High inborn aerobic capacity does not protect the heart following myocardial infarction


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High aerobic capacity does not protect the heart following myocardial infarction (MI) compared with rats with lower inborn aerobic capacity (inborn aerobic capacity; myocardial infarction; cardio-protection; calcium cycling/excitation-contraction coupling; inborn aerobic capacity; myocardial infarction; cardio-protection). High aerobic capacity does not protect the heart following myocardial infarction (MI) compared with rats with lower inborn aerobic capacity (inborn aerobic capacity; myocardial infarction; cardio-protection; calcium cycling/excitation-contraction coupling; inborn aerobic capacity; myocardial infarction; cardio-protection). High aerobic capacity does not protect the heart following myocardial infarction (MI) compared with rats with lower inborn aerobic capacity (inborn aerobic capacity; myocardial infarction; cardio-protection; calcium cycling/excitation-contraction coupling; inborn aerobic capacity; myocardial infarction; cardio-protection). High aerobic capacity does not protect the heart following myocardial infarction (MI) compared with rats with lower inborn aerobic capacity (inborn aerobic capacity; myocardial infarction; cardio-protection; calcium cycling/excitation-contraction coupling; inborn aerobic capacity; myocardial infarction; cardio-protection).

High aerobic capacity measured as maximal oxygen uptake (\(\dot{V}O_{2\text{max}}\)) is reported to reduce the risk of developing cardiovascular disease (CVD), regardless of reported activity level (28), and is considered as an important prognostic parameter for patients with pronounced CVD (20, 22, 27, 36). The inborn variation in \(\dot{V}O_{2\text{max}}\) is determined by a complement of genes (24), and heritability is estimated to predict ~50% of the \(\dot{V}O_{2\text{max}}\) (6, 7).

In 1996, Koch and Britton (25) started two-way artificial selective breeding to develop rat strains that only contrast for intrinsic (i.e., inborn) aerobic treadmill running capacity. After 11 generations of selection, the low-capacity runner (LCR) rats had developed features of the metabolic syndrome (48) and, in addition, cardiomyocyte properties with resembling characteristics, as previous observations in heart failure rats (19, 47, 48). In contrast, the rats selected as high-capacity runner (HCR) rats displayed an athletic phenotype that included expansion of \(\dot{V}O_{2\text{max}}\). Subsequent work from generations 12–28 has revealed that the LCR score higher than the HCR for a wide range of complex disease risks, such as hepatic steatosis, increased susceptibility to ventricular fibrillation, and diminished longevity (26). Thus this model is highly adequate for studying inborn effects of aerobic capacity on phenotype alterations.

Endurance training before and after myocardial infarction (MI) improves survival and restricts left ventricle (LV) remodeling (13, 15, 49). It is, however, not known if the cardio-protective effect is restricted to acquired aerobic capacity by endurance training, or if inborn capacity may yield the same beneficial outcome.

We used the LCR and HCR rat model to determine the role of inborn aerobic capacity on cardiac contractile function and Ca\(^{2+}\) handling in LCR vs. HCR rats after MI by ligation of the left anterior descending coronary artery (LAD). We hypothesized that the higher aerobic capacity in HCR rats would yield a cardio-protective effect after MI compared with the LCR rats that already have established risk for CVD.

METHODS

Animals. The rats used in the present study were selected and bred over 22 generations for either HCR or LCR starting from a N:NIH stock obtained from the National Institutes of Health (USA), as previously described (25, 48). In brief, the selection is based on an exercise capacity test at 11 wk of age, where rats with the 20% highest and 20% lowest scores are selected to generate the next generation for each strain. Concurrent breeding of HCR and LCR at every generation allows them to serve as reciprocal controls for unknown environmental changes. Female rats were randomized for sham (SH) or MI surgery, giving the following groups: HCR-SH, HCR-MI, LCR-SH, and LCR-MI. The Norwegian council for Animal Research approved the study, which was in accordance with Use of Laboratory Animals Laboratory Animals by the European Commission Directive 86/609/EEC.

