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Educational Case

Educational Case: Aortic valve stenosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.sciencedirect.com/journal/academic-pathology/about/pathology-competencies-for-medical-education-pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Cardiovascular-heart, Valvular dysfunction, Aortic stenosis, Hypertrophy, Adaptation, Cellular response to injury

Primary objective

Objective CH5.1: Valve Stenosis. Discuss the underlying causes, clinicopathologic features, and complications associated with cardiac valvular stenosis.

Competency 2: Organ System Pathology; Topic: Cardiovascular-Heart (CH); Learning Goal 5: Valvular Dysfunction.

Secondary objective

Objective ACD1.1: Adaptation. Discuss the pathogenesis of hyperplasia, hypertrophy, atrophy, and metaplasia, and compare and contrast their possible physiologic and pathologic causes.

Competency 1 Disease Mechanisms and Processes; Topic: Adaptation and Cell Death (ACD); Learning Goal 1: Cellular Response to Injury.

Patient presentation

A 54-year-old man is brought to the emergency department following an episode of brief loss of consciousness, while running six blocks to catch the bus. Fortunately, there was someone at the bus stop who witnessed his fall and called for help. The patient has never experienced anything like this before. However, when asked about his medical history, the patient shares that over the past year, he has been feeling fatigued and slightly out of breath with occasional palpitations, especially when exercising, which he thought was due to aging. The patient does not exercise as much as he would like to, but when he does get the chance, he often has to stop to catch his breath. The patient has no known current medical conditions, and the only medication that he takes is a daily over-the-counter multivitamin.

Diagnostic findings, Part 1

The patient's blood pressure is 148/62 mmHg, his pulse is 84 beats per minute, his temperature is 98.6 °F (37 °C), his respiratory rate is 18 breaths per minute, and his SpO2 is 98%. On physical examination, the patient is awake, alert, and oriented. He does not appear to be in acute distress. The patient's skin is warm, pink, and dry. The patient's head is normocephalic and atraumatic. The chest wall is symmetric and normal in appearance. On cardiac exam, a harsh systolic crescendo-decrescendo murmur is best heard at the right upper sternal border in the second intercostal space, with radiation to the carotids. Pulses are weak, with a slight delay from the radial to the femoral pulse. There are no signs of trauma or respiratory distress. The lung sounds are clear in all lobes

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bilaterally without rales, rhonchi, or wheezes. Motor function is normal with muscle strength 5/5 bilaterally to upper and lower extremities. Sensation is intact bilaterally. Cranial nerves 1–12 are intact. No gait abnormalities are appreciated.

Questions/discussion points, Part 1

What is considered in the differential diagnoses for this patient?

This patient experienced syncope, a transient loss of consciousness with spontaneous recovery. The differential diagnosis follows the four general causes of syncope: neuronal, orthostatic, cardiogenic, and idiopathic.[2]

What is the etiology of neuronal syncope?

Neurally mediated syncope, also known as reflex syncope, occurs when there is a failure in the autoregulation of blood pressure, allowing for decreased cerebral perfusion and transient loss of consciousness. The most common form of neurally mediated syncope is known as vasovagal syncope. These episodes are triggered by stressors, such as fear, pain, or intense emotion. Other forms of neurally mediated syncope include situational syncope and carotid sinus hypersensitivity.

What is the etiology of orthostatic syncope?

Orthostatic syncope is caused by cerebral hypoperfusion prompted by rapidly standing from a seated or supine position or by standing for a prolonged period of time. Standing causes blood to pool in the lower extremities, resulting in decreased venous return, which in turn results in decreased cardiac output. Healthy patients trigger a rapid sympathetic response to compensate for this; however, patients with slowed sympathetic responses will experience a sudden decrease in blood pressure, which causes reduced perfusion that can result in syncope. This can occur in an illness of autonomic dysfunction, volume depletion, and endocrine dysfunction; it is more common in older patients.

What is the etiology of cardiogenic syncope?

Cardiac syncope can be divided into two subcategories: abnormalities in electrical conduction or abnormalities in structure. Abnormalities in electrical conduction cause dysrhythmias, in which the heart pumps in an irregular pattern, resulting in decreased cardiac output. There are certain classes of drugs that have been known to cause syncope due to dysrhythmias, such as tricyclic antidepressants, antiarrhythmics, and sympathomimetics.[3] Similarly, structural abnormalities of the heart can result in decreased cardiac output by preventing blood from flowing efficiently.

