‘Ultra’ Coronary Arteries: Bigger and Better?

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In this issue of Circulation, Haskell and colleagues report the results of an intriguing study of the coronary arteries of ultradistance runners. They performed quantitative coronary arteriography at rest and after maximal pharmacological coronary vasodilation with nitroglycerin in 11 middle-aged runners who trained approximately 50 miles per week for an average of 13 years and had completed the Western States ultramarathon. The results were compared with 11 sedentary control subjects who were referred for evaluation of chest pain but had angiographically normal coronary arteries. At rest, the right coronary artery in the runners was bigger, although combined cross-sectional area of the right, left main, left anterior descending, and circumflex coronary arteries was not different between the groups. Of particular importance was that after an infusion of nitroglycerin, an endothelium-independent coronary vasodilator,2 the total cross-sectional area of the coronaries of the runners increased by approximately twice that of the control subjects, demonstrating a significantly greater vasodilator reserve capacity.

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Increased occupational5,6 or recreational5,6 physical activity reduces the risk of cardiac death in individuals who have not yet demonstrated any manifestations of coronary heart disease, i.e., primary prevention. The American Heart Association therefore now recognizes a sedentary lifestyle as an independent and potentially modifiable risk factor for coronary disease.7 The present study may offer some insight into one mechanism for the apparent protection of increased physical activity.

This study is unique in that it provides the first evidence in living humans that prolonged endurance training may substantially affect coronary artery anatomy and physiology. Although animal studies abound,8 there have been remarkably few studies on the effect of endurance training on human coronary arteries. As discussed by the authors, autopsy studies have suggested that long-term endurance training may increase the size of epicardial coronary arteries. In particular, the case of “Mr. Marathoner” Clarence De Mar, who ran the Boston marathon 34 times up to the age of 66 years and who at autopsy had unusually large coronary arteries,9 promulgated the myth that runners were immune from coronary artery disease.10 Thus, the observation in the present study that resting total cross-sectional area was not larger in the runners is somewhat surprising. The authors suggest that the similar left ventricular mass between runners and control subjects may explain this finding. However, it may also reflect the difference between autopsy studies and those performed during life.

One of the most important factors influencing coronary blood flow and therefore vasomotor tone and vessel size is myocardial metabolism, as reflected by myocardial oxygen consumption (MVO2).11,12 The MVO2 required to sustain the actively contracting heart is approximately 10 times that of the noncontracting heart.13 Wyatt and Mitchell14 have shown in dogs that coronary diameter is linearly related to heart rate, an index of MVO2, emphasizing the critical importance of comparing coronary artery size under similar metabolic conditions. In the present study, the athletes were studied at a 50% lower heart rate and a 15% lower systolic blood pressure than the control subjects, reflecting an approximately 65% lower MVO2.15 It is possible, therefore, that at any given MVO2 (including autopsy, i.e., MVO2=0), coronary artery size is larger in the endurance athlete. If heart rate had been increased at rest (using atropine, for example) in the endurance athletes so that their MVO2 was equivalent to that of the control subjects, the coronary artery size might have been larger in the athletes.

It is interesting to note that despite this difference in MVO2, the right coronary artery was significantly larger in the runners compared with control subjects. Douglas et al15 have recently reported right ventricular dilation after prolonged exercise in contrast to the left ventricle, which decreased in size after the Hawaii Ironman Triathlon. They hypothesized that this was due to a disproportionate increase in pulmonary artery pressure and right ventricular work during exercise.16 It is intriguing to hypothesize that the increase in the right coronary artery area in these ultramarathoners may be due to chronic hypertrophy of the right ventricle as opposed to the left ventricle in response to prolonged and intense endurance training.

Probably more important than the anatomic changes in coronary size in the present study was the identification of increased coronary vasodilator reserve in the ultramarathoners. Neural (sympathetic and parasympathetic efferent activity), metabolic, and endothelial modulators of coronary vascular resistance both in large epicardial conductance vessels and smaller resistance arterioles allow for the dynamic adjustment of coronary blood flow to match changes in myocardial oxygen consumption.

