JAOA Review article

The muscle hypothesis: a model of chronic heart failure appropriate for osteopathic medicine

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Chronic heart failure is one of the most serious medical problems in the United States, affecting some 4 million persons. In spite of its common occurrence, and comprehensive literature regarding this condition, no unifying hypothesis has been accepted to explain the signs and symptoms of chronic heart failure. The cardiocirculatory and neurohormonal models place an emphasis on left ventricular ejection fraction and cardiac output and do not provide appropriate explanations for the symptoms of breathlessness and fatigue.

The muscle hypothesis supplements these conventional models. It proposes that abnormal skeletal muscle in heart failure results in activation of muscle ergoreceptors, leading to an increase in ventilation and sensation of breathlessness, the perception of fatigue, and sympathetic activation. At least one fourth of patients with chronic heart failure are limited by skeletal muscle abnormalities rather than cardiac output.

Cardiac rehabilitation exercise can lead to an increase in exercise capacity that is superior to that gained from digitalis or angiotensin-converting enzyme inhibitors. Exercise tends to reverse the skeletal muscle myopathy of chronic heart failure and reduces the abnormal ergoreflex. Other interventions that have been shown to have a favorable outcome include localized muscle group training, respiratory muscle training, and dietary approaches. The possibility that osteopathic manipulative treatment might be of benefit is an attractive, but untested, possibility.

(Key words: chronic heart failure, cardiac rehabilitation, muscle hypothesis)

Chronic heart failure is a clinical syndrome characterized by symptoms of fatigue and breathlessness. It has been defined as a syndrome or condition characterized by (1) signs and symptoms of intravascular and interstitial volume overload, including shortness of breath, rales, and edema, or (2) manifestations of inadequate tissue perfusion, such as fatigue and poor exercise tolerance.[1]

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Heart failure is among the most common medical problems in the United States, affecting some 4 million people. Despite substantial literature on this common health problem, no single unifying hypothesis has been accepted to explain the mechanism of heart failure. This is probably because the clinical syndrome of heart failure represents the final common event for a widely diverse group of cardiovascular conditions.

To a large degree, the models that have been used to explain heart failure have reflected the diagnostic or therapeutic modalities available at their times. Initially, heart failure was viewed as a problem of excessive salt and water retention caused by abnormalities of renal blood flow (the cardiorenal model).[2] With the development of right heart catheterization and measurement of cardiac output, heart failure was then defined in terms of reduced cardiac output and excessive peripheral vasoconstriction, leading to the cardiocirculatory model (or hemodynamic model) for heart failure (*Figure 1*). Subsequently, these models have been supplemented by the neurohormonal model of heart failure. A recent perspective on mechanisms and models in heart failure placed these three models in the clinical context of symptom relief and prevention of disease progression, while adding new strategies based on genetics and the reversal of the heart failure phenotype[3] (*Figures 2* and *3*).

This article presents the muscle hypothesis, a different model of heart failure that proposes the possibility that abnormal skeletal muscle in heart failure results in inappropriate activation of muscle ergoreceptors. This, in turn, leads to an enhanced signal to ventilation and resultant breathlessness, causes a sense of fatigue, and results in sympathetic activation (*Figure 4*).[4]

Measurement of left ventricular performance is a critical step in the evaluation and management of patients with suspected or clinically apparent heart failure.[1] Combined use of history, physical examination, chest radiography, and electrocardiography is not reliable in determining whether a patient's symptoms and physical findings are due to dilated cardiomyopathy, left ventricular diastolic dysfunction, valvular heart disease, or a noncardiac etiology. Most patients with heart failure have an ejection fraction less than 40%. However, patients with an ejection fraction greater than 40% can still have heart failure because of valvular disease or left ventricular diastolic dysfunction.