1 Contact L. G. Koch (lgkoch@med.umich.edu) or S. L. Britton (brittons@umich.edu) for information on the LCR and HCR rats; these rat models are maintained as an international collaborative resource at the University of Michigan, Ann Arbor, MI.
MI surgery. MI was performed by permanent occlusion of LAD during 1.5% isoflurane anesthesia, and the success of inducing an permanent LAD occlusion was evaluated by echocardiography after 1 wk, as earlier described (23). Following MI, the animals remained sedentary in their cages before they were killed after 12 wk. One week before sacrificing the animals, the rats were examined by echocardiography to determine cardiac function. We included rats with MI larger than 40% of the LV to ensure consistency in the study population. There were no differences in the number of excluded animals or infarct size between the HCR and LCR.

$V_{O_{2\max}}$ All animals remained sedentary for 12 wk following the MI surgical procedure. At the end of the experimental period, we measured $V_{O_{2\max}}$ during uphill (25°) treadmill running in a metabolic chamber (48 before sacrificing the animals). The $V_{O_{2\max}}$ test procedure is a previously described and validated method (19, 46).

Echocardiography. Echocardiography was measured by Vevo 770 VisualSonics (Toronto, Canada) during isoflurane (2%) anesthesia. LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were recorded with parasternal long-axis B-mode echocardiography, which allowed calculation of the fractional shortening (FS) [% = ([LVEDD - LVESD]/LVEDD) x 100] as an index of systolic LV function.

Cardiomyocyte isolation, Ca$^{2+}$ measurements, and cardiomyocyte dimension measurements. The animals were killed during isoflurane (3%) anesthesia and heparinized (0.2 ml heparin) before removal of the heart. Cardiomyocytes from the LV were isolated by retrograde Langendorff perfusion and enzymatic digestion of collagenase (Worthington Biochemical), as previously described (18). To ensure that we only studied viable cardiomyocytes remote from the ischemic infarct area, we removed both the infarct and the boarder zone area (~1–2 mm from the boarder of the infarction). Cell experiments were performed in 1.8 mmol/l Ca$^{2+}$ HEPES-based solution. Cardiomyocytes were field stimulated by bipolar electrical pulses at 1–2 Hz in 1.8 mmol/l Ca$^{2+}$ HEPES-based solution and continuously perfused at 37°C. Cardiomyocyte shortening was measured by video-based sarcomere spacing (SarcLen Sarcomere Length Acquisition Module, Ionoptix, Milton, MA) using an inverted epifluorescence microscope (Nikon TE-2000E, Tokyo, Japan). Ca$^{2+}$ handling measurements by fura 2-AM (2 μmol/l, Molecular Probes, Eugene, OR) was measured by a photomultiplier tube acquisition add-on module (PMTACQ, IonOptix; Optoscan, Cairn Research, Kent, UK). Rod-shaped cardiomyocytes with no visible damage and response up to 2-Hz stimulation were included.

Cell dimensions were measured with Nikon Eclipse E400 Microscope with a DSFI2l camera (Nikon NIS Elements Basic Research, version 3.0 software, Nikon Instruments).

