CURRENT TOPICS

Effects of Physical Training on Myocardial Vascularity and Perfusion

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SUMMARY Physical training is thought to be a stimulus for coronary vascular growth and coronary collateral development. This report is a summary of knowledge in the area. Studies in experimental animals with normal hearts indicate that physical training promotes increased myocardial capillary density and also causes enlargement of the surface coronary vessels. The physiologic effect of these changes on coronary vascular reserve and protection of segments of the heart against myocardial ischemia has not been established. Physically trained dogs and pigs do not appear to be protected against the effects of coronary occlusion, in that the ischemic area appears to be as large in trained animals as in untrained animals for any given coronary lesion. One study in physically trained rats appears to show protection against myocardial infarction, but whether this is related to coronary vascular changes has not been established. Experiments in dogs subjected to chronic narrowing or gradual occlusion demonstrate that physical training in these models does promote collateral blood flow as measured by retrograde flow in open-chest experiments. Studies using the microsphere technique in closed-chest animals confirms increased collateral flow to ischemic areas in some animals, but the magnitude of the increases appears to be small and varies greatly from animal to animal.

Studies in athletes suggest that myocardial blood flow is lower at any submaximal level of training in athletes than in sedentary persons. Studies in patients with coronary artery disease have generally failed to show an increase in coronary blood flow or in perfusion of ischemic areas after physical training programs, but the techniques used might not have been sensitive enough to detect changes.

The evidence in the experimental animals is sufficiently promising to indicate that the search should be continued to define physical training programs that will most stimulate myocardial vascularity and coronary collaterals in humans.

THE HYPOTHESIS that physical training programs are beneficial to the heart is based on evidence that chronic repeated exercise increases myocardial vascularity and protects the myocardium against ischemic insults. It has been suggested that training promotes coronary collateral vessel development so that when coronary artery disease is already established, collateral vessels would permit more abundant blood flow to a potentially ischemic area of myocardium and protect that area against ischemic injury and infarction.

The purpose of this paper is to review our knowledge of how myocardial vascularity and coronary collaterals respond to physical training.

Evidence of Increased Cardiac Vascularity in Experimental Animals

Early studies indicated that physical training increased myocardial vascularity in dogs and guinea pigs. Using coronary cast techniques, training was shown to increase the ratio of vascular space to myocardial mass in male and female rats trained by swimming or by running. As little as 2 days of exercise per week in rats was sufficient to cause some of these effects. In some of these studies, an absolute increase in capillary density was observed in the absence of cardiac hypertrophy.

Bloor and Leon explored the relationship of age to capillary fiber ratio in rats trained by swimming. They found that daily or twice-weekly swimming caused an increase in the capillary–myocardial fiber ratio in very young, young adult and old rats, but in the younger rats this change was due to an absolute increase in the number of capillaries and in the old rats to a decrease in the number of myocardial fibers. Tomanek found that the number of myocardial capillaries decreases with advancing age of rats, but the capillary–myocardial fiber ratio and total number of capillaries was greater in conditioned rats in any age group. The cross-sectional areas of the coronary collateral arteries and of the major coronary arteries were also increased.

In further studies in rats, Leon and Bloor studied the composition of the myocardium after 10 weeks of training by swimming and then after 10 weeks of detraining programs. As in their earlier work, they found that myocardial capillaries increased with 10 weeks of swimming, but if that was followed by a 10-week rest period, the number of capillaries had returned to the control state. If after 10 weeks of training, swimming was continued either for 60 minutes once a week or 30 minutes twice a week, they showed an intermediate level of increased myocardial capillarity, but with a swimming program of 15 minutes five times a week, myocardial capillaries returned approximately to the control level. Thus, there was an apparent dose-response relationship for maintenance of myocardial capillary abundance after capillarity had been in-
creased due to physical training. These workers also found that the increase in the extracoronary collateral luminal cross-sectional area was maintained only with swimming 60 minutes once a week but not with less vigorous regimens. Therefore, like myocardial capillarity, continued physical training was required to maintain the advantage on extracoronary collaterals. This effect on vascularity is similar to that observed on myocardial performance and actomyosin ATPase activity, where the training stimulus in rats needed to be maintained almost at the full level of exercise or else there was a rapid regression of the training effect toward the control state.