What is the etiology of idiopathic syncope?

Idiopathic syncope is a term that is used to describe a spontaneous syncope without a known cause. Up to 50% of syncopal episodes remain idiopathic.[2]

What is the most likely cause of syncope in our patient?

Our patient is a healthy 54-year-old man who fainted after running six blocks to catch a bus. In this patient who had a syncopal episode after running several blocks, vasovagal syncope is unlikely because he did not experience any of the known triggers. Orthostatic syncope is unlikely because it did not occur immediately after standing, or after standing in one place for a prolonged period. Therefore, cardiac syncope remains the most likely cause of the patient's syncope. This is further supported by the findings on the physical exam, including a heart murmur, palpitations, and a late and weak pulse, commonly referred to as “pulsus parvus et tardus.” This means that on physical examination, the pulse is not as strong as expected and late relative to the heart's contraction, hence it is called weak (parvus) and late (tardus).

What is the next step to confirm our presumptive diagnosis?

An echocardiogram is the next best step to confirm the diagnosis. Using ultrasound technology, an echocardiogram can examine all four chambers of the heart for structural abnormalities. It also can assess wall movement and measure blood flow very accurately. In our patient, this may either rule out cardiac pathology as a cause for the syncope or provide conclusive details on the cardiac pathology.

Diagnostic findings, Part 2

An echocardiogram is performed, which reveals an aortic valve with moderate calcifications. The valve is bicuspid. The aortic-valve area is mildly decreased to 1.6 cm^2. Peak velocity across the valve is increased to 2.9 m/sec, with mean gradient increased to 24 mmHg. Ejection fraction is within the normal range at 55–60%. The tricuspid, pulmonary, and mitral valves are unremarkable. The left ventricle shows moderate concentric hypertrophy. The left atrium is normal in size. The right ventricle is normal in size and function.

Fig. 1 is an echocardiographic image of the left ventricular outflow tract in the parasternal long axis view. The thickened, echogenic aortic valve cusps are due to calcification and stenosis. The restricted mobility and distortion of the valvular apparatus result in a decreased aortic valve area.

Questions/discussion points, Part 2

What is the significance of the echocardiogram findings?

This echocardiogram supports the cardiac etiology for the syncope and provides evidence of a specific structural pathology. Three pathological changes occur in valve stenosis; the aortic valve area decreases while maximum velocity and mean gradient increase. According to the 2020 American College of Cardiology/American Heart Association

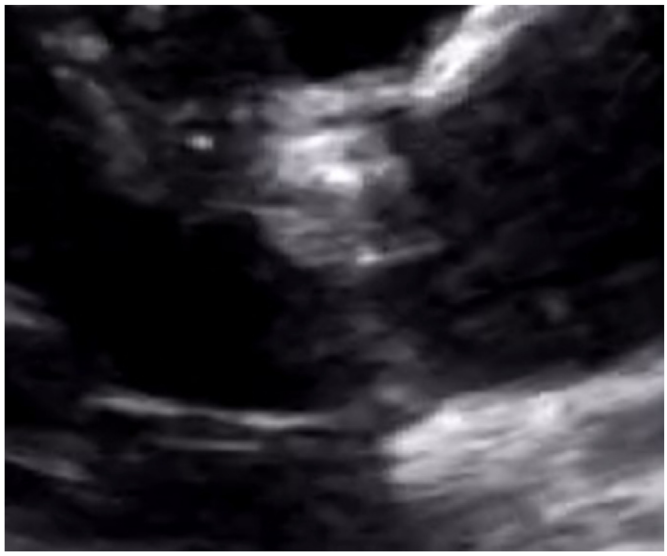

Fig. 1. Echocardiogram in the parasternal long axis view showing thickened, echogenic aortic valve cusps. Please note that image was taken from a patient with senile aortic stenosis, however, the thickened, calcified cusps would appear similarly in our fictional patient with bicuspid aortic stenosis. Image courtesy of David Carroll. Carroll D, aortic stenosis (transthoracic echocardiography). Case study, Radiopaedia.org (Accessed on 02 Oct 2024) https://doi.org/10.53347/rID-63358 Permalink: https://radiopaedia.org/articles/89930, rID:89930.