Quantitative measurements of diastolic Ca$^{2+}$ leak. We determined diastolic Ca$^{2+}$ leak from sarcoplasmic reticulum (SR) by the established Shannon et al. (42) protocol. Briefly, to bring the cellular Ca$^{2+}$ content to a steady state, we stimulated the cardiomyocytes electrically at 1 Hz in normal HEPES-based 1.8 mmol/l Ca$^{2+}$ concentration solution for 60 s. After the last electric stimulus, we rapidly switched the perfusion to a 0 Na+ /0 Ca$^{2+}$ containing solution and measured diastolic Ca$^{2+}$ concentration in quiescent nonstimulated cardiomyocytes (1 min) by tetracaine (1 mmol/l). The 0 Na+ /0 Ca$^{2+}$ solution prevents the Na+ /Ca$^{2+}$ exchange (NCX), which is the primary Ca$^{2+}$ influx and efflux mechanism at rest, whereas tetracaine blocks the Ca$^{2+}$ leak over the ryanodine receptors (RyR). The quantitative difference between diastolic Ca$^{2+}$ concentration with and without tetracaine determines leak. After the 1-min period in 0 Na+ /0 Ca$^{2+}$ ± tetracaine solution, we added caffeine (10 mmol/l) to assess the SR Ca$^{2+}$ content. Diastolic Ca$^{2+}$ leak is presented as diastolic Ca$^{2+}$ concentration in relation to total SR Ca$^{2+}$ content. In a subset of experiments, autacamide-2 related inhibitory peptide (AIP, 1 μM, Sigma Aldrich) was used for specific Ca$^{2+}$/calmodulin-dependent protein kinase II (CaMKII) inhibition, and H-89 (3 μM, Sigma Aldrich) for protein kinase A (PKA) inhibition. Cardiomyocytes were preincubated with AIP or H-89 1 h before the experiments.

Quantitative measurements of Ca$^{2+}$ removal during diastole. We used the rate constant of Ca$^{2+}$ decline in three different solutions to quantify the contribution from SR Ca$^{2+}$-ATPase (SERCA-2a), NCX, mitochondrial unipporter, and sarcocalcemic Ca$^{2+}$-ATPase: 1) rate constant of Ca$^{2+}$ decline during electrical stimulation in normal HEPES 1.8 mmol/l Ca$^{2+}$ solution, with all contributors active; 2) addition of 10 mmol/l caffeine in normal HEPES 1.8 mmol/l Ca$^{2+}$ solution that offset the SR and re-uptake by SERCA-2a; and 3) addition of 10 mmol/l caffeine in a 0 Na+ /0 Ca$^{2+}$ solution that offset both SERCA-2a and NCX.

Confocal imaging of Ca$^{2+}$ release synchrony. Cardiomyocytes loaded with fluo 3-AM (10 μmol/l, Molecular Probes) were used to determine Ca$^{2+}$ release synchrony. For the Ca$^{2+}$ release synchrony analysis, one to three Ca$^{2+}$ transients/cell were used, and the line scan of each Ca$^{2+}$ transient was divided into ~25 equal strips (~4 μm/strip). Time from stimulation to 50% Ca$^{2+}$ release was measured for each strip, and the standard deviation of the measurement was used as a measure of Ca$^{2+}$ release synchronicity across the cell.

Statistics. Statistical analyses were performed by ANOVA using Bonferroni post hoc test. To determine whether there was a significantly more pronounced effect by MI between the two phenotypes (i.e., HCR and LCR), we performed an independent sample two-tailed t-test on the delta (Δ) change induced by MI between the LCR (LCR-SH – LCR-MI) and HCR (HCR-SH – HCR-MI). The use of “relative effect of MI” in this context is, therefore, used to show the Δ change occurring on each single parameter as a consequence of inducing MI in each line of animals (HCR and LCR). In these analyses, we have used the assumption that the sham animals are the zero point reference within the LCR and HCR groups.

Data are presented as means ± SD. P < 0.05 was considered statistically significant.

RESULTS

Intrinsic aerobic capacity and in vivo cardiac contractility. Aerobic capacity, measured as $V_{O_{2\max}}$, was significantly lower in LCR-SH compared with HCR-SH (P < 0.01, Fig. 1). $V_{O_{2\max}}$ was reduced after MI in both HCR and LCR rats compared with their respective sham-groups (by 20 and 36%, respectively, P < 0.01, Fig. 1). Cardiac function measured by echocardiography demonstrated reduced systolic function after MI in both HCR and LCR rats (Table 1). Compared with respective sham group, LV FS was decreased by 49% in

![Fig. 1.](http://jap.physiology.org/)
Cardiomyocyte size. Cardiomyocyte width and length were not significantly different between sham groups. MI induced a significant increase in cardiomyocyte width and length in both HCR and LCR rats (P < 0.01, Table 1).

