Review of Published Cases of Syncope and Sudden Death in Patients With Severe Aortic Stenosis Documented by Electrocardiography

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The ECG findings during sudden collapse (syncope or sudden death) in severe aortic stenosis (AS) are not well defined. We conducted a comprehensive review of the literature for ECG data during sudden collapse in patients with AS and provided a case report of our own. There were 37 published cases of syncope or sudden death in patients with severe AS which were documented by ECG. Brady- or ventricular arrhythmias were documented in 34 cases (92%). Bradyarrhythmia (n = 24; 71%) was more common at the time of collapse than ventricular tachyarrhythmia (n = 10; 29%). There was slowing of the sinus rate before bradyarrhythmia in the vast majority of patients with bradyarrhythmia but not in those presenting with ventricular tachyarrhythmia (75% vs 0%; p <0.001). ECG evidence of ischemia (ST-segment depression or elevation) was present in most patients with bradyarrhythmia but not in those with ventricular tachyarrhythmia (75% vs 0%; p = 0.011). In conclusion, our findings suggest that left ventricular baroreceptor activation plays a dominant role in the pathophysiology of sudden collapse in patients with severe AS and suggest that ischemia may play a role as well. **(Am J Cardiol 2021;148:124−129)**

Sudden collapse is an ominous finding in a patient with severe aortic stenosis (AS). The most feared outcome is sudden cardiac death. Despite the many advances in the evaluation and treatment of AS over the last century, sudden death remains a significant cause of mortality in these patients. Here we present the case of a patient who experienced sudden cardiac arrest during a treadmill exercise test and was found to have severe AS. We reviewed the literature for ECG data to gain potential insight into the mechanisms of sudden collapse in patients with AS. While cases of sudden collapse during ECG recording are rare, several have been observed in patients with AS over the years. ECG findings at the time of collapse include normal sinus rhythm, sinus bradycardia, varying degrees of A-V block, asystole, idioventricular rhythm, and ventricular arrhythmias.

Case Presentation

A 65-year-old man with known hypertension, hyperlipidemia, and exertional chest "tightness" for 3 months presented with witnessed syncope while carrying groceries up one flight of stairs. Cyanosis was noted by a witness during this event. Afterward the patient experienced nausea and lightheadedness for 5 to 10 minutes. His symptoms completely resolved after receiving intravenous fluids in the emergency department. Electrocardiogram (ECG) in the emergency department demonstrated normal sinus rhythm with minimal 0.5 mm ST depression in the inferior leads (II, III, aVF).

Prior to work-up for a valvular etiology, he was referred for stress testing with myocardial perfusion imaging for evaluation of angina pectoris and underwent exercise testing using a standard Bruce protocol. He had appropriate heart rate response in Stage 1 and developed diffuse ST depression along with ST elevation in lead AVR. In stage 2, he developed a gradual decline in heart rate, resulting in sinus bradycardia. At that time, the patient complained of lightheadedness and the test was aborted. He lost consciousness shortly after he was lowered to a stretcher. ECG revealed asystole (Figure 1. **Panels A and B**). Chest compressions were immediately started and the patient received 2 doses of epinephrine (1 mg each) and 2 cycles of cardiopulmonary resuscitation (CPR, 2 minutes each). The patent regained full consciousness and was neurologically intact. Echocardiogram revealed a bicuspid aortic valve with severe stenosis (peak velocity 5 m/sec, peak gradient 101 mm Hg, mean gradient 66 mm Hg, and calculated aortic valve area of 0.56 cm^2). Coronary angiography revealed no coronary artery disease (CAD). He underwent uncomplicated surgical aortic valve replacement and was asymptomatic 20 months later.

Methods

We reviewed the literature using the PubMed database with the search terms "aortic stenosis + syncope" and "aortic

