EDITORIAL

Is dyspnea the new angina? The ever-changing profile of patients referred for CAD evaluation

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The prevalence, severity, and manifestation of coronary artery disease (CAD) have been changing. In the past several decades, there has been a decline in the incidence of cardiac death and myocardial infarction.[1,2] Simultaneously, the presentation of stable CAD has evolved as well. It is increasingly clear that the Diamond and Forrester estimates of pretests likelihood of CAD from the 1970s markedly overestimate the probability of CAD in present-day patient populations,[3,4] and the more contemporary European Society of Cardiology pretest probability predicts obstructive CAD, cardiovascular events, and myocardial perfusion abnormalities more accurately.[5,6] Furthermore, the prevalence and severity of myocardial perfusion abnormalities on SPECT myocardial perfusion imaging (MPI) studies have progressively decreased over the past 3 decades.[7,8] These observations may be attributable to decrease in tobacco use, increase in statin use, and more aggressive management of hypertension. Furthermore, the clinical suspicion threshold to test patients for CAD may have been dialed down over the years to include patients with lower likelihood of CAD, further diluting the prevalence and severity of CAD in contemporary patient populations.[9,10] Concomitant to these trends, the patient population has been aging along with an increased prevalence of diabetes mellitus and obesity, decreased exercise capacity, and increased utilization of pharmacologic stress modality among patients undergoing stress MPI.[10]

In this issue of the journal, Rozanski et al investigated the presenting symptoms of $> 60,000$ patients referred for stress SPECT-MPI between 1991 and 2017 at Cedars-Sinai Medical Center, Los Angeles, CA, USA.[11] The authors also analyzed the presenting symptoms of > 6500 patients referred for coronary CT angiography (CCTA) between 2011 and 2017 at the same institution. A total of 690 patients who underwent both tests were included in the study. For patients who underwent repeat testing, only the first test in each imaging modality cohort was included in the analysis. Four symptom categories were captured: typical angina, atypical angina, non-anginal pain, and dyspnea only. The SPECT cohort was divided into four 6-year intervals (1991–1997, 1988–2004, 2005–2010, 2011–2017) and the CCTA cohort was analyzed as one 6-year period (2011-2017), parallel with the last SPECT-MPI 6-year period. Follow-up was longer for the SPECT-MPI patients (12.5 years), compared to the CCTA cohort (3.7 years). However, results for only 5-year survival are presented. The SPECT-MPI cohort data showed decreasing prevalence of typical angina (16.2% to 3.1%) and non-anginal pain (20% to 2.9%). Atypical angina increased from 28.6% to 52.4%, and dyspnea only increased from 5.9% to 14.5%. The proportion of ''asymptomatic'' patients remained similar (close to 30%) over the observation period. Notably, when all the chest pain syndromes are combined (typical angina, atypical angina, and non-anginal), the frequency is similar in the first 3 time periods: 64.8%, 64.6%, and 66.8%, respectively; only the last period showed a decrease to 58.4%. The CCTA cohort, in comparison with the concurrent 2011–2017 SPECT group, had more frequent non-anginal pain (32.5% vs 2.9%) and less frequent atypical angina (18.4% vs 52.4%). Typical angina was present in 6% of the CCTA patients compared to 3.1% in the SPECT group, while dyspnea-only

presentation was similar in frequency (13% vs. 14.5%). The presence of significant ischemia (>10%) by SPECT decreased over time from 19.7% to 3.8%. Among the CCTA cohort, severe (≥70%) and intermediate (50-69%) epicardial coronary stenoses (obstructive disease) were diagnosed in 12.1% and 11.5% of patients, respectively. During the 5-year follow-up, 14.1% of the patients died. Fewer of those who died were revascularized (13.8% vs. 17.8%). Compared to other symptom groups, dyspnea-only was associated with highest all-cause mortality among both revascularized and non-revascularized subjects.

How should we interpret those findings? It is now accepted that CAD presentation, extent of the disease, and prognosis have changed over the past >30 years. The study cohort is a microcosm reflecting general national trends in the patient population and the nature of CAD among those referred for non-invasive assessment of ischemic heart disease. Indeed, the study confirms better risk factors modification during the study epoch that mimics national trends, i.e., decreased tobacco use, increased statins use, and lower resting blood pressure. Furthermore, the pretest likelihood of CAD among patients referred to either modality has declined, as the proportion of patients with non-anginal chest pain has risen from 20% in 1991–1997 to 35.4% (2.9% MPI + 32.5% CCTA) in 2011–2017. The latter change may reflect applying lower clinical threshold for CAD testing in modern era. In the same time period, increases in the rates of obesity and diabetes mellitus were observed. Increasing rates of obesity and diabetes mellitus may have changed patient symptoms with more dyspnea and less perception of pain. Unfortunately, no data are available on the presence of congestive heart failure, lung disease, or valve disease in this large dataset. The study suggests a change in the referral pattern of patients with non-anginal pain from SPECT-MPI (20%) in 1991–1997 to primarily CCTA (32.5%) and less MPI (2.9%) in 2011–2017. This change suggests leveraging the negative predictive value of CCTA in patients with low likelihood of CAD.