Cardiomyocyte contractility and Ca\(^{2+}\) transients. LCR-SH was characterized by depressed cardiomyocyte contractile function and relaxation, as well as impaired Ca\(^{2+}\) handling compared with HCR-SH (Fig. 3). The relative reduction in cardiomyocyte FS was 39% in HCR-MI (P < 0.01, Fig. 3A) and 34% in LCR-MI (P < 0.01, Fig. 3A), compared with respective sham group. The Δ change induced by MI relative to their respective sham groups was significantly larger in HCR than LCR rats (P < 0.01, Fig. 3A). Also, the Δ effect of MI on time to 50% relengthening during diastole was larger in HCR (P < 0.05, Fig. 3B). Despite this larger effect of MI in HCR rats, it is important to note that time to 50% relengthening was still significantly faster than observed in LCR-MI (P < 0.01, Fig. 3B) and not significantly different from LCR-SH. Ca\(^{2+}\) transient amplitude was reduced by 37% in HCR after MI (P < 0.01, Fig. 3C), whereas a 20% reduction was observed in LCR-MI rats (not significant, Fig. 3C). Again, the Δ effect of MI relative to their respective sham was more pronounced in HCR than LCR rats (P < 0.05, Fig. 3C). Similar to time to 50% relengthening, Ca\(^{2+}\) decay during diastole was prolonged after MI in both HCR (P < 0.01, Fig. 3D) and LCR (P < 0.01, Fig. 3D). Ca\(^{2+}\) decay was not different between HCR-MI and LCR-SH. Diastolic Ca\(^{2+}\) levels were not different between any group (Fig. 3E), whereas SR Ca\(^{2+}\) content was higher in HCR-SH compared with all other groups (P < 0.01, Fig. 3F). MI reduced SR Ca\(^{2+}\) content with the same impact in HCR and LCR (both 20%, P < 0.01, Fig. 3F).

To determine Ca\(^{2+}\) release properties, we measured the time to 50% peak Ca\(^{2+}\) amplitude and the Ca\(^{2+}\) release synchrony along the cardiomyocyte length. We did not find any significant difference on time to 50% Ca\(^{2+}\) amplitude between groups (Fig. 4A). The difference for synchrony of Ca\(^{2+}\) release was only different between HCR-MI and LCR-SH (Fig. 4B). Diastolic Ca\(^{2+}\) handling. Since the transition from normal function to heart failure usually shift the Ca\(^{2+}\) cycling distribution between SR and sarcoplasmic Ca\(^{2+}\) handling proteins...
we quantified SERCA-2a and NCX rate of Ca\textsuperscript{2+} removal during diastole. We found that SERCA-2a Ca\textsuperscript{2+} removal rate was significant higher in HCR-SH compared with all other groups (P < 0.001, Fig. 5A). After MI, SERCA-2a Ca\textsuperscript{2+} removal decreased by 47% in HCR (P < 0.001, Fig. 5A) and 44% in LCR (P < 0.05, Fig. 5A) compared with respective sham. The \( \Delta \) change relative to their respective sham groups on SERCA-2a Ca\textsuperscript{2+} removal following an MI was largest in HCR-SH compared with all other groups (P < 0.05, Fig. 5A).

