Characterization of atrial histology in a patient with hypertrophic cardiomyopathy: Possible evidence of a primary atrial myopathy

Stephen Keane, MB,* Aurelie Fabre, MD, PhD,† David Keane, MB, PhD, FHRS*

*From the *Department of Cardiology, St. Vincent's University Hospital, Dublin, Ireland, and †Department of Pathology, St. Vincent's University Hospital, Dublin, Ireland.*

Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous genetic myocardial disorder characterized by primary left ventricular hypertrophy. HCM is the most common inherited cardiovascular disorder, affecting about 1 in 500 in the general population, and is a leading cause of sudden cardiac death in young people.[1] In addition to ventricular arrhythmias, HCM is associated with a high incidence of atrial fibrillation (AF).[2]

Phenotypic expression of HCM in the left ventricle can lead to asymmetric septal hypertrophy, apical hypertrophy, and concentric hypertrophy. In association with hypertrophied ventricular segments, patchy ventricular fibrosis is commonly found. Secondary effects of the above include left ventricular diastolic dysfunction and ultimately, in some patients, progression to systolic dysfunction; ventricular outflow tract obstruction; and systolic anterior motion of the anterior mitral leaflet and mitral regurgitation.[3] The above secondary effects can lead to atrial hypertension, increased atrial wall stress, and atrial dilatation, which are felt to contribute to the high incidence of AF in HCM.[4,5]

Not only is the incidence of AF in patients with HCM high, but the outcomes of catheter ablation of AF in patients with HCM has been consistently disappointing, as highlighted by 2 meta-analyses.[6–8] The recurrence rate of AF after ablation in HCM patients has been consistently higher than in other patient cohorts, including those with heart failure with reduced ejection fraction (HF-rEF) and those with heart failure with preserved ejection fraction (HF-pEF). The underlying mechanisms of the high rate of AF recurrence post ablation in HCM are unknown. Specifically, it is unknown if AF in HCM is exclusively secondary to the consequences of ventricular dysfunction or whether it could be attributable in part to primary direct phenotypic expression of HCM in the atria.

To explore additional potential factors contributing to the high incidence of AF in HCM and the high rate of AF recurrence post ablation, we performed a detailed histological analysis of the atria, as well as the ventricles, in a patient with HCM and AF who underwent an orthotopic heart transplant. We describe the atrial histological characteristics in this patient and the possible contributory role these findings may play in AF in HCM.

KEY TEACHING POINTS

- Patients with hypertrophic cardiomyopathy (HCM) have a high incidence of atrial fibrillation (AF), which is associated with a deterioration of clinical status.
- Patients with hypertrophic cardiomyopathy have a high recurrence rate of AF post catheter ablation.
- The underlying mechanisms of the high rate of AF recurrence post ablation in HCM are unknown.
- We describe the atrial histology of a patient with HCM who underwent a heart transplant.
- The findings of biatrial myocyte hypertrophy and disarray indicate that HCM can result directly in a primary atrial myopathy, which could potentially contribute to the high incidence of AF in these patients.

Case report

We report a 46-year-old man who was diagnosed with HCM at age 22 years. His presenting complaint was dyspnea on minimal exertion and his primary care doctor noted a murmur. He does not have a family history of HCM. His initial

KEYWORDS Atrial fibrillation; Atrial myopathy; Catheter ablation; Hypertrophic cardiomyopathy; Heart transplant; Heart failure; Pulmonary vein isolation

(Heart Rhythm Case Reports 2021;7:413–417)

Conflicts of Interest: All authors have none to declare. **Address reprint requests and correspondence:** Dr Stephen Keane, Cardiology Department, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland. E-mail address: stephenkeane4@gmail.com.

https://doi.org/10.1016/j.hrcr.2021.03.017

electrocardiogram in our institution showed inferolateral T-wave inversion (Figure 1) and his echocardiogram showed asymmetric septal hypertrophy with the interventricular septum measuring 30 mm and preserved systolic function.