Joint Committee on Clinical Practice Guidelines, the cut-off for mild and severe aortic stenosis are aortic-valve area $\geq$1.5 cm^2 (mild) and $\leq$1.0 cm^2 (severe); peak velocity $\geq$2.0 m/s (mild) and $\geq$4.0 m/s (severe); and mean gradient of <20 mmHg (mild) and $\geq$40 mmHg (severe).[4] Our patient would therefore be classified as having mild aortic stenosis. Additionally, moderate concentric hypertrophy was noted on the echocardiogram, which is in no way pathognomonic of aortic stenosis; however, it is commonly a result of aortic stenosis.

Aortic stenosis is a structural disease whereby it is more difficult for the blood in the left ventricle to enter the aorta. As we explained earlier, the decreased cardiac output can lead to inadequate cerebral perfusion and syncope, especially upon exercising.

What adaptive process is responsible for the patient's myocardial enlargement?

Both hypertrophy and hyperplasia are ways by which cells respond and adapt to changes in their environment. Both can be physiologic, such as a response to endurance training and pregnancy, or pathologic, such as in response to chronic hypertension and aortic stenosis. Hypertrophy is an increase in the size of the existing cells due to increases in cellular material, without any increase in the number of cells. In the case of myocytes, the increased cellular material consists of additional sarcomeres. Hyperplasia is an increase in the number of cells. Often, hyperplasia and hypertrophy coexist and are triggered by the same external stimulus. In our case, however, cardiac muscle is not capable of hyperplasia since myocytes are nondividing cells. Therefore, the heart can adapt only by hypertrophy. More specifically, our patient was found to have concentric hypertrophy.

Other adaptive processes include atrophy and metaplasia. Atrophy refers to a decrease in size or number and metaplasia refers to replacement of one mature epithelium with another. These terms do not pertain to the adaptive processes seen in this case.

What is concentric hypertrophy and what are some possible causes of concentric hypertrophy?

Concentric hypertrophy occurs when sarcomeres are added in parallel as a means to increase contractile strength of the cardiac muscle. With this form of hypertrophy, the muscular walls of the heart enlarge, resulting in a smaller lumen. Fig. 2 shows this form of hypertrophy with a side-by-side image of a normal heart. As the myocytes enlarge due to the increased stress, the left ventricular wall thickness increases while the lumen decreases. Left ventricular thickness of greater than 1.5 cm on gross examination supports a diagnosis of left ventricular hypertrophy. Concentric hypertrophy is necessary for the heart to overcome impedance to forward flow. This is a common complication of long-standing, untreated hypertension where the heart needs to pump harder to overcome the increased afterload. Sarcomeres can also be added in parallel in certain disease states, such as in hypertrophic cardiomyopathy, as described below.

In contrast, eccentric hypertrophy occurs when sarcomeres are added in series, resulting in an enlarged heart with an expanded lumen. Eccentric hypertrophy is an adaption that occurs in response to an increased fluid load. This commonly occurs in diseased states with inadequate pumping, such as systolic heart failure or regurgitation.

Why is aortic stenosis associated with concentric hypertrophy?

Due to the unforgiving stenotic aortic valve, the pressure in the left ventricle needed to open the valve is increased. In response to the increased pressure demand, the myocardium adapts by adding sarcomeres in parallel in order to increase contraction and pressure, resulting in left ventricular concentric hypertrophy. This occurs in all three of the main causes of aortic stenosis that are discussed below.

What is the typical pathogenesis of aortic stenosis?

Aortic stenosis develops due to the valves being subject to constant mechanical stress, particularly at the hinge points, which causes wear and tear and collagen breakdown. The process begins with endothelial injury due to mechanical stress and allows for progression of lipid deposition, inflammation, fibrosis, and calcification.[5] Over time, due to the repeated scarring and healing, more and more of the functional valve is replaced by nodular calcific deposits. In most cases, this is a slow process that usually does not present until 70 years of age, but it can be accelerated in certain abnormal states, as will be described below. Fig. 3, taken during the heart examination of an autopsy patient, shows pathological findings similar to those described in our fictional patient. Note the bicuspid valve with calcific deposits forming small, round, well-circumscribed nodules on the valve leaflets. These calcific nodules cause the cusps to become rigid and more difficult to open. Valve replacement or balloon valvuloplasty are effective treatments for

