The paintings of the Belgian surrealist René Magritte (1898 to 1967) juxtapose 2 incongruous, illogical, or even contradictory objects: a steam locomotive projecting from a domestic fireplace (Time Transfixed, 1939); a bright daytime sky over a nighttime scene of a dimly lighted street (The Empire of Light, 1954); or a picture of a pipe with a caption on the canvas that reads, in French, “This is not a pipe” (The Treachery of Images, 1929). On the basis of conventional wisdom, the current palette of therapy for heart failure also would seem incongruous, illogical, or even contradictory if it included exercise therapy. However, change is at hand.

Conventional wisdom excluded the role of exercise training in the management of heart failure. The definition of heart failure—inadequate cardiac output/function to meet the metabolic demands of the body—efficiently fits the commonly reported and observed clinical symptom of reduced exercise capacity in patients with heart failure: the heart cannot keep up with the needs of the body that increase with physical activity. The measurement of functional capacity, objectified by exercise testing with measurement of maximal oxygen uptake (VO₂max) as the hallmark of body metabolism, demonstrates progressive limitation with the degree of heart failure (1). It serves, for example, to identify appropriate candidates for cardiac transplantation and to determine the degree of disability (2).

This limitation in exercise capacity was turned-around as a management paradigm: cardiology textbooks routinely advocated the restriction of physical activity and eschewed exercise training in patients with heart failure. The inclusion of an excellent chapter in a congestive heart failure textbook (3) that advocated limited exercise rehabilitation and training based on available evidence-based medicine perhaps marked the tipping point away from the conventional view. Subsequently, an American College of Cardiology/American Heart Association (ACC/AHA) guideline statement (2) recommended exercise training in patients with heart failure. A formalized recognition of this recommendation is part of the current ACC/AHA guidelines (4) for patients with current or prior symptoms of heart failure with reduced systolic function: exercise training is a Class I recommendation (Level of Evidence B). What is the evidence basis for this sea change in exercise training as therapy for heart failure, what are the limitations of the recommendations (both patient- and payer-centered), and what should clinicians now do with this information?

Studies of exercise training suggest some beneficial effects. The ACC/AHA statement (2), noted previously, reviewed 15 exercise trials in systolic dysfunction heart failure that included from 17 to 99 patients (total of 426) patients, the typical range of study patients in such trials. These trials used a wide range of training programs that differed by setting, types of activity, intensity, and duration, the latter ranging from 4 to 24 weeks. It found a modest improvement in VO₂max that occurred after a few weeks (range 12% to 31%) that was sustained for a number of months if the training program continued. A Cochrane review of 29 studies with 1,126 patients similarly reported that exercise training resulted (in the subset of studies providing data) in modest increases of VO₂max (range ~10% to 30%), duration of exercise, work capacity, and distance on the 6-min walk. Improvements in VO₂max were greater for a training program of greater intensity and duration. Health-related quality of life improved in patients in 7 of 9 trials that measured this outcome (5). Although safety was not stated as a primary objective of the studies included in this meta-analysis, 17 of the trials stated that no adverse event occurred, whereas 1 trial reported complications associated with training, but these complications were confined to the most severe patients with ejection fractions <30%. A recently published meta-analysis identified 35 studies, published between 1991 and 2004, that included 1,486 patients and found results similar to those reported previously in this paper. In a subset of studies that included cardiac performance, no benefit on ejection fraction or end-systolic volume was found, whereas end-diastolic volume decreased significantly, but only by approximately 1% (6).

As to the basis for these improvements in VO₂max and other measures of exercise capacity, the major benefit of exercise training is likely to occur through a partial reversal of physical deconditioning, which is an invariable concomitant of severe heart failure. Deconditioning may directly or synergistically (with cardiac dysfunction) worsen many of the adverse organ system changes that occur in heart failure: skeletal muscle mass and metabolism, vascular function (endothelial function, in particular, has been cited), respi-
ratory function and gas exchange, thermoregulation, and neuroendocrine homeostasis (7–16). Although the targets of exercise training are largely noncardiac, beneficial effects on the heart may occur through circulatory coupling that we now understand and routinely accept as determinants of cardiac function in heart failure.

The current study extends previous findings. The meta-analysis by Haykowsky et al. (17) in this issue of the Journal covers some familiar ground—exercise capacity and VO_{2\text{max}} in heart failure training studies—but adds some new information: effects on cardiac function and its relationship to modality of exercise training. As a background to their report, there are 2 broad categories of exercise modalities used in trials of training effect. Studies incorporate either “endurance” (sometimes called “aerobic” or “dynamic”) or “isotonic,” which use large muscle groups during either a walking-type or cycling-type of exercise) training, whereas a smaller set of trials use “strength” (sometimes called “circuit” or “weight”) training, or both types of training.

