Exercise training increases L-type calcium current density in coronary smooth muscle


Vascular Biology Laboratory, Dalton Cardiovascular Research Center, Departments of Physiology and Veterinary Biomedical Sciences, University of Missouri, Columbia, Missouri 65211


Exercise training increases L-type calcium current density in coronary smooth muscle. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H2159–H2169, 1998.—Exercise training produces numerous adaptations in the coronary circulation, including an increase in coronary tone, both in conduit and resistance arteries. On the basis of the importance of voltage-gated Ca\(^{2+}\) channels (VGCC) in regulation of vascular tone, we hypothesized that exercise training would increase VGCC current density in coronary smooth muscle. To test this hypothesis, VGCC current was compared in smooth muscle from conduit arteries (>1.0 mm), small arteries (200–250 \(\mu m\)), and large arteries (75–150 \(\mu m\)) from endurance-trained (Ex) or sedentary miniature swine (Sed). After 16–20 wk of treadmill training, VGCC current was determined using whole cell voltage-clamp techniques. In both Ex and Sed, VGCC current density was inversely related to arterial diameter, i.e., large arterioles > small arteries > conduit arteries. Exercise training increased peak inward currents approximately twofold in smooth muscle from all arterial sizes compared with those from Sed (large arteriole, \(-12.52 \pm 2.05\) vs. \(-5.74 \pm 0.99\) pA/pF; small artery, \(-6.20 \pm 0.97\) vs. \(-3.18 \pm 0.44\) pA/pF; and conduit arteries, \(-4.22 \pm 0.30\) vs. \(-2.41 \pm 0.55\) pA/pF; 10 mM Ba\(^{2+}\) external). Dihydropyridine sensitivity, voltage dependence, and inactivation kinetics identified this Ca\(^{2+}\) current to be L-type current in all arterial sizes from both Sed and Ex. Furthermore, peak VGCC current density was correlated with treadmill endurance in all arterial sizes. We conclude that smooth muscle L-type Ca\(^{2+}\) current density is increased within the coronary arterial bed by endurance exercise training. This increased VGCC density may provide an important mechanistic link between functional and cellular adaptations in the coronary circulation to exercise training.

ENDURANCE EXERCISE TRAINING produces numerous adaptations in the regulation of coronary arterial tone (8, 23, 30, 37). Although these adaptations appear complex and heterogeneous throughout the coronary circulation, in general, exercise training is associated with enhanced vasodilation and reduced vasoconstriction to vasoactive agonists (23, 37). Although the cellular mechanisms underlying these training-induced adaptations have not been completely described, numerous studies have demonstrated a central role for dihydropyridine-sensitive, voltage-gated Ca\(^{2+}\) channels (VGCC) in the regulation of arterial tone (for review, see Ref. 33). Vasoconstrictor agonists including serotonin, endothelin, and norepinephrine increase arterial tone directly and/or indirectly through activation of VGCC (3, 17, 18, 35). Conversely, many vasodilators such as adenosine (12) decrease arterial tone, in part, through activation of K\(^{+}\) channels, which hyperpolarize the cell membrane and inactivate VGCC and Ca\(^{2+}\) influx (33). In addition, VGCC contribute significantly to both development and maintenance of myogenic tone (20, 46). Previously, we demonstrated an enhanced myogenic response in resistance (30) and conduit (9) coronary arteries of endurance-trained swine. Furthermore, Haskell et al. (15) provided evidence for an increased basal tone in conduit coronary arteries of endurance-trained humans. Thus it appears that enhanced coronary tone may be a general adaptation to endurance training.

Given the central role of VGCC in the regulation of coronary arterial tone and the increase in coronary tone after exercise training, we hypothesized that exercise training would increase VGCC current in coronary smooth muscle. Therefore, the present study determined VGCC current densities in isolated smooth muscle cells from conduit arteries (>1.0 mm), small arteries (200–250 \(\mu m\)), and large arteries (75–150 \(\mu m\)) after endurance exercise training. In support of our hypothesis, we found that exercise training increased L-type Ca\(^{2+}\) current density to a similar extent in smooth muscle from all arterial sizes.