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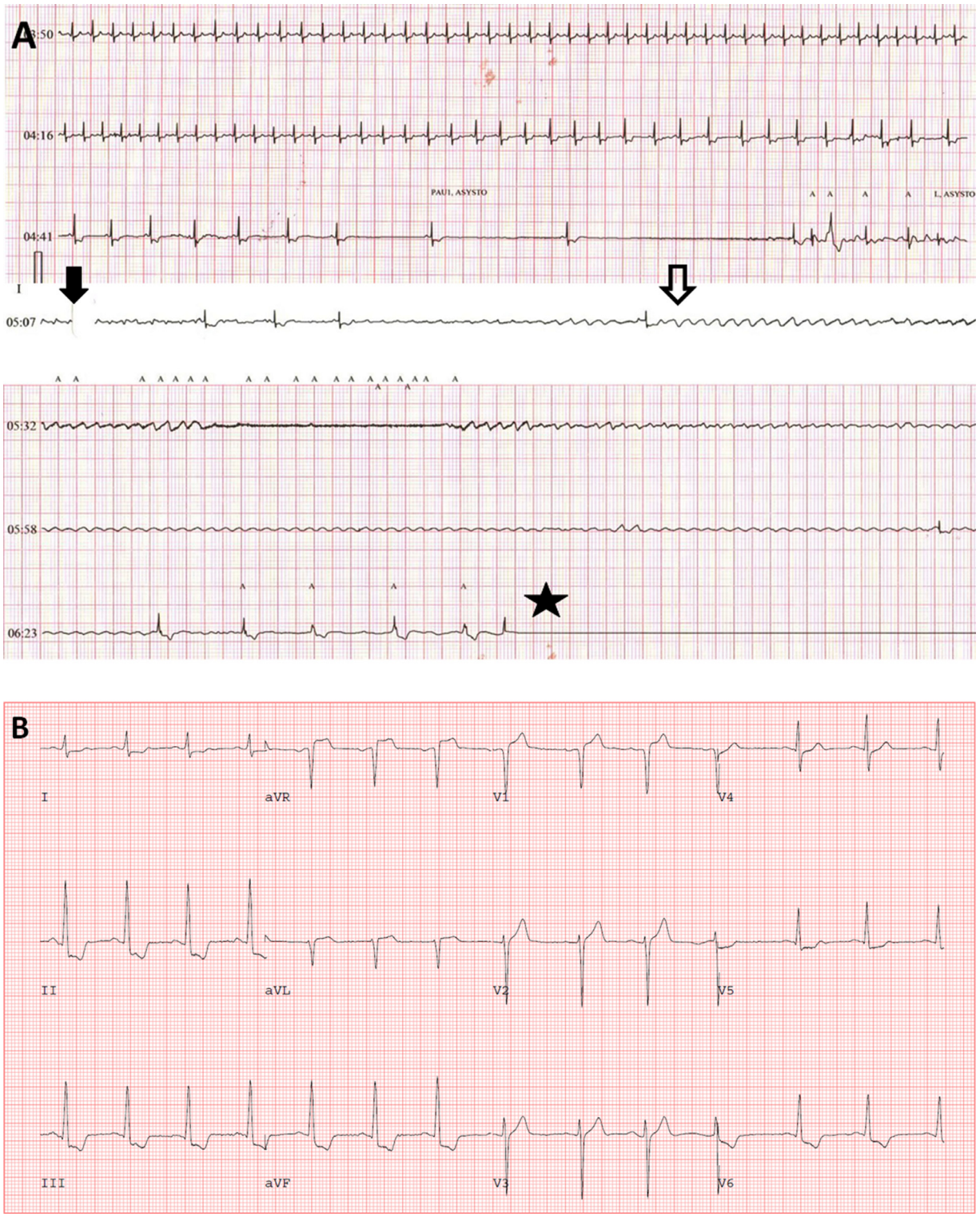

Figure 1. ECG recorded during Bruce Protocol Treadmill Exercise Testing. **Panel A.** The lead II rhythm strip begins in early Stage 2 in which sinus tachycardia and ST depressions are seen. Around 4 minutes and 20 seconds, the patient developed a gradual decline in heart rate, resulting in sinus bradycardia and prolonged sinus pauses. At that time, the patient complained of lightheadedness and the test was aborted. He lost consciousness shortly after he was lowered to a stretcher. ECG revealed asystole (solid arrow). Chest compressions were started immediately (artifact is demonstrated by the hollow arrow) and the patient received ACLS. The ECG became disconnected during CPR (star). He regained full consciousness about 4 minutes later. **Panel B.** 12-lead ECG recorded at 04:33 demonstrates slowing of sinus rate and ST changes.

stenosis + sudden death." For the purposes of our review, we considered syncope and sudden cardiac death on a spectrum of "sudden collapse" related to severe aortic stenosis, with similar underlying mechanisms. Abstracts were reviewed for relevance. References from included publications were also reviewed for relevance and considered for inclusion. Cases were included in our analysis if there was documentation of the event (syncope or sudden death) by ECG.