In their meta-analysis of 14 trials that included measurement of cardiac performance in 812 patients, the authors found an overall improvement in both VO_{2\text{max}} (~20%) and ejection fraction (~3% absolute). However, the authors noted heterogeneity in their pooled outcome and sought to determine its basis. They found that endurance training studies demonstrated these beneficial effects, whereas studies that used combined exercise modalities (i.e., both endurance and strength) did not. Furthermore, in the subset of studies that reported ventricular volumes, a decrease of end-diastolic and –systolic volumes occurred in those that used endurance training, whereas trials with combined training were inconclusive, although the smaller number of patients who participated in such studies limited the strength of the statistical analysis.

The authors concluded that aerobic exercise training reverses, to some extent, adverse ventricular remodeling in systolic dysfunction heart failure. However, a novel aspect of their study was the finding that strength (or combined modality) training did not demonstrate favorable effects. They hypothesized that the heightened systolic and diastolic pressure loading that occurs with strength training prevented the beneficial effects of exercise observed in the studies included in their meta-analysis and could have effects on the outcomes reported in other pooled trials of exercise training in heart failure patients. What are the limitations of these trials, and what do they portend for future research in and treatment of heart failure?

Problems in design of exercise trials limit interpretation of outcome. Exercise training trials of heart failure enroll small numbers of patients, thereby requiring meta-analyses, with their limitations, to provide the statistical affirmation that we now require for evidence-based medicine. However, another prominent and seemingly insuperable problem presents itself in evaluating the true effect of exercise training: studies lack patient blinding. An unblinded patient enrolled in a trial who is aware that his or her exercise training treatment arm may receive benefit or even perceive that an outcome based on this treatment could benefit or please the trial investigator, may promote an enhanced degree of cooperative behavior that could influence outcome, the so-called “Hawthorne effect” (18). Furthermore, although training sessions are not customarily viewed as “patient care,” it is hard to ignore the therapeutic benefit of a visit with (or even the presence of) a caregiver, even if stated for another purpose. Patients could skew outcome by, for example, increased compliance in nonstudy treatments, such as diet and medication, and thereby beneficially influence study end points, especially because standard therapy with angiotensin-converting enzyme inhibitors and beta-blockers each improve exercise capacity, whereas the latter also improves ventricular function (19).

Another limitation is that many earlier studies were conducted without maximal drug therapy. For example, in the meta-analysis of Haykowsky (17), only 4 of the 14 studies used beta-blockers in more than 50% of the study population, and only 2 of 14 used beta-blockers in more than 70%. Furthermore, I am not aware of any exercise training study that includes patients who have biventricular pacing. It will be important to observe the outcome of future trials that incorporate all proven modalities of heart failure as baseline therapy in both treatment arms of an exercise training study.

Future prospects for exercise training in heart failure. The positive outcomes in exercise training studies on VO_{2\text{max}} and, as reported in this issue of the Journal, on ventricular function, likely serve as surrogate markers for increased functionality and decreased symptoms in patients with heart failure. Without minimizing the value of these results to quality of life, most contemporary studies of treatments for heart failure emphasize “hard” end points such as the number of heart failure hospitalizations and survival. Most single-center exercise training studies of heart failure patients did not include these end points, either because of design or small sample size. However, a recent European collaborative meta-analysis examined death from all causes in 805 patient data sets from 41 nonoverlapping exercise training trials of heart failure. In these endurance training trials, exercise significantly reduced both mortality and death plus hospital admission with hazard ratios of 0.65 and 0.72, respectively, and the upper bound confidence intervals <1.0 for both; that is, the outcomes were statistically significant (20).

Now, a large, multicenter, randomized National Heart, Lung, and Blood Institute-sponsored clinical trial has been undertaken to definitively assess the effect of exercise training on the clinically relevant end points of mortality, hospitalization, and quality of life in patients with heart failure: HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) (21). Subsequent to baseline assessment to determine whether they can safely exercise, 3,000 patients are randomized to either usual care or exercise training, the latter consisting of supervised
facility-based endurance (cycling or walking) exercise training sessions. After completing the supervised sessions, patients initiate, and then transition to, solely home-based exercise, with some refresher sessions as reinforcement. Patients are followed for up to 4 years. A number of substudies are planned. The outcomes of this study should strongly advise because, compared with habitual exercisers, patients who initiate exercise after being habitually sedentary demonstrate a 100-fold increased risk for infarction and a 50-fold increase risk for sudden death (22,23). Unstated conditions of this recommendation are the motivation of the patient to participate in such a training program, to monitor themselves for side effects, and to avoid excessive anticipation of benefit. The latter is important because cultural and media bias present highly trained sports figures as attaining Herculean status, whereas the likely benefit of an exercise training program in a heart failure patient will be small.

Still another problem remains for the both provider and patient: exercise training for patients with heart failure currently is not cost reimbursed by the Centers for Medicare and Medicaid for cardiac rehabilitation services for patients with heart failure in the absence of an acute ischemic event. This is a barrier to nonhome programs, but one that may be addressed if the evidence base becomes sufficient to convince payers of its value, as perhaps could occur upon completion of the HF-ACTION trial.

Conclusions. So, is heart failure and exercise training contradictory or conventional? Looking forward to the likely beneficial effect of exercise training, as well as additional beneficial therapies available to treat heart failure, we may one day look upon such a patient and say, “This is not a heart failure patient.”

**References**