Diastolic SR Ca\textsuperscript{2+} leak. SR Ca\textsuperscript{2+} leak was minor in HCR-SH, but increased by 177% after MI (from 2.6% RyR Ca\textsuperscript{2+} leak in HCR-SH to 7.2% in HCR-MI, P < 0.01, Fig. 6A). The diastolic SR Ca\textsuperscript{2+} leak in LCR-SH was significantly larger compared with HCR-SH and was further increased by 67% after MI (from 6.1% in LCR-SH to 10.2% RyR Ca\textsuperscript{2+} leak in LCR-MI, P < 0.01, Fig. 6A). In heart failure, increased phosphorylation of the RyR by CamKII is shown to be a key mechanism for increased diastolic SR Ca\textsuperscript{2+} leak (2); therefore, we incubated the cells with the CaMKII inhibitor, AIP. We found that diastolic SR Ca\textsuperscript{2+} leak remained unchanged in HCR-SH, whereas it was normalized in HCR-MI, LCR-SH, and LCR-MI (Fig. 6B). In addition, to evaluate the effect of

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Fig. 4. Ca\textsuperscript{2+} release properties in LV cardiomyocytes. Time to 50% Ca\textsuperscript{2+} amplitude (A), and synchronization of twitch Ca\textsuperscript{2+} release along the cell length assessed by the standard deviation (SD) of Ca\textsuperscript{2+} release along the line scan over the length of the cardiomyocyte (B) are presented as means ± SD. Number of animals in each group: HCR sham, n = 5; HCR MI, n = 5; LCR sham, n = 6; and LCR MI, n = 6; number of cells from each animal: n = 6–8.
PKA phosphorylation on Ca\(^{2+}\) leak, we also incubated the cells with the PKA inhibitor, H-89, and found no significant effects (Fig. 6C).

**DISCUSSION**

The objective of the present study was to investigate if contrasting for high or low inborn aerobic capacity would yield different remodeling on cardiac contractile function and Ca\(^{2+}\) handling after MI; i.e., potential for cardio-protection in rats with high inborn aerobic capacity and, conversely, more severe deterioration in rats with low inborn aerobic capacity. We found that MI led to a severe reduction in \(\dot{V}O_{2}\text{max}\) and LV function, as well as cardiomyocyte function and Ca\(^{2+}\) handling in both of the groups. In contrast to our hypothesis, HCR rats with high inborn aerobic capacity suffered the same, or even a greater, loss after an MI than LCR rats on \(\dot{V}O_{2}\text{max}\), cardiac contractile function, and Ca\(^{2+}\) handling properties when relating to the respective sham groups. However, rats with high inborn aerobic capacity displayed an advantageous end point outcome compared with their LCR counterparts as the cardiac function in HCR after MI was comparable to the sham-operated LCR for almost all parameters.

**Aerobic capacity and global cardiac function after MI.** As earlier reported, \(\dot{V}O_{2}\text{max}\) was lower in LCR-SH compared with HCR-SH rats (48). In the present study, \(\dot{V}O_{2}\text{max}\) was reduced to the same extent in both animal lines after MI, which was explained by an equal deteriorated global cardiac contraction, assessed by reduced LV FS and EF. However, despite similar reduction on \(\dot{V}O_{2}\text{max}\) and cardiac contraction when relating to their respective sham after MI in LCR and HCR, the levels from HCR-MI rats were still functionally higher than those of LCR-MI and similar to those of LCR-SH. Low EF is associated with ventricular enlargement after MI, or LV dilatation caused by infarct expansion (21, 35). In addition to EF, LVESV is considered a meaningful prognosticator after MI, as it predicts the extent of LV remodeling (35). We observed an equal increase in LVESV in both HCR and LCR after MI, suggesting similar prognosis. Accordingly, in vivo measurements of cardiac function indicated that high-inborn aerobic capacity was not associated with cardio-protective effects after MI in terms of reduced cardiac function and remodeling of the heart relative to their respective sham.