Two review authors independently examined the titles and abstracts of all the potential studies to be included, identified by the search strategy. Inconsistencies were resolved by a third author. Then, the complete text of the relevant primary studies was evaluated and data were extracted. The information about the authors, name of the article, journal, year, issue, and volume was included. The following data were retrieved from each case: age, sex, presenting symptoms, history of coronary artery disease, and ECG data including: rhythm at the time of collapse and presence or absence of preceding ST segment changes and/or slowing of the sinus rate prior to collapse.

The baseline characteristics for each case were extracted from the original manuscripts. The data from all cases reports were pooled. In this pooled cohort baseline characteristics were reported as frequency with percentage (%) for categorical variables and median with interquartile ranges for continuous variables. We used chi-square and Wilcoxon rank sum tests to evaluate for differences in categorical and continuous baseline characteristics, respectively. Analysis was performed in Stata software version 14.2 (StataCorp, College Station, Texas).

Results

Our search revealed 2,639 results for possible inclusion. We identified 37 cases which had either a published ECG at the time of collapse (30/37) or a clear description of the ECG at the time of collapse (7/37). The median age of the cohort was 64 years and 57 percent were men. In cases in which they were documented, classically taught cardinal symptoms of aortic stenosis were common with 86% (31/36), 36% (8/22), and 19% (4/21) percent of patients having documented symptoms of syncope, angina, or heart failure, respectively. 34 of 37 cases (92%) had clear documentation of either bradyarrhythmia or ventricular arrhythmia at the time of collapse and were further analyzed. Of 3 cases which were excluded, normal sinus rhythm was present in 2 and both "ventricular standstill'' and "ventricular arrhythmia'' were documented in 1. Individual case details including the presence of published EKG can be found in Supplemental Table 1.[1–22]

In this series, bradyarrhythmia (24/34; 71%) was more common at the time of collapse than ventricular tachyarrhythmia (10/34; 29%). Patients presenting with bradyarrhythmia were more likely to have a history of syncope than those presenting with ventricular tachyarrhythmia (96% vs 67%; $p = 0.02$). Preceding slowing of the sinus rate was also present in the vast majority of patients presenting with bradyarrhythmia and absent in those presenting with ventricular tachyarrhythmia (75% vs 0%; $p < 0.001$). Signs of ischemia defined as preceding ST-segment deviation (i.e., ST-segment depression or elevation) were present in the vast majority of patients presenting with bradyarrhythmia and absent in those presenting with ventricular tachyarrhythmia (75% vs 0%; $p = 0.01$). Our results are summarized in Table 1.

Discussion

The main findings of this study are three-fold. First, to our knowledge the current study is the first to demonstrate that bradyarrhythmias, rather than ventricular arrhythmias are more commonly documented at the time of collapse in patients with significant aortic stenosis. Second, our study demonstrates that the source of bradycardia is most likely extrinsic (i.e., secondary to increased vagal tone) rather than intrinsic (i.e., secondary to native conduction system disease). This is highlighted by the finding that 75% of patients with bradyarrhythmia had preceding slowing of the sinus rate prior to collapse. Lastly, we demonstrate a potential role of ischemia, as documented by the frequent occurrence of ST segment deviation (i.e., depression or elevation in 75% of cases) in patients presenting with bradyarrhythmia. Notably, the latter two findings were absent in patients presenting with ventricular arrhythmia and suggests that ventricular arrhythmias likely occur from a different mechanism.

Several suggestions have been made regarding the mechanism of sudden collapse in patients with severe AS. Johnson AM. was the first to highlight the role of left ventricular (LV) "baroreceptors" in the initiation of syncope and sudden death in patients with aortic stenosis.[23] Current evidence suggests that when LV mechanoreceptors located in the inferolateral wall are activated, impulses travel via vagal afferent fibers to the medulla resulting in inhibition of sympathetic tone and parasympathetic stimulation.[24] Similar to the carotid or aortic baroreceptors, the LV mechanoreceptors respond to elevation in systolic pressure by eliciting bradycardia and hypotension (Figure 2). Such a reflex in patients with severe aortic stenosis may lead to a deleterious cascade of events ultimately leading to circulatory collapse.[25,23]

