EDL muscle of infarcted animals in the present study could be due to a deficient release of NO, which can be corrected by increased muscle activity induced by electrical stimulation. This interpretation is at least partly supported by the fact that training induces an increase in endothelial NO synthase in skeletal muscle arterioles (40). However, in the present study, increased muscular activity impaired, rather than improved, the response of these arterioles to vasodilators and vasoconstrictors.

Although the attenuated vasodilation to the lower dose of Ado in terminal arterioles (4A) in MI animals was reversed by stimulation, dilation in response to the higher dose was even smaller in MI+Stim compared with MI rats. Ado produces vasodilation by acting on A1 receptors in smooth muscle (21), but it can also act on endothelium (46). Thus recent studies have emphasized a role for A2 receptors (1), but whether the release of NO is involved is a point of some controversy (3). After exercise training, a somewhat (23) or significantly (40) attenuated response of intramuscular arterioles to Ado was observed in rat spinotrapezius and gracilis muscle, respectively. Sun et al. (40) postulated that chronically elevated Ado levels in exercised muscles from trained animals could result in downregulation of smooth muscle A1 receptors and a desensitization in tissue response.

Even more controversial is the explanation of the more pronounced vasoconstriction of arterioles in response to ACh in the MI+Stim group, which could indicate a further impairment of endothelial function. It is recognized that chronic alterations in blood flow and wall shear stress provide stimuli for adaptation of the vascular endothelium with impaired NO production and/or release during reduced muscle perfusion states as seen with MI and heart failure (9, 30) and improve endothelial function with the elevated muscle perfusion associated with exercise training (5, 28). Thus we might have expected that the increased muscle activity associated with electrical stimulation would attenuate the previously observed vasoconstrictor response to ACh (42) resulting from MI, but this was not the case. Exercise has been shown to have different effects on the arteriolar response to ACh depending on the duration of training and type of vessel being evaluated (24). Although dilatation was attenuated in smaller (20 µm) arterioles in rat spinotrapezius muscle after 8 wk, it was enhanced in all arterioles evaluated after 16 wk of training. It is also possible that, although the fairly strenuous electrical stimulation protocol used in this study is well tolerated in muscles with normal blood flow, it can possibly damage already dysfunctional endothelium in chronic hypoperfusion states as reported previously in ischemic muscle (16).

Table 3. EDL weight, oxidative characteristics, and capillarity in control, myocardial infarcted, and infarcted-stimulated rats

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>EDL wt, mg</th>
<th>EDL/BW, mg/g</th>
<th>%Oxidative Fibers</th>
<th>C/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td>5</td>
<td>132 ± 6</td>
<td>0.46 ± 0.02</td>
<td>55.1 ± 2.8</td>
<td>1.34 ± 0.06</td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>149 ± 4*</td>
<td>0.49 ± 0.01</td>
<td>56.6 ± 2.1</td>
<td>1.47 ± 0.13</td>
</tr>
<tr>
<td>MI + Stim</td>
<td>4</td>
<td>143 ± 8</td>
<td>0.51 ± 0.02</td>
<td>56.2 ± 2.9</td>
<td>1.59 ± 0.08*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. EDL, extensor digitorum longus muscle; C/F, capillary-to-fiber ratio. *P < 0.05 vs. Con.
Electrical stimulation further accentuated the more pronounced constrictor response to the lowest concentration of NE in both classes of arterioles in infarcted animals. This increased vasoconstriction resembles the responses observed with exercise training by McAllister and Laughlin (28) in rings from femoral and brachial arteries taken from pigs trained just for 7 days. Increased adrenergic constriction was also noted in feed arteries and first-order arterioles from spinotrapezius muscle in trained rats (23). It is known that plasma epinephrine and NE concentrations increase during exercise (47) and circulating catecholamines are also increased in animals with myocardial infarction (27). In a manner similar to exercise, strenuous electrical stimulation may trigger the release of catecholamines, which was shown to cause endothelial cell swelling (2) and possibly impair endothelial function. This could explain the increased constrictor effect of NE, in agreement with previous findings (18, 41). Finally, because NE activates both $\alpha_1$-receptors on vascular smooth muscle and $\alpha_2$-receptors on smooth muscle and endothelium, with the latter attenuating vasoconstriction (45), any damage to the endothelium could accentuate the effect of NE on $\alpha_1$-receptors.

Skeletal muscle. The lack of change in percentage of oxidative fibers in EDL from the MI group with moderate LV dysfunction in the present study is supported by the finding of Delp et al. (4), who only saw a transformation of type II/D/X to type II/B fibers in skeletal muscles from rats with much larger infarcts and left ventricular end-diastolic pressures indicative of pump failure. We (15) and others (37) have previously reported no change in the proportion of oxidative fibers in EDL or tibialis anterior muscles from animals stimulated at the same frequency as used in the present experiments for 7 days. Thus lack of a change in the MI + Stim group was not surprising. We also documented an increase in capillarization over the same time period in this group, which, although significant, was somewhat less than stimulation-induced increases that we have reported previously in normal EDL (16). In our most recent study with this particular stimulation protocol, the increased C/F ratio was accompanied by increased arteriolar density due to arteriolarization of capillaries (10). Because capillary supply in skeletal muscles is either reduced (9) or unchanged (33, 38) post-MI, the increase in C/F ratio induced by chronic stimulation, together with the restored diameter of arterioles, and, to a certain degree, the restored capacity for dilation represents some potential for improved muscle perfusion. It is also possible that the altered response of arterioles to ACh in MI + Stim compared with MI animals could be due to the fact that some observations were made on immature arterioles transformed from capillaries that had possibly not yet acquired fully functional endothelium.

In summary, we have reported the effects of electrical stimulation on EDL microcirculation in infarcted rats in which blood flow to this muscle is reduced (30) in a manner similar to that seen after ligation of the iliac artery (16). Although a beneficial effect was seen with respect to both capillarization and restoring diameter of 3A and 4A arterioles, electrical stimulation failed to correct most of the abnormal responses of these microvessels in infarcted rats, which, in some instances, actually worsened.

Electrical stimulation is an attractive alternative to dynamic exercise for increasing blood flow through selective muscle beds in heart failure patients as it can be achieved without increasing total cardiac output (26). This is considered to be a major advantage where increasing cardiac output is undesirable, dangerous, or even impossible with such patients, depending on the extent of ventricular dysfunction. Interestingly, Maillefer et al. (26) documented an improved exercise performance after 5 wk of electrical stimulation in patients with chronic heart failure. This was achieved without any change in gastrocnemius muscle phosphocreatine (PCr)/PCr + P, ratio or pH either at rest, or immediately after exercise, as measured by $^{31}$P-nuclear magnetic resonance spectroscopy. These findings were interpreted as being indicative of a lack of effect of the muscle stimulation program on muscle metabolism. As electrical stimulation also failed to elevate cardiac output at any point of the 5-wk duration of the program it could be that a less strenuous, intermittent protocol of longer duration can achieve an improvement in muscle performance via its effect on muscle perfusion, attenuating the increase in limb vascular resistance in heart failure (9, 29, 30). Further studies are required to evaluate whether an intermittent, less strenuous stimulation protocol can correct the abnormal microvascular responses seen in locomotor skeletal muscles post-MI.

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