Ventricular Arrhythmias in Adult Aortic Stenosis*

Prevalence, Mechanisms, and Clinical Relevance

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With the longer life expectancy of the population, calcific aortic stenosis (AS) has become an increasingly prevalent condition. It is well known that AS in the adult has a progressive course with a long asymptomatic period. However, when severe AS becomes symptomatic, the prognosis is usually poor in the absence of valve replacement and sudden death is a feared complication. It has been hypothesized that malignant ventricular arrhythmias could be responsible for the high incidence of sudden death in symptomatic patients with aortic stenosis. The purpose of this review is to analyze the prevalence, the electrophysiologic mechanisms, and the possible role of ventricular arrhythmias in the development of symptoms and in the outcome of adult subjects with aortic stenosis.

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Key words: aortic stenosis; electrophysiologic mechanisms; left ventricular hypertrophy; sudden death; syncope; ventricular arrhythmias

Abbreviations: ACE=angiotensin-converting enzyme; AS=aortic stenosis; EAD=early afterdepolarization; LVH=left ventricular hypertrophy

With the longer life expectancy of the population, calcific aortic stenosis (AS) has become an increasingly prevalent condition. It is well known that AS in the adult has a progressive course with a long asymptomatic period. However, when severe AS becomes symptomatic, the prognosis is usually poor in the absence of valve replacement, with an average survival ranging between 1 and 3 years,1 because both the medical treatment and the balloon valvuloplasty have only a short-term efficacy. Furthermore, death observed among symptomatic unoperated-on patients is frequently sudden, with an incidence ranging from 8 to 34%;2,3 conversely, sudden death appears only occasionally in asymptomatic subjects (0 to 5% of adult and 7.5% of children).1,4,5 It has been hypothesized that malignant ventricular arrhythmias may be responsible for the high incidence of sudden death in AS patients, as well as in those with coronary artery disease or cardiomyopathy. However, although a higher prevalence of ventricular arrhythmias has been documented in AS patients compared with control subjects, the mechanisms underlying these arrhythmias and their impact on the natural history of disease are still debated. The purpose of this review is to analyze the prevalence of ventricular arrhythmias and their possible role in the development of symptoms and outcome of adult subjects with AS.

Prevalence of Ventricular Arrhythmias in Adult AS

Several studies showed that premature ventricular contractions, documented by Holter monitoring, are frequent in patients with aortic valvular disease (Table 1). In the early 1980s Santiga et al6 and von Olshausen et al7 documented a high prevalence of ventricular arrhythmias in patients with severe AS and/or aortic regurgitation without significant coronary artery disease. The frequency and complexity of ventricular arrhythmias were closely related to myocardial function and thus were more common in patients with higher left ventricular systolic stress and reduced systolic function. On the contrary, the severity of arrhythmias was not related to the etiology of valve stenosis, the transvalvular gradient, or the severity of aortic regurgitation.

These observations were later confirmed by Klein,8 Kostis et al,9 and more recently by Martinez-Useros et al,10 Michel et al,11 and our group (unpub-
lished data). Of interest, in all these studies, no relation was observed between severity of arrhythmias and syncope or sudden death during follow-up. However, Schwartz et al,12 in 1969, reported that the ECG of AS patients recorded during syncope often documented ventricular tachycardia or even ventricular fibrillation reverting to sinus rhythm spontaneously. If the malignant ventricular arrhythmias persisted longer, sudden death eventually occurred. Also, von Olshausen et al13 have recently described seven AS patients who suddenly died during Holter monitoring; in six of them, the cause of death was a malignant tachyarrhythmia (monomorphic or polymorphic ventricular tachycardia) and only in one patient was death associated with bradyarrhythmia. Increased ectopic ventricular activity with complex forms (couplets and nonsustained ventricular tachycardia) and a significant acceleration in heart rate were observed within the last hours before tachyarrhythmic sudden death, thus reinforcing the hypothesis that a strong link exists between frequency and complexity of ventricular arrhythmias and risk of sudden death in these patients. However, it must be mentioned that all the patients in this study had moderate to severe heart failure and impaired left ventricular systolic function, thus the arrhythmias leading to the sudden death could be related to the left ventricular dysfunction itself more than to the outflow obstruction.13