Fig. 2. Cross-section of a heart with concentric hypertrophy compared to a normal heart. The thickness of the muscular left ventricular wall increases, and the volume of the lumen decreases. LVH, Left Ventricular Hypertrophy. "PEIR Digital Library". Pathology Education Instructional Resource. Published, 1 August 2013, Accessed, 9 Jun 2024, < https://peir.path.uab.edu/library/picture.php?/11101/search/3157> © Copyright UAB Department of Pathology. All rights reserved.

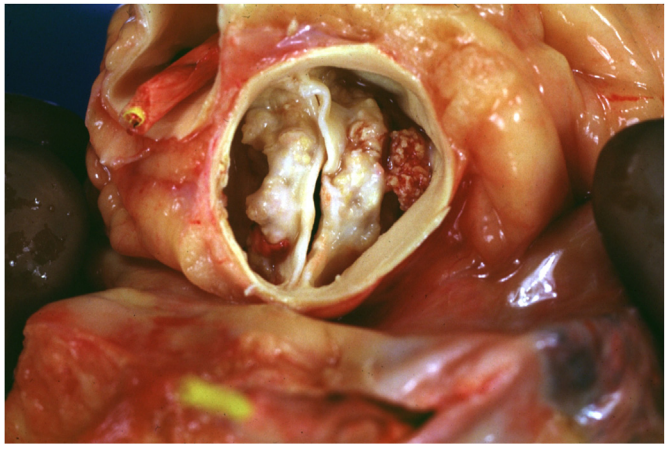

Fig. 3. Calcifications on this bicuspid aortic valve form multiple small nodules on both cusps. These cause the cusps to become rigid and difficult to open. "PEIR Digital Library". Pathology Education Instructional Resource. Published, 1 August 2013, Accessed, 9 Jun 2024, <https://peir.path.uab.edu/library/picture.php?/2076/tags/123-aortic_stenosis_bicuspid> © Copyright UAB Department of Pathology. All rights reserved.

valvular stenosis and should be recommended to patients experiencing significant symptoms of aortic stenosis, such as syncope, angina, and congestive heart failure.[6] These symptoms are discussed below.

Why did our patient develop stenosis at a relatively young age?

The echocardiogram showed a bicuspid aortic valve (BAV). Instead of the typical 3 semilunar leaflets of the aortic valve, our patient only has 2 functional leaflets. Patients with BAV are more susceptible to aortic stenosis, leading them to become symptomatic at younger ages. This can possibly be attributed to bicuspid valves being subject to greater levels of mechanical stress because there is less surface area to share the impact of the valves closing against each other. In fact, calcified BAV comprises roughly 50% of aortic stenosis found in adults.[7,8]

BAV is the most common congenital cardiac defect,[8,9] with a prevalence in the general population of 1–2%.[10,11] BAV is associated with a number of congenital or hereditary diseases such as ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, Turner syndrome, and Marfan syndrome.[11] Additionally, loss-of-function mutations in *NOTCH1* have been associated with BAV in a few families.[12]

What are the three common causes of aortic stenosis?

As shown in Table 1, there are 3 common causes of aortic stenosis: senile (degenerative) aortic stenosis, bicuspid aortic stenosis, and rheumatic heart disease (postinflammatory scarring).[13]

Senile (degenerative) aortic stenosis is the typical chronic scarring of the valve due to recurring scarring and healing. As the name suggests, the stenosis typically manifests in these patients at an older age (70s and 80s). The prevalence of 80-year-old patients with aortic stenosis was found to be roughly 10%.[14]

Bicuspid aortic stenosis has a very similar pathophysiology to senile (degenerative) aortic stenosis; however, since these patients have valves that incur more stress than the typical valve, the stenosis typically manifests at a relatively younger age (40s and 50s). Similarly, unicuspid aortic valve, a rare congenital malformation, may cause aortic stenosis at even younger ages than those with bicuspid aortic valves.[15]

Rheumatic heart disease is an immune-mediated disorder that may occur following *Streptococcus pyogenes* (GAS) infection in the pharynx or skin. While the exact disease mechanism is not fully understood,[16] antibodies formed against the M protein found in GAS may cross-react with proteins found in heart valves, which leads to valvulitis. The chronic healing and scarring that ensue can cause the valves to fuse, resulting in bicuspid valves and possibly even a unicuspid valve, hence it is sometimes referred to as an acquired bicuspid aortic valve. While it most commonly affects the mitral valve, the aortic valve can also be affected. Rheumatic heart disease is no longer very common in the United States; it is more often found in underdeveloped countries.

