Atrial Fibrillation and Diffuse Left Ventricular Fibrosis, a Causal Association?*

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Late gadolinium enhanced magnetic resonance imaging (MRI) is an established technique for quantification of dense myocardial fibrosis (1). Cohesive regions of myocardial fibrosis, such as infarcted myocardium, are characterized by expanded extracellular matrix due to replacement of normal myocytes with collagen. Gadolinium contrast agents perfuse into and wash out of normal myocardium relatively rapidly. However, because of increased extracellular matrix and decreased capillary density, gadolinium contrast is retained within fibrotic myocardium (2). Late gadolinium enhanced MRIs are obtained by using an inversion recovery pulse that suppresses the signal from normal myocardium and results in hyperenhancement of signal from the gadolinium retained in dense myocardial fibrosis (3). If the myocardial fibrosis is diffuse rather than focal, however, gadolinium contrast may be evenly retained throughout the diffusely fibrotic myocardium. Thus, normal myocardium for appropriate selection of the inversion time may be absent. Additionally, the signal intensity variation of diffusely fibrotic areas compared with that of normal tissue may be minimal. As a result, diffuse myocardial fibrosis may be overlooked despite substantial retention of gadolinium. In contrast, the T1 mapping technique detects diffuse myocardial fibrosis by providing a quantitative measure of the myocardial T1 relaxation times. Diffuse myocardial fibrosis shortens the T1 relaxation time because of retention of gadolinium contrast in increased interstitial spaces. Prior studies have used T1 mapping to quantify diffuse fibrosis in patients with heart failure, aortic regurgitation, adult congenital heart disease, nonischemic cardiomyopathy, and myotonic muscular dystrophy (4–8). It is important to note that histopathologic processes other than diffuse myocardial fibrosis, such as fatty infiltration, edema, amyloid protein deposition, and iron deposition, also influence the myocardial T1 relaxation time. Additionally, the post-contrast myocardial T1 time may vary as a function of parameters such as contrast dose, delay time of MRI scan after contrast injection, patient hematocrit, and glomerular filtration rate.

In this issue of the Journal, Ling et al. (9) examined the association of diffuse myocardial fibrosis of the left ventricle with atrial fibrillation. The authors performed myocardial T1 mapping in 67 patients with atrial fibrillation (60% paroxysmal, 40% persistent) and 23 healthy volunteers. Patients with persistent atrial fibrillation had larger left atrial volume and lower left ventricular ejection fraction when compared with patients with paroxysmal atrial fibrillation and healthy volunteers. The post-contrast left ventricular T1 relaxation time was significantly different across groups: shortest in patients with persistent atrial fibrillation, modestly short in patients with paroxysmal atrial fibrillation, and longest in healthy volunteers. The subgroup of patients with lone atrial fibrillation also had shorter left ventricular T1 relaxation times when compared with age- and sex-matched controls. In multivariable analysis, age, atrial fibrillation category, and left ventricular ejection fraction were independently associated with the post-contrast left ventricular T1 relaxation time.

Ling et al. (9) provided strong evidence for an association between atrial fibrillation and the presence of diffuse left ventricular myocardial fibrosis. They asserted 2 possible explanations for the association they uncovered: 1) diffuse interstitial fibrosis may occur as a result of atrial fibrillation and tachycardia-mediated cardiomyopathy; or 2) diffuse interstitial fibrosis may reflect the presence of an underlying cardiomyopathy that precedes and contributes to the development of atrial fibrillation. Certainly, the association may also be due to a combination of the above explanations. Alternatively, unmeasured confounding due to a third factor that is independently associated with atrial fibrillation and diffuse fibrosis may have led to the association. Given the implications of the investigators’ findings upon strategies for the follow-up and treatment of patients with atrial fibrillation, it is important to consider the weight of evidence for any causal effect of atrial fibrillation upon diffuse ventricular fibrosis. The English epidemiologist, Sir Austin Bradford Hill, proposed several criteria required as minimum evidence for the presence of a causal association between 2 variables (10). The first of these criteria concerns the strength of association. Although it is difficult to compare the magnitude of association across variables, the magnitude of association between the presence of any atrial fibrillation

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and the myocardial T1 relaxation time (−75.2 ms) in the multivariable model appears remarkably strong. Another criterion is the specificity of association. Atrial fibrillation is associated with a myriad of other comorbidities, and it is difficult to dissect the effect of each comorbidity condition upon diffuse ventricular fibrosis. However, shorter T1 relaxation times in patients with lone atrial fibrillation than in healthy volunteers appears to support the specificity of this association. The biological gradient, or dose-response relationship criterion, has been nicely demonstrated in the stronger magnitude of association between the T1 relaxation time and persistent versus paroxysmal categories of atrial fibrillation. The biological plausibility criterion was highlighted by Hill (10) as a criterion we cannot demand because "what is biologically plausible depends upon the biological knowledge of the day." Nevertheless, it is certainly biologically plausible that atrial fibrillation may lead to diffuse ventricular fibrosis through multiple mechanisms, including tachycardia-mediated cardiomyopathy, reduced atrial contribution to cardiac output and thus increased work of ventricles, chronic microemboli, chronic atrioventricular dyssynchrony, and chronic interventricular dyssynchrony due to aberrant conduction. Another important criterion is coherence, or the compatibility of the cause and effect interpretation of data with the generally known facts of the natural history and biology of the disease. That atrial fibrillation may have an etiologic role in formation of diffuse ventricular fibrosis is not incompatible with our current knowledge of the morbidity and mortality that is associated with atrial fibrillation.

Some of the Hill criteria for causality remain untested with regard to the association of atrial fibrillation with diffuse ventricular fibrosis. Because this is the first report of an association between atrial fibrillation and diffuse myocardial fibrosis, Hill’s criterion of consistency of association has not yet been assessed. Another important criterion that cannot be assessed by the presented cross-sectional study is the temporality of association, which will require examination of ongoing population-based cohorts with MRI T1 mapping as well as atrial fibrillation incidence data. Future studies of left ventricular T1 relaxation in patients with atrial fibrillation randomized to rhythm versus rate control may satisfy the experiment criterion. Finally, studies of the association of other atrial and ventricular arrhythmias with diffuse ventricular fibrosis will be necessary to strengthen the argument for causality from an analogy standpoint.

The possibility that atrial fibrillation may have a causal role in the development of diffuse ventricular myocardial fibrosis is one that cannot be ignored. Such a causal role would significantly change our understanding of this arrhythmia and provide stronger rationale for the development of antiarrhythmic agents as well as ablation methodologies for improved rhythm control. Future studies that focus on uncovering the direction of association between atrial fibrillation and diffuse myocardial fibrosis are warranted.

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