Physical Activity in the Prevention of Heart Failure:

Another Step Forward

Running title: Intwala et al.; Physical Activity and Heart Failure

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In 1988, Sullivan and colleagues from Duke University took a bold and novel step forward in the treatment of heart failure with the publication of their comprehensive seminal study of exercise training in 12 patients with heart failure (left ventricular ejection fraction 24 +/- 10%). Whereas exercise was previously proscribed in such patients, using invasive hemodynamic measurements, radionuclide angiography and metabolic measures including gas exchange and lactate analysis, these intrepid investigators demonstrated that ambulatory patients with heart failure can significantly improve their exercise tolerance largely through training–induced changes that occur in the periphery. They concluded that exercise training “may represent a useful therapeutic option in stable patients [with heart failure]”. This study served as a major stimulus for nearly 3 decades of subsequent research that has consistently demonstrated improvements in functional capacity, subjective symptoms, and quality of life with exercise training in heart failure patients. Mechanistic studies have uncovered changes that occur in the central and peripheral circulation, exercising muscles, autonomic nervous system, and other integrated systems that lead to such improvements. These studies have prompted the question: Does exercise training affect mortality among patients with heart failure and reduced ejection fraction? This important issue has since been addressed by the NIH funded, multi-centered, randomized and controlled HF-ACTION trial which measured the effects of exercise training on clinical outcomes in stable, medically optimized patients with heart failure and LVEF 35%. After adjusting for pre-specified predictors of mortality, a significant 11% reduction in the composite primary endpoint of all-cause mortality or all-cause hospitalization was found. Accordingly, exercise training is now recognized as a valuable adjunct in the therapeutic approach to the patient with stable heart failure, and is recommended by the American College of Cardiology Foundation and the American Heart Association at a Class 1 level.
In this issue of Circulation, Pandey et al. take another step forward in providing novel
and important information that demonstrates a dose-response relationship between physical
activity and the prevention of heart failure. The authors included a robust selection of trials
comprising 370,460 participants from 12 cohort studies (mean age range 44–76 years; 53%
female; 14 year mean follow-up) to assess the quantitative relationship between physical activity
(MET-min/week) and heart failure risk. A thorough outcome assessment was employed in the
aforementioned studies that included self-reported heart failure with clinical adjudication, ICD-9
& 10 codes for HF admissions and adjudication based on chart review. Physical activity
expenditure rates were categorized as Light (3 METs), Moderate (5 METs), and Vigorous (9
METs). Physical activity dose was derived from the product of mean activity intensity (METs)
and duration of activity in minutes. They employ a very detailed and careful method of
estimating the dose of physical activity as derived from each study. Participants were stratified
according to levels of minimal physical activity that have been recommended per the 2008 US
Federal Guidelines, i.e. 500 MET-min/week. Compared to those who reported no leisure time-
activity, the risk of heart failure was reduced by 10%, 19%, and 35% in those engaging in 500,
1000, and 2000 MET-min/week, respectively. Furthermore, subgroup analysis examining the
association between the highest level compared to lowest of physical activity and heart failure
risks revealed no difference in effect relative to age (< 55 years vs. ≥55 years; P = 0.64), sex
(men vs. women; P = 0.51), and geography (Europe vs. United States; P = 0.38). Although this
meta-analysis only includes two randomized control trials with the remainder of trials being
observational, the authors conducted extensive sensitivity and subgroup analyses, and report
consistency in their findings.

The authors provide compelling evidence which suggests that incrementally more
physical activity provides a protective benefit in preventing heart failure, and that levels of
physical activity greater than current guideline recommendations provide even greater benefit.
The present study reveals remarkably similar reductions in heart failure, as those reported for
coronary heart disease. A linear dose response was observed across a wide dose range
suggesting that any physical activity is better than none. No upper or lower threshold effect was
observed.

In order to better understand the findings of this study and its implications, a brief
discussion of terms may be useful. The Surgeon General’s report on physical activity and health
defines physical activity as skeletal muscle contraction resulting in bodily movement which
requires energy use. Physical activity can be further classified according to specific metabolic
and mechanical aspects of contraction. Metabolically, physical activity can be classified as
anaerobic (energy derived in absence of oxygen) or aerobic (energy derived in the presence of
oxygen). Mechanically, physical activities can be viewed as those that produce limb movement
without a change in muscle tension (isotonic exercise) and those that produce muscle tension
without limb movement (isometric exercise). A combination of these forms of muscle
contraction are employed with most activities.

Intensity is defined as the rate of energy expenditure during physical activity, and is most
commonly defined relative to resting energy expenditure, where one MET is equal to the resting
metabolic expenditure of approximately 3.5 mL O2/kg/min. Absolute intensity is determined by
the rate of energy expenditure during exercise, and is usually expressed in METS or kcal/minute.
Light activities are defined as < 4 METs, moderate as 4-6 METs, and vigorous as > 6 METs.
Relative intensity is defined by individual’s levels of cardiorespiratory fitness, expressed as the
relative percentage of maximal exercise capacity which is maintained during exercise, reported
as percentage of maximal heart rate or a percentage of VO_{2\text{max}}. Walking is frequently reported as a moderate-intensity physical activity; however, in actuality the intensity may differ from individual to individual. For example, brisk walking at a speed of 3 miles/hour has an absolute intensity of approximately 4 METs, which meets criteria for moderate intensity. However, in relative terms, the intensity would be considered light for a healthy 20-year-old individual, but would be classified as vigorous for an 80-year-old. Moderate relative intensity activities generally occur at 40-60% VO_{2\text{max}}.^{10}

The present study focuses on physical activity dose, where dose refers to the total volume of energy employed in physical activity per unit of time. Dose reflects total physical activity volume and is the product of the intensity and duration of an activity over a given time period. It is most commonly expressed in terms of kilocalories/week or MET-minutes/week.