*Cardiomyocyte contractility, relaxation, and Ca\(^{2+}\) transients.* Impaired global cardiac function is commonly mediated by diminished function of individual cardiomyocytes and dysfunctional Ca\(^{2+}\) handling. Our laboratory has previously reported that cardiomyocytes from LCR rats resemble cardiomyocytes from post-MI failing hearts (19, 48). In line with this, we found that LCR-SH had similar cardiomyocyte contractility and Ca\(^{2+}\) handling as HCR-MI on most parameters. However, in contrast to our hypothesis, we observed that the HCR rats had a larger \(\Delta\) reduction in cardiomyocyte FS and time to functional relengthening compared with their respective sham groups than the \(\Delta\) reduction after MI in LCR rats.

The lower FS in HCR-MI, LCR-SH, and LCR-MI compared with HCR-SH was probably caused by the reduced Ca\(^{2+}\) transient amplitude through depletion of the SR Ca\(^{2+}\) content (4). Time to 50\% Ca\(^{2+}\) decay during diastole was also prolonged in these groups, leading to impaired cardiomyocyte relengthening.

The reduced time to 50\% Ca\(^{2+}\) decay, explained by lower rate constant of SERCA-2a Ca\(^{2+}\) removal, probably partly

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**Fig. 5.** Rate constant of Ca\(^{2+}\) removal by SR Ca\(^{2+}\)-ATPase (SERCA-2a; A), and Na\(^+\)/Ca\(^{2+}\) exchange (NCX; B) are presented as means \(\pm\) SD. \(*P < 0.05\) and \(**P < 0.01\), different from all other groups. To determine whether the effect of inducing an MI in the two different phenotypes was statistically different, we compared the \(\Delta\) difference (HCR-sham – HCR-MI and LCR-sham – LCR-MI) with the respective sham groups as zero point control within the groups. Number of animals in each group: HCR-sham, \(n = 5\); HCR-MI, \(n = 5\); LCR-sham, \(n = 6\); and LCR-MI, \(n = 6\); number of cells from each animal: \(n = 6–8\).

**Fig. 6.** Diastolic SR Ca\(^{2+}\) leak in vehicle HEPES (1.8 mmol/l Ca\(^{2+}\)) solution (A), after incubation of autacamide-2-related inhibitory peptide (AIP) + HEPES (B), and after incubation of H-89 + HEPES (C) is presented as means \(\pm\) SD. \(*P < 0.05\), different from all other groups. Number of animals in each group: HCR-sham, \(n = 5\); HCR-MI, \(n = 5\); LCR-sham, \(n = 6\); and LCR-MI, \(n = 6\); number of cells from each animal: \(n = 6–8\).
caused the observed reduction in SR Ca\(^{2+}\) content, leaving less Ca\(^{2+}\) available for cardiomyocyte contraction (17). Reduced SERCA-2a activity is usually accompanied by increased NCX activity, which is commonly seen in failing hearts (16, 30, 38). Increased NCX activity contributes to Ca\(^{2+}\) removal from cytosol to provide relaxation and to avoid Ca\(^{2+}\) overload in the absence of normal SERCA-2a function. Increased NCX-mediated Ca\(^{2+}\) removal during diastole may have negative inotropic effects, as it facilitates extrusion of Ca\(^{2+}\) across the sarcolemma that, in turn, leads to lower SR Ca\(^{2+}\) content. This may be sufficient to reduce the Ca\(^{2+}\) released from the SR for a given L-type Ca\(^{2+}\) channel current trigger (5, 17, 30, 39). Hence, our data indicate that increased NCX rate constant of Ca\(^{2+}\) removal may contribute to the reduction of SR Ca\(^{2+}\) content displayed in HCR-MI, LCR-SH, and LCR-MI in the present study.

