

Featured Review

Journal of Atrial Fibrillation



www. jafib.com

Atrial Fibrillation in Hypertrophic Obstructive Cardiomyopathy - Antiarrhythmics, Ablation and More!

Gangadhar Malasana MD¹, John D. Day MD², T. Jared Bunch MD²

¹Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah. ²Intermountain Heart Rhythm Specialists, Department of Cardiology, Intermountain Medical Center, Murray, Utah.

Abstract

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the cardiac sarcomere with an autosomal dominant pattern of inheritance. Patients with HCM are at high risk of developing atrial fibrillation (AF) particularly in the setting of advanced diastolic dysfunction and left atrial enlargement. AF is a marker of increased mortality and morbidity and results in a significant reduction in quality of life. Antiarrhythmic medications improve symptoms and reduce AF recurrence, but few are safe and there exists little data to guide their long-term use in HCM. Non-pharmacologic approaches have emerged and have equal or greater efficacy than pharmacologic approaches. Although these approaches are promising, the long-term impact on atrial function needs to be carefully studied as it may impact quality of life in patients that age in the setting of a progressive diastolic disease disorder. Nonetheless, with the significant impact of AF in HCM, rhythm control strategies are often required. The understanding of rhythm control strategies in HCM, an often rapidly progressive diastolic dysfunction disorder, may provide insight in how to treat the much more prevalent AF patient with hypertensive cardiomyopathy. Regardless of treatment strategy (rhythm or rate control) patients are a moderate to high risk of thromboembolism and until data are available to suggest otherwise require long-term warfarin anticoagulation.

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the cardiac sarcomere with an autosomal dominant pattern of inheritance. There are more than 450 familial hypertrophic cardiomyopathy-causing mutations identified in 20 genes, that encode cardiac isoforms of sarcomere and sarcomere-related gene products. ¹ Of these, cardiac-myosin binding protein-C is the most commonly affected gene (15–50%) ;², ³, ⁴β-MHC is the next most com-

mon (13–25%) ,^{2, 3, 5} followed by mutations in cardiac troponin isoforms I and T(4–15%). ^{2, 5, 6, 7, 8, 9}

Pathophysiology of HCM

The genetic defects involved in HCM lead to myofibril disarray and cause ventricular hypertrophy over time. Although significant phenotypic variation exists, the most common form of HCM involves hypertrophy of the septum extending to the outflow tract. In approximately 25% of pa-

Corresponding Address :T. Jared Bunch, M.D. Intermountain Heart Rhythm Specialists, Intermountain Medical Center, Eccles Outpatient Care Center, 5169 Cottonwood St, Suite 510, Murray, Utah, 84107.

tients the muscle thickening is evenly distributed throughout the ventricle and in approximately 10%, myocardial thickening is predominantly at the apex of the heart.¹⁰ The myofibril disarray present in the septum and even in other distinct areas of the myocardium that may or may not be hypertrophied but can contribute to ventricular arrhythmogenic substrate and/or diastolic dysfunction and heart failure symptoms.

In patients with HCM, dynamic left ventricular outflow tract obstruction is an important pathophysiologic feature that distinguishes obstructive HCM from nonobstructive disease and is closely correlated with long-term adverse outcomes .¹¹ Despite structural impairment, outflow obstruction through the Venturi phenomenon during systole can also result in systolic anterior motion of the mitral valve resulting in mitral valve regurgitation, valve leaflet fibrosis, and valve degen-

Figure 1:

eration. ^{12,13} The combined state of structural and valvular heart disease can result in heart failure symptoms, ventricular arrhythmias, apical thrombi, and premature death .^{14, 15, 16, 17, 18}In patients with the acquisition of other disease states such as coronary artery disease the pathologic process may be accelerated. ¹⁹

Clinical manifestations of HCM

The clinical manifestations of HCM vary considerably resultant from a broad spectrum of morphologic and hemodynamic abnormalities (Figure 1). Common symptoms are dyspnea on exertion, chest pain, orthopnea and paroxysmal nocturnal dyspnea, palpitations, fatigure, postural lightheadedness, presyncope and/or syncope. Most patients are diagnosed with HCM because of routine screening due to a family history of HCM. Overtime, asymptomatic patients can become