MATERIALS AND METHODS

Animals. Adult female miniature swine weighing 25–40 kg were obtained from the breeder (Charles River) and housed in pens at the College of Veterinary Medicine, University of Missouri, Columbia, MO. All pigs included in this study were familiarized with treadmill exercise over a 1- to 2-wk period. Treadmill performance tests were administered to each animal. Pigs were then randomly divided into two groups. One group (Ex, \(n = 9\)) underwent a progressive treadmill training program used previously in our laboratory (25, 30, 36). The second group of pigs was restricted to their pens (6 \(\times\) 12 ft) for 16–20 wk and served as sedentary controls (Sed, \(n = 10\)). Animal protocols were approved by the University of Missouri Animal Care and Use Committee in accordance with the “Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training.”

Training procedures. During the first week, the pigs from the Ex groups ran on the treadmill at 3 miles per hour (mph), 0% grade for 20–30 min (endurance) and at 5 mph for 15 min (sprint). The speed and duration of running were gradually increased over the first 12 wk at a rate dependent on the tolerance of each pig. During the final 4–8 wk of training, a typical training session consisted of the following 85-min workout: 1) 5-min warm-up run at 2.5 mph, 2) 15-min sprint at speeds of 5–8 mph, 3) 60-min endurance run at 4–5 mph, and 4) 5-min warm-down run at 2 mph. Ranges are given because the exercise training program was individualized to each animal’s exercise ability. The pigs were given positive reinforcement for exercise by feeding after each training bout.
Treadmill performance test. Efficacy of training was determined by administering treadmill performance tests before and at the completion of the training (Ex) or pen confinement (Sed). The performance tests consisted of the following four stages (performed continuously): stage 1, 3.1 mph, 0% grade for 5 min; stage 2, 3.1 mph, 10% grade for 10 min; stage 3, 4.3 mph, 10% grade for 10 min; and stage 4, 6 mph, 10% grade until exhaustion. Typically, animals ran briefly into stage 4 before training and extended this time posttraining. Total running time to exhaustion (i.e., stages 1–4) was recorded.

Skeletal muscle oxidative enzyme activity. At the time the animals were killed, muscle samples were taken from the lateral head of the triceps brachii and deltoid, frozen in liquid N₂, and stored until processed. Citrate synthase activity was measured spectrophotometrically from whole muscle homogenates.

Preparation of coronary arteries. Pigs were anesthetized with ketamine (30 mg/kg) and pentobarbital sodium (35 mg/kg) and administered heparin. The hearts were removed and placed in iced (4°C) Krebs bicarbonate solution during vessel isolation. Conduit (≥1.0-mm ID) segments of right coronary artery were trimmed of fat and connective tissue in sterile modified Eagles Minimal Essential Storage Media containing 20 mM HEPES (pH 7.1) and 0.2 mM EGTA. Cells were enzymatically dispersed for 45–60 min in a shaking water bath at 37°C. The enzyme solution was then replaced with enzyme-free low-Ca²⁺ solution. Cells were enzymatically dispersed by incubation for 45–60 min in a shaking water bath at 37°C. Immediately after dispersion the enzyme solution was replaced with enzyme-free low-Ca²⁺ solution, and isokochrhole女孩子as were digested with gentle trituration by micropipette. For conduit coronary arteries, arteries were opened longitudinally and pinned, lumen side up, onto a silicone rubber substratum in a 2 ml of low-Ca²⁺ enzyme solution. Cells were enzymatically dispersed for 45–60 min in a shaking water bath at 37°C. The enzyme solution was then replaced with enzyme-free low-Ca²⁺ solution, and isolated single cells were obtained by repeatedly directing a stream of low-Ca²⁺ solution over the artery via pasteur pipette. All solutions used for conduit and resistance vessels were identical. Cell suspensions were stored in low-Ca²⁺ (0.5 mM) buffer at 4°C until use (0–6 h).