**Mechanism of Ventricular Arrhythmias in AS**

**Risk of Ventricular Arrhythmias in Left Ventricular Hypertrophy**

The Framingham Heart Study showed that hypertensive patients with left ventricular hypertrophy (LVH) are at increased risk of premature cardiovascular death and this is frequently sudden.14-16 Accordingly, the hypothesis that ventricular arrhythmias may be responsible for sudden death was formulated.17-20 Nevertheless, the role of ventricular arrhythmias in the pathogenesis of sudden death in patients with LVH is still unclear. Recently, Bikkina et al21 demonstrated that the presence of asymptomatic frequent and/or complex ventricular arrhythmias, in subjects with LVH and free of clinically apparent coronary heart disease, is associated with a doubling of all-cause mortality. Coste et al22 performed programmed ventricular stimulation in patients with essential hypertension with and without LVH on echocardiogram. Ventricular stimulation induced intraventricular reentry beats in 92% of hypertensive subjects with and only in 17% of those without LVH, indicating that the increase in myocardial mass may represent an anatomic substrate for ventricular arrhythmias. In 40 hypertensive patients with documented LVH and history of syncope and aborted sudden death, Vester and coauthors23 performed programmed ventricular stimulation inducing ventricular tachycardia or ventricular fibrillation in 30% of them. Furthermore, it is well known that in patients with hypertrophic cardiomyopathy, the rate of inducibility of ventricular tachycardia is high, ranging between 40% and 82% in different studies.24,25 These data support the hypothesis that LVH may provide a substrate for malignant ventricular arrhythmias and sudden death, independently of the etiology.

**LVH: The Arrhythmogenic Substrate**

Arterial hypertension and AS, by virtue of chronic systolic pressure overload, result in increased wall stress. Myocardial hypertrophy, which occurs as consequence of the hemodynamic abnormality, is thought to be a compensatory process that leads to normalization in wall stress. Structural remodeling of the main myocardial components—myocytes, colla-
gen, and microvessels—is initially adaptive, but may have deleterious consequences at a later stage.26 Adverse effects of long-term hypertension include depressed myocardial contractility and altered diastolic function, an increased collagen content, abnormal electrophysiologic properties, and decreased myocardial perfusion due to a reduction in coronary vasodilator reserve.27,28 The impaired coronary reserve observed in LVH is related in hypertension, but not in AS, to an intramyocardial arteriole wall thickening and to an increase in perivascular fibrosis.29 Thus, the reduced coronary reserve, the inappropriate capillary density compared with the ventricular myocyte hypertrophy, and the increased wall stress may lead to myocardial ischemia, myocyte death, and scar formation.

Electrophysiologic Mechanisms for Ventricular Arrhythmias in LVH

Several cellular mechanisms have been proposed to explain the propensity for ventricular arrhythmias in LVH.30 In 1983, Cameron et al27 documented that, in feline LVH induced by aortic banding, regions of normal myocardium were associated with multiple areas of fibrosis. Using microelectrode techniques, the authors showed that the prolongation of action potentials was the most prominent electrophysiologic abnormality in the hypertrophied cells. The contiguity of cells with normal and abnormal action potentials was thought to provide a heterogeneous substrate for the genesis of ventricular arrhythmias. Recently, using a similar experimental model of LVH, Kowey et al31 confirmed the presence of a prolonged monophasic action potential duration in hypertrophic myocardium, but also showed that hypertrophic myocytes had a larger dispersion of refractoriness and a lower ventricular fibrillation threshold. The dispersion of refractoriness could be responsible for development of functional reentry in LVH. In fact, the initiation of reentry could be related to block of premature impulse in fibers with long refractory period and conduction in fibers with shorter refractory period, eventually returning to the initial point of block after the excitability recovers there.

