it is a more reliable marker of cardiorespiratory fitness. It is assumed that the difficulties that the study population had with balance, strength, and spasticity were better accommodated by cycle ergometry. In line with this assumption is the mean age-predicted maximum heart rate, which was 91.8 ± 10.7% compared with 65.1 ± 8.9%, respectively, using cycle ergometry and 6MWT. The level of perceived exertion, as measured by the 16-point Borg rating of perceived exertion scale, was also significantly greater during cycle ergometry. The authors discuss the fact that an exercise treadmill test with harness support minimizes the requirement for maintaining balance and may be an alternative to cycle ergometry. This qualification is intuitive, and further comparison of the two tests is warranted. However, the current study seems to indicate that cycle ergometry is the better assessment modality and perhaps the preferred training method for improving cardiorespiratory fitness in the population of patients with chronic stroke and residual disability.

One of the most significant findings in the study (and perhaps the true bottom line for all of us who concern ourselves with the care of patients discussed in the article by Pang et al) is the exceedingly poor cardiorespiratory fitness of these individuals. When compared to norms in age-matched healthy populations, the VO2max in the study population was approximately 20 to 25% lower and in the region of the 10th percentile.

The mean percentage of body fat is increased in this population, and the lean body mass is decreased. This situation is especially critical considering that the study subjects were all at a higher level of function compared to the stroke population in general.

Now that we have been educated and given the appropriate tools, we have the imperative to develop programs for patients that can lead to improved fitness. Appropriate trials that build on the data in the article by Pang et al to determine the impact of fitness enhancement on pertinent outcomes should be encouraged.

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Role of Endothelin-1 in Acute Myocardial Infarction

The presence of the endothelin (ET) system was first discovered in 1988.1 The ET system includes ET-1, ET-2, ET-3, and ET-4. ET-1, a 21 amino acid peptide, represents the major isoform of the ET system, as it is the most potent vasoconstrictor known.2 ET-1 is cleaved from its precursor by the action of ET-converting enzyme. ET-1 acts through two receptors, ET-A and ET-B. Activation of the ET-A receptor leads to an increased intracellular calcium concentration inducing vasoconstriction and cellular proliferation. Contrary, ET-B receptors are inhibitory, and are involved in the clearance of ET-1 and inhibition of the ET-converting enzyme. Additionally, activation of ET-B receptors results in release of vasodilatory mediators such as nitric oxide and prostacyclin. Thus, ET-1 has both vasoconstrictive and vasodilatory effects, but the vasoconstrictive effect predominates, more so in the vessels with dysfunctional endothelium; the loss of nitric oxide may augment the vasoconstrictive activity of ET-1.

ET-1 plays a role in both the physiologic and pathologic conditions of the cardiovascular system. Human and canine epicardial coronary arteries display a baseline ET-1–dependent tone, which is an ET-A receptor-dependent process.3 In healthy coronary arteries, administration of ET-1 causes biphasic coronary response characterized by a transient dilatation of large and small vessels followed by a sustained constriction. With higher doses, the vasoconstrictive response predominates, both in the coronary as well as the periph-

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eral circulation. In a human experiment in which ET-1 was administered IV in doses of 0.2, 1, and 8.0 pmol/kg/min, coronary blood flow was reduced by 23%, coronary vascular resistance increased by 48%, and mean arterial pressure increased from 95 to 106 mm Hg with the highest ET-1 infusion rates. The reduction in coronary blood flow and increase in coronary vascular resistance were parallel to the decrease in coronary sinus oxygen levels. The threshold dose of ET-1 for causing significant coronary effects was 1.0 pmol/kg/min, a dose that raised plasma levels by fourfold. Thus, ET-1 at nonphysiologic plasma levels results in a mismatch between oxygen supply and demand in coronary circulation, although at physiologic levels it plays a major role in maintaining the healthy vascular tone.

The effects of ET-1 on heart are multiple, and are more or less a function of the plasma level of ET-1. With normal ET-1 plasma levels, it exerts a positive inotropic effect because of an ET₁-dependent increase in intracellular calcium; however, the elevated plasma levels of ET-1 result in a decline in cardiac output because of the predominant peripheral and coronary vasoconstrictive effect resulting in increased afterload and reduced myocardial perfusion, respectively. This has been substantiated by the observations in which ET antagonism worsened myocardial contractility in healthy humans with normal ET-1 plasma levels but improved contractility in patients with advanced ventricular dysfunction. Moreover, cardiac output increases when ET-1 is coadministered with vasodilators, likely because of unmasking of its inotropic effects. ET-1 also stimulates secretion of atrial natriuretic peptide through ET-A receptors. In addition, ET-1 promotes growth of the cardiac myocytes, especially in the presence of hypoxia.