He was initially managed as heart failure with diastolic dysfunction (HF-pEF), which over the following decade progressed to a dilated cardiomyopathy with reduced ejection fraction (HF-rEF). He developed recurrent AF in his late 20s and subsequently underwent catheter ablation for AF in 2007, 2013, and 2018 (including isolation of the pulmonary veins and box isolation of the posterior left atrial wall), following which he remained in sinus rhythm. Atrial hypertrophy (as reflected by atrial electrogram voltage and response to radiofrequency applications) was noted at the time of posterior left atrial wall box isolation in 2013 and reconnection to the posterior left atrial wall was found in 2018, which required reisolation along with a left atrial anteroseptal line and a right atrial cavotricuspid line.

He developed worsening congestive cardiac failure in his early 30s secondary to HF-rEF, and severe mitral regurgitation required admission to hospital on multiple occasions for intravenous diuresis. Cardiac magnetic resonance imaging in 2008 revealed severely reduced left ventricular function with post-contrast images showing extensive hyperenhancement, indicating fibrosis throughout the anteroseptal, inferoseptal, and interventricular septum. An implantable cardiac defibrillator (ICD) was inserted in 2008. He subsequently developed a left bundle branch block and the device was upgraded to a cardiac resynchronization therapy defibrillator with wireless stimulation endocardially (WiSE CRT-D; EBR Systems, Sunnyvale, CA) in 2014. His heart failure was optimized with diuretics, sacubitril/valsartan, spironolactone, and β-blockade. His mitral regurgitation was managed with a transcatheter mitral valve repair (MitraClip; Abbott Laboratories, Abbott Park, IL) in 2018 to which he had a limited response (Figure 1).

An echocardiogram in 2018 showed a left ventricular ejection fraction of 30% with anteroseptal, inferoseptal, and posterior hypokinesis. The left and right atrial volumes were estimated to be 62 and 25 mL, respectively.

Despite optimal medical therapy; catheter ablation, which restored sinus rhythm; cardiac resynchronization therapy; and a transcatheter mitral valve repair, his condition continued to deteriorate and he was referred for heart transplantation assessment. In August 2020 he underwent orthotopic heart transplantation. He is currently asymptomatic and well 6 months postprocedure. The patient's explanted heart was studied.

Macroscopic pathology

The left ventricle thickness was 8–10 mm with clearly demarcated patchy fibrosis, particularly in the interventricular septum (Figure 2A and 2B). The pectinate muscles in the right and left atrial appendages were noticeably hypertrophied (Figure 2C and 2D).

An atrial pacing lead was located in the right atrial appendage (Supplemental Figure S1) and an ICD lead was located in the right ventricle. A MitraClip device was seen between the anterior and posterior mitral leaflets (Figure 2E). The pacing electrode for the WiSE-CRT-D device was embedded in the inferolateral wall of the left ventricle. The coronary arteries had mild subintimal atheroma.

Histology

All cardiac chambers, including the atria, displayed myocyte disarray, cardiomyocyte hypertrophy, and thickened intramural vessels. Diffuse interstitial fibrosis was noted in all chambers, most prominently in the interventricular septum. The left and right atria also had the above findings, consistent with HCM (Figure 3 and Supplemental Figure S2). Along the previously ablated inferior transverse linear lesion of left atrial posterior wall box isolation, focal calcification and