The present report by Rozanski et al adds to the growing body of literature documenting the changing burden and presentation of CAD. Although the study does not fully explain the drivers behind the observed trends, it convincingly brings to attention new aspects of the presentation of an old disease. The study confirms that patients with typical angina continue to have highest rates of inducible myocardial ischemia and obstructive CAD. However, only one third of patients with typical angina had obstructive CAD. Therefore, the study confirms other contemporary reports showing that typical angina is only associated with intermediate pretest likelihood of obstructive CAD, not high likelihood.

Perhaps a more intriguing observation is the rise in the proportion of patients presenting with dyspnea only. In fact, dyspnea was associated with the lowest survival rates among both patients who did and did not undergo coronary revascularization.

The negative prognostic implications of dyspnea as the presenting symptom among patients referred for SPECT-MPI is underrecognized. In a cohort of nearly 18,000 subjects undergoing SPECT-MPI at Cedars-Sinai Medical Center, Abidov et al reported adverse prognostic implications of dyspnea, as compared to chest pain symptoms.[12] The authors found that the rates of cardiac death and all-cause death were significantly higher among patients with dyspnea compared to those with other symptoms at presentation, irrespective of previously known CAD status. Among patients with no known history of CAD, those with dyspnea had four times higher risk of sudden cardiac death than asymptomatic patients and more than twice the risk of patients with typical angina; this increase in risk was independent of other significant factors.[12] Notably, the report by Abidov et al comes from a Cedar-Sinai Medical Center cohort which seems to overlap with the cohort in the present report by Rozanski et al. The prognostic implications of dyspnea have been further confirmed by Argulian et al in a meta-analysis of 6 studies, encompassing 5,753 patients with dyspnea and 24,491 patients with chest pain.[13] The authors found that although there was no statistically significant difference in the incidence of ischemia on stress imaging in patients with dyspnea compared to those with chest pain (37.4% vs 30.2%), patients with dyspnea had higher all-cause mortality compared with patients with chest pain (annual mortality 4.9% vs 2.3%, odds ratio of 2.57).

Dyspnea is a well-recognized angina equivalent, particularly among patients with diabetes and women. In the context of the present report, it is likely that dyspnea is a manifestation of a constellation of comorbidities that have been on the rise in recent decades, including obesity, diabetes mellitus, hypertension, and impaired exercise tolerance. These comorbidities are often associated with increasing need for pharmacologic stress testing, which is known to be associated with increased mortality risk.[14–16] It is unclear from the present study whether other chronic diseases, such as heart failure and lung diseases, played a role in the observed dyspnea-associated mortality. Certainly, ischemia and CAD burden alone do not explain why dyspnea is associated with the highest mortality, as those patients do not have the highest rates of severe ischemia on MPI or severe coronary stenoses on CCTA. Irrespective of the pathophysiology, the reported data indicate that clinicians should be aware that patients presenting with dyspnea

represent a high-risk group with increased risk of mortality.

The authors challenge us to re-think our conventional approach to the diagnostic and prognostic evaluation of epicardial CAD and leave us with several questions to address in future research. Clearly, the data need to be confirmed by more than one institution. Investigating multimodality CAD imaging methods (PET, stress Echo, MRI, CCTA, CAC, invasive coronary angiography) is necessary to better understand shifts in referral patterns, dependent of local availability, expertise, and economic pressures, and to comparatively evaluate short- and long-term prognostic value of each modality. Future investigations should focus on obtaining detailed descriptions of symptoms, particularly for ''asymptomatic'' patients and those with dyspnea. More data on medication use, comorbidities, left ventricular function, valvular abnormalities, and cause of death will bring us closer to the answers. Finally, the benefits of various CAD management tools should be investigated in subjects with non-conventional CAD presentation, particularly patients with dyspnea or those with no apparent angina equivalent symptoms.

The present report challenges the current paradigm of assessing patients with known or suspected CAD utilizing stress testing. Based on the Bayes theorem, various stress testing studies are best suited to evaluate patients with intermediate pretest likelihood of CAD, not low likelihood. The declining prevalence of typical angina accompanied with decreasing burden of myocardial ischemia and obstructive CAD forces us to reexamine the effectiveness of stress MPI in contemporary patient populations. The study contests the conventional wisdom of typical angina being the feared symptom of CAD. With the decline of typical angina and emergence of dyspnea with associated high mortality rates, one wonders whether dyspnea is the new angina, a feared symptom of the modern era.

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