Whole cell voltage clamp. Whole cell currents were determined with a standard whole cell voltage-clamp technique as used routinely (42–44). Cells were initially superfused with physiological saline solution (PSS) containing (in mM) 2 CaCl₂, 138 NaCl, 1 MgCl₂, 5 KCl, 10 HEPES, and 10 glucose, pH 7.4, during gigaseal formation. After whole cell configuration, the superfusate was switched to PSS with tetraethylammonium chloride (TEACl) substituted for NaCl and either 2 mM Ca²⁺ or 10 mM Ba²⁺ as the charge carrier. The pipette solution contained (in mM) 120 CsCl, 10 TEACl, 1 MgCl₂, 20 HEPES, 2 Na₃ATP, 0.5 Tris-GTP, 5 EGTA, and 0.2 fura 2 pentapotassium salt, pH 7.1. Fura 2 was included in the pipette to verify whole cell dialysis. Ionic currents were amplified by a List EPC-7 patch-clamp amplifier with a 0.5–50 GΩ variable feedback resistance head stage. Whole cell currents were filtered through an eight-pole low-pass filter with a cutoff frequency of 400 Hz, digitized at 495-µs intervals, and stored on computer. Current densities (pA/pF) were obtained for each cell by normalization of whole cell current to cell capacitance to account for differences in cell membrane surface area. Capacity currents were measured for each cell during 10-ms pulses from a holding potential of −80 mV to a test potential of −70 mV. Capacity currents were filtered at a low-pass cutoff frequency of 8.4 kHz and digitized at 25-µs intervals. Leak subtraction was not performed. Data acquisition and analysis were accomplished using a Labmaster analog-to-digital converter and microcomputer equipped with AxoBASIC 1.0 data acquisition software (Axon Instruments). All experiments were conducted at room temperature (22–25°C). Cells were continually superfused under gravity flow. Stock solutions of nifedipine were dissolved in 100% ethanol and diluted 1,000-fold for final solutions.

Statistics. Data are expressed as means ± SE with data from each animal averaged and counted as one observation (n). Data presented for sedentary controls represent a subset of previously published data demonstrating an inverse relationship between coronary arterial diameter and smooth muscle VGCC density in sedentary swine (6). For the purposes of the present investigation, data obtained on cells from sedentary animals whose time of death corresponded with the exercise-trained group were analyzed on a per-animal basis (i.e., all cells for each vessel category for each animal were averaged and counted as 1 observation). There was no significant difference between the sedentary animals or cells from the previous study and the subset utilized in the present investigation. Data presented for exercise-trained animals have been previously published only as an abstract (7). ANOVA was used for comparisons between groups with unpaired t-test used for post hoc analysis. A P value <0.05 was set as the criterion for significance in all comparisons.
VGCC in coronary smooth muscle. Figure 2 shows a representative family of currents obtained under the experimental conditions described using 10 mM external Ba\(^{2+}\) as the charge carrier. Successive depolarization steps from a holding potential of \(-280\) mV to a final test potential of \(+50\) mV in 10-mV increments produced inward currents showing a peak near \(+10\) mV and slow inactivation. With Ca\(^{2+}\) as the external charge carrier, the time for the sustained current to decay to one-half peak amplitude at a test potential of \(0\) mV was similar in conduit arteries, small arteries, and large arterioles (200 ± 22, 203 ± 25, and 212 ± 11 ms, respectively) and was unaffected by exercise training (191 ± 25, 180 ± 13, and 206 ± 12 ms, respectively). These values for current inactivation are similar to those previously reported for L-type current in smooth muscle and are \(~15\) fold greater than those for T-type current (44). Thus the whole cell currents measured in the present study demonstrated current-voltage (I-V) relationships and slow inactivation characteristics consistent with L-type Ca\(^{2+}\) current (2, 5, 26, 44).

