Risk Stratification for Sudden Cardiac Death
A Puzzle Beyond p Values*

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In their elegant paper in this issue of the Journal, Laukkanen et al. (1) report on a seemingly strong association between maximal oxygen consumption and risk of sudden cardiac death. The corresponding p value was <0.001. Case closed?

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First, some background. Despite dramatic advances in preventing and treating cardiovascular disease, sudden arrhythmic cardiac death remains a major public health threat in the U.S., affecting between 184,000 and 462,000 people every year (2). By its very nature, death occurs shortly after the onset of symptoms, leaving little time for effective medical interventions. Therefore, there continues to be a great deal of interest in identifying effective, clinically useful markers of risk, as prevention appears to be the only viable approach to decrease substantially this disorder’s devastating effects.

The best-known predictor of death is depressed left ventricular ejection fraction, which has been well documented to be associated with a dramatically increased risk of sudden death (3). Ejection fraction has been used to select patients for prevention trials (4) and has also been used by payers to determine coverage for automated implantable cardioverter-defibrillators. Nonetheless, ejection fraction is limited by low sensitivity, as the majority of people who suffer from sudden cardiac death have a preserved ejection fraction (2).

Over the past 10 to 15 years, investigators have studied numerous other noninvasive risk-stratification techniques including QRS duration, QT interval and dispersion, signal-averaged electrocardiography, short- and long-term heart rate variability, ventricular ectopy and nonsustained ventricular tachycardia on Holter monitoring, heart rate turbulence, heart rate recovery after graded exercise, T-wave alternans, and baroreceptor sensitivity. To date, there is no evidence that any of these techniques provide clinical utility to guide selection of therapy (2).

We now come to the paper of Laukkanen et al. (1), who report on the use of exercise testing with measurement of maximal oxygen consumption for prediction of sudden cardiac death in the community. The investigators followed 2,682 men, 40 to 60 years of age, who lived in or near the Finnish town of Kuopio between 1984 and 1989. The men were generally healthy, with only 7% having a history of prior myocardial infarction and <1% undergoing previous coronary bypass surgery. All subjects underwent a symptom-limited exercise tolerance test with direct analyses of respiratory gases. The study was well done, with systematic collection of multiple important baseline characteristics, careful exercise and gas exchange measurements according to a rigorous protocol, long-term follow-up, a large number of outcome events, blinded adjudication of deaths, and a remarkably high rate of documentation of terminal arrhythmia as assessed by electrocardiography or exclusion of other causes of death by autopsy.

During 17 years of follow-up, 146 men experienced sudden cardiac death. The investigators found that an increase of 1 metabolic equivalent in maximal oxygen consumption predicted a 22% reduction in the risk of sudden cardiac death. By traditional hypothesis testing, the association between maximal oxygen consumption and sudden death risk was substantial, with a reported p value <0.001.

Fortunately, the authors did not stop, but chose to take their analyses further, beyond the p value. Following up-to-date standards in clinical epidemiology (5), they determined the ability of maximal oxygen consumption to improve discrimination and reclassification. Discrimination refers to the ability to correctly distinguish between higher- and lower-risk subjects. Reclassification refers to the ability to correctly reassign risk given the additional information provided by the test.

The investigators found that maximal oxygen consumption led to only a modest increase in discrimination, with the C-index (a measure that is analogous to the area under a receiver-operating characteristic curve) increasing from 0.760 to 0.767. Furthermore, measurement of maximal workload led to an essentially identical increase in discrimination, with the C-index increasing from 0.760 to 0.766. Gas exchange technology yielded a trivial improvement in discrimination (C-index difference of only 0.001).

When the investigators analyzed the ability of maximal oxygen consumption to reclassify risk, they found that, if anything, the test yielded misinformation. Among 52 subjects who died from sudden cardiac death and who were classified by risk factors as being at only intermediate risk, only
3 were correctly reclassified as being at high risk, whereas 8 were incorrectly reclassified as being at low risk. Correspondingly, the “net reclassification index” showed no significant change ($p = 0.7$), and if anything, trended in the wrong direction with a value $<0$.

In summary, despite statistical significance by traditional hypothesis testing, measurement of maximal workload and maximal oxygen consumption does not appear to provide clinically meaningful information on long-term risk of sudden cardiac death among middle-aged men.

Why the failure? Maximal oxygen consumption reflects complex physiological pathways involving respiratory, cardiac, autonomic, hematologic, and skeletal muscle function; the test may not be specific enough to accurately detect future fatal cardiac arrhythmia. The investigators measured only 1 baseline value of maximal oxygen consumption; it is possible that serial measurements may have improved prediction. The investigators did not include electrophysiological measures such as T-wave alternans and heart rate variability; it is possible that a combined panel of measurements including exercise and electrophysiological measures may have yielded substantially improved degrees of discrimination and reclassification.

The investigators are to be particularly commended for comparing the predictive properties of maximal workload and maximal oxygen consumption. Measurement of maximal workload is much less technology-intensive than measurement of gas exchange, yet yielded essentially identical prediction. This finding is remarkably consistent with a recent report on patients undergoing metabolic exercise testing as part of a cardiac transplantation evaluation; exercise treadmill time was practically as good as maximal oxygen consumption for prediction of all-cause mortality (6). These kinds of studies, along with others, argue that, in medicine, more is not necessarily better (7).

Our battle against sudden cardiac death is far from over. While automated implantable cardioverter-defibrillators certainly save lives (4), we are still lacking effective risk stratification and preventive interventions for the majority of people who will ultimately experience sudden cardiac death. The well-done but negative study of Laukkanen et al. (1) is a potent reminder of the need for basic, translational, and clinical research to redefine paradigms for confronting this ongoing public health scourge. It also serves to caution us of the dangers of excessive reliance on p values.

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