Fig. 4 is a computerized rendering comparing a normal aortic valve with the three common causes of aortic stenosis.

Table 1
Common causes of aortic stenosis.

	Senile (degenerative) aortic stenosis	Rheumatic aortic stenosis	Bicuspid aortic stenosis
Cause	Chronic recurrent scarring and healing	Autoimmune injury of the heart valves following group A *Streptococcus*	Congenital defect.
Pathological changes	Hardened, scarred, and calcified tricuspid valves	Inflammation and scarring causes fusion of valves, resulting in an acquired bicuspid valve	Hardened, scarred, and calcified bicuspid valves.
Presentation	Patient is typically older (70's and 80's)	Most commonly affects the mitral valve. Patient may be middle aged (40s and 50s). More commonly seen in underdeveloped countries.	Patient may be middle age (40s and 50s).
Complications	Long standing aortic stenosis can result in cardiomegaly, syncope, angina, and congestive heart failure		

What are potential sequelae of aortic stenosis?

Longstanding aortic stenosis can result in cardiomegaly, syncope, angina, and congestive heart failure.

Syncope is due to the stenotic aortic valve resisting forward flow into the aorta and systemic circulation, resulting in decreased cardiac output. During exercise, there is a greater oxygen demand, and if the stenotic valve prevents adequate oxygenated blood from entering systemic circulation and meeting the increased oxygen demand, hypoperfusion and syncope can ensue.

Concentric hypertrophy can occur as an adaptation to meet the increased pressure required to pump out blood, as explained above. In turn, this decreases the compliance of the left ventricle and causes increased pressure in the ventricle for any given amount of fluid, resulting in increased left ventricular end-diastolic pressure. Diastolic pressure is the driving force for blood to enter the coronary arteries. However, the elevated left ventricular end-diastolic pressure opposes this forward flow, resulting in decreased stroke volume that leads to decreased perfusion of the coronary arteries. In addition, the number of capillaries is not proportionately increased in pathologic cardiac hypertrophy, further decreasing supply of oxygen. If perfusion to the myocytes becomes severely diminished, the patient will experience angina.

Congestive heart failure due to aortic stenosis can be both systolic and diastolic. Systolic heart failure may occur due to the outflow obstruction, resulting in heart failure with a reduced ejection fraction. Diastolic heart failure may occur due to the decreased compliance as a result of

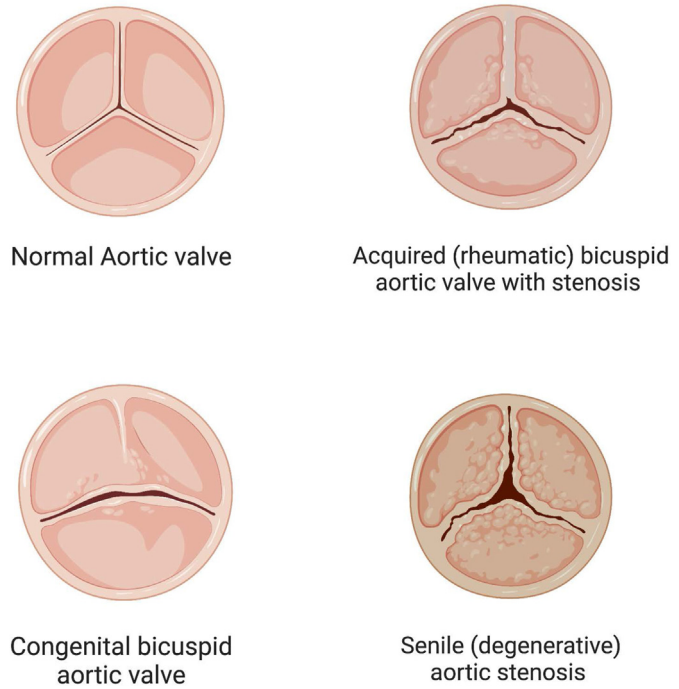

Fig. 4. Computerized rendering, created with BioRender.com, comparing a normal aortic valve to the valves found in bicuspid aortic stenosis, senile (degenerative) aortic stenosis, and rheumatic heart disease. Fusion of the commissures is seen in congenital bicuspid aortic valve and also in acquired rheumatic stenosis. However, the former is due to improper formation of the commissure during development, while in the latter it is acquired due to chronic healing and scarring.