Exercise training and VGCC density. Figure 3 shows representative current traces comparing voltage-gated Ca\(^{2+}\) current in coronary smooth muscle from conduits (Fig. 3A), small arteries (Fig. 3B), and large arterioles (Fig. 3C) from sedentary and exercise-trained animals. The magnitude of both the peak and sustained current was increased in cells from trained animals in all arterial sizes. The effect of exercise training on I-V relationships for coronary myocytes from conduit arteries, small arteries, and large arterioles is shown using either 10 mM external Ba\(^{2+}\) (Fig. 4A) or 2 mM external Ca\(^{2+}\) (Fig. 4B) as the charge carrier. Exercise training increased peak VGCC density approximately twofold in all arteries. In both groups, VGCC density increased as arterial diameter decreased, indicating a heterogeneous distribution of VGCC within the coronary arterial network as previously reported (6).
and VGCC density. Approximately 45–65% of the variation in VGCC density could be accounted for by differences in endurance capacity, with the strongest correlation found in the large arterioles. In fact, when data from large arterioles of trained animals were analyzed separately, over 90% of the variation in VGCC density was accounted for by the response to training ($r^2 = 0.93$).

Relative contribution of L-type Ca$^{2+}$ current. Smooth muscle has been reported to contain both T-type and L-type Ca$^{2+}$ channels (44). L-type Ca$^{2+}$ channels are highly sensitive to block by dihydropyridines such as nifedipine, whereas T-type channels are insensitive to this class of drugs (2). To determine the relative contribution of dihydropyridine-sensitive L-type Ca$^{2+}$ channels to whole cell VGCC current, inhibition of whole cell VGCC current by nifedipine was examined. Sensitivity of whole cell VGCC to nifedipine in porcine coronary smooth muscle cells is shown in Fig. 7. With a holding potential of $-80 \text{ mV}$, peak inward current at $+10 \text{ mV}$ was inhibited in a concentration-dependent fashion ($IC_{50} \approx 32 \text{ nM}$). Although L-type Ca$^{2+}$ channels are highly sensitive to nifedipine, this sensitivity is highly voltage dependent. The holding potential of $-80 \text{ mV}$ used in the present study (chosen to avoid possible differences in inactivation characteristics between groups) is relatively hyperpolarized, necessitating a higher dihydropyridine concentration to produce maximal inhibition. In addition, a maximally effective concentration of nifedipine avoids possible differences in dihydropyridine sensitivity between groups. Therefore, a maximally effective concentration of nifedipine (3 µM) was used for comparison between groups. Figure 8 shows the effect of 3 µM nifedipine on Ca$^{2+}$ current in smooth muscle cells from conduit arteries (Fig. 8, A and D), small arteries (Fig. 8, B and E), and large arterioles (Fig. 8, C and F) from both sedentary (Fig. 8, A–C) and exercise-trained (Fig. 8, D–F) animals. Peak inward current at $+10 \text{ mV}$ in the presence of 3 µM nifedipine was effectively abolished in cells from all arterial sizes from both trained and sedentary animals (% inhibition: Sed, 96 ± 2, 98 ± 2, and 91 ± 4; Ex, 99 ± 2, 98 ± 2, and 103 ± 11 for conduit, small artery, and large arterioles, respectively). Thus dihydropyridine-sensitive L-type Ca$^{2+}$ current appears to be the dominant VGCC current in coronary smooth muscle of all arterial sizes, supporting previous studies showing a predominance of L-type Ca$^{2+}$ current in most vascular smooth muscle (6, 19, 26, 28).