The studies cited above do not prove that the increased vascularity is of any physiologic significance. Pencaprgkul, Bersohn, Schaible and Scheuer showed increased coronary flow capability of hearts from rats trained either by swimming or running when perfused with aqueous perfusion medium in an isolated working rat heart apparatus. These studies indicated that maximum coronary flow capacity was greater in hearts of physically trained rats than in hearts of controls. Aqueous perfusion medium permits study under maximum coronary vasodilation states, but does not prove that this increased capacity is available in vivo in blood perfused hearts. Yipinsiotis et al. studied blood-perfused rat hearts in situ using the microscope technique, and vasodilated the coronary vessels by making the rats hypoxic. No greater coronary flow was observed in the hearts of physically trained rats; however, maximum vasodilation probably was not achieved. Spear et al. explored the same problem in hearts of rats trained by running and found no changes in coronary blood flow under baseline conditions between hearts of sedentary and trained rats. However, during hypoxia and when blood pressure was maintained by infusion of methoxamine, coronary flow and coronary conductance tended to be higher in the hearts of trained rats than in sedentary controls. Again, maximal coronary vasodilation was not achieved, and although their findings suggest that the greater vascularity might be of physiologic significance, the magnitude of difference was small.

The majority of studies on myocardial vascularity have been conducted in rodents, although the earlier work of Petren et al. suggested the same effects in dogs. Myocardial vascularity was explored in more detail in dogs by Wyatt and Mitchell. They trained dogs for 8 weeks on a treadmill and examined the hearts histologically. The cross-sectional area of the extramural coronary arteries in the trained dogs was greater than that in sedentary dogs and myocardial capillary density tended to be higher, but the latter was not a statistically significant difference. With deconditioning of these dogs, the circumflex artery cross-sectional area decreased significantly toward the control value and myocardial capillary density also diminished significantly, indicating that training and detraining do affect the vascularity of the heart in dogs. Stone studied whether this change has physiologic significance. He trained dogs on a treadmill for varying periods and then measured their coronary blood flow velocity as a function of heart rate during atrial pacing studies. Flow velocity in the circumflex coronary artery at any given heart rate was significantly higher in dogs trained 4–5 weeks than in untrained dogs. However, when coronary flow velocity was studied with the dogs running on a treadmill, flow velocity was lower during exercise at any specific submaximal exercise level in partially trained dogs (4–5 weeks of exercise) than in dogs trained 8 weeks or in untrained dogs. It is difficult to interpret the findings in this report in terms of maximum coronary flow, because maximum coronary reserve was not studied in a definitive manner. The lesser blood flow during submaximal exercise may be due to the effects of training on heart rate and blood pressure.

Physical training results in a relative bradycardia at rest or during submaximal exercise, and frequently is accompanied by a lesser blood pressure response to exercise. Therefore, the determinants of myocardial energy consumption and coronary blood flow are lower in the physical training state at rest or during submaximal exercise. Liang et al. found that myocardial blood flow in dogs trained for 5 weeks was lower at rest than in sedentary control dogs. A lesser coronary flow might also be expected during submaximal exercise. At maximum exercise, the determinants of myocardial energy demand and coronary blood flow are frequently the same before and after training.

Therefore, the increased coronary cross-sectional area and myocardial capillary vascularity have not been shown to be of physiologic significance in experiments in animals, perhaps because hearts have not been studied under maximum coronary vasodilation conditions.

Studies During Myocardial Hypoxia or Ischemia

Another way to explore whether coronary vascular changes are of physiologic significance is to study the myocardium while it is ischemic or hypoxic. Spear et al. did find slight improvements in myocardial blood flow in physically trained rats under hypoxic conditions. McElroy et al. studied infarct size after ligating the anterior descending coronary artery in sedentary and physically trained rats. They observed increased myocardial vascularity in the physically trained rats. The infarct was approximately 30% smaller in hearts of physically trained rats than in sedentary controls, suggesting a protective effect of physical training. This does not prove that this is related to an increase in coronary collateral formation; Scheuer and St佐sido demonstrated that hearts of physically trained rats subjected to global hypoxia maintained performance better than hearts of sedentary controls, and when hearts were perfused under global ischemic conditions in the isolated working rat heart apparatus, myocardial function also was preserved, even though the level of ischemia was the same in sedentary and conditioned hearts. Therefore, a protective effect may be partially due to an intrinsic alteration in the heart muscle that is independent of improved myocardial oxygen delivery.

Cohen et al. attempted to explore this subject in
dogs with normal coronary arteries trained on a treadmill training program for 8–12 weeks. Both moderate and strenuous training programs were studied. At the end of the training period, the hearts were subjected to occlusion of the left anterior descending coronary artery, and blood flow to the ischemic area was measured by the microsphere technique. There was no significant difference in the coronary blood flow to the ischemic area in either of the trained groups vs control; in fact, collateral flow tended to be lower to the ischemic area in the trained dogs, although this difference was not statistically significant. The endocardial–epicardial flow ratios also were similar in the ischemic areas, and when retrograde flow and coronary conductance were studied they also were not different. This study would suggest that a physical training program in dogs with normal coronary arteries does not promote collateral development that would subsequently protect a portion of the heart against ischemic insult. Burt and Jackson25 also studied retrograde flow in dogs that had normal coronary arteries and were trained by treadmill exercise. The maximal rate of retrograde flow after acute coronary ligation was not different in control and trained dogs, although total retrograde flow appeared to be greater in the physically trained dogs. Similarly, Sanders et al.26 found no increase in collateral blood flow in hearts of pigs with normal coronary arteries when studied during acute coronary occlusion after 10 months of physical training.