The role of the LV "mechanoreflex" in the pathophysiology of aortic stenosis has been demonstrated in numerous studies.[23,24,26,27] Paradoxical peripheral vasodilation was shown to occur in patients with AS during exercise as opposed to vasoconstriction in patients without AS.[26] The same mechanism has also been shown to be a cause of hypotension related to inferior/inferolateral myocardial infarction (MI) or ischemia, exhaustive exercise, vasovagal syncope, the bradycardia of digitalis, nitrates or other drugs, and bradycardia experienced during coronary angiography.[23,27]

The role of ischemia in patients with significant AS is multifaceted. Firstly, coronary flow reserve has been demonstrated to be abnormal in patients with significant AS, history of angina, and no CAD as demonstrated by Fallen et al[28]. Second, ischemia has been shown to trigger hypotension via reflex pathways as demonstrated in patients with frequent coronary vasospasm during periods of documented inferior or inferolateral ischemia as opposed to other regions of the heart.[27] Given the diffuse subendocardial ischemia that frequently occurs with exertion in patients with AS, ischemia may serve as a second stimulus of vagal afferents arising from the left ventricle further predisposing these patients to sudden collapse. This theory is

Table 1
Characteristics of patients with bradyarrhythmia vs ventricular arrhythmia

Variable	Level	Bradyarrhythmia	Ventricular arrhythmia	p value
		N = 24	N = 10	
Age, median (IQR)		65 (60, 68)	62 (51, 67)	0.49
Women/men		13 (54%)	5 (56%)	0.94
		11 (46%)	4 (44%)	
Prior syncope	Absent	1 (4%)	3 (33%)	0.022
	Present	23 (96%)	6 (67%)	
Angina pectoris	Absent	10 (59%)	4 (80%)	0.39
	Present	7 (41%)	1 (20%)	
Prior congestive heart failure	Not available	9 (38%)	3 (33%)	0.067
	Absent	14 (58%)	3 (33%)	
	Present	1 (4%)	3 (33%)	
Presentation	Sudden death	5 (21%)	4 (40%)	0.25
	Syncope	19 (79%)	6 (60%)	
Prior myocardial infarction/presence of obstructive coronary artery disease	Not available	11 (46%)	5 (50%)	0.52
	Absent	9 (38%)	2 (20%)	
	Present	4 (17%)	3 (30%)	
Angina pectoris (before or after event)	Not available	8 (33%)	5 (50%)	0.62
	Absent	8 (33%)	3 (30%)	
	Present	8 (33%)	2 (20%)	
Slowing of sinus rate preceding collapse	Not available	4 (17%)	8 (80%)	<0.001
	Absent	2 (8%)	2 (20%)	
	Present	18 (75%)	0 (0%)	
ST segment deviation*	Absent	5 (25%)	3 (100%)	0.011
	Present	15 (75%)	0 (0%)	

* ST Segment criteria: elevation of ≥0.2 mV or depression ≥0.1 mV in ≥2 contiguous leads.