Diastolic SR Ca\(^{2+}\) leak. In HCR-SH rats, diastolic SR Ca\(^{2+}\) leak was minor, but increased significantly after MI. Despite this increase, the Ca\(^{2+}\) leak was, however, not different from LCR-SH. In LCR-MI, the SR Ca\(^{2+}\) leak was significantly larger than that in all other groups. The increased Ca\(^{2+}\) leak from SR may, in addition to the shift in Ca\(^{2+}\) handling between SERCA-2a and NCX, have contributed to the reduced SR Ca\(^{2+}\) content and subsequent Ca\(^{2+}\) transient amplitude in HCR-MI, LCR-SH, and LCR-MI compared with HCR-SH (1, 11).

The RyR is directly phosphorylated by the multifunctional CaMKII (31). In heart failure, CaMKII activity is increased, causing phosphorylation of RyR that may lead to spontaneous Ca\(^{2+}\) release and afterdepolarizations of the ventricle (2). By acutely inhibiting CaMKII with AIP in isolated cardiomyocytes, we found that SR Ca\(^{2+}\) leak was abolished. In addition, we inhibited the effect of PKA, previously shown to increase the open probability of the RyR, causing increased Ca\(^{2+}\) leak (32, 41). We did, in contrast to those studies, not find any effect of PKA inhibition on SR Ca\(^{2+}\) leak. The increased SR Ca\(^{2+}\) leak appears, therefore, to be caused by CaMKII in the present study. As emphasized by other studies, CaMKII probably serves as an important target for preventing spontaneous Ca\(^{2+}\) release that may trigger ventricular arrhythmias and additionally for rescuing defective Ca\(^{2+}\) handling and hence cardiac function (43, 44).

Cardioprotection by aerobic capacity appears to be exercise dependent. The data from the present study are not consistent with a cardio-protective effect of high inborn aerobic capacity; when comparing the change following MI relative to the respective sham groups the in vivo cardiac function, cardiomyocyte function and Ca\(^{2+}\) handling were similar, or, even more profoundly, affected on several parameters in HCR than in LCR rats.

In 1980, Morris et al. (37) reported greater survival rate in fit compared with sedentary subjects after MI. Later, other experimental animal studies suggested that exercise training preconditioning the heart and protects it against ischemia-reperfusion injury (8, 9, 12, 13, 29, 40, 50), as well as promotes healing of the infarcted area (13, 33). The protective role of a high \(\bar{V}O_{2\text{max}}\) in relation to CVD morbidity and mortality may be such be a result of adaptive responses to exercise training that serve as cardiac preconditioning rather than by \(\bar{V}O_{2\text{max}}\) level alone. Our data indicate, therefore, that high inborn \(\bar{V}O_{2\text{max}}\) without the adaptive response to exercise training do not elicit the expected cardio-protective effect on MI tolerance, even though \(\bar{V}O_{2\text{max}}\) is reported more closely related to mortality risk than physical activity levels per se (28, 34). Thus cardio-protection is likely dependent on acute effects provided by exercise training, as it vanishes at cessation of regular exercise (29).

It is difficult from our data to directly explain why high inborn aerobic capacity does not show the same protective effect as exercise training. A potential explanation for the lack of detectable protection in the present study is that the phenotypic changes developed through generation in rats selected for low aerobic capacity [including characteristics similar to the metabolic syndrome (22)] may have triggered mechanisms that, to some extent, may precondition the heart against ischemic damage. These mechanisms were not explored in the present study, but previous studies with this model have shown that the immune response is exaggerated in LCR (45), and especially TNF-\(\alpha\) (14) and interleukin-10 (10), which have been shown to have preconditioning effects on ischemia-reperfusion injury and is significantly upregulated in the LCR rats (26).

Conclusion. This study demonstrates that the effect of MI in HCR rats was similar or even more pronounced on cardiac and cardiomyocyte contractile function, as well as on Ca\(^{2+}\) handling properties, compared with observations in LCR. Thus our data do not support a cardio-protective effect of higher inborn aerobic capacity. The cardio-protective role associated with high aerobic capacity seems, therefore, not to depend on inborn characteristics, but rather on acquired aerobic capacity and cardiac preconditioning.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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