Morbidity and Mortality from Atrial Fibrillation in Hypertrophic Cardiomyopathy Symptoms Increased Mortality Heart Failure Dyspnea Stroke Palpitations Cardiac Arrest Postural Lightheadedness Ventricular Presyncope/Syncope Arrhythmias Chest Pain Reduced quality of life Structural Changes Electrophysiologic Changes Atrial enlargement Progression of atrial fibrillation Loss of atrial filling with subty pe (paroxysmal to chronic) prolonged diastolic filling times Sinus node dysfunction Systolic/Diastolic heart failure Ventricular tachyarrhythmias Conduction system Aberrant conduction abnormalities

25

symptomatic with 25% developing incapacitating symptoms or death over an 8 year followup in one large study .²⁰ In patients with HCM, age at onset of symptoms, gender, the presence of obstruction, and genetic mutations impact progression of disease and expected outcomes ²¹ Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis .²² Nonetheless, in patients specifically referred for evaluation of HCM, heart failure symptoms and outflow tract gradients are common, particularly when exercise testing is used in the diagnostic assessment. ²³

Pathophysiology of Atrial fibrillation in HCM

In patients with HCM, atrial fibrillation (AF) is a common arrhythmia. A few studies have sought to understand the incidence of AF in patients with HCM. In a case-control study of 104 HCM patients, AF was present in approximately 5 percent of patients at the time of diagnosis of HCM and developed in an additional 10 percent during the subsequent five years of follow-up. ²⁴ A second study of 480 consecutive HCM patients, AF occurred in 22 percent over 9 years of follow-up. ²⁵ In both patient populations the AF subtype was more likely paroxysmal likely reflecting

closer follow-up and the incidence is significantly higher than that projected from similar age-based general populations. Forty two percent of HCM patients with paroxysmal AF at presentation progress to chronic AF. In one study, the average progression time from paroxysmal to chronic AF was 5 years. Occurrence of AF increased progressively with age and was predominant in patients >60 years of age. Strong predictors of AF in HCM included age, functional class, left atrial size.

It is not surprising that AF is much more common in patients with HCM. These patients have various degrees of left ventricular hypertrophy and diastolic dysfunction, left atrial enlargement, and atrial fibrosis ^{26,27} An interesting observation was the atrial fibrosis present in HCM is often out of proportion to the degree of heart failure present and is similar in extent to that observed non-HCM patients with advanced heart failure .27 An area that requires further study is if atrial myofibril disarray is due to the ventricular disease only and if it is this atrial myofibril disarray that places patients at increased risk of AF. Similarly, little is known regarding the myocardial anatomic structure of the pulmonary vein ostia in HCM patients. Investigation into the genetic risk of an atrial myopathy and sarcomeric protein mutations in the atrium may help identify patients at early risk of AF.

An interesting finding is that dynamic outflow

Medication	Class	Summary
Disopyramide	Ia	Unclear efficacy in the treatment of AF in patients with HCM. Improves outflow tract obstruc- tion and symptoms in HCM. Side effects are common
Sotalol	III	Short-term efficacy for supraventricular Arrhythmias in HCM. Exercise tolerance improve- ment. No observed toxicities in limited trial data
Amiodarone	III	Long-term efficacy for AF. Reduces embolic rates and cardioversions in a small study. Long-term toxicities are well known. Lower doses may allow long-term use if side effects develop.
Dofetilide	III	No available data in patients with HCM
Dronedarone	III	No available data in patients with HCM. Avoid in patients with advanced systolic failure. Unclear safety in patients with advanced diastolic failure.

 Table 1
 Summary of antiarrhythmic medication efficacy and utility in patients with hypertrophic cardiomyopathy

obstruction in HCM does not predict AF. ²⁸ These data that suggest that patients likely need an atrial predisposition coupled with the ventricular cardiomyopathy to develop early atrial arrhythmias.