To further test the relative contribution of L-type Ca$^{2+}$ current in coronary arterial myocytes, we examined the effect of steady-state depolarization on the I-V relationship. Currents derived from T-type and L-type voltage-gated Ca$^{2+}$ channels in smooth muscle can be separated by holding potential (2, 19, 44). Compared with L-type channels, T-type channels activate and peak at more negative membrane potentials and are inactivated by steady holding potentials less than $-40 \text{ mV}$ (2, 44). Thus the presence of two types of voltage-gated Ca$^{2+}$ channels can be discerned by a positive shift in the I-V relationship when the holding potential is increased (44). Normalized I-V relationships obtained
at holding potentials of $-80$ mV and $-30$ mV were superimposable in arteries of all sizes and were unaffected by training (Fig. 9). The lack of a positive shift in the I-V relationship with sustained depolarization to $-30$ mV confirms the absence of a significant T-type $\text{Ca}^{2+}$ current and supports a predominance of L-type $\text{Ca}^{2+}$ current in coronary arteries from both trained and sedentary animals.
DISCUSSION

Substantial evidence exists supporting the role of chronic exercise in reducing the incidence and severity of coronary vascular disease (1, 13). Although recent studies have greatly expanded our understanding of the impact of exercise on coronary arterial regulation, relatively little is known about the intrinsic cellular changes within the coronary vasculature associated with these functional adaptations. The present study provides novel evidence that endurance exercise training increases voltage-gated Ca\(^{2+}\) channel current density in coronary arterial smooth muscle. In light of the well-documented importance of voltage-gated Ca\(^{2+}\) channels in regulation of vascular tone in both normal and disease states (27, 33), this information could provide a vital mechanistic link between exercise training and associated functional adaptations within the coronary circulation.

Arterial tone, via control of vascular resistance, is the major determinant of total blood flow and distribution within the coronary circulation. Various vasoactive...
Exercise training and coronary Ca\(^{2+}\) current

Fig. 7. Dihydropyridine inhibition of VGCC current. A: inhibition of normalized Ba\(^{2+}\) current \(I_{Ba}/I_{Ba\text{max}}\) by 0.1 (top) and 1.0 (bottom) \(\mu M\) nifedipine (Nif). Effect of 0.01 \(\mu M\) nifedipine is shown for comparison. After whole cell access (time 0), \(I_{Ba}\) elicited by depolarization to +10 mV from HP of –60 mV increased to a steady-state plateau, which was unaffected by 0.01 \(\mu M\) nifedipine. Subsequent application of either 0.1 or 1.0 \(\mu M\) nifedipine resulted in reversible inhibition. B: VGCC current was inhibited by nifedipine in a concentration-dependent manner. Data were fitted with a sigmoidal curve (IC\(_{50}\) = 32 nM). Data are expressed as means ± SE; n = 3 cells/concentration, obtained from conduit arteries of sedentary control animal.

stimuli including norepinephrine (32), serotonin (14), endothelin (17) and pressure (22, 27) increase arterial smooth muscle tone through depolarization and activation, directly or indirectly, of VGCC. In addition, vasodilators such as endothelium-dependent hyperpolarizing factor (11), nitric oxide (4), and adenosine (12) have been shown to activate K\(^+\) channels, resulting in hyperpolarization, inactivation of VGCC, and vasodilation. Thus the relative activation of VGCC can affect both vasoconstriction and vasodilation. The present study found an approximately twofold increase in peak voltage-gated Ca\(^{2+}\) current density in coronary smooth muscle after exercise training. This training-induced increase was similar in magnitude in conduit arteries, small arteries, and large arterioles.