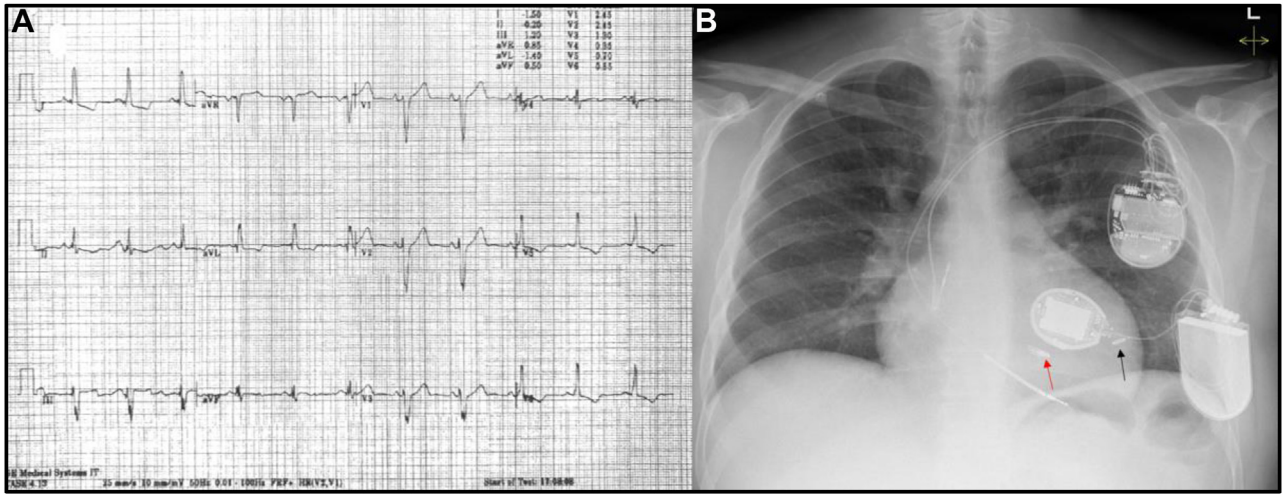

Figure 1 **A:** Initial electrocardiogram our institution with inferolateral ST changes and high-amplitude P waves. **B:** Chest radiograph with an implantable cardiac defibrillator, WiSE-CRT device (EBR Systems, Sunnyvale, CA; receiver electrode indicated by black arrow), and MitraClip (Abbott Laboratories, Abbott Park, IL; indicated by red arrow).

