Elevated N-Terminal Pro-B-Type Natriuretic Peptide Levels: The Effect of Chronic Obstructive Pulmonary Disease

We read with great interest the recent article by Daniels et al. (1) in which the investigators reported that detectable cardiac troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were both associated with increased all-cause and cardiovascular death in healthy older adults.

NT-proBNP was previously identified as a prognostic cardiac risk marker associated with increased mortality. NT-proBNP is released by cardiac myocytes in response to wall stress in conditions associated with volume overload as in heart failure and chronic kidney disease, pressure overload as in patients with heart valve abnormalities, and ischemia owing to coronary disease. In the present study, the association remained even after participants with baseline coronary heart disease were excluded, which was 30% of the subjects with elevated (≥450 pg/ml) NT-proBNP levels.

However, the authors might have overlooked the effect of chronic obstructive pulmonary disease (COPD) on NT-proBNP levels. COPD is associated with cardiovascular disease and is an independent risk factor for cardiovascular morbidity and mortality (2). We recently investigated the relationship between COPD, both the presence and severity, and NT-proBNP levels in 376 patients. To mitigate the influence of heart failure, chronic kidney disease, and myocardial ischemia, we adjusted for history of angina pectoris, myocardial infarction, heart failure, and renal function. In addition, all patients had resting left ventricular function of more than 40% using echocardiography. The severity of COPD was assessed using pulmonary function tests with the GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification. We found COPD to be an independent risk factor for increased NT-proBNP levels, and the levels increased with the severity of COPD.

The underlying mechanism is likely to be pulmonary hypertension and right ventricular dysfunction caused by pulmonary arterial pressure overload (3). COPD may induce wall stretching, ventricular dilation, and/or increased vascular pressures, which may promote the secretion of the neurohormone NT-proBNP. Because COPD is common in the elderly population (affecting nearly 35% of this population) (4), the addition of spirometric data to the analysis by Daniels et al. (1) would have been very interesting and informative. The less severe forms of COPD are often asymptomatic and therefore frequently underestimated, especially in the elderly. Thus, the presence of underlying COPD might have contributed to the observed correlation between NT-proBNP and outcome in this elderly population.

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REFERENCES


Reply

We thank Dr. van Gestel and colleagues for their interest in our work (1). They wonder whether the presence of underlying chronic obstructive pulmonary disease (COPD) might have contributed to the strong association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) and outcomes in the Rancho Bernardo Study. We did not find this to be the case.

Dr. Van Gestel and colleagues stated that COPD affects nearly 35% of the elderly population; however, the article that they reference actually found this incidence only in current smokers (2). The cumulative incidence of COPD was only 14% in ex-smokers and 12% in never-smokers.
The Rancho Bernardo Study had a low prevalence of smoking, with only 4% reporting a current smoking habit. Consistent with this, the prevalence of COPD in our cohort, as determined by self-report and review of history and medications, was extremely low at only 6%. Median NT-proBNP levels did not differ based on the presence or absence of COPD (208 pg/ml vs. 171 pg/ml, p = 0.20), and adjusting for a history of COPD did not significantly influence the association of NT-proBNP with all-cause death and cardiovascular death: hazard ratios per 1-U log increase in NT-proBNP levels were 1.70 (95% confidence interval [CI]: 1.24 to 2.33, p = 0.001) versus 1.67 (95% CI: 1.21 to 2.29) for all-cause death and 1.97 (95% CI: 1.19 to 3.26, p = 0.009) versus 1.93 (95% CI: 1.17 to 3.19) for cardiovascular death in Cox proportional hazards models adjusted for age, sex, and other cardiovascular risk factors with and without COPD in the model.

Spirometry was not performed at the same Rancho Bernardo Study visit when NT-proBNP was measured, which could have led to an underestimation of the true prevalence of COPD. However, elevated natriuretic peptide levels in the setting of COPD are likely due to right ventricular dysfunction secondary to pulmonary hypertension; thus, individuals with asymptomatic COPD are unlikely to have significantly elevated levels of natriuretic peptide and would therefore be unlikely to explain a significant proportion of the association of NT-proBNP with all-cause and cardiovascular mortality (3).