Cardiac amyloidosis is caused by the aggregation and deposition of misfolded proteins in the extracellular space of the myocardium. The heart is one of multiple organs that may be involved in systemic amyloidosis and is usually the main cause of significant morbidity and mortality. Transthyretin amyloidosis (ATTR), one of the most common forms of cardiac amyloidosis, is increasingly recognized as an important cause of heart failure with preserved ejection fraction.1 It is generally believed that for heart failure to occur, the severity of amyloid deposition in a diseased heart has to be great enough to cause abnormal wall thickening, which is easily identifiable by echocardiography.

ATTR is caused either by wild-type transthyretin (TTR), a disease limited to the heart and predominantly of elderly males, or by mutant TTR, a disease with autosomal dominant inheritance, which may cause an isolated cardiomyopathy, isolated neuropathy, or combined disease. Numerous variants of TTR have been identified, among which is the substitution of isoleucine for valine at position 122 (V122I). This mutation has a prevalence of 3.4% in the North American population of African descent and is generally recognized as causing an infiltrative–restrictive cardiomyopathy, usually in the seventh decade and above.2 In this issue of Circulation: Heart Failure, Dungu et al3 provide data that further substantiate the importance of the V122I allele as a cause of heart failure in those of African descent. In a retrospective study of all Afro-Caribbean patients with heart failure presenting over 7 years to a heart failure clinic in a single academic cardiac center in the United Kingdom (n=211), the authors found that V122I ATTR was the fourth most common cause of heart failure in this group, occurring in 11.4% of patients, only slightly less than the 12.3% diagnosed as hypertensive cardiomyopathy. They also confirmed that V122I amyloid cardiomyopathy was associated with a worse prognosis compared with other common causes of heart failure. Amyloid cardiomyopathy was initially suspected by a typical echocardiographic appearance, often with additional evidence by cardiac magnetic resonance, and subsequently confirmed by genotyping or cardiac biopsy. The authors are to be congratulated in bringing this striking percentage to our notice, because we suspect that few cardiologists would have estimated that such a high percentage of Afro-American or Afro-Caribbean patients in an unselected outpatient population had heart failure because of amyloidosis.

Yet, further contemplation of the number of patients seen over the 7-year period of their study raises another question. Not why were so many patients seen, but why so few? The catchment area of the hospital studied is 1.5 million people. Assuming that 13.3% are of African descent (based on the demographics of Greater London) with a gene prevalence of 3.4%, then >6700 should carry the amyloidogenic gene. Even if only 20% of that population was >65 years old, >1300 people should be at risk of a rapidly progressive autosomal dominant amyloid cardiomyopathy, yet only 18 diagnoses were made over a 7-year period, despite a high index of suspicion and careful diagnostic approach. Why might this be?

Three possibilities come to mind. Either the gene has a low penetrance or it does not manifest as a classical amyloid cardiomyopathy (and, hence, is missed) or both. The possibility of a low penetrance seems, on a cursory reading, to be highlighted in a recent analysis of 3856 black Americans participating in the ongoing, observational ARIC study (Atherosclerosis Risk in Communities). Among 46 known gene carriers studied by echocardiography at visit 5 (when most were in their 70s), only 3 (7%) had echocardiographic features suggestive of an infiltrative cardiomyopathy. Although this might suggest a low penetrance of the gene, it is intriguing to note that V122I carriers had a statistically increased risk of heart failure during the later years of the study compared with noncarriers (hazard ratio 1.47; P=0.04).4 This paradox, namely the rarity of classical amyloid phenotype by echocardiography, yet a significant heart failure risk in the genotype, should be viewed as challenging our current thinking of how and when heart failure occurs in a heart with amyloid deposition. It may well...
be that our understanding of the disease phenotype is incorrect, and the gene can cause heart failure without the classical profound increase in wall thickness seen in typical amyloid cardiomyopathy. There are other data that support such a concept. The BEST (Beta-Blocker Evaluation in Survival Trial) studied treatment with bucindolol or placebo in 2708 patients with New York Heart Association functional class III or IV systolic failure with a left ventricular ejection fraction ≤ 35% and a dilated ventricle. African Americans comprised 23% of the study population. Cardiac amyloidosis was an exclusion criterion, and the classical appearance of cardiac amyloidosis, which is a nondilated ventricle with a relatively preserved left ventricular ejection fraction, did not meet the study criteria. Rather than a lower prevalence of the gene in the study population, the prevalence of the V122I allele in individuals >60 years of age was 10%, much greater than the reported carrier rate in the general African American population. Unless the entrance criteria were widely violated, this finding implies that carriers of V122I may be at risk of heart failure associated with a nontypical phenotype. One possible mechanism is that a relatively small amount of amyloid deposition, inadequate to produce the usual echocardiographic appearance, may increase the likelihood of heart failure, possibly by a two-hit mechanism of amyloid deposition plus a second insult, such as ischemia or hypertension.

This paradigm shift in how TTR amyloid may be a precipitant of heart failure, if correct, may be of even greater significance for wild-type amyloid deposition because it is more common. In the elderly population, autopsy studies consistently show a double figure prevalence of cardiac TTR amyloid that increases with decade lived, and an association has been suggested between the presence of such deposits and the diagnosis of heart failure with a preserved ejection fraction during life. Recently, using 99m Tc-3,3-diphenyl-1,2-propanodicarboxylic acid nuclear imaging, a sensitive and specific test for detecting ATTR, a prevalence of wild-type cardiac amyloidosis of 13% was found in an unselected heart failure group admitted to a single hospital with heart failure with a preserved ejection fraction. Thus, the description by Dungu et al of the high prevalence of V122I as a cause of heart failure in patients of African descent is more than an interesting observation. It offers key insights into an under-recognized cause of heart failure in a large ethnic population and serves as an example of the need for heart failure evaluations and therapies tailored to specific patient characteristics. Genetic testing for a TTR mutation is a simple and easily available blood test and should be strongly considered whenever faced with an African American patient with unexplained heart failure. Recognition of the presence of amyloid cardiomyopathy is particularly important now because, as described by the authors, several promising potential treatments for both wild-type and mutant ATTR are currently being actively investigated. These therapies may soon change the course of this disease in the same way that chemotherapy has extended the life of patients with AL amyloidosis. In addition, by raising the question of the curious paucity of patients with typical V122I cardiac amyloidosis, it brings to mind the Sherlock Holmes story, in which the failure of the dog to bark led to a solution of an otherwise seemingly insoluble murder. If our musings on the possible role of subclinical or atypical amyloid deposits prove to be unfounded, we hope that at least they will have stimulated thought. If they are shown in the future to have some merit, then we can safely say that a pathology once considered an obscure orphan disease may turn to be a major culprit in the large and growing population of patients with heart failure and a preserved ejection fraction.

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References


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