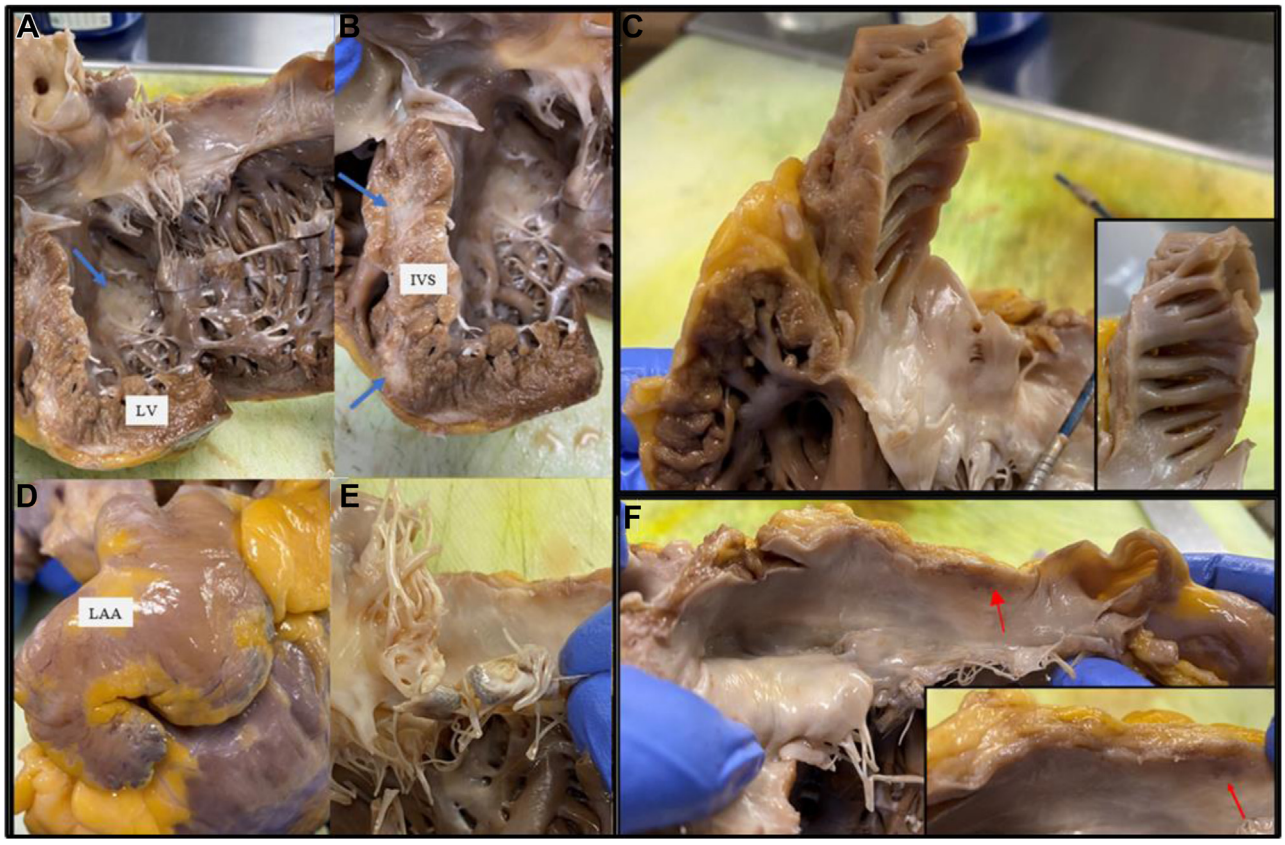

Figure 2 **A, B:** Left ventricle (LV) and intraventricular septum (IVS) displaying hypertrophy and patchy myocardial endocardial and mural fibrosis (blue arrows). **C:** Hypertrophied pectinate muscles in the right atrial appendage. **D:** Left atrial appendage (LAA). **E:** Left atrium with a MitraClip (Abbott Laboratories, Abbott Park, IL). **F:** Left atrium with previous ablation sites (red arrows).

chronic inflammatory changes were seen. The insertion site of the left ventricular subendocardial CRT-EBR electrode-receiver showed minimal inflammation.

Discussion

Our findings of myocyte disarray, myocyte hypertrophy, and interstitial fibrosis consistent with HCM within the atria are novel and not previously reported. Our findings suggest that the changes in atrial dimensions, thickness, and function in HCM may not only be a consequence of left ventricular dysfunction but may also arise from possible primary direct phenotypic expression of HCM in the atria. Our pathologic and histologic findings of advanced right atrial involvement (in addition to left atrial involvement) further support a primary atrial pathologic effect of HCM.

Santangeli and colleagues[9] reported that, in patients with HCM undergoing AF ablation, after pulmonary vein isolation and posterior left atrial wall box isolation there is a significant incidence of right atrial triggers of AF in addition to the interatrial septum and left atrial appendage. Their clinical observation would be supported by our marked right atrial findings. It would be reasonable to hypothesize that myocyte hypertrophy and disarray and fibrosis within the atria may contribute to the electrophysiological substrate for AF.

HCM was first described in 1958 and was first histologically described by Ferrans and colleagues[10] in 1972 who noted disorganized left ventricular myocardial architecture with hypertrophied cardiomyocytes. Although a high degree of myocyte hypertrophy and disarray is pathognomic of HCM, the detection of mild myocyte disarray is not exclusive to HCM and has been detected to a small degree in the hearts of patients with other cardiovascular diseases, such as hypertension or ischemic heart disease.[11–13]

A previous histological study in 2000 by Varnava and colleagues[14] found extensive myocyte disarray, fibrosis, and small vessel disease in the ventricles of hearts after sudden death with autopsy findings of HCM or post transplant, but they did not find atrial myocyte disarray in the left atrial free wall. In the ventricles, they found the distribution of myocyte disarray to vary widely within each heart. The reasons for the positive atrial myocyte disarray findings in our case, in contrast to their previous report, are unclear, but could include potential differences in individual genotype or phenotypic expression or distribution of disarray within the atria.