Although the training-induced increase was most apparent at membrane potentials positive to the reported physiological range for vascular smooth muscle, i.e., –60 to –30 mV (33, 34), it is important to note that apparent thresholds for Ca\(^{2+}\) current activation in whole cell voltage-clamp configurations are really detection thresholds. VGCC activity is a continuous function of membrane potential, with no true threshold (16, 33). Therefore, it is probable that the training-induced differences in whole cell Ca\(^{2+}\) current can be extrapolated to more negative membrane potentials. Furthermore, important physiological vasoconstrictors such as norepinephrine and serotonin shift the voltage dependence for activation of VGCC to more negative membrane potentials (33, 35). On the basis of these findings, we predict an enhanced role of VGCC in regulation of coronary vascular tone after endurance exercise training. Although numerous physiological stimuli associated with acute exercise and exercise training could be responsible for the increase in VGCC density, it is interesting to note that dihydropyridine-sensitive VGCC number has been reported to be increased by β-adrenergic stimulation (39). The increased sympathetic activation and circulating catecholamines associated with exercise may be a contributing stimulus for training-induced increases in VGCC current. This training-induced increase in VGCC current density may be specific for coronary smooth muscle, because endurance training did not alter VGCC current in rat cardiac myocytes (29).

Smooth muscle contains two distinct types of voltage-gated Ca\(^{2+}\) current (2, 5, 44). The channel subtype responsible for whole cell currents can be distinguished by several characteristics including dihydropyridine sensitivity and time- and depolarization-dependent inactivation characteristics. L-type channels are highly sensitive to inhibition by dihydropyridines (2, 33), whereas T-type channels are insensitive to this class of drugs (16, 33). Furthermore, T-type channels are activated by small depolarizations and inactivate quickly, whereas L-type channels require greater depolarization for activation and inactivate slowly (5). The whole cell currents in all arterial sizes in the present study were abolished by the dihydropyridine nifedipine and showed characteristic L-type voltage dependence of activation and slow inactivation (2, 33, 44). These characteristics are strongly indicative of L-type Ca\(^{2+}\) channels being the predominant channel type in smooth muscle of all coronary arterial sizes. This conclusion is in agreement with other studies showing a predominance of L-type Ca\(^{2+}\) channels in most vascular smooth muscle (2, 6, 19, 28) including coronary myocytes (26). Exercise training had no effect on either current characteristics or sensitivity to nifedipine, indicating a similar predominance of L-type channels in arteries from trained and sedentary animals.

Although not directly addressed in this study, the expected physiological consequence of this training-
induced increase in L-type VGCC current would be an overall increase in contractile response to the numerous vasoconstrictor stimuli that activate VGCC. Exercise training was shown to increase myogenic tone in resistance arteries similar in size to the large arterioles of the present study (30), and dihydropyridine-sensitive Ca\textsuperscript{2+} channels are required for development and maintenance of myogenic tone (20, 46). Therefore, the increased myogenic response of resistance arteries after exercise training may be caused, in part, by an enhanced VGCC current. The strong correlation between training status and VGCC density in the large arterioles (Fig. 6C) supports the hypothesis that training-induced increases in VGCC density contribute to the previously reported enhanced myogenic tone and increased VGCC current density in response to training. Further studies will be needed to directly test this hypothesis.

Aside from increases in basal coronary tone, the overall functional adaptation of the coronary circulation to exercise training has been generalized as reduced vasoconstriction and enhanced vasodilation to various vasoactive agents (23, 24, 37). After exercise training, in vitro studies showed reduced contractile responses in coronary arteries to norepinephrine (36) and endothelin (8), both of which are known to activate VGCC (21). These findings appear difficult to reconcile with the increase in VGCC density found in the present study. However, recent studies of vascular smooth muscle are uncovering a role for intracellular Ca\textsuperscript{2+} not exclusively in vasoconstriction but, under certain conditions, as a mechanism for vasodilation (10, 31, 47). By compartmentalizing intracellular Ca\textsuperscript{2+} into restricted subcellular spaces, i.e., the subsarcolemmal space, and away from the Ca\textsuperscript{2+}-dependent contractile apparatus, localized increases in Ca\textsuperscript{2+} can activate Ca\textsuperscript{2+}-activated K\textsuperscript{+} (K\textsubscript{Ca}) channels to limit depolarization and vasoconstriction or produce vasodilation. Thus, under certain conditions, increasing Ca\textsuperscript{2+} influx could be a mechanism to limit vasoconstriction or induce vasodilation.