Limitations of the ejection fraction

Because the ejection fraction (EF) is used to establish a diagnosis of left ventricular systolic dysfunction, clinicians have extrapolated from this that the degree of left ventricular dysfunction will define the clinical course and prognosis. Al-

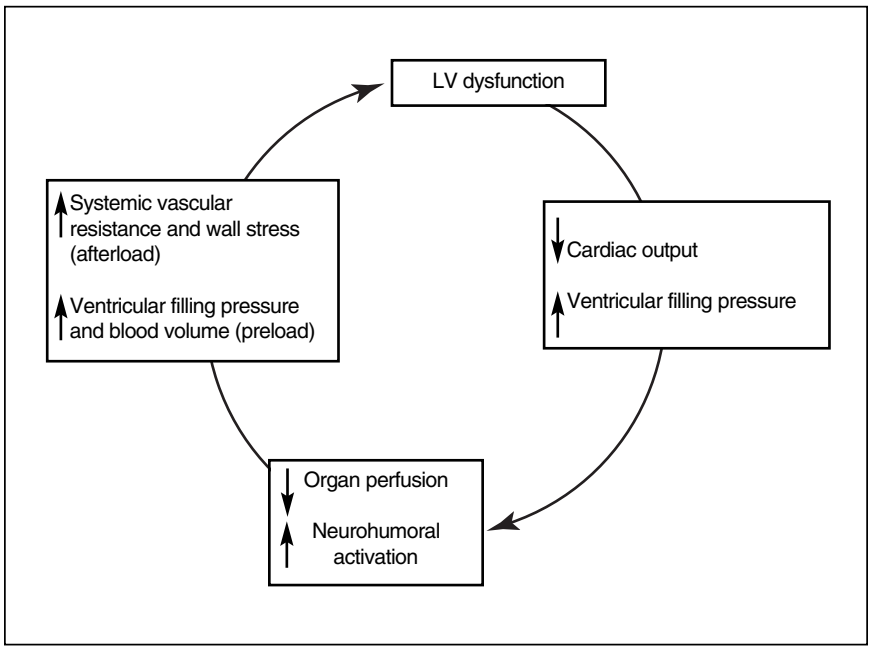

Figure 1. *A traditional model for heart failure. Left ventricular dysfunction leads to a decrease in cardiac output and increase in left ventricular filling pressure. The decrease in organ perfusion leads to neurohumoral activation, and diminished skeletal muscle blood flow causes fatigue. The consequence of altered hemodynamics in heart failure leads to an increase in preload and afterload, which in turn worsen left ventricular dysfunction.*

though the ejection fraction does have prognostic value,[5,6] there are distinct limitations to placing a strong reliance on the EF—whether for establishing a prognosis or guiding therapy.

One of the goals of heart failure management is to reverse the hemodynamic abnormalities associated with the clinical syndrome. However, the therapy that has the best effect on the ejection fraction does not necessarily have the best outcome. For example, digoxin[7] and the combination of hydralazine hydrochloride and isosorbide dinitrate[8] cause a greater increase in the ejection fraction than do angiotensin-converting enzyme (ACE) inhibitors, but the clinical outcome is inferior.

The EF may also be a poor predictor of functional status and prognosis. In patients with heart failure, there is no relationship between the left ventricular EF and exercise capacity (*Figure 5*).[9] Further, there is no relationship between the resting cardiac output and calf blood flow in patients with chronic heart failure (*Figure 6*). The survival of patients referred for cardiac transplantation is much better predicted by the patient's exercise capacity[10-12] than it is by the EF. The assessment of exercise tolerance need not be complicated. The Studies of Left Ventricular Dysfunction (SOLVD) trial demonstrated that the distance walked in 6 minutes was a better predictor of prognosis than were either the EF or the New York Heart Association classification in a group of patients with heart failure of various causes.[13]

An additional component to the hemodynamic model is the cardiac output as it pertains to exercise capacity. Although depressed cardiac output may be the primary determinant of exercise intolerance in some patients, exercise testing yields counterintuitive results in others. Patients with chronic heart failure at peak exercise are able to increase their cardiac output in response to a further increase in exercise load. At peak treadmill exercise, if arm exercises are added, both the cardiac output and the peak oxygen consumption increase further. This indicates that left ventricular function is not the feature that limits exercise in this group of patients with heart failure.[14]

Inadequate explanation of chronic heart failure symptoms

The traditional view of how the symptoms of chronic heart failure develop is that the initial myocardial damage (myocardial infarction, hypertension, cardiomyopathy, etc.) causes low output and fluid retention. The fluid retention results in breathlessness as fluid "leaks" into the lungs, and the low output state results in fatigue because of inadequate muscle perfusion. A number of observations suggest that this model may be inaccurate.[14] Certainly, the breathlessness cannot be easily explained in patients with well-treated heart failure who are at dry weight and without evidence of increased body water, but who have breathlessness with exertion. An alternative approach is to consider abnormalities of ventilation in patients with heart failure.