AF is the most common sustained arrhythmia in patients with HCM. Systematic review and meta-analysis revealed an AF prevalence of 22%, but in population-based analysis it is reported to be as high as 38%. The development of AF in patients with HCM is associated

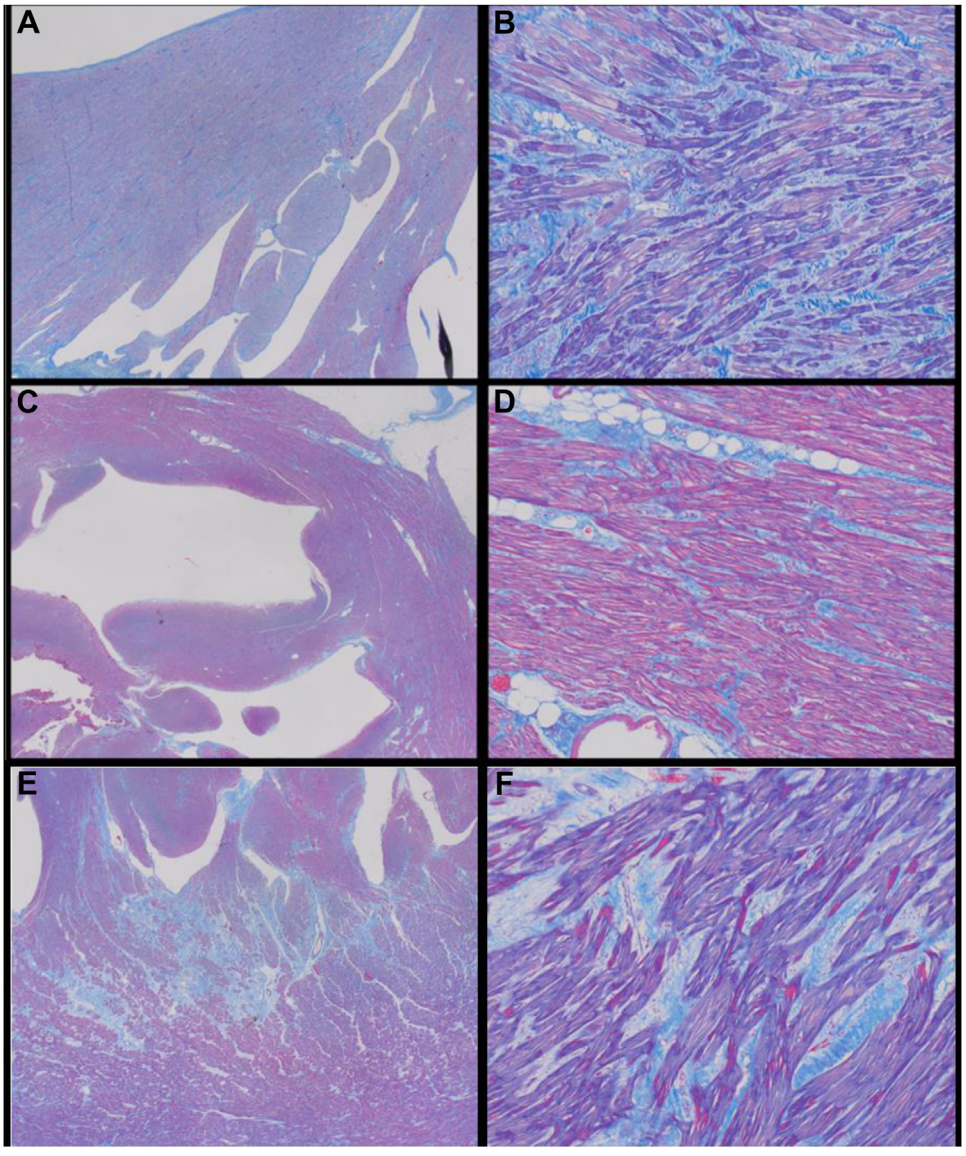

Figure 3 **A, B:** Left atrial histology with Masson trichrome stains showing fibrosissin blue. There is myocyte hypertrophy and disarray, and diffuse interstitial fibrosis. **C, D:** Right atrial histology with myocyte hypertrophy and disarray, and diffuse interstitial fibrosis. **E, F:** Left ventricle histology with marked fibrosis (blue), myocyte hypertrophy, and disarray.