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requirements. Because the myocardium operates at near maximal oxygen extraction, an increase in blood flow is the only mechanism by which such requirements can be met. In normal coronary arteries with intact endothelial function, maximal flow in response to pharmacological stimulation can increase to approximately 3.5-4.0 times control values.17 In the present study, the authors measured change in coronary cross-sectional area that is related to flow by a factor of the radius of the vessel to the fourth power. If we assume that the length and the pressure drop across the vessel remain unchanged, then the reported increase in area of the left anterior descending coronary artery would lead to approximately twice the increase in flow in the athletes (265%) compared with the control subjects (134%), depending on the magnitude of nitroglycerin-induced changes in the caliber of small, intramyocardial resistance arterioles. This increase in maximal flow to cardiac muscle is similar to the increase in maximal conductance of skeletal muscle identified cross-sectionally in endurance athletes18 and longitudinally with endurance training.19 Whether this is a structural or functional adaptation, however, is not clear. Maximal conductance in skeletal muscle does appear to be associated with a number of other adaptations of the endurance athlete, including eccentric hypertrophy of the heart and carotid baroreflex control of vascular resistance,20,21 suggesting that the large vasodilator reserve in both cardiac and skeletal muscle may be closely related.

Nitrovasodilators such as nitroprusside or nitroglycerin used in the present study to induce maximal coronary vasodilation act by generating nitric oxide, the putative endothelium-derived relaxing factor, but do not require an intact endothelium to exert an effect.13 They differ from endothelium-dependent vasodilators such as acetylcholine, the response to which may be grossly abnormal in the setting of atherosclerosis.22 One important caution about interpreting the greater vasodilator response in the ultraendurance athletes in the present study is the fact that the control subjects were patients being evaluated for chest pain who had angiographically normal-appearing coronary arteries. Some of these patients may have abnormal coronary vasomotion as evidenced by a reduced vasodilator response to metabolic23 or pharmacological stimuli,24 which may contribute to their chest pain syndrome. However, recent studies have shown that this abnormal response is primarily due to endothelium dysfunction—the response to endothelium-independent vasodilators such as used in the present study appears to be normal.25 It would be interesting and physiologically important to know whether a similarly greater coronary artery flow reserve could be demonstrated in response to endothelium-dependent vasodilators such as acetylcholine in ultraendurance athletes.

The authors are appropriately cautious in interpreting the clinical implications of their findings. One concern is the “dose” of exercise necessary to protect against coronary artery disease. In the Harvard alumni study cited by the authors,3 cardiac death rates decreased linearly with increasing physical activity from 500 to >2,000 kcal of energy expenditure per week (equivalent to walking or running approximately 20 miles per week). There was no apparent benefit in terms of cardiovascular mortality for those men exercising more than this level, and death rates tended to increase with exercise durations similar to the ultramarathoneers from the present study. Furthermore, Blair et al4 have shown that for both men and women, the largest benefit in terms of survival is associated with a relatively low level of physical fitness.5 In this study, a maximal treadmill work rate equivalent to approximately 10 METS (metabolic equivalent of the task) in men and 9 METS in women conferred virtually all the advantage for preventing cardiovascular disease, with a large proportion of the protection already present at 7 METS for both sexes.

Levine et al21 have demonstrated that at least for skeletal muscle, there is not an increase in maximal conductance or blood flow with moderate levels of physical conditioning.21 If this is also true for cardiac muscle, then the amount of exercise or level of fitness required to improve survival is less than that necessary to stimulate adaptations that increase maximal blood flow in response to physiological or pharmacological stress, arguing against this adaptation response as the mechanism for reduced cardiovascular mortality with fitness or regular exercise.

Recent insights into the pathophysiology of myocardial infarction and acute coronary insufficiency suggest that these acute syndromes occur as a result of sudden rupture into an atherosclerotic plaque with associated intravascular thrombosis.26 Thus, although the presence of larger coronary arteries with increased flow reserve might be expected to delay the onset of angina, particularly during exercise, it would not necessarily be expected to reduce the incidence of myocardial infarction. In fact, for patients enrolled in cardiac rehabilitation after an acute coronary event, exercise training appears to improve survival primarily by reducing the incidence of sudden death27 rather than by reducing myocardial infarction. It is likely that increases in vagal tone associated with endurance training28 is another mechanism responsible for a large portion of this effect.29,30 Powerful supporting evidence for this hypothesis comes from Vanoli et al,30 who studied an elegant model using conscious dogs that survived an induced myocardial infarction. In over 100 animals, they showed that stimulation of the vagus nerve virtually eliminated ventricular fibrillation during ischemic exercise.

In summary, this study by Haskell et al provides new and provocative data regarding the effect of extreme endurance training on human coronary anatomy and physiology that extend observations made previously only in animals. The clinical significance of these observations is yet to be determined.

References

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