Impact of AF in HCM

The occurrence of AF represents an important clinical turning point in a HCM patient and has significant impact on quality of life and mortality with both short and long term consequences. In a case series of 52 patients with HCM and new onset AF, the acute onset of AF was associated with worsening of symptoms in 89% of patients and 93% of patients reverted to their original symptom class after either rhythm restoration or rate control .²⁴

The impact of AF has been well studied in a large community based HCM study involving 480 patients that were followed up for 9.1 years .²⁵AF developed in 107 patients during this period. AF onset was associated with new or worsening clinical manifestations in 84% of the 107 patients. Clinic

cal manifestations included dyspnea, chest pain, and functional deterioration in a majority of patients as well as severe symptoms of heart failure, pulmonary edema, impaired consciousness and syncope in others. In this study, 74 patients died of HCM-related causes, including 38 (35%) among the 107 AF patients (sudden death in 13, heart failure-related death in 17, and stroke-related death in 8). AF was associated with markedly increased risk for HCM-related death (3% versus 1%, p=0.001) when compared to patients in SR and was explained by an excess stroke- and heart failure-related mortality (p=0.001). There was increased incidence of Ischemic strokes among AF patients than among those in sinus rhythm (21% versus 2.6%, OR 17.7), causing death in 8 patients and permanent disability in 11. Also patients developing AF before 50 yrs of age were at greater risk of strokes. Similar increase in stroke risk was also noted in HCM patients with AF.²⁵

Similar findings were noted in an epidemiological study involving 744 consecutively enrolled



and largely unselected patients across 3 centers followed up for 8 years .²⁹ HCM-related death occurred in 86 patients (12%, sudden and unexpected in 51% of these patients), progressive heart failure (36%), and HCM-related stroke associated with AF (13%) .²⁹ Data from these studies highlight the profound impact of AF in these setting of HCM as it relates to both morbidity and mortality. Although unknown, these findings suggest that efforts to maintain sinus rhythm may improve outcomes by favorably impacting disease related morbidity and mortality

Treatment of AF in HCM patients

Therapeutic options in HCM patients with AF are similar to those for patients without HCM. However, due to the association between AF and progressive HF symptoms, mortality, and stroke, an aggressive approach to the maintenance of sinus rhythm is often preferred .³⁰

There exists a paucity of data to guide antiar-Figure 3: rhythmic therapy in patients with HCM (Table 1). There are no systematic randomized trials to compare the efficacy and safety of these medications and the information available is largely gleemed from observational studies of a single drug.

Amiodarone

Due to often significant left ventricular hypertrophy and the potential for proarrhythmia, class III antiarrhythmic medications are often used. Of these agents, amiodarone is effective and often used despite a relatively young population. In a case series of 52 consecutive patients with HCM ²⁴ 46 developed AF and sinus rhythm was restored in 29 patients (63%) with amiodarone. Of these patients, sinus rhythm was maintained in 22 of 29 patients during a 5.5 year follow up period. Over this follow-up period, patients who were treated with amiodarone had fewer alterations in drug therapy, less embolic episodes, and required less cardioversions. In another small study with 53 patients with HCM, amiodarone successfully



treated paroxysmal AF/supraventricular tachycardia in 8/9 patients without provocation of ventricular arrhythmias over a 27 month follow-up period .³¹ In this study, Amiodarone was discontinued in 3 patients secondary to side effects, but was restarted later at a lower dose and was well tolerated .³¹ However extrapolation of known side effects of amiodarone that are dose and duration dependent from other AF populations makes use of this medication long term in the young HCM patients concerning.

Sotalol

Sotalol may also be helpful in preventing AF in HCM patients. In a small study of 30 patients, sotalol eliminated supraventricular arrhythmias in 6 of 7 patients and suppressed ventricular arrhythmias in 7 of 13 patients. As important, 25 patients had better exercise tolerance on sotalol than on placebo. At a 6 month follow-up period the antiarrhythmic medication remained effective. In one patient, sotalol induced bronchospasm and had to be discontinued.³²