with a deterioration in clinical status and increased risk of stroke, inappropriate ICD shocks, and mortality.[2,15]

The exact mechanism of why patients with HCM have such a high AF burden is not fully understood. Patients with HCM in sinus rhythm are known to have increased P-wave duration and amplitude, indicating possible atrial hypertrophy, and have a higher incidence of biphasic or triphasic signal-averaged P waves, which may indicate intra-atrial conduction delay (Supplemental Figure S3).[16]

Progressive left atrial dilatation secondary to left ventricular diastolic dysfunction and mitral regurgitation (often related to systolic anterior motion of the valve) is thought to predispose to AF in patients with HCM. Left atrial dysfunction and enlargement have been shown to be independent predictors of AF in HCM.[2]

The histological findings in our report offer another potential contributory factor to the development of AF in HCM and warrant further study.

Conclusion

We herein describe the atrial histology of a patient with HCM. Our findings of biatrial myocyte hypertrophy and disarray (in addition to fibrosis) indicate that HCM can result directly in a primary atrial myopathy (beyond the consequences of left ventricular dysfunction), which could potentially contribute to the high incidence of AF in these patients.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2021.03.017.

References

1. Maron BJ, Gardin JM, Flack JM, et al. Assessment of the prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA Study. Circulation 1995;92:785.
2. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart 2014;100:465–472.
3. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol 1995;26:1699.
4. Sachdev V, Shizukuda Y, Brenneman CL, et al. Left atrial volumetric remodeling is predictive of functional capacity in nonobstructive hypertrophic cardiomyopathy. Am Heart J 2005;149:730–736.
5. Yang H, Woo A, Monakier D, et al. Enlarged left atrial volume in hypertrophic cardiomyopathy: a marker for disease severity. J Am Soc Echocardiogr 2005;18:1074.
6. O'Neill L, Hensey M, Nolan W, Keane D. Clinical outcome when left atrial posterior wall box isolation is included as a catheter ablation strategy in patients with persistent atrial fibrillation. J Interv Card Electrophysiol 2015;44:63–70.
7. Providencia R, Elliott P, Patel K, et al. Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. Heart 2016;102:1533–1543.
8. Zhao DS, Shen Y, Zhang Q, et al. Outcomes of catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a systematic review and meta-analysis. Europace 2016;18:508–520.
9. Santangeli P, Di Biase L, Themistoclakis S, et al. Catheter ablation of atrial fibrillation in hypertrophic cardiomyopathy: long-term outcomes and mechanisms of arrhythmia recurrence. Circ Arrhythm Electrophysiol 2013;6:1089.
10. Ferrans VJ, Morrow AG, Roberts WC. Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis: a study of operatively excised left ventricular outflow tract muscle in 14 patients. Circulation 1972;45:769–792.
11. Bulkley BH, Weisfeldt ML, Hutchins GM. Asymmetric septal hypertrophy and myocardial fiber disarray. Features of normal, developing and malformed hearts. Circulation 1977;56:292–298.
12. Van der Bel-Kahn J. Muscle fibre disarray in common heart diseases. Am J Cardiol 1977;40:355–364.
13. Hughes S. The pathology of hypertrophic cardiomyopathy. Histopathology 2004;44:412.
14. Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. Heart 2000;84:476–482.
15. McClelland S, O'Connor SA, Donohue S, et al. Prevalence and impact of atrial fibrillation in a cohort of patients with hypertrophic cardiomyopathy in Ireland. J Atr Fibrillation 2020;13:37–43.
16. Cecchi F, Montereggi A, Olivotto I, et al. Risk for atrial fibrillation in patients with hypertrophic cardiomyopathy assessed by Signal-averaged P-wave. Heart 1997;78:44–49.