Cardiac muscle is basically anisotropic, that is its electrophysiologic properties vary according to the direction of myocardial syncytium32,33 with different axial resistance along and perpendicular to the fiber axis. During conduction of the impulse, axial current flows from one myocardial cell to an adjacent cell through the gap junctions of the intercalated disks. The anisotropic properties involved are determined by the alignment of cardiac myocytes, the distribution of gap junctions, and the geometry of extracellular space. This structural organization is reflected in a lower axial resistivity and a higher conduction velocity in the longitudinal direction of myocardial fibers rather than crosswise. On the contrary, the slower conduction in the transverse direction is due to higher axial resistivity, which may be partly explained by fewer and shorter gap junctional contacts in a side-to-side direction. The anisotropy of cardiac muscle affects not only conduction velocity but may also contribute to the occurrence of unidirectional block. Spach et al34 have indicated that in anisotropic muscle, the safety factor for conduction is lower in the longitudinal direction of rapid conduction than in the transverse direction of slow conduction resulting in a preferential conduction block of premature impulses in the longitudinal direction. With aging and pathologic conditions—as in the border zone of healed myocardial infarction or in ventricular hypertrophy—the development of connective tissue septa within myocardial cells and bundles decreases the electrical coupling of adjacent groups of parallel fibers changing the anisotropic structure from uniform to nonuniform. Spach et al35 documented, in nonuniform anisotropic cardiac muscle, that premature activation resulted in conduction block in the longitudinal direction while conduction in the transverse direction continued. Therefore, anisotropic conduction properties of cardiac muscle may contribute to create an arc of unidirectional block around which the impulse can circulate and successfully initiate reentry.

Although reentry may contribute to the genesis of ventricular arrhythmias in LVH, there is additional evidence that mechanisms other than reentry may be involved. Stretch-induced arrhythmias may appear in LVH when the stretching of the fibers exceeds their optimal point, such as during sudden changes in volume or pressure load.35 The mechanism suggested to cause arrhythmias under these conditions is the mechanoelectrical feedback, that is the development of electrophysiologic and arrhythmogenic changes during or after changes in mechanical loading conditions.36,37 In hypertrophied myocardial cells, stretch-regulated channels could moderate currents by one or more of several mechanisms, including direct activation of an inward current or inactivation of an outward current, and favor the development of triggered upstrokes arising from early or delayed afterdepolarization.38-40

The progressive prolongation of the action potential is a hallmark of hypertrophied myocardium and the delayed repolarization provides a substrate for development of arrhythmias arising from triggered activity.39 Triggered activity is a pacemaker activity induced by afterdepolarizations that are transient depolarizing shifts in membrane potential occurring
either during the first part of repolarization (early afterdepolarization [EAD]) or after repolarization is complete (delayed afterdepolarization). Particularly, EAD could be involved in the genesis of malignant ventricular arrhythmias in LVH. The prolongation of both the action potential duration and the repolarization phase is the most prominent electrophysiologic abnormality of hypertrophic myocytes and the main step required for the appearance of EAD-induced triggered activity. The prolongation of the repolarization phase requires a reduction of the net outward ionic current, basically resulting from an increase of one or more inward currents (mainly due to Ca++ and Na+ currents), a decrease of one or more outward currents (mainly the Ikk and Ikl potassium currents) or both. The final result, in presence of a slow driving rate and a low extracellular potassium level, could be a depolarizing current carrying the charge for the EAD that can eventually result in a self-sustaining rhythm.

CLINICAL RELEVANCE OF SYNCOPE AND SUDDEN DEATH IN AS PATIENTS: POSSIBLE ROLE OF VENTRICULAR ARRHYTHMIAS

Syncope

Syncope is one of the cardinal manifestations of AS and its reported incidence, mostly during exercise, ranges from 14 to 25%. Despite its high prevalence, its pathogenesis has been controversial. Since Gallavardin first described syncope in AS patients with the classic physical findings of reduced systolic pressure, absence of pulses and apical impulse, and disappearance of murmurs with return to the baseline after recovery, various pathogenetic mechanisms responsible for syncope have been proposed. These include arrhythmias, left ventricular failure, carotid sinus hypersensitivity, conduction abnormalities and activation of cardiac mechanoreceptors.