Disopyramide

Disopyramide is a class Ia antiarrhythmic medication that is negatively inotropic. Disopyramide was first used for patients with obstructive HCM in 1982 largely due to its' effects on inotropy. Disopyramide has been shown to provide symptomatic benefit (at 300 mg to 600 mg per day with a dose-response effect) by reducing systolic anterior motion of the mitral valve, outflow obstruction, and mitral regurgitant volume.³³⁻³⁶ Disopyramide has been recommended to be used in conjunction with a low dose beta blocker as it may be potentially pro-arrhythmic by accelerating AV nodal conduction and increasing the ventricular rate in AF. However, disopyramide use in a large multi center trial of 188 patients with obstructive HCM ³⁷, 66% of the patients had a 50% reduction in outflow gradient with amelioration of symptoms that was maintained over 3 years and did not increase the risk of sudden cardiac death. However, anticholinergic side effects with disopyramide were common in this study and consisted of constipation (11%), xerostomia (32%), and urinary delay/ retention (23%). Unfortunately, in non-HCM populations the long-term maintenance of sinus rhythm with disopyramide is poor ³⁸; a finding that is likely worse in patients with HCM with coexistent diastolic dysfunction.

New class III antiarrhythmics such as dofetilide and dronedarone may also have utility in the treatment of AF in HCM patients, although their clinical efficacy and safety in this population is not known. Due to the significant limitations of current antiarrhythmic medications in patients with HCM, coupled with the consequences of atrial tachyarrhythmias in HCM, there exists a significant need to define new pharmacologic and nonpharmacologic approaches.

Percutaneous Catheter AF ablation

Catheter ablation with pulmonary vein isolation to treat AF is being performed with increasing frequency and safety. The technique has emerged as a first-line therapy in medically-refractive AF³⁹ and in one trial was an effective initial treatment compared to medication.⁴⁰ In a recent comprehensive systemic review of 63 studies that examined both ablation and antiarrhythmic medications for treatment of AF, the single-procedure success rate of ablation off all antiarrhythmic therapies was 57% and for multiple procedures the success rate increased to 71%. In comparison, the success rate for antiarrhythmic therapies at 1 year was 52%. Of interest, major complications with catheter ablation occurred in 4.9% of patients compared to a rate of 30% of adverse, but less severe, events that occurred with drug therapy. ⁴¹The primary objectives of catheter ablation are to eliminated triggers of AF and modify the underlying substrate that is responsible for arrhythmia maintenance. Often the procedure requires extensive ablation in the left atrium particularly in those with extensive substrate or chronic AF.

Catheter ablation for treatment of AF in patients with HCM has been reported from multiple centers. The procedural success rates vary greatly from the different centers from 45-79% . ⁴²⁻⁴⁶The variance in reported outcomes from these multiple centers likely is due to patient characteristics, inclusion of patients that had prior ablations, technique approach, and the follow-up duration. In aggregate, there appears to be additive benefit in a more aggressive ablative strategy in those

with more advanced disease (Figure 2). Unfortunately with broad variance in ablation strategy, the optimal approach still needs to be defined. We advocate a stepwise approach with more aggressive linear ablation in those with chronic disease, severe left atrial enlargement, or presentation with prior ablative attempts. In understanding the importance of aggressive rhythm control attempts, in our study ⁴⁶, one of the most prominent findings was the significant improvement in quality of life that was sustained over the follow-up period after catheter ablation. This finding reflects not only the procedure as a whole, but the highly symptomatic state of HCM patients with AF.

Given the variable results with catheter ablation we previously tried to understand if echocardiography characteristics and/or progression of diastolic disease helped determine outcomes. The presence of diastolic function and severe left atrial enlargement were associated with worse outcomes. As important, in those patients with advanced diastolic disease and chronic AF the procedural approach impacted outcomes. This finding is reflective of the significant atrial arrhythmia substrate with HCM. If patients had severe left atrial enlargement, advanced diastolic dysfunction, or chronic AF additional linear ablation was required to obtain favorable outcomes as well as multiple ablative attempts (Figure 3). Recently atrial strain has emerged as an intriguing technique to evaluate atrial function. Strain may be additive in understanding atrial myopathy and assist in atrial ablation approach .47 Most of these HCM patients will require more aggressive ablation approaches as left atrial enlargement and distolic dysfunction are common. For AF ablation in general, an area that requires study is the long-term effects of aggressive ablation on atrial transport function. In patients highly dependent on the atrial contraction component of ventricular filling, loss of transport may impact quality of life and disease-related morbidity significantly. As we do not understand the long-term consequence of aggressive ablation, a stepwise approach may be preferable to minimize extent of ablation if possible especially in young patients with HCM.