The ventilatory response to exercise in 55 patients with chronic heart failure was compared to 24 controls by Clark and colleagues.[15] Ventilation was increased in patients with heart failure at each stage of exercise. They achieved a lower peak oxygen consumption than control patients, and during exercise had a higher ratio of peak ventilation to expired CO_2 than did control patients. Dead space ventilation as a fraction of tidal volume was increased in patients at peak exercise. These abnormalities were not due to pulmonary pathologic mechanisms, however, as shown by lower end tidal CO_2 at each stage of exercise, and higher levels of alveolar oxygen tension compared to controls.

Patients with heart failure have an increased ventilatory response at all stages of exercise. Although this is accompanied by an increase in dead space ventilation relative to tidal volume, there is also hyperventilation relative to arterial blood gases. The more limited patients are with heart failure, the more they hyperventilate and reduce arterial CO_2. Their exercise capacity is not limited by

impaired pulmonary function. Likewise, peripheral chemoreceptors are not the main mediators of this increased ventilation, and other nonperipheral chemoreceptor-mediated mechanisms are involved.[16,17]

Inspiratory muscle weakness might also contribute to the symptoms of breathlessness in patients with heart failure. Respiratory muscle strength, limb muscle strength, and inspiratory muscle endurance were compared in 20 patients with chronic heart failure and 10 healthy controls. Respiratory muscle endurance was reduced in patients with chronic heart failure, probably as a reflection of a generalized skeletal myopathy.[18]

The ventilatory and heart rate responses to exercise are better predictors of heart failure mortality than is peak oxygen consumption. Robbins and colleagues followed up 470 patients with heart failure who were not taking beta-blockers or intravenous inotropes. During the 18 months of the study, 71 deaths occurred. With multivariate analysis, the best independent predictors of mortality were a steep ratio of ventilation to CO_2 production and a low chronotropic index (heart rate increase with exercise).[19]

Fatigue

The exercise intolerance of patients with heart failure has proven to be a complex problem. Exertional fatigue appears to be due to inadequate skeletal muscle flow, decreased cardiac output, and/or subnormal flow responses,[20] as well as skeletal muscle changes.[21-23] The muscle derangements include atrophy, reduced mitochondrial-based enzymes, reduced mitochondrial size, an increase in type II (fast-twitch) fibers, and abnormal metabolic responses to exercise despite an appropriate increase in blood flow. Recent studies also have demonstrated specific changes in skeletal muscle myosin heavy chain composition[24] and abnormalities in nitric oxide synthetase.[25] Although many of the skeletal muscle changes are the result of deconditioning, one study has shown that the magnitude of myosin heavy chain redistribution is not related to disuse atrophy but instead correlates with the severity of heart failure.[24] It is estimated that at least one fourth of patients are limited by skeletal muscle changes rather than decreased cardiac output and underperfusion.[14] These data may explain why certain patients do not respond to inotropes or vasodilators, and establishes the role of cardiac exercise rehabilitation in patients with heart failure, as will be discussed subsequently.