concentric left ventricle hypertrophy, which causes increased pressure for any given amount of fluid in the ventricle. This can lead to pressure and fluid backup into the left atrium and the pulmonary veins, causing pulmonary edema.

What conditions can mimic aortic stenosis?

Hypertrophic cardiomyopathy is a genetic disorder that results in thickening of the myocardium. It is often the result of autosomal dominant mutations in genes encoding proteins of the sarcomere, such as the MYH7 (β-myosin heavy chain) and MYBPC3 (myosin binding protein C) genes. These mutations lead to asymmetric septal hypertrophy with a thickened myocardium, especially in the region of the interventricular septum, causing obstruction of the left ventricular outflow tract. Additionally, due to the decreased space for the blood to travel, there is increased velocity due to the continuity equation, $A_1V_1 = A_2V_2$. The increased velocity, along with the negative pressure that is generated, cause the anterior leaflet of the mitral valve to be pulled towards the septum, further blocking the outflow of blood. This outflow obstruction presents with a similar murmur and similar symptoms to aortic stenosis.

How can we differentiate aortic stenosis from hypertrophic cardiomyopathy on physical exam?

These two pathologies can be differentiated in conditions of decreased preload. In aortic stenosis, the murmur will become softer with decreased preload because there is less blood being forced through the stenotic valve. In contrast, the murmur in hypertrophic cardiomyopathy will become harsher with decreased preload. This is because the obstruction of the outflow tract in hypertrophic cardiomyopathy is partially mitigated by distension of the heart due to increased ventricular pressure. Thus, with decreased preload, the heart is less distended, and the murmur paradoxically becomes harsher. Therefore, we can ask the patient to perform the Valsalva maneuver to help differentiate between the two pathologies. In the Valsalva maneuver, a forced exhalation against a closed airway increases the thoracic pressure, causing decreased venous return and a decreased preload.

Teaching points

- Multiple complications are associated with longstanding, untreated aortic stenosis, including cardiomegaly, syncope, angina, and congestive heart failure
- There are 3 general causes of aortic stenosis: senile (degenerative) aortic stenosis, bicuspid aortic stenosis, and rheumatic heart disease
- The pathogenesis of aortic stenosis is due to the heart valves being subject to constant mechanical stress, which causes collagen breakdown with repeated scarring, healing, and calcium deposition
- Senile (degenerative) aortic stenosis is a chronic process and thus typically manifests in older patients, in the eighth or ninth decade of life
- Bicuspid aortic valves are subject to greater levels of mechanical stress and are thus more prone to developing aortic stenosis at younger ages. Bicuspid aortic stenosis can become symptomatic in the fifth or sixth decade of life
- Aortic stenosis requires a higher pressure in the left ventricle in order to get the blood out of the heart and into systemic circulation
- Hypertrophic cardiomyopathy should not be confused with concentric hypertrophy. Hypertrophic cardiomyopathy is caused by mutations in genes encoding proteins of the sarcomere and results in hypertrophy that is most pronounced in the interventricular septum. Concentric hypertrophy is an adaptive response to increased afterload, and hypertrophy is found in the luminal walls
- Hypertrophic cardiomyopathy can mimic aortic stenosis on physical exam. We can differentiate between these 2 pathologies via the Valsalva maneuver
- Hypertrophy is enlargement of the cells; hyperplasia is an increase in the number of cells. Myocytes are nondividing cells and are thus not capable of hyperplasia, rather they adapt to an increased demand for contraction by undergoing hypertrophy
- There are 4 general causes of syncope: cardiogenic, neural, orthostatic, and idiopathic. Of the known causes of syncope, vasovagal episodes are the most common

Declaration of competing interest

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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