Another area that requires further study is the underlying atrial anatomy in patients with HCM and if this contributes to outcomes. Unfortunately, most of the pathologic data revolves around the ventricular cardiomyopathy. Understanding the anatomy further will help in choice of ablation tools, duration of energy delivery, endpoints sought, and strategy.

Surgical AF ablation and Maze procedure

There are less data available regarding surgical based antiarrhythmic procedures in HCM patients. It is unclear if surgical myectomy will favorably impact long-term risk of AF. The impact of the surgical approach, if apparent, will likely require long-term investigation as the presence or severity of an outflow tract gradient does not appear to be associated with an increased incidence of AF [48]. In one small case series of septal alcholol ablation, 3 patients had improvement of AF burden after the procedure.⁴⁹

The surgical Maze procedure, similar to catheter ablation, provides an effective nonpharmacologic approach. In a case series of 10 patients that underwent a combination Maze III procedure and myectomy, 80% were in sinus rhythm at a mean of 15 months.⁵⁰ Complications in the relatively higher risk cohort were higher than with catheter ablation in that two developed complete heart block requiring a pacemaker and one died 3 months later due to ventricular fibrillation.

There are no case series to understand the efficacy of a surgical minimally invasive Maze procedure in patients with HCM. This procedure is a potentially attractive option as the left atrial appendage can be removed. Likely the ablation approach, whether with cryothermal or radiofrequncy energy sources, will need to be extensive, similar to the catheter-based approaches, in order to treat all the arrhythmia substrate.

Rate control

Beta blockers, nondihydropyridine calcium channel blockers or both are usually used to treat the ventricular rate. Digoxin can increase inotropy which may exacerbate heart symptoms in patients with HCM that have preserved systolic function. In patients that have refractory AF with rapid ventricular rates, atrioventricular node ablation and permanent pacing is an alternative.

Unfortunately, patients with HCM have various levels of diastolic dysfunction that progresses in

severity over time. The organized atrial contraction is often an important contributor to left ventricular filling in patients with diastolic dysfunction. ⁵¹ Loss of the atrial component of filling despite control of the ventricular rate may still significantly impact quality of life and prompt the need to reconsider aggressive rhythm control strategies as the primary approach to improve outcomes.

Thromobo-embolism prevention

Ischemic strokes occur up to eight times more frequently with AF in HCM than in sinus rhythm. ²⁴ The risk of stroke increases with age; in the Framingham Study, the annual risk of stroke attributable to AF increased from 1.5% in participants aged 50 to 59 years to 23.5% for those aged 80 to 89 years. In HCM, the risk of AF is higher with an incidence of 2%/yr and prevalence of 22%. In another large community based cohort of 900 patients with HCM, the overall incidence of stroke and peripheral arterial embolic events was 0.8%/ year and 1.9% for patients >60 years. As expected, the cumulative incidence of these events was significantly higher in non-anticoagulated patients as compared with patients on warfarin (31% vs. 18%; p < 0.05).⁵² HCM patients who develop AF should be considered to be at moderate to high risk and should be anticoagulated with warfarin. Further study is required to understand if aggressive measures to keep patients in SR decrease stroke risk in the setting of anticoagulation.

With emerging advances and successes of nonpharmacologic approaches to restore sinus rhythm, there arises the question of discontinuing warfarin anticoagulation. The recent Heart Rhythm Society guidelines ³⁹ conclude that the long-term use of warfarin anticoagulation should be based upon the underlying patient risk. Patients with HCM are now low risk, a profile that would suggest they can be effectively and safely treated with aspirin only. Given, their baseline moderate risk status, warfarin should be continued until data are available to suggest otherwise or the risk of bleed is greater than the risk of stroke based upon the presented epidemiologic studies

Conclusion

Patients with HCM are at high risk of developing

AF particularly in the setting of advanced diastolic dysfunction and left atrial enlargement. AF is a marker of increased mortality and morbidity and results in a significant reduction in quality of life. Antiarrhythmic medications improve symptoms and reduce AF recurrence, but few are safe and there exists little data to guide their long-term use in HCM. Non-pharmacologic approaches have emerged and have equal or greater efficacy than pharmacologic approaches. Although these approaches are promising, the long-term impact on atrial function needs to be carefully studied as it may impact quality of life in patients that age in the setting of a progressive diastolic disease disorder. Nonetheless, with the significant impact of AF in HCM, rhythm control strategies that are often aggresive with associated risk are required. The understanding of rhythm control strategies in HCM, an often rapidly progressive diastolic dysfunction disorder, may provide insight in how to treat the much more prevalent AF patient with hypertensive cardiomyopathy.

