Beyond traditional cardiovascular risk factors: Could frailty and other morbidities explain the worse prognosis in patients undergoing pharmacologic stress?

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Received Nov 3, 2020; accepted Nov 3, 2020
doi:10.1007/s12350-020-02441-5

See related article, pp. 840–852

Performance of exercise as the mode of stress in SPECT myocardial perfusion imaging studies brings enormous benefits! The exercise capacity in metabolic equivalents a patient is able to achieve during stress testing is the most powerful prognostic marker and predicts mortality and other cardiovascular events across multiple populations, including healthy individuals and in patients with cardiovascular disease irrespective of age, gender, and extent of coronary disease.[1] Our lab has previously shown that the ability to achieve a high exercise workload of ≥10 METS identifies a group with a very low 0.4% prevalence of significant ≥10% left ventricular ischemia and a low prevalence of high-risk CAD on invasive coronary angiography.[2,3] Moreover, those patients able to achieve ≥10 METS have an excellent prognosis over more than 2.5 years.[4] Other studies have shown that lower functional capacity is associated with increased risk for myocardial infarction, unstable angina, and coronary revascularization.[5] Functional capacity estimated using the Duke Activity Status Index (DASI) provides independent and incremental prognostic value for prediction of both significant coronary angiographic disease and long-term adverse clinical events.[6]

A number of additional parameters assessed by exercise stress provide powerful diagnostic and prognostic information additive to imaging results, including exercise ST segment deviation and rapidity of recovery post-stress,[7,8] exercise-induced angina,[9] blood pressure response to exercise,[10] heart rate recovery,[11] and chronotropic incompetence.[12] The role of pharmacologic stress MPI in the risk stratification of patients is well-established, with excellent diagnostic accuracy.[6,12] However, the wealth of incremental diagnostic and prognostic information provided with exercise stress mandates that this mode of stress should be strongly preferred and should be used whenever possible.

Despite the clear benefits with exercise stress, the proportion of patients undergoing pharmacologic stress SPECT MPI has increased steadily over the past few decades relative to exercise imaging, from an initial third of patients to now more than 50% of stress imaging tests.[13,14] This trend is hypothesized to be occurring due to the aging of the population and increasing prevalence of obesity.[15] Moreover, patients undergoing pharmacologic stress have increased risk factors for CAD, including high-risk markers such as diabetes mellitus, chronic kidney disease, and peripheral vascular disease, all of which impair the ability to exercise.[16]

This differential profile of the pharmacologic stress patient suggests that this subgroup may have a different risk with any given perfusion imaging finding compared with those who can undergo an adequate exercise protocol. Indeed, several studies have found that patients

Funding This manuscript was supported by NIH T32 EB003841.
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J Nucl Cardiol 2022;29:853–6.
1071-3581/$34.00

undergoing pharmacologic stress MPI have a higher event rate with both normal and abnormal imaging results.[17,18] Both MI and cardiac deaths rates are significantly higher in patients undergoing pharmacologic MPI.[17]

In a previous study, Rozanski et al. actively investigated the differential prognostic risk with pharmacologic vs exercise stress.[16] In their propensity-matched cohort analysis of patients with normal SPECT MPI imaging results, the observed annualized mortality rate in patients undergoing adenosine stress was more than twice that of subjects undergoing exercise (3.9% vs 1.6%, $P < .0001$). The authors note that there are substantial confounding factors leading to this increased morbidity, including higher-risk demographics and a greater prevalence of cardiovascular risk factors in those undergoing pharmacologic stress test. Assessing the prognostic effect of pharmacologic stress is complicated by substantial referral bias, as pharmacologic test tends to be ordered for older individuals with higher rates of traditional cardiovascular risk factors. To date, a direct comparison of the stress modalities with an adequate analysis plan to avoid referral bias is not available.

In the current issue of the Journal, Rozanski et al. extend their analysis of this important area, delving into the differential impact of pharmacologic vs exercise stress on all-cause mortality over 13.3 ± 5.0 years follow-up in a large, single-center prospective evaluation of 39, 179 subjects undergoing SPECT MPI. In this analysis, they use a propensity analysis plan to adjust for referral bias to better understand the contributors to the increased risk with pharmacologic stress.

For the entire cohort, 4,699 deaths (12.0%) occurred within 5 years of the initial SPECT scan. More deaths occurred in the pharmacologic patients, with a higher annualized mortality rate compared to exercise patients. (5.1% vs 0.9%). Similar findings were reported in pharmacologic vs exercise patients within the propensity cohort (3.9% for pharmacologic vs 1.2% for exercise). Rozanski et al. assessed comparative mortality according to the mode of stress in two ways: by risk adjustment comparisons of exercise vs pharmacologic patients in the entire cohort (adjusted by clinical characteristics) and by comparing the outcomes of pharmacologic vs exercise patients in a propensity-matched cohort. Similar results were obtained by both approaches. Both among non-ischemic patients and for each level of inducible myocardial ischemia, pharmacologic patients had substantially increased mortality risk compared to exercise patients. The cohort also included an ''adeno-walk'' protocol for adenosine patients who were deemed able to perform limited exertion. This subgroup was found to have an intermediate survival risk compared to the patients that exercised or underwent adenosine testing without walking.