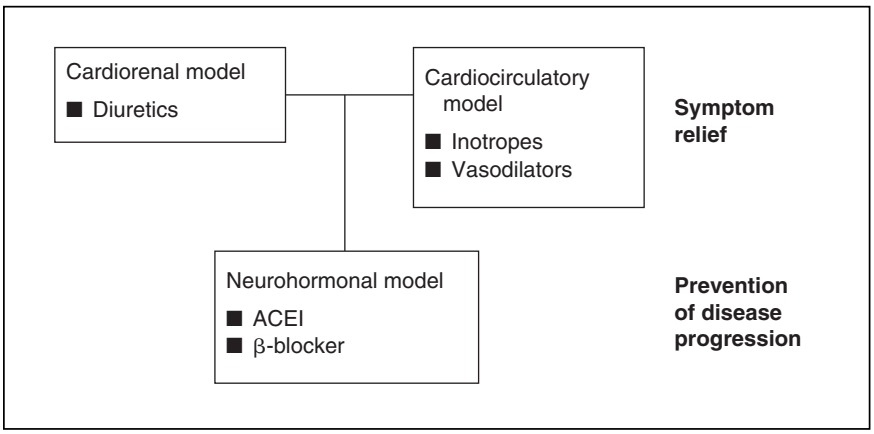

Figure 2. *Treatment of abnormalities defined by the cardiorenal model with diuretics, and of the cardiocirculatory model with inotropic agents and vasodilators leads to improvement in symptoms. Although vasodilator treatment may improve survival, compared to controls, the benefit occurs early, without evidence of continuing improvement over time, indicating that this treatment approach does not prevent disease progression. The use of angiotensin-converting enzyme inhibitors (ACEI) and beta-blocker does have a favorable survival benefit, and prevents or retards disease progression. Used with permission from Mann.*[3]

Muscle hypothesis

The "muscle hypothesis" proposes the possibility that abnormal skeletal muscle in heart failure results in activation of muscle ergoreceptors, which leads to an enhanced signal to ventilation and results in sympathetic activation.[26] The afferents from skeletal muscle are sensitive to metabolic effects of muscular exercise. They then modulate hemodynamic, ventilatory, and autonomic responses. These are small myelinated and unmyelinated afferents, of group III and IV afferents. They arise from "free" or "naked" nerve terminals that are associated with collagen structure and skeletal muscles or with blood and lymphatic vessels and are presumed to be engaged in feedback control, where muscle work regulates energy supply. The central reflection of these pathways is in the ventral lateral medulla, including the lateral reticular nucleus. These receptors are overactive during exercise, and they play a larger role in responses to exercise in patients with chronic heart failure as compared with control subjects. The overactivated muscle signal in heart failure due to abnormalities in exercising muscle causes an increased ventilatory drive.[27]

The muscle afferents are histologically inseparable from pain fiber afferents, so they may serve sensory as well as reflex functions, mediating the sensation of fatigue and the exaggerated ventilatory and cardiovascular responses to exercise.[28] This system could mediate a sympathoexcitatory and vasoconstrictor response to exercise. However, the subnormal blood flow response to exercise and pharmacologic vasodilatation is complex and may include persistent vasoconstrictor drive, edema of resistance vessel walls, a relative paucity of peripheral blood vessels, a deficient nitric oxide vasodilator, and enhancement of the vasoconstrictor endothelin.[20]

Investigators explored a neural link to explain the muscle hypothesis of exercise intolerance in chronic heart failure by studying 92 stable patients with heart