References

1 Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. Nat. Clin. Pract. Cardiovasc. Med.2008; 5: 158–168. CrossRef PubMed

2. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, Benaiche A, Isnard R, Dubourg O, Burban M, Gueffet JP, Millaire A, Desnos M, Schwartz K, Hainque B, Komajda M; EU-ROGENE Heart Failure Project. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy, Circulation 2003; 107:2227–2232. CrossRef PubMed

3. Van Driest SL, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Sarcomeric genotyping in hypertrophic cardiomyopathy, Mayo. Clin. Proc. 2005; 80: 463–469. CrossRef PubMed

4. Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 2004; 44:1903–1910. CrossRef PubMed 5. Van Driest SL, Jaeger MA, Ommen SR, Will ML, Gersh BJ, Tajik AJ, Ackerman MJ. Comprehensive analysis of the betamyosin heavy chain gene in 389 unrelated patients with hypertrophic cardiomyopathy, J. Am. Coll. Cardiol. 2004; 44:602–610. CrossRef PubMed

6.Van Driest SL, Ellsworth EG, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy, Circulation 2003;108:445–451. CrossRef PubMed 7. Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, Spirito P, Matsumori A, Moravec CS, Seidman JG, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy, N. Engl. J. Med. 1995; 332:1058–1064. CrossRef PubMed

8. Ho CY, Seidman CE, A contemporary approach to hypertrophic cardiomyopathy, Circulation 2006;113:e858–62. CrossRef PubMed

9. Oudet C, Petrovic A, Stutzmann J, Time-dependent effects of a 'functional'-type orthopedic appliance on the rat mandible growth, Chronobiol. Int.1984;1:51–57. CrossRef PubMed

10. Kitaoka H; Doi Y; Casey SA; Hitomi N; Furuno T; Maron BJ Comparison of prevalence of apical hypertrophic cardiomyopathy in Japan and the United States. Am J Cardiol 2003; 92(10):1183-6. CrossRef PubMed

11. Maron MS; Olivotto I; Betocchi S; Casey SA; Lesser JR; Losi MA; Cecchi F; Maron BJ, Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003; 348(4):295-303. CrossRef PubMed

12. Schwammenthal E; Nakatani S; He S; Hopmeyer J; Sagie A; Weyman AE; Lever HM; Yoganathan AP; Thomas JD; Levine RA Mechanism of mitral regurgitation in hypertrophic cardiomyopathy: mismatch of posterior to anterior leaflet length and mobility. Circulation 1998; 98(9):856-65.

13. Yu EH; Omran AS; Wigle ED; Williams WG; Siu SC; Rakowski H Mitral regurgitation in hypertrophic obstructive cardiomyopathy: relationship to obstruction and relief with myectomy. J Am Coll Cardiol 2000;36(7):2219-25. CrossRef PubMed

14. T. Nakamura, K. Matsubara and K. Furukawa et al., Diastolic paradoxic jet flow in patients with hypertrophic cardiomyopathy: evidence of concealed apical asynergy with cavity obliteration, J Am Coll Cardiol 1992;19:516–524.

15. K. Matsubara, T. Nakamura, T. Kuribayashi, A. Azuma and M. Nakagawa, Sustained cavity obliteration and apical aneurysm formation in apical hypertrophic cardiomyopathy, J Am Coll Cardiol 2003; 42:288–295. CrossRef PubMed

16. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, Lesser JR, Udelson JE, Ackerman MJ, Maron BJ. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy, Circulation 2008;118:1541–1549. CrossRef PubMed

17. Fighali S, Krajcer Z, Edelman S, Leachman RD, Progression of hypertrophic cardiomyopathy into a hypokinetic left ventricle: higher incidence in patients with midventricular obstruction, J Am Coll Cardiol 1987; 9:288–294.