Plasma levels of ET-1 are elevated in patients with acute myocardial infarction. Following an uncomplicated acute myocardial infarction, ET-1 is markedly elevated within hours, peaks at 6 h, and returns to normal within 24 h. In complicated myocardial infarction, such as with pulmonary edema, reinfarction, or cardiogenic shock, plasma ET-1 levels remain elevated for a longer period; in fact, the highest plasma levels of ET-1 have been observed in patients in cardiogenic shock with acute myocardial infarction. The elevated plasma levels of ET-1 observed during acute myocardial infarction are a result of stimulated both cardiac and extracardiac production of ET-1. An increased myocardial expression of prepro-ET-1 messenger RNA has been observed in animal models, suggesting stimulated cardiac production during myocardial infarction. In a rat ischemia-reperfusion model, plasma ET-1 increased after 50 min of coronary occlusion and was augmented further after reperfusion, suggesting a reperfusion-related washout phenomenon. However, the main source of elevated ET-1 plasma levels in acute myocardial infarction seems to be extracardiac, possibly by reduced pulmonary clearance and increased ET-1 production regulated by baroreflexes, as a positive correlation has been reported between both the cardiac filling pressures and pulmonary vascular resistance and the plasma ET-1 levels. In addition, angiotension II, activated in acute myocardial infarction, is also a potent stimulator of ET-1.

The role of ET-1 in acute myocardial infarction is both beneficial and detrimental. ET-1 seems to play an important role in causation of myocardial infarction, in postinfarct scar formation, in left ventricular remodeling, and in prognosis of myocardial infarction. ET-1 is a causative factor in stenosis of atherosclerotic coronary arteries, contributing to the pathophysiology of the acute myocardial infarction. In an angiographic human study, intracoronary delivery of an ET-A receptor blocker resulted in a marked 21% dilatation of stenotic coronary arteries at 60 min, compared to 7% dilatation of angiographically smooth epicardial coronary arteries. After myocardial infarction, the physiologic role of ET-1 is in stabilization of scarring and is likely due to a combination of its inflammatory, proliferative, and fibrotic effects, the characteristics necessary for healing of myocardial infarction. ET-1 is a chemotactic factor for macrophages, and it stimulates neutrophil adhesions. After a myocardial infarction, ET-1 levels in the infarcted area are many-fold higher than those in healthy myocardium, which suggests the favorable effects of ET-1 in scar healing and stabilization. ET-1 promotes myocardial fibrosis by enhancing cardiac fibroblast proliferation, adhesion molecule expression, and extracellular matrix deposition, and therefore, plays a role in postinfarct remodeling after acute myocardial infarction. At the same time, elevated plasma levels of ET-1 early after myocardial infarction may cause vasoconstriction of coronary and systemic arteries, further increasing the afterload and myocardial ischemia causing scar expansion. These deleterious vascular effects seems to predominate, as it has been noted in studies using animal ischemia-reperfusion models that ET-receptor blockade has either favorable effects on myocardial infarction size, incidence of arrhythmia, and myocardial function, or has no effect. In humans, a significant correlation has been observed between the transcardiac extraction of ET-1 in the acute phase of myocardial infarction and the left ventricular ejection fraction and left ventricular end-diastolic volume index after 1 month, indicating a possible strong role of ET-1 in evolution of infarct and postinfarct ventricular remodeling. Similarly, in a human study, plasma levels of ET-1 measured after myocardial infarction were found to be a strong...
predictor of 1-year survival independent of clinical and biochemical variables previously associated with a poor prognosis.

Prognostic role of ET-1 in acute myocardial infarction where the culprit coronary artery was therapeutically opened was not known. In a report published in this issue of the CHEST (see page 1491), Yip and associates have tested this hypothesis in 186 patients with ST-segment elevation myocardial infarction who were treated with primary percutaneous coronary intervention. Patients were classified into two groups with reference to the median plasma value of ET-1 after acute myocardial infarction in the study group. There was no control group; therefore, the plasma levels of ET-1 in study population were not compared with those in healthy population. Patients were followed up for 30 days for occurrence of adverse clinical outcomes and mortality. The study demonstrated that ET-1 was an independent prognostic factor for adverse clinical outcomes and mortality even after successful opening of the culprit epicardial coronary artery. There could be two possible explanations of this observation. First, it is well known that opening of the culprit epicardial coronary artery does not reflect the reperfusion at the cellular levels. The reperfusion at the cellular level actually limits the myocardial damage, and is more precisely reflected by the resolution of the ST-segment elevation, not by the coronary angiography. Second, opening of the culprit epicardial coronary artery with balloon angioplasty would not circumvent the vasoconstrictive effect of the high plasma ET-1, which is mainly on the small coronary arteries. Can ET-1 blockers do it? Theoretically, the blockade of ET system could be a valuable therapeutic target to attenuate the process of postinfarction remodeling, but animal studies on this subject have not given conclusive results.13–18 and the clinical applicability of this possibility waits thorough clinical testing in large trials.

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