The observations reported by Pandey et al. are consistent with prior studies on physical activity in prevention of coronary heart disease and heart failure.\textsuperscript{11-13} For example, a review of 63 prospective cohort studies of physical activity and cardiovascular disease risk examining more than 890,000 subjects (>600,000 women, >180,000 non-white, and >25,000 with age ≥65) showed, compared with the least active subjects, the most active men and women had median risk reduction of approximately 30 to 40%.\textsuperscript{11} More recent studies have aimed to objectively quantify the amount of physical activity using devices that measure movement and the dose-relationship for risk reduction. In a prospective study to assess whether ambulatory activity was associated with lower risks of cardiovascular events in adults at high risk for type 2 diabetes and cardiovascular disease, the authors found that every 2000 step/day increment at baseline was associated with a 10% lower event rate. Furthermore, each 2000 step/day increase during the subsequent 12 months was associated with an additional 8% lower event rate regardless of age,
gender, or baseline level of activity. A recent meta-analysis assessed the quantity of physical activity for risk reduction and found those who engaged in 150 or 300 min/wk of moderate-intensity leisure-time physical activity had 14% and 20% reduction in coronary heart disease, respectively, compared to those who reported no leisure-time physical activity. The benefits of exercise training in chronic heart failure have been extensively studied and have shown improved exercise capacity, lower HR response to submaximal exercise, improved LV function and reverse remodeling, enhanced quality of life and marked reduction in symptoms. Mechanistic studies have proposed the effects may be mediated by decreased inflammatory markers, neurohormonal adaptations, and direct effects on central and peripheral circulatory systems. Interestingly, one of the most common etiologies of heart failure is ischemic heart disease, thereby prevention of coronary artery disease confers further risk reduction to heart failure. The biologic link between exercise and CHD protection has been attributed to improved antioxidative protection, changes in mitochondrial metabolism, favorable lipid changes (increase HDL, decrease LDL) and control of known atherosclerotic risk factors. A major limitation of assessing physical activity is via self-reporting methods, as this may lead to over- or under-estimations of true physical activity. Direct physical activity measurements by mobile health technologies can be employed to develop better estimates of physical activity frequency, intensity, duration and dose. In fact, these novel wearable healthcare technologies have recently become popular in the general population to promote physical activity, and in research to objectively quantify physical activity. These commercially available, nearly ubiquitous devices include various forms of heart rate monitors, pedometers, and accelerometers. In a meta-analysis of pedometer users, including nearly 3000 subjects, pedometer use was associated with a significant increase in physical activity, approximately
2000 steps or 1 mile, over a mean duration of 18 weeks. Furthermore, the accuracy of smartphone applications and wearable devices were recently assessed in a unique trial where adult participants were asked to walk on a treadmill set at 3.0 mph for 500 and 1500 steps, each twice, wearing/carrying one of the top ten selling applications or devices in the United States. These researchers found a relative difference in mean step counts of -0.03% to 1.0% for accelerometers and pedometers, -22.7% to -1.5% for wearable devices, and -6.7 to 6.2% for smartphone applications. The advances in healthcare technology will allow clinicians and researchers to assess physical activity with more accuracy and precision.

The present report by Pandey et al. contains some limitations that are worthy of comment, and are acknowledged by the authors. First, physical activity investigations were determined by employing questionnaires and self-reported frequency which are subject to measurement error. While the dose of physical activity is reported, the intensity of activity was not. Hence, it is unclear whether performance of low intensity activities for longer durations is as beneficial as performing vigorous intensity activities for shorter duration, as both would yield a similar reported dose. Second, this meta-analysis focuses only on leisure–time physical activity, and not other forms like domestic, occupational, or commuting activity. In fact, many domestic activities like yard work (3-6 METs) and occupational activities, like carpentry (3-7 METs), no doubt contribute to overall activity dose, and perhaps may reduce the risk of heart failure as well. Finally, the types and severity of heart failure were not qualified. Future research studies can better explore the relationship between physical activity dose and the risk of heart failure by incorporating reliable physical activity measurement devices that allow determination of activity intensity as well. Categorization of activity type (domestic, occupational, commuting and leisure–time) would also answer important questions that may further refine physical activity
recommendations. Finally, more specific determination of heart failure outcomes, including etiology, reduced or preserved ejection fraction, and severity on presentation would be useful.

In conclusion, we believe this is a pivotal and well-done study that is consistent with the past three decades of research revealing the benefits of physical activity. We hope this study will encourage practitioners to continue to promote physical activity by implementing interventions, such as the assessment of physical activity during routine office visits, and the prescription of increased physical activity and perhaps regular exercise as a routine part of everyday life in order to modify future heart failure risk. The present study suggests a novel preventive approach that may perhaps help to curb the rise in heart failure incidence, and provides substantial evidence to be considered in future iterations of national guidelines.

Conflict of Interest Disclosures: None

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