18. Hoffman JI, Buckberg GD, The myocardial supply:demand ratio—a critical review, J Am Coll Cardiol 1978; 41:327–332.

19. Sorajja, P, Ommen, SR, Nishimura, RA, et al. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. Circulation 2003; 108:2342. CrossRef PubMed

20 . Maron BJ; Casey SA; Poliac LC; Gohman TE; Almquist AK; Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA 1999;281(7):650-5. Cross-Ref PubMed

21. Anan R, Shono H, Kisanuki A, Arima S, Nakao S, Tanaka H. Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in thecardiac troponin T gene have variable cardiac morphologies and a favorable prognosis. Circulation 1998; 98: 391-7.

22.Olivotto I; Maron MS; Adabag AS; Casey SA; Vargiu D; Link MS; Udelson JE; Cecchi F; Maron BJ. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46(3):480-7. CrossRef PubMed

23. Maron MS; Olivotto I; Zenovich AG; Link MS; Pandian NG; Kuvin JT; Nistri S; Cecchi F; Udelson JE; Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114(21):2232-9. CrossRef PubMed

24. Robinson K; Frenneaux MP; Stockins B; Karatasakis G; Poloniecki JD; McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. J Am Coll Cardiol 1990;15(6):1279-85.

25. Olivotto I; Cecchi F; Casey SA; Dolara A; Traverse JH; Maron BJ. Impact of atrial fibrillation on the clinical course of hy-

pertrophic cardiomyopathy. Circulation 2001; 104 (21):2517-24. CrossRef PubMed

26 Tani T; Tanabe K; Ono M; Yamaguchi K; Okada M; Sumida T; Konda T; Fujii Y; Kawai J; Yagi T; Sato M; Ibuki M; Katayama M; Tamita K; Yamabe K; Yamamuro A; Nagai K; Shiratori K; Morioka S, Left atrial volume and the risk of paroxysmal atrial fibrillation in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2004;17(6):644-8. CrossRef PubMed

27. Ohtani K; Yutani C; Nagata S; Koretsune Y; Hori M; Kamada T. High prevalence of atrial fibrosis in patients with dilated cardiomyopathy. J Am Coll Cardiol 1995; 25(5):1162-9. CrossRef PubMed

28. Savage DD; Seides SF; Maron BJ; Myers DJ; Epstein SE. Prevalence of arrhythmias during 24-hour electrocardiographic monitoring and exercise testing in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation 1979; 59(5):866-75.

29. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of Hypertrophic Cardiomyopathy–Related Death Revisited in a Large Non–Referral-Based Patient Population. Circulation 2000;102: 8581.

30. Maron, BJ, McKenna, WJ, Danielson, GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003; 42:1687. CrossRef PubMed

31. McKenna WJ, Harris L, Rowland E, Kleinebenne A, Krikler DM, Oakley CM, Goodwin JF. Amiodarone for long-term management of patients with hypertrophic cardiomyopathy. Am J Cardiol. 1984;54(7):802-10. CrossRef PubMed

32.. Tendera M, Wycisk A, Schneeweiss A, Polonski L, Wodniecki J. Effect of sotalol on arrhythmias and exercise tolerance in patients with hypertrophic cardiomyopathy. Cardiology. 1993;82(5):335-42. CrossRef PubMed

33. Sherrid MV, Pearle G, Gunsburg DZ. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. Circulation 1998;97:41–7.

34. Sherrid M, Delia E, Dwyer E. Oral disopyramide therapy for obstructive hypertrophic cardiomyopathy. Am J Cardiol 1988;62:1085–8. CrossRef PubMed

35 Pollick C, Kimball B, Henderson M, Wigle ED. Disopyramide in hypertrophic cardiomyopathy. I. Hemodynamic assessment after intravenous administration. Am J Cardiol 1988;62:1248–51. CrossRef PubMed

36. Pollick C. Muscular subaortic stenosis: hemodynamic and clinical improvement after disopyramide. N Engl J Med 1982;307:997–9.