This study represents the latest in an important series of analyses published by this group examining the essential clinical and test characteristics and the prognostic features of MPI results. The findings of this study confirm that pharmacologic patients remain at higher increased risk compared to exercise patients following the performance of propensity matching to identify patients of comparable age and clinical risk profiles. This analysis adds to previous investigations to further confirm that the ability to exercise at the time of stress testing is an important, independent prognostic factor that translates into differences in mortality.[16,18–21]

The authors account for differences in age, gender, traditional CAD risk factors, comorbidities, and functional capacity through propensity matching. These markers are highly relevant when assessing the prognostic impact of exercise vs pharmacologic testing. Traditional cardiovascular risk factors increase the risk for the development of CAD and thus impact mortality, particularly given that this is the most common cause of death in the United States.[22] Other comorbidities, particularly those that cause chronic inflammation or put strain on the cardiorespiratory system, can also contribute to the development of CAD and increase CAD-related mortality.

However, there are numerous causes and contributors to mortality that extend beyond CAD. Many of these comorbidities lead to the inability to exercise and mandate pharmacologic stress. Highly morbid conditions such as frailty, deconditioning, chronic pulmonary disease, anemia, advanced systemic inflammatory diseases or progressive neurological conditions were not analyzed in the present manuscript and are important prognostic independent factors to be considered.

Frailty is a common reason for the choice of pharmacologic stress and has substantial implications for morbidity and mortality. It involves a state of overall weakening and fatigability and translates into increased vulnerability to disease and decreased tolerance of therapies.[23] As established in previous studies, frailty is an important risk factor for cardiovascular disease especially in older individuals.[24] A systematic review by Afilalo et al[25] found that frailty was associated with a two to threefold increased risk of CVD. Frailty is also a strong predictor of mortality independent of CVD. Thus, comorbidity is highly relevant but also common. The prevalence of frailty is high, ranging from 10% to 60%, depending on the CVD burden, as well as the tool and cutoff chosen to define frailty.[26] The value of frailty in guiding cardiovascular care is beginning to recognized, although there is no consensus for a validated assessment tool to facilitate identifying this comorbidity and

no established effective response once it has been identified.

Another relevant comorbidity leading to selection of pharmacologic stress is deconditioning or poor functional capacity. Functional capacity provides independent and incremental prognostic value for prediction of both significant coronary angiographic disease and long-term adverse clinical events[6] and is the most powerful predictor of mortality over other established risk factors for cardiovascular disease.[1] It is inversely associated with all-cause mortality and cardiovascular mortality, both in the general population and in older adults.[27–29] In clinical practice, a growing number of patients referred for exercise stress MPI have limited functional capacity due to obesity, orthopedic problems and increasing rates of other comorbidities such as peripheral vascular disease.

Notably patients with chronic lung disease are at increased risk for CAD. Chronic obstructive pulmonary disease (COPD) affects 5% of the adult population.[30] Data from multiple studies across different jurisdictions indicate that one of the leading but underrecognized causes of death in COPD is ischemic heart disease.[31] The prevalence of cardiovascular comorbidities is increased by twofold in chronic obstructive pulmonary disease (COPD) patients.[32] Many studies have shown the interaction of COPD and ischemic heart disease, including an analysis by Campo et al. showing that patients with both COPD and ischemic heart disease have an increased risk of mortality and other outcomes including myocardial infarction and COPD exacerbation when compared to patients with only COPD or only IHD.[33] Moreover, other chronic pulmonary conditions are associated with higher prevalence of CAD, such as idiopathic pulmonary fibrosis.[34] There is not only a higher prevalence of CAD in patients with idiopathic pulmonary fibrosis, but patients with this lung disease and significant CAD appear to have worse outcomes.

Another group that was excluded from the Rozanski et al. analysis were patients with liver disease. Non-alcoholic fatty liver disease (NAFLD) is the most common hepatic disorder in the developed world. Adams et al. reported that survival of NAFLD patients was lower than expected survival in general population.[35] Recent studies have stressed the importance of fatty liver as an independent predictor of some cardiovascular outcomes. A recent study showed that patients with NAFLD are at an increased risk for CVD compared to matched controls.[36] Indeed, data from the Multi-Ethnic Study of Atherosclerosis (MESA) suggested that while patients with NAFLD have a high risk for incident CVD, NAFLD per se was not a predictor of CVD independent from traditional CVD risk factors such as high cholesterol and smoking.[37]

Inflammatory myopathies, arthropathies, and other rheumatologic diseases impact the ability to exercise, As postulated in the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, inflammatory diseases should be considered a risk-enhancing factor for ischemic heart disease and should be incorporated into risk considerations.[38] Investigations have shown that patients with these conditions such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriatic arthritis, polymyositis, dermatomyositis, and inflammatory bowel disease are at an elevated risk for the development of CAD.[39]

In these challenging patients with multiple comorbidities, it will be important to have a more comprehensive risk assessment. Combined protocols with low-level of exercise likely will be of an advantage in this group of patients with questionable ability to achieve adequate workload. Defining the optimal tool set to measure frailty and deconditioning and methods to account for non-traditional but high-risk comorbidities is a high priority.

Exercise capacity is the more powerful predictor of mortality, and exercise stress should remain the preferred stress approach, as it provides an evaluation of multiple prognostic factors beyond the presence and extent of coronary artery disease. Traditional CVD risk factors play an important role in risk stratification but other non-traditional factors such as frailty, deconditioning, and pulmonary, liver, and inflammatory diseases should be incorporated, as these comorbidities likely have an important impact in overall prognosis. Future research is needed in this area to better define how to incorporate and mitigate risk in these patients.

NEW KNOWLEDGE GAINED

Frailty, lung disease, and other non-traditional cardiovascular risk factors are important potential contributors to the increased risk of patients undergoing pharmacologic stress myocardial perfusion imaging.

Disclosures

Dr Bourque owns equity in Locus Health and is a consultant for Pfizer and General Electric.

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