Collateral Development with Chronic Ischemic Lesions

Ischemia is a potent stimulus to coronary collateral formation. The hypothesis that physical training promotes coronary collaterals was stimulated by the report of Eckstein,27 in which the circumflex coronary artery of dogs was narrowed. Half of the dogs were exercised and the others remained sedentary. Retrograde flow to the ischemic area was measured at the end of the training period. There was an inverse relationship in both sedentary and trained dogs between the amount of retrograde flow to the ischemic vessel and the amount of antegrade flow through the narrowed area. However, for any degree of narrowing, the retrograde flow was less in hearts of sedentary dogs than in hearts of trained dogs, indicating that training had promoted coronary collateral development to the ischemic area. However, myocardial perfusion could not be measured in these studies and aortic blood pressure was not controlled; thus, the results could not be considered conclusive.

Heaton et al.28 ligated the circumflex coronary artery and narrowed a branch of the anterior descending coronary artery in dogs and later studied the awake, intact animals using the microsphere technique both at rest and during exercise, before and after a training program. They compared the results with those in a group of sedentary control dogs. The only positive result that was observed was during exercise in the trained animals. Myocardial blood flow to the endocardium was significantly higher after the training program than before, but there was no significant difference in epicardial blood flow or transmural blood flow. When control and trained dogs were compared before or after training, myocardial blood flow to the endocardium was not significantly different. Therefore, although a statistically significant increase in blood flow to the endocardium was demonstrated in the trained dogs, the magnitude of change was only slightly greater than that in control animals. Whether this effect is important in terms of improved myocardial performance or protection against ischemia remains to be shown.

Cohen et al.29 studied purebred beagles in which the left circumflex coronary artery was narrowed to a level that did not decrease resting coronary blood flow but markedly attenuated the postocclusive hyperemic response. In this model, ischemia developed only during exercise. Half of the dogs were trained for 12 weeks on a treadmill and the other half were kept sedentary. The closed-chest dogs were then studied during rest and exercise by the microsphere technique, while the circumflex coronary artery was abruptly occluded by a balloon-occluding device controlled from outside the dog. While the dogs were resting, collateral blood flow increased into the circumflex area in only one of six dogs in the sedentary group, but increased significantly in four of seven in the trained group. The ratio of blood flow to the ischemic area to that in the normal area increased over the 12-week period in two of the six sedentary dogs and increased significantly in four of seven of the trained dogs. These results demonstrate that when a carefully created ischemic lesion is in place during training, collateral blood flow increases. However, the response was not homogeneous; collateral flow also increased in one of the sedentary dogs and failed to increase in some of the trained dogs. This raises the possibility that even in this homogeneous genetic group of animals, there is a heterogeneous response of collateral vessels.

Whether collateral development is actually stimulated by physical training after coronary occlusion has also been investigated. Kaplinsky et al.30 ligated the coronary artery of experimental animals before training. They found no angiographic evidence of increased coronary collateral vessels after training. Neill and Oxendine31 studied dogs subjected to 5–8 weeks of treadmill training after an ameroid constrictor was placed around the left circumflex artery. They used the microsphere technique to study transmural myocardial blood flow distribution in the basal state and during tachycardia induced by cardiac pacing. These workers found that there was no difference in transmural blood flow distribution at rest or during tachycardia in the trained vs the sedentary dogs. However, retrograde blood flow from the occluded vessel in the open-chest dog was higher in the trained animals. Neill and Oxendine concluded that collateral vessel formation increased, as demonstrated by the retrograde blood flow studies, confirming the report of Eckstein,27 but this was not of physiologic importance; in the intact myocardium, the increased collateral formation could not be translated to an increase in myocardial blood flow.