37. Mark V. Sherrid MD, Ivan Barac MD, William J. McKenna MD, Perry M. Elliott MD, Shaughan Dickie DCR,Lidia Chojnowska MD PHD, Susan Casey RN and Barry J. Maron MD Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005; 45(8):1251-1258.

38. Karlson BW, Torstensson I, Abjörn C, Jansson SO, Peterson LE. Disopyramide in the maintenance of sinus rhythm after electroconversion of atrial fibrillation. A placebo-controlled one-year follow-up study. Eur Heart J. 1988; 9(3):284-90.

39. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up: a report

of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2007; 4: 816–861. CrossRef PubMed

40. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A: Radiofrequency ablation versus antiarrhythmic drugs as first-line treatment for symptomatic atrial fibrillation. JAMA 2005; 293:2634-2640. CrossRef PubMed

41. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I, Treatment of Atrial Fibrillation With Antiarrhythmic Drugs or Radiofrequency Ablation. Two Systematic Literature Reviews and Meta-Analyses. Circulation: Arrhythmia and Electrophysiology. 2009;2:349-361. CrossRef PubMed

42. Gaita F, Di Donna P, Olivotto I, Scaglione M, Ferrero I, Montefusco A, Caponi D, Conte MR, Nistri S, Cecchi F: Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy. Am J Cardiol 2007; 99: 1575 -1581. CrossRef PubMed

43. Kilicaslan F, Verma A, Saad E, Themistoclakis S, Bonso A, Raviele A, Bozbas H, Andrews MW, Beheiry S, Hao S, Cummings JE, Marrouche NF, Lakkireddy D, Wazni O, Yamaji H, Saenz LC, Saliba W, Schweikert RA, Natale A: Efficacy of catheter ablation of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. Heart Rhythm 2006; 3:275-280. CrossRef PubMed

44. Liu X, Ouyang F, Mavrakis H, Ma C, Dong J, Ernst S, Bansch D, Antz M, Kuck KH: Complete pulmonary vein isolation guided by three-dimensional electroanatomical mapping for the treatment of paroxysmal atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. Europace 2005; 7:421-427. CrossRef PubMed

45. Callans DJ, Gerstenfeld EP, Dixit S, Lin D, Cooper J, Russo A, Verdino R, Marchlinski FE: Efficacy of pulmonary vein isola-

tion in patients with hypertrophic cardiomyopathy. Circulation 2006; 114:704.

46. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM, Rea RF, Shen WK, Powell BD, Ommen SR, Monahan KH, Haroldson JM, Packer DL. Substrate and Procedural Predictors of Outcomes after Catheter Ablation for Atrial Fibrillation in Patients with Hypertrophic Cardiomyopathy J Cardiovasc Electrophysiol. 2008; (10):1009-14.

47. Paraskevaidis IA, Farmakis D, Papadopoulos C, Ikonomidis I, Parissis J, Rigopoulos A, Iliodromitis EK, Kremastinos DT. Twodimensional strain analysis in patients with hypertrophic cardiomyopathy and normal systolic function: a 12-month follow-up study. Am Heart J. 2009;158(3):444-50. CrossRef PubMed

48 Savage DD; Seides SF; Maron BJ; Myers DJ; Epstein SE. Prevalence of arrhythmias during 24-hour electrocardiographic monitoring and exercise testing in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation 1979; 59(5):866-75.

49. Hosokawa Y, Takano H, Ohno T, Takayama M, Takano T. Impact of percutaneous transluminal septal myocardial ablation on refractory paroxysmal atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. Angiology. 2008; 59(3):329-34. CrossRef PubMed

50. Chen MS, McCarthy PM, Lever HM, Smedira NG, Lytle BL. Effectiveness of atrial fibrillation surgery in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2004; 93(3):373-5. Cross-Ref PubMed

51. Bonow RO; Frederick TM; Bacharach SL; Green MV; Goose PW; Maron BJ; Rosing DR. Atrial systole and left ventricular filling in hypertrophic cardiomyopathy: effect of verapamil. Am J Cardiol 1983 May 1;51(8):1386-91. CrossRef PubMed

52. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, Casey SA, Gohman TE, Bongioanni S, Spirito P. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;39:301–7. CrossRef PubMed