# Physical activity and coronary collateral circulation

Francesco Barillà, Enrico Mangieri, Gaetano Tanzilli, Loreta Prosseda, Pietro Paolo Campa Second Section of Cardiology, Institute of Cardiac Surgery, "La Sapienza" University of Rome, Rome, Italy

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Introduction

Address:

#### Dr. Francesco Barillà

II Cattedra di Cardiologia Istituto di Cardiochirurgia Università degli Studi "La Sapienza" Policlinico Umberto I Viale del Policlinico, 155 00161 Roma It has been widely demonstrated that a moderate level of physical activity reduces the risk factors in patients with coronary artery disease (CAD), improves the functional work capacity and reduces both the progression of the disease and the mortality rate<sup>1</sup>. Indeed, the American Heart Association has recently concluded that inactivity should be considered a risk factor for CAD. Among currently available therapies for CAD, the observed 25% risk reduction with exercise is comparable to 20% achieved with aspirin, 20% with  $\beta$ -blockers, and 15% with angiotensin-converting enzyme inhibitors.

However, despite the well-known beneficial effects of exercise training in patients with CAD, the question of whether exercise induces improvement of myocardial perfusion in the absence of coronary lesion regression is still unsolved, and the question of whether or not exercise training stimulates the development of coronary collateral circulation (CCC) remains open to debate. Salomon<sup>2</sup> argued that improvement in CCC could result from physiological responses to the progression of CAD, rather than to the direct effect of exercise, and concluded that no evidence exists that exercise increases CCC in humans. Salomon s statements, however, are not supported by subsequent experimental and clinical studies.

## Animal studies

Eckstein<sup>3</sup> reported a beneficial effect of exercise on the development of CCC in dogs with a surgically induced narrowing of the circumflex coronary artery. By using

retrograde flow to estimate collateral blood flow, this author showed that a moderate to severe narrowing of the artery is necessary for collateral growth induction. In addition, he demonstrated that exercise increases the extent of CCC above the amount expected from the narrowing artery itself. Neill and Oxendine<sup>4</sup> also investigated the effects of exercise on collateral formation in dogs, using an aneroid constrictor on the circumflex artery and a tracer microsphere for measuring coronary blood flow. In spite of an improvement in collateral growth in trained group animals, no increase of perfusion in the ischemic area was seen, and the authors concluded that exercise can promote CCC even in the absence of perfusion improvement in the ischemic myocardium. In beagles with coronary occlusion, Scheel et al.5 observed that exercise after a 3-month convalescent period promotes epicardial and intramyocardial collateral growth. This phenomenon allowed restoration of the coronary reserve that reached 52% of initial capacity in the trained animals, as compared to 34% in the untrained animals. These data suggest that in the presence of a reduced coronary reserve exercise can cause structural changes in coronary collateral vessels. Such an improvement of CCC could have a protective effect in the collateral-dependent myocardium when there is a limited increase in metabolic demand. The contradictory results of the above experimental studies are explained by Cohen<sup>6</sup>. He hypothesized that in the presence of normal coronary arteries, as is the case of the above studies, the coronary reserve is large enough to avoid myocardial ischemia during exercise, which is an important stimulus for exercise-induced collateral growth.

Recently, White et al.<sup>7</sup> have found that exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in the heart. The substances required to initiate the angiogenesis process during exercise are the growth factors. These hormones stimulate the proliferation of vascular cells and increase the expression of proteases that are an important factor for vessel remodeling. Since increasing levels of both vascular endothelium growth factor and fibroblast growth factor were found in animal skeletal muscle after a single bout of exercise, one could speculate that these hormones are involved in the vascular adaptation to chronic exercise.

## **Human studies**

Data from human studies are also intriguing. Conventional exercise has been shown to enhance myocardial perfusion and to reduce the incidence of ischemic heart disease<sup>1</sup>. In contrast, strenuous exercise in sedentary subjects may lead to platelet activation as well as platelet hyperreactivity. These changes with the concomitant increase in plasma levels of catecholamines can precipitate an acute ischemic event.

Several mechanisms have been proposed to explain the enhanced myocardial perfusion in patients with CAD during routine exercise. They include regression of CAD, recruitment of CCC, and enhanced blood flow. Most studies have failed to document a net regression of coronary lesions, even when lipid lowering strategies were associated with exercise training. On the other hand, a decreased incidence of myocardial ischemia was observed in patients with progression of the disease. These findings suggest that improvement of myocardial perfusion may be achieved independently of changes in coronary lesions.

Recruitment of collateral vessels during maximal exercise is considered the one possible mechanism, but angiographic studies do not support this hypothesis. However, it is well known that coronary angiography is not the proper technique to evaluate collateral channel development, since only vessels with a diameter > 100  $\mu$ m are visualized. In addition, collateral channels in the subendocardial layers may not be opacified with standard angiography.

Schuler et al.<sup>8</sup> studied the effects of low-fat diet and regular exercise in 18 patients. After 1 year of this program they demonstrated that some patients showed an improvement of myocardial perfusion, in spite of progression of coronary lesions. Ferguson et al.<sup>9</sup> postulated that the positive effects of physical training in patients with CAD may be related to the slow progression of coronary disease rather than to the development of new collateral vessels. Other authors<sup>10</sup> observed that the development of CCC during exercise was present especially in patients treated previously with heparin. More recently, in two groups of randomized patients, Niebauer et al.11 demonstrated that there were no significant differences in the development of collaterals during the exercise program. However, the progression of the disease was significantly related to an increase in collateral growth while the regression was significantly related to a decrease in collateral development. Since in this study patients with progression of the disease exercised for > 3 hours a week and patients with regression of CAD exercised > 5-6 hours a week, this raises the question of whether an exercise program is able to induce CCC when a regression of CAD occurs. Improvement of myocardial perfusion was found in another study12 in patients with progression of CAD during intense exercise, although coronary angiography failed to demonstrate an increase in CCC. On the basis of previous investigations, it seems reasonable to believe that the angiographic approach is not the proper technique to evaluate collateral vessel development. The limited patient population of previous studies, and the relatively short training period may account for the negative results of the majority of these studies.

## Summary

Several animals and clinical investigations as well as studies in patients with peripheral artery disease<sup>13</sup> have recently provided evidence that exercise stimulates vascular collateralization in humans. Since myocardial ischemia has been shown to be the most efficacious stimulus for vascular collateral development, a paradoxical question arises: should exercise training intensity be set above the anginal or ischemic electrocardiographic threshold? Or, should the training program be more prolonged than that utilized in previous studies?

Further studies by using different protocols for exercise training and more sensitive tools to assess the development of collateral channels are necessary to better clarify the relation between exercise training and coronary collateral growth in patients with CAD.

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