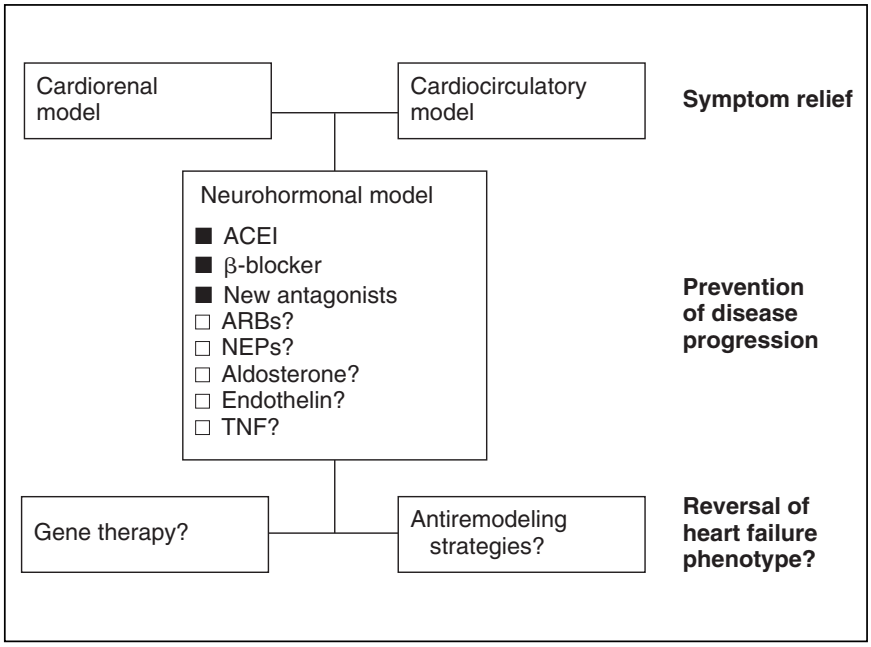

Figure 3. *A comprehensive model of treatment strategies proposed by Douglas L. Mann, MD.[3] Future modes of therapy will likely involve strategies that more effectively antagonize known neurohormonal systems, or alternatively antagonize other biologically active systems (aldosterone, endothelin, and tumor necrosis factor). It is possible that antiremodeling or gene therapeutic strategies or both may be used with existing heart failure strategies. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NEP, neutral endopeptidase inhibitor.*

failure and comparing them to 28 age-matched controls. Exercise tolerance was measured by bicycle ergometry; the ergoreflex activity was evaluated with two dynamic handgrip tests. Three minutes of local circulatory occlusion were used during the second study to isolate the neural component to the ergoreflex (as opposed to circulating metabolites). Isometric handgrip was associated with a prolonged increase in systolic and diastolic blood pressure, an increase in ventilation, and increase in leg vascular resistance. The intensity of the reflex was higher in New York Heart Association Class II and III heart failure patients than in Class I patients.[29]

Role of exercise training in chronic heart failure

It is estimated that at least one fourth of patients with chronic heart failure are limited by skeletal muscle changes rather than decreased cardiac output and underperfusion. This may explain why certain patients do not respond to inotropes or vasodilators, and establishes the role of cardiac rehabilitation exercise in patients with heart failure.