At present, one of the most plausible pathogenetic mechanisms for syncope during exercise in AS patients is activation of left ventricular baroreceptors with concomitant arterial hypotension and consequent bradycardia. This hypothesis was derived from the observation in animal experiments that the increase in left ventricular pressure during exercise and the stimulation of intraventricular nonmyelinated C-fibers can promote reflex vasodilatation, hypotension, and bradycardia. This phenomenon, the Bezold-Jarisch reflex, can explain the pathogenesis of exertional syncope in AS patients. In fact, during muscular exercise, sensory receptors in skeletal muscle transmit impulses to the CNS to initiate vasodistraction. This excitatory reflex helps to maintain arterial pressure in the presence of metabolic vasodilatation in exercising muscle; therefore, during leg exercise, the somatic pressor reflex normally produces vasoconstriction in the resting forearm. Mark et al. in 1973, tested the hypothesis that this circuit was altered in patients with AS and syncope. They found that the forearm vasoconstriction response during exercise is inhibited or reversed and it usually normalizes after valve replacement. Richards et al. confirm this finding, studying AS patients with ECG, pulmonary, and systemic pressure monitoring during exercise and concluded that left ventricular baroreceptor stimulation is the underlying mechanism for syncope. Ross and Braunwald have shown that the average survival in AS patients after syncope is 3 years. Successful aortic valve replacement is generally associated with an improvement in symptoms and survival. Nevertheless, Sharma et al. have documented that syncope might not necessarily be eliminated by valve replacement. After aortic valve replacement, left ventricle mass regression and chamber remodeling appear to take place over months to years. In the early postoperative period, a reduction in afterload and an associated increase in fractional shortening may enhance the mechanoreceptor activation and therefore neurocardiogenic syncope, despite relief of outflow obstruction.

Furthermore, it is possible that reflex hypotension and bradycardia may sometimes induce a severe reduction in coronary perfusion of hypertrophied left ventricle and the consequent myocardial ischemia may trigger ventricular arrhythmias or bradyarrhythmias similar to those seen in acute myocardial infarction, even in absence of significant coronary artery stenosis.

Finally, it must be underlined that syncope in AS patients is not always associated with exercise and different pathogenetic mechanisms could be responsible, such as ventricular arrhythmias or conduction disturbances. The latter have been hypothesized on the basis of both the contiguity between valvular-perivalvular calcification and His-Purkinje system and the high prevalence of conduction disturbances (including left axis deviation, bundle branch block, and atrioventricular block) in AS.

Sudden Death

In adult AS, sudden death occurs in 15 to 20% of all patients at an average age of 60 years. Among symptomatic unoperated-on patients, sudden death occurs with a prevalence of 8 to 34%. However, sudden death in asymptomatic patients is uncommon; its incidence is reported to be 0 to 5% in adults and 7.5% in children.

At present, the mechanism of sudden death in AS...
is still unknown, although substantial data attribute a possible role either to an abnormal Bezold-Jarisch reflex with hypotension and bradycardias or to malignant tachycardias. Furthermore, LVH increases myocardial oxygen consumption while reducing coronary blood flow reserve. This supply-demand mismatch may predispose to myocardial ischemia and to malignant arrhythmias.

Von Olshausen et al recently examined Holter monitoring findings in seven patients with AS and sudden death. Six of them were due to ventricular tachyarrhythmias: monomorphic or polymorphic ventricular tachycardia or torsade de pointes. All seven patients exhibited signs of congestive heart failure. In this regard, sudden death appears to bear similarities to the mechanisms of sudden death in patients with other forms of systolic dysfunction. Accordingly, the authors hypothesized that ventricular arrhythmias in AS patients appear to be related to left ventricular dysfunction and might signal subclinical impairment of left ventricular function.

Influence of Aortic Valve Replacement on Ventricular Arrhythmias

Although aortic valve replacement usually results in a substantial clinical improvement and reduction in mortality, sudden cardiac death still remains a common cause of late death with an incidence of 8 to 44%. Studies have been carried out to identify preoperative or postoperative findings useful to predict the long-term survival and particularly the occurrence of sudden death following aortic valve replacement.

Frequent and complex ventricular arrhythmias have been related to reduced left ventricular ejection fraction and to elevated peak systolic wall stress in patients with AS who have not undergone surgery. Following aortic valve replacement, a strong relationship has been observed between complex ventricular arrhythmias and left ventricular performance. In fact, there is no increase in the frequency of premature ventricular contraction late after operation in patients with preoperatively normal left ventricular ejection fraction; furthermore, a trend toward a decrease in frequency and complexity of ventricular arrhythmias is observed if valve replacement is followed by a marked improvement of left ventricular function. 