More recently, Scheel et al.32 created coronary stenosis in dogs with a left circumflex coronary artery ameroid constrictor, but they did not begin an exercise
program until 3 months later. After 8 weeks of training, they studied retrograde flow and coronary conductance to all areas of the coronary vascular system using a carefully controlled isolated perfused dog heart preparation. In the trained dogs, there was a marked increase in retrograde flow to the occluded circumflex area from the anterior descending region, the right coronary artery region, and the septal vessels. Retrograde flow also increased in the sedentary group compared with a group of control dogs without prior coronary occlusion, but the increase was much more marked in the trained dogs. Thus, the potential for developing coronary collaterals is great if exercise is started 3 months after coronary occlusion, but an increase in collateral blood flow technique cannot always be translated into meaningful myocardial perfusion in the closed-chest animal with an intact coronary bed. Since Scheel et al. used only the retrograde flow technique, further studies are necessary using the same experimental time sequence, but measuring collateral flow to ischemic myocardium in closed-chest animals. Schaper trained dogs for 50 days before placement of aortomacular constrictors. After 100 days of further training, no difference was observed in retrograde flow patterns when these hearts were compared with hearts of untrained dogs with aortomacular constrictor treatment of the same duration.

Thus, the information about training effects on coronary collateral development in dog hearts is inconsistent, perhaps because ischemia itself is such a potent stimulus to collateral growth in dog hearts that a physical training effect is overridden by the ischemic effect. In man, where collateral vessel response to ischemia may not be as abundant, physical training could provide more of an additive effect. This possibility must be tested either in animal models that react more like man; or, when sensitive noninvasive methods are available, studies will be performed in humans.

Studies in Humans

Heiss et al., in a study of normal males, measured coronary blood flow in 11 athletes and 11 untrained students. Myocardial blood flow was lower in the trained athletes both at rest and during exercise. It is not clear whether blood flow was measured at maximum exercise, and since the level of tension-time index was lower both at rest and during exercise in the trained subjects, the results could be in part explained by the lesser myocardial energy demands in trained subjects at any submaximal level of exercise.

Most of the studies of coronary flow in physical training in man have been conducted in patients with coronary artery disease. Sim and Niell studied eight patients with angina pectoris before an 11–15 week training program. They found that coronary blood flow was similar before and after the training program both at rest and during tachycardia induced by pacing. Coronary angiography also failed to demonstrate a change in the coronary collateral vessels.

Ferguson et al. studied patients with coronary artery disease before and after a 16–26 week training program. The patients were exercised acutely on a bicycle ergometer while coronary sinus blood flow was measured. Coronary sinus blood flow at rest was the same before and after the physical training program, but during submaximal exercise, coronary sinus blood flow was less after than before training. At maximum exercise, coronary sinus blood flow was the same after training as before training. When blood flow was examined as a function of myocardial energy demand as measured by the rate-pressure product, the ratio of coronary sinus blood flow to energy demand was similar at any level of exercise before and after the training program. Thus, it appeared that the change in myocardial blood flow was due to the alteration in energy demand.

The effects of physical training in men with coronary artery disease have been studied using angiography, and although some increase in coronary collaterals was visualized in some patients, an increase has also been reported in patients with coronary artery disease who have not been subjected to a physical training program. It is difficult to evaluate whether physical training per se has a greater effect than ischemia alone as measured by coronary angiography, which is relatively insensitive.

One would hope that the use of radionuclide testing provides a more sensitive tool that can be applied both during rest and exercise to evaluate the development of collateral flow to ischemic areas in humans with coronary artery disease. The studies using radionuclide perfusion have been relatively limited. Nolewajka et al. used radiolabeled microaggregates before and after an experimental period in a group of control and trained patients with ischemic heart disease. They found no evidence of collateral vessel development in either group. Verani et al. studied 30 patients with documented coronary artery disease before and after a 12-week treadmill program. Although physical training improved exercise performance, there was no difference between resting or exercise myocardial perfusion index as studied by thallium-201 scintigraphy before and after the training program. Froelicher et al. reported that six of 16 patients with coronary artery disease subjected to a physical training program of at least 3 months showed some improvement in myocardial perfusion by thallium-201 testing during acute exercise.

Conclusions

There is unequivocal evidence that in experimental animals, chronic physical exercise results in increased capillary growth in the myocardium and causes enlargement of extramural vessels. The role of this increased vascularity in terms of greater myocardial perfusion or protecting the heart against ischemic segments has not been established. Once an area of ischemia is established, it is clear that at least with some training protocols in dogs, coronary collateral growth can be potentiated by chronic exercise. The type of stimulus needed for this potentiation is unclear. The evidence that physical training enhances collateral
vessel formation in humans with coronary artery disease is, at best, equivocal. The reasons for this may be that we have not had sensitive enough tools with which to measure collateral flow, or the correct physical training programs may not have been used.

Continued research is required to more clearly develop specific principles or training programs that can help protect the heart and to explore protocols in humans that might increase collateral vessel formation.

Acknowledgment
The author gratefully acknowledges Carol Gundlach for her editorial assistance and Janet Ellen Holwell for her secretarial assistance.

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J Scheuer

_Circulation_. 1982;66:491-495
doi: 10.1161/01.CIR.66.3.491

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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