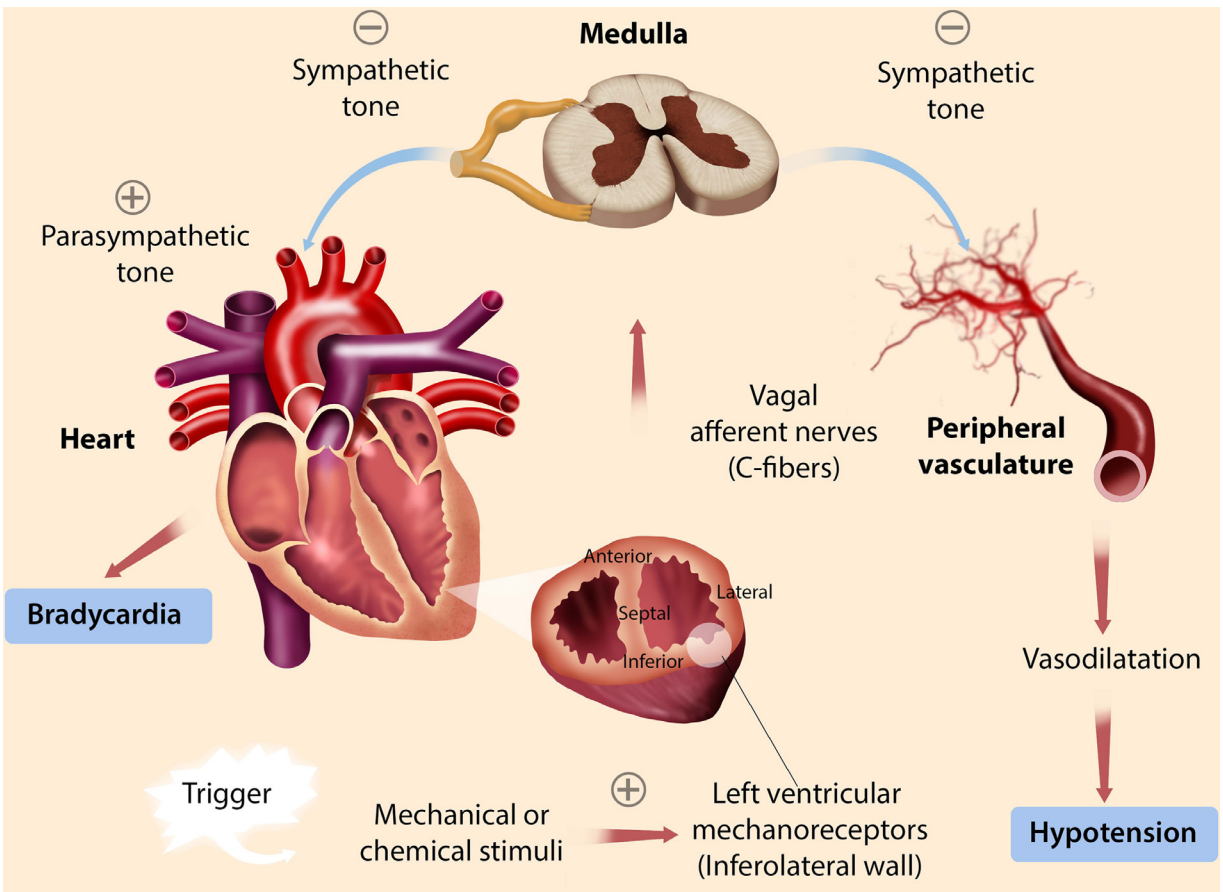

Figure 2. The left ventricular mechanoreflex pathway.

supported by findings in the current study that ST-segment depression or ST-segment elevation were present in the vast majority of patients presenting with bradyarrhythmia and absent in those presenting with ventricular tachyarrhythmia (75% vs 0%; p = 0.011).

The minority (29%) of patients in our study presented with ventricular arrhythmias. While ventricular arrhythmias are known to occur in patients with CAD and LV dysfunction, there is an increased incidence of complex ventricular arrhythmias in patients with severe AS and no CAD when compared with normal subjects.[29] The chronic pressure-overload state of AS along with hypertrophy of the ventricle lead to increased wall stress and reduced capillary density per unit mass of myocardium. This ultimately leads to diffuse subendocardial ischemia and may serve as a nidus for ventricular arrhythmia.

Our retrospective study has several limitations. It is subject to publication bias, missing data, and other inherent limitations of a retrospective cohort study composed of the heterogeneous publications included. However, the authors feel our cohort to be the most complete collection of documented ECG evidence during syncope or sudden death in patients with aortic stenosis. The authors acknowledge these limitations, but also highlight that the findings are supportive of the known pathophysiology of aortic stenosis from extensive basic science and clinical studies.

Our comprehensive review of the literature is the first of its kind to detail the ECG findings in reported cases of patients with severe AS and sudden collapse. In our review, the majority of patients presented with bradyarrhythmias, rather than ventricular arrhythmias. Preceding slowing of the sinus rate was seen in 75% of patients with bradyarrhythmia. Our findings suggest that the source of bradycardia is most likely extrinsic (i.e., secondary to increased vagal tone) rather than intrinsic (i.e., secondary to native conduction system disease) and support the role of the LV mechanoreflex in the pathophysiology of sudden collapse from AS. Lastly, our findings support the role of ischemia as a second trigger (in addition to pressure overload) in triggering the LV mechanoreflex. Notably, the latter two findings were absent in patients presenting with ventricular arrhythmia and suggests that ventricular arrhythmias likely occur from a different mechanism. Most importantly, this manuscript demonstrates that caution is warranted in administering beta blockading medications to patients with severe AS as they are prone to bradyarrhythmias.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.023.

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