Drug Therapy of Ventricular Arrhythmias in AS Patients

To our knowledge, no studies have been performed in AS patients either on the efficacy of antiarrhythmic therapy in suppressing ventricular arrhythmias or on the utility of pharmacologic treatment to prevent syncope or sudden death. It is well known that complex ventricular arrhythmias are infrequent in the absence of organic heart disease and, in this setting, they are probably not associated with an adverse outcome. Conversely, in patients with AS, the prognostic role of complex ventricular arrhythmias is still debated, although there is growing evidence that they are related to left ventricular function and can be involved in the genesis of sudden cardiac death. Symptomatic patients are at high risk of cardiac death, often sudden, and therefore valve replacement should be performed promptly. Nevertheless, in the presence of documented complex ventricular arrhythmias and signs of left ventricular impairment, antiarrhythmic therapy could be considered an option if valve replacement cannot be performed expeditiously. Furthermore, in elderly patients not amenable to surgical correction...
because of severe end-stage left ventricular dysfunction, antiarrhythmic drugs may suppress malignant ventricular arrhythmias.

In recent years, there has been growing concern about the proarrhythmic effects of class I antiarrhythmic agents in patients with left ventricular dysfunction.\textsuperscript{70,71} Attention has therefore begun to shift to antifibrillatory class III compounds, like amiodarone, essentially acting by prolonging myocardial repolarization and decreasing the dispersion of refractoriness with little or no effects on cardiac inotropism. The ability of amiodarone to decrease total mortality after myocardial infarction is documented as well as its peculiar antifibrillatory property in cardiac arrest survivors.\textsuperscript{72–74} Furthermore, the efficacy of amiodarone on mortality reduction has been tested recently also in patients with congestive heart failure with variable results.\textsuperscript{75,76} Nevertheless, it is our opinion that amiodarone with both its peculiar electrophysiologic properties and low negative inotropic effects could be used with caution to treat ventricular arrhythmias in the setting of moderate to severe left ventricular impairment due to AS.

However, it should be emphasized that to decrease the risk of sudden death in symptomatic patients with complex ventricular arrhythmias, valve replacement should be performed. Antiarrhythmic therapy with amiodarone could be considered, in our opinion, in patients with complex arrhythmias when surgical procedure is not an immediate option or in patients who are not deemed suitable operative candidates.

Recognizing that sudden death is rare in asymptomatic patients with AS, is there a role for “antiarrhythmic” therapy in asymptomatic patients with complex ventricular arrhythmias? In these patients, the detection of complex ventricular arrhythmias could indicate that the chronic pressure overload has already altered the electrophysiologic properties of the left ventricle. In fact, the progressive fibrosis occurring in AS patients may create the substrate for both current and late fatal ventricular arrhythmias. Theoretically, angiotensin-converting enzyme (ACE) inhibitors, if they are successful in slowing the progression of LVH, can potentially change the electrophysiologic property of myocardium.\textsuperscript{77} Recent studies on experimental models of AS showed that long-term therapy with ACE inhibitors can reduce myocyte hypertrophy and interstitial fibrosis.\textsuperscript{78,79} Furthermore, ACE inhibitors reduce the conduction velocity delay of hypertrophic myocytes decreasing their junctional gap resistance and improving the cell-to-cell coupling.\textsuperscript{80} These findings may lead to a decrease both in dispersion of refractoriness and in vulnerability to reentry arrhythmias.

Therefore, it could be hypothesized that in patients with noncritical AS, therapy with low doses of ACE inhibitors might lead to a substantial change in the arrhythmogenic substrate responsible for sudden death. Clearly, clinical studies must be performed to establish the safety and efficacy of this approach.

OTHER ‘PREDICTORS’ OF POOR PROGNOSIS AND SUDDEN DEATH IN AS PATIENTS

Identification of AS patients at high risk for sudden cardiac death is of paramount importance. Thus, there is increased interest in risk stratification techniques able to identify those patients at higher risk of sudden death even in the asymptomatic phase of the disease.