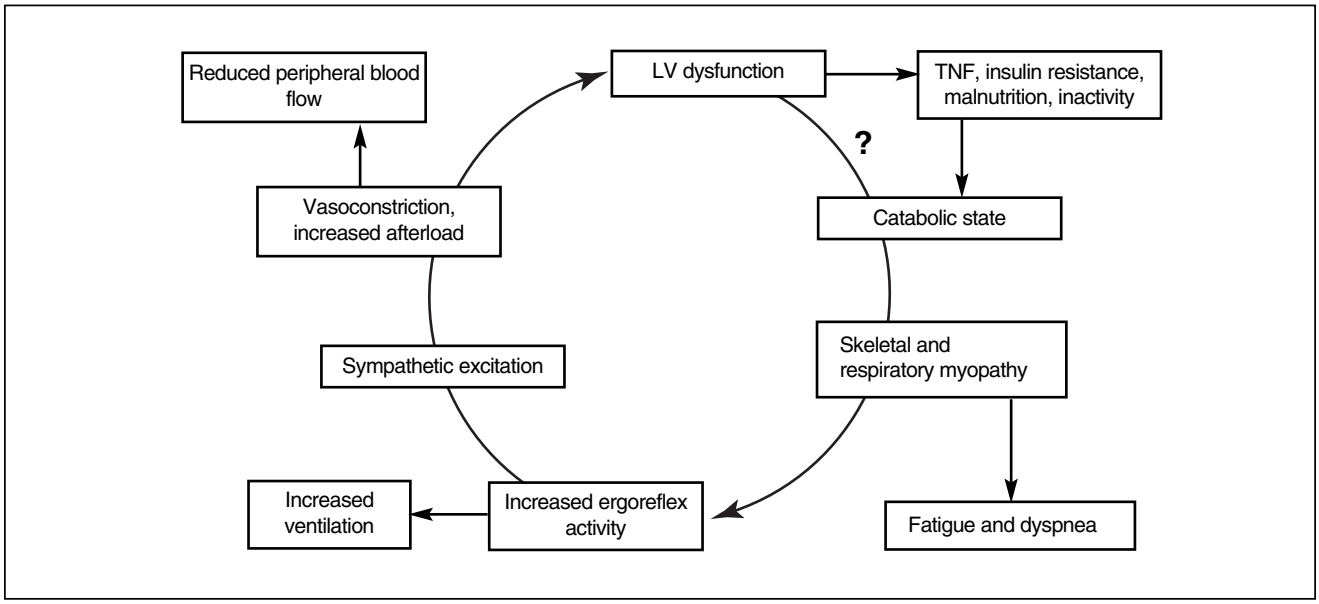

Figure 4. *The muscle hypothesis of chronic heart failure. In this hypothesis, an initial reduction in left ventricular function activates catabolic and reduces anabolic factors that cause skeletal muscle myopathy. This in turn leads to exercise intolerance and sympathoexcitation that, through the combined effects of the persistent catabolic state and of profound inactivity, further worsens skeletal muscle structure and function, and may eventually lead to a progressive effect on remodeling of the left ventricle. Used with permission from Coats et al.[57]*

Randomized, controlled trials have assessed the effects of exercise training in patients with symptomatic heart failure.[30-37] These studies have demonstrated improvement in exercise capacity (measured by peak exercise duration or peak oxygen consumption)[30-37] and also show favorable changes in autonomic nervous system function,[36] regional blood flow,[33] endothelial function,[38] and skeletal muscle function.[39-40]

During long-term moderate exercise training, heart failure patients randomized to the exercise group had an increase in their peak exercise oxygen consumption and an improvement in the myocardial thallium score. Measures of their quality of life improved parallel to the increase in peak oxygen consumption.[37] Exercise training has also been shown to lead to attenuation of the harmful process of left ventricular remodeling in postinfarction patients, perhaps through a chronic decrease in sympathetic nervous system tone.[41]

The effects of training in chronic heart failure programs have been summarized by Wielenga and colleagues.[42] Exercise training has no effect on central hemodynamics (pulmonary artery pressure, pulmonary wedge pressure), but it does increase cardiac output at submaximal and peak exercise compared to baseline, and with exercise is associated with a lower double product (the value arrived at by multiplying the heart rate by the blood pressure). Sympathetic nervous system activity is decreased, with an increase in vagal activity. There is no change in resting leg blood flow, but with exercise, there is a decrease in leg vascular resistance. Skeletal muscle demonstrates an increase in strength and oxidative capacity. After exercise training, there is a reduction in the enhanced ergoreflex response to exercise.

Unexpectedly, women with moderate heart failure have a normal proportion of fast-twitch skeletal muscle fibers, but this is associated with a decrease in the cross-sectional area of both the slow- and fast-twitch fibers. Exercise training increased the cross-sectional area up to the reference range, and the relative number of fast-twitch fibers decreased by 12%. In women, exercise training increased muscle strength by 16%. The increase in peak oxygen consumption was directly related to the increase in muscle fiber cross-sectional area.[43]

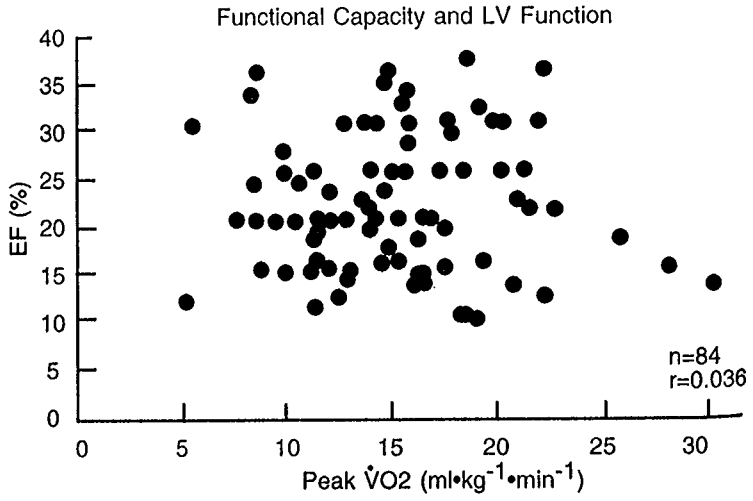

Figure 5. *Lack of correlation between functional capacity and left ventricular (LV) ejection fraction. Exercise capacity measured by metabolic gas analysis during exercise stress and expressed as peak oxygen consumption (V_{O_2}) in mL of $O_2 \times kg^{-1} \times min^{-1}$. Note large range of exercise capacity in a group of patients with severe LV dysfunction; ejection fraction (EF) is clearly not a major determinant of functional capacity in patients with heart failure. (Courtesy of T. Barry Levine, MD.[58])*