Figure 8. Similar efficacy of dihydropyridine inhibition across arterial size and training status. Typical experimental tracings showing block of inward current by the dihydropyridine nifedipine (3 µM) are given. Step depolarizations to +10 mV from HP of -80 mV before (C) and after (●) nifedipine are shown for cells from conduit arteries (A and D), small arteries (B and E), and large arterioles (C and F) from Sed (A–C) and Ex (D–F) animals. Nifedipine completely abolished inward current at +10 mV in all arteries from both groups, demonstrating predominance of dihydropyridine-sensitive Ca\textsuperscript{2+} channel current (L-type) in coronary smooth muscle in arteries from both Sed and Ex animals. Similar inhibition was seen at all membrane potentials (data not shown). Capacitance transients are eliminated for clarity. Dotted line, zero-current level.
muscle. With the use of simultaneous intracellular 
Ca$^{2+}$ and contractile techniques, we previously re-
ported a reduced averaged myoplasmic Ca$^{2+}$ (Cam) and 
contractile response to endothelin after exercise train-
ing (8). Paradoxically, although contraction and bulk 
Cam were reduced by training, Ca$^{2+}$ influx was dramati-
cally increased, providing indirect evidence for in-
creased sarcolemmal Ca$^{2+}$ cycling after exercise train-
ing. As proposed by Rasmussen et al. (38), sarcolemmal 
Ca$^{2+}$ cycling produces a high subsarcolemmal Ca$^{2+}$ 
(Cas) concentration without a substantial increase in 
Cam. The resulting increase in Cas could, therefore, 
limit contraction by activation of K$_{Ca}$ channels, which 
hyperpolarize the membrane and limit contraction 
(10). Recently, a similar role for sarcoplasmic reticulum  
(SR) Ca$^{2+}$ release, i.e., Ca$^{2+}$ sparks, in limiting depolar-
ization and vasoconstriction by activation of K$_{Ca}$ chan-
nels has been proposed (31). Sturek and colleagues (41, 
42) found that exercise training increased slow SR Ca$^{2+}$ 
release, i.e., SR Ca$^{2+}$ unloading, in coronary smooth 
muscle, which can produce increased Cas and K$_{Ca}$ 
channel activation (43). Together, these data support a 
model for limiting contraction and/or enhancing vaso-
dilation by increasing Ca$^{2+}$ influx. The increased VGCC 
density in smooth muscle after training described in 
the present study fits well within such a model.

In conclusion, the current study provides direct electro-
physiological evidence that endurance exercise train-
ing increases L-type VGCC current density in coronary 
smooth muscle. This training adaptation was similar in
coronary myocytes from conduit arteries (>1.0 mm), small arteries (200–250 µm), and large arterioles (75–150 µm). Furthermore, L-type Ca\textsuperscript{2+} current density was directly correlated with endurance capacity. In light of the importance of VGCC in regulation of coronary arterial tone and, consequently, total and regional blood flow, these findings should provide an important mechanistic link between cellular and functional adaptations of the coronary circulation to exercise training.

The authors thank Pam Thorne and Tammy Strawn for invaluable assistance in this project.

This work was supported by National Heart, Lung, and Blood Institute Grants HL 52490 (M. H. Laughlin, M. Sturek, and D. K. Bowles), HL-41033 (M. Sturek), and HL-02872 (M. Sturek).

Address for reprint requests: D. K. Bowles, E102 Veterinary Medicine, Univ. of Missouri, Columbia, MO 65211.

Received 17 November 1997; accepted in final form 31 August 1998.

REFERENCES


36. Oldman, C. L., J. L. Parker, H. R. Adams, and M. H. Laughlin. Effects of exercise training on vasomotor reactivity of...