In the past few years, the detection of late potentials by signal-averaged ECGs has been considered a powerful means to identify patients at risk of life-threatening arrhythmias in heart disease of varying etiologies, being a sensitive noninvasive marker of arrhythmogenic substrate for reentry circuits.\textsuperscript{81–85} In 1987, Brune et al\textsuperscript{86} documented a higher prevalence of late potentials in hypertensive patients than in normal subjects. Recently Palatini et al\textsuperscript{87} studied 107 hypertensive subjects with LVH: the prevalence of late potentials was significantly greater than in control subjects (25% vs 6%) and was related both to the detection of complex ventricular arrhythmias on Holter monitoring and to the recording of impaired left ventricular filling on Doppler echocardiography.

We recently recorded signal-averaging ECG in a group of patients with severe isolated AS documenting a higher prevalence of late potentials than in control subjects (25% vs 4%)\textsuperscript{88} (Fig 1). No relation between late potentials and echocardiographic indexes of LVH was found. It is possible that the extent of fibrosis and the presence of electrophysiologically silent scars in subendocardium of AS patients could be responsible for areas of delayed myocardial activation detectable by signal-averaged ECG as a potential substrate for reentrant arrhythmias. Further studies on a larger group of patients with AS are needed to confirm our data and to evaluate the prognostic role of signal-averaged ECG.

Finally, the possible role of the autonomic nervous system in the genesis of sudden death in AS patients must be mentioned. Impaired autonomic control may be an independent risk factor for sudden cardiac death in patients with different heart diseases;\textsuperscript{89,90} in particular, in patients with coronary heart disease, an increase in sympathetic activity has been shown to be related to a decrease in the fibrillatory threshold of the ventricle.\textsuperscript{91} Recently, Mandawat et al\textsuperscript{92} documented that heart rate variability is significantly
reduced also in patients with LVH related either to hypertension or aortic valve disease. The authors were unable to demonstrate any association between impaired autonomic balance and prevalence of ventricular arrhythmias. The hypothesis that abnormalities of cardiac autonomic function may contribute to the mechanism of sudden death in patients with LVH needs to be verified.

**Conclusions**

Several studies have documented that the prevalence of ventricular arrhythmias is higher in AS patients compared with control subjects. Less clear and still debated is the clinical relevance and the prognostic role of ventricular arrhythmias in the natural history of adult AS. Substantial data point out that severity of ventricular arrhythmias could be related to the underlying left ventricular performance more than to the valvular disease per se. There is evidence that in a small group of patients, particularly those with left ventricular dysfunction and symptoms of congestive heart failure, ventricular arrhythmias may be involved in the genesis of syncope or sudden death. Other studies have not implicated ventricular arrhythmias as playing an important role in sudden death in AS patients. Furthermore, there is general agreement that development of symptoms in patients with severe AS is an indication for valve replacement considering the high mortality rate observed in these patients. Because valve replacement is indicated in symptomatic AS patients, it is extremely difficult to study prospectively the prognostic role of ventricular arrhythmias without valve replacement. Conversely, in asymptomatic patients, the prognosis is excellent, sudden death as a first symptom is unusual, and cardiac surgery should not be considered until symptoms develop. However, this recommendation does not consider the theoretical disadvantages of waiting for symptoms in terms of long-term survival after surgery. In fact, myocardial fibrosis proceeds rapidly in the presence of severe AS, may persist for years after valve replacement, and may produce an arrhythmogenic substrate for current and late fatal arrhythmias. At present, the best predictor of sudden death in patients with severe AS is still the development of symptoms. However, detecting myocardial fibrosis in asymptomatic patients could be important in reducing the incidence of sudden death. In this setting, a possible role could be played by recording of late potentials. By detecting the increased interstitial fibrosis of the left ventricle as zones of myocardial activation delay, they could become noninvasive markers of arrhythmogenic substrate also in patients with AS, as well as in other diseases. Therefore, an early identification of LVH and/or dysfunction by echocardiogram associated with the recording of both late potentials and complex ventricular arrhythmias could identify a small group of patients with AS.
in whom aortic valve replacement may be indicated even during the asymptomatic phase of disease. This approach needs to be verified in larger groups of patients.

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