Additional metabolic disturbances in chronic heart failure include insulin resistance, deficient insulin-like growth factor-1, immune activation, cytokine release, and muscle ergoreflex alterations.[44] Each of these features can worsen the symptoms and prognosis in patients with heart failure, and all theoretically can be improved with a customized exercise program. Endurance exercise training also leads to a reduction in circulating neural hormones, which may then have a beneficial effect on long-term prognosis.[45]

With exercise training of 1 to 6 months, a significant increase in exercise duration has been demonstrated in the trained subjects. The observed increase of 26% to 37% is almost double that reported with ACE inhibitors or digoxin.[46,47] Some of the skeletal abnormalities are due to deconditioning, and they are partly reversed by exercise training. Training has also been shown to reduce the exaggerated ergoreflex activity, thereby improving the response to exercise.[48]

Interventions with regard to the musculoskeletal system

The exercise prescription for patients with heart failure is similar to other types of heart disease—the patient should engage in aerobic activity that allows him or her to accumulate 30 minutes of exercise three times per week. Often these patients do not tolerate well their first week of exercise. They may need additional rest or may need to delay other household or leisure-time activity. Because of coexisting disease, or exacerbation of symptoms, patients with heart failure may experience interruption of their exercise program.

Exercise for patients with heart failure has been recommended by an expert panel of the Agency for Healthcare Quality Research (formerly the Agency for Health Care Policy and Research).[49] It needs to be incorporated into a comprehensive program of outpatient management for heart failure. Today, such a program includes more than the standard therapy of ACE inhibitor, diuretic,

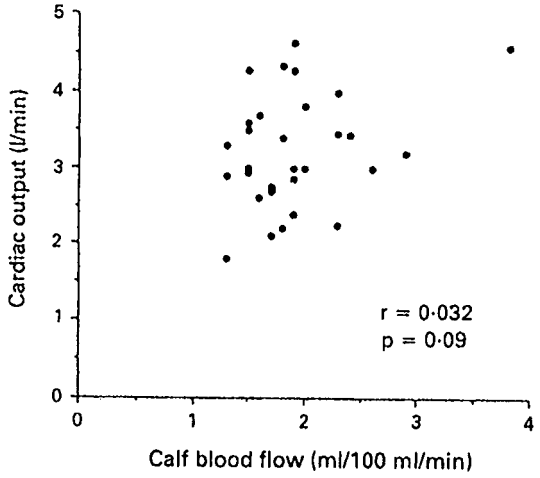

Figure 6. *Lack of relation between resting cardiac output and calf blood flow in patients with chronic heart failure. Used with permission from Muller et al.*[59]

digitalis, beta blocker, and spironolactone. Additional components of a comprehensive program include diet instruction, salt restriction, nurse-directed telemedicine follow-up, and occasionally visits to freestanding heart failure clinics.

The increased exercise capacity with ACE inhibitors or angiotensin II receptor blocking agents does not occur immediately, indicating that it is not related to improved cardiac output. Rather, it has now been demonstrated that the increase in exercise capacity is accompanied by a shift in myosin heavy chain of leg skeletal muscle toward slow, more fatigue-resistant isoforms. The magnitude of myosin heavy chain 1 changes correlates with the net peak oxygen consumption gain, suggesting that the improved exercise capacity may be caused by favorable biochemical changes in skeletal muscle.[50] Likewise, the improvement in exercise tolerance that occurs following cardiac transplantation is not immediate, but delayed by several weeks, also suggesting favorable alterations in skeletal muscle function rather than improved cardiac output as the basis for that functional improvement. The exercise performance in patients with heart failure may be further augmented by sympatho-inhibition with the use of clonidine hydrochloride, as noted by Lang and colleagues.[51] Intravenous administration of clonidine decreased systemic blood pressure, lowered pulmonary capillary wedge pressure, and increased exercising leg blood flow while decreasing leg vascular resistance. Serum norepinephrine levels dropped 40%, and there was no change in cardiac output. At comparable workloads, there was a decrease in peak oxygen consumption and pulmonary lactate levels (indicating a decrease in skeletal muscle lactate production).

The demonstration of reduced respiratory muscle endurance in patients with chronic heart failure[18] has encouraged some investigators to incorporate respiratory muscle training as part of the cardiac rehabilitation exercise prescription.[52] Recognizing the abnormal metabolism of skeletal muscle in chronic heart failure, some researchers have investigated dietary approaches to improvement in exercise tolerance. At least in short-term studies, a change in diet composition to slow glycogen use leads to an improvement in exercise capacity.[53]

Osteopathic implication

Since the encoding of the four basic tenets of osteopathic medicine in 1953,[54] several other concepts have been added to the central precepts of osteopathic medicine. One of these is the recognition that the neuromusculoskeletal system is the primary machinery of life. As described by Irvin M. Korr, PhD, the traditional emphasis of medicine on the viscera tends to convey the impression that human activity and human behavior are composites of visceral functions, such as myocardial contraction, peristalsis, digestion, vasomotion, and glomerular filtration. The fact is that the ultimate instrument of human action and behavior is the musculoskeletal system. Every human act consists of coordinated contractions and relaxations of skeletal muscles, most of them activating bony levers. Human behavior is, ultimately, the continually changing patterns of muscular contractions and relaxations.[55]

Because the muscle hypothesis of chronic heart failure places a central role on peripheral mechanisms,[26] especially involving muscle ergoreceptors, this model of heart failure is appropriate for evaluation and testing by members of the osteopathic medical profession. The obvious question that arises is this: What is the most appropriate intervention with regard to derangements of musculoskeletal function that are associated with chronic heart failure? The obvious answer is those interventions that are most effective. Although it would be attractive to say that the most appropriate strategy is to apply osteopathic manipulative treatment (OMT), research at the present time indicates that the intervention with proven efficacy is cardiac rehabilitation exercise training and localized muscle group training as described previously. On a theoretical basis, other interventions into the musculoskeletal system, such as yoga, tai chi, and dietary approaches, may also be worthy of study.

It is intriguing to consider the possibility that OMT could play a role in the management of patients with chronic heart failure. Few studies have been conducted.[56] However, the developing literature concerning the muscle hypothesis of heart failure and the effects of exercise training provide a road map that could lead to the development of a conceptual model for testing the efficacy of OMT. Manipulative treatment would be directed at the paraspinal musculature, the appendicular system, and the respiratory diaphragm. The magnitude of effect of OMT could then be compared to other interventions, such as cardiac rehabilitation exercise. The intermediate outcomes

would be changes in palpatory findings of the musculature, the peak oxygen consumption with exercise, exercise duration, the slope of ventilation to carbon dioxide production, and measurements of autonomic nervous system tone, such as heart rate variability. The health outcomes would be the patient's quality of life, New York Heart Association classification, and functional status. Because of the delayed course of improvements in musculoskeletal function in response to intervention, the response to OMT would have to be followed up over an interval of 4 to 8 weeks, or possibly longer.

Summary

Heart failure is among the most common medical problems in the United States. Its clinical syndrome is characterized by symptoms of fatigue and breathlessness. The conventional cardiorenal, cardiocirculatory, and neurohormonal models of heart failure do not adequately explain these symptoms. The muscle hypothesis is a different model of heart failure that supplements these conventional theories. It proposes the possibility that abnormal skeletal muscle in heart failure results in activation of muscle ergoreceptors, leading to an enhanced signal to ventilation and sensation of breathlessness, the perception of fatigue, and sympathetic activation. Cardiac rehabilitation exercise can lead to an increase in exercise capacity by reversing the skeletal muscle myopathy of chronic heart failure and reducing the abnormal ergoreflex.

Acknowledgment

The author thanks Mary Barnard for providing transcription for this article.

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