A 71-year-old man with a history of hypertension, hyperlipidemia, and bicuspid aortic valve endocarditis treated with prosthetic valve replacement in 2012 presented to the internal medicine clinic for his annual physical examination. His home medications included aspirin (81 mg), pantoprazole (40 mg), paroxetine (37.5 mg), rosuvastatin (20 mg), and terazosin (10 mg) daily. Review of systems was notable for increasing exertional and supine shortness of breath. He also reported occasional chest discomfort on the right side with and without exertion. He had no fevers, chills, diaphoresis, palpitations, syncope, abdominal pain, changes in his bowel/urinary habits, or skin abnormalities.

Vital signs included blood pressure of 118/62 mm Hg, a bounding pulse rate of 93 beats/min, temperature of 36.8 °C, and oxygen saturation of 96%. On physical examination, the patient was a well-appearing man in no acute distress. His skin was warm, and no thyromegaly, cervical adenopathy, carotid bruit, or jugular vein distention was noted. Cardiovascular examination revealed normal rate and regular rhythm; the S1 and S2 were normal, but a notable grade 2/4 early diastolic decrescendo murmur was detected, most prominently heard over the right second intercostal space. Pulmonary examination revealed bilateral lower lobe rales. His abdomen was soft and nontender with normal bowel sounds. He was alert and oriented. Because of the presence of a new diastolic murmur and symptomatic congestive heart failure on examination, he was advised to go to the emergency department.

1. Which one of the following is the most likely cause of this patient’s diastolic murmur?
   a. Pulmonary regurgitation (PR)
   b. Aortic regurgitation (AR)
   c. Aortic stenosis (AS)
   d. Mitral stenosis
   e. Mitral regurgitation

Cardiac auscultation serves as the most widely used method of screening for valvular heart diseases. Murmurs are described by their shape (ie, crescendo, decrescendo, both, or continuous), the timing in systole or diastole, location and pitch, and audible intensity grade. A heart murmur may be benign or indicate valvular or structural abnormalities of the heart. Diastolic murmurs, however, are almost always pathologic.

The most common causes of diastolic murmurs are PR and AR. Pulmonary regurgitation is described as an early decrescendo blowing diastolic murmur. Pulmonary regurgitation is most commonly caused by pulmonary hypertension.

The diastolic murmur of AR tends to be a high-pitched diastolic decrescendo murmur that begins with A2. Its duration in diastole depends on whether the AR is acute or chronic as well as the severity of the regurgitation.

Differentiation of PR murmur from AR can be difficult by auscultation alone. The correlation of the patient’s history with the physical examination plays an important role. The presence of known aortic pathology in this patient makes AR the most likely cause of his diastolic murmur.

The murmur associated with AS tends to be heard over the right second intercostal space. The AS murmur is a harsh systolic ejection murmur and may be transmitted to the carotid arteries. Because the murmur in our patient is diastolic, AS is unlikely.

Mitral stenosis causes a mid-diastolic murmur with an associated rumbling characteristic and an opening snap. This murmur is best heard over the cardiac apex and not the right second intercostal space.
patient’s murmur was not associated with an opening snap.

Mitral regurgitation is characteristically a high-pitched holosystolic murmur best heard at the apex. Our patient’s murmur was diastolic rather than systolic.

In the emergency department, laboratory studies yielded the following (reference ranges provided parenthetically): hemoglobin, 12.1 g/dL (13.2 to 16.6 g/dL); leukocyte count, $6.8 \times 10^9$/L (3.4 to 9.6 $\times 10^9$/L); platelets, $256 \times 10^9$/L (135 to 317 $\times 10^9$/L); sodium, 136 mmol/L (135 to 145 mmol/L); potassium, 4.8 mmol/L (3.6 to 5.2 mmol/L); creatinine, 1.16 mg/dL (0.74 to 1.35 mg/dL); bicarbonate, 24 mmol/L (22 to 29 mmol/L); glucose, 99 mg/dL (70 to 140 mg/dL); serum urea nitrogen, 16 mg/dL; plasma lactate, 0.9 mmol/L (0.5 to 2.2 mmol/L); troponin T, 29 ng/L ($\leq 15$ ng/L); N-terminal pro-B-type natriuretic peptide, 4032 pg/mL ($\leq 103$ pg/mL).

2. Which one of the following is the best initial diagnostic test for investigation of heart murmur?
   a. Electrocardiography
   b. Transthoracic echocardiography (TTE)
   c. Chest radiography
   d. Cardiac magnetic resonance imaging (MRI)
   e. Cardiac computed tomography (CT)

   Although electrocardiography is excellent for aiding in the diagnosis of conduction disorders and acute myocardial infarction, it would not be the initial test to evaluate for structural heart issues. The presence of left ventricular hypertrophy with repolarization abnormality, however, would support the diagnosis of chronic AR.

   Echocardiography is the most appropriate test for the initial evaluation of a heart murmur. According to the 2020 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, TTE or transesophageal echocardiography (TEE) is essential not only for confirming the presence of the AR but also for determining the severity of the regurgitation and the etiology.

   It visualizes the aortic root and enables evaluation of left ventricular size and systolic function.\(^1\)

   Although chest radiography provides adjunctive information about the effects of valvular dysfunction (ie, diagnosis of heart failure), it does not provide diagnostic information with regard to the nature of valvular disease.

   Cardiac MRI is indicated if there has been inadequate evaluation of suspected valvular disease with TTE or TEE. It is not recommended as a first-line test.\(^2\) Similar to MRI, cardiac CT can be used to evaluate structural valve disease but is not considered a first-line study.

   The patient underwent TTE, which revealed severe aortic insufficiency, increased left ventricular size, and an ejection fraction of 46% (previously 55%). Electrocardiography revealed left atrial enlargement but no other notable abnormalities. Computed tomographic angiography of the chest to rule out pulmonary embolism yielded normal findings. The patient was admitted to the cardiology service for further monitoring. Lisinopril and furosemide were administered for his new-onset heart failure with subjective improvement in his symptoms of dyspnea. On day 2 of hospitalization, however, he had an acute increase in creatinine from his baseline of 1.16 mg/dL to 1.94 mg/dL.

3. Which one of the following best explains the increase in this patient’s creatinine level?
   a. Type 1 cardiorenal syndrome (CRS)
   b. Type 2 CRS
   c. Type 3 CRS
   d. Type 4 CRS
   e. Type 5 CRS

   Cardiorenal syndrome is a complex medical condition in which an insult to either the heart or the kidneys causes dysfunction in the other organ. The timing of the inciting event can be either acute or chronic and is dependent on multiple factors including hemodynamics, neurohormonal markers, and inflammatory signals.\(^3\)
Type 1 CRS is also known as acute CRS. It is caused by an acute heart failure exacerbation leading to an acute kidney injury (AKI). In the case of our patient, his increased creatinine level was likely caused by the administration of furosemide decreasing his preload. This decrease of his preload in the context of severe AR likely resulted in a lack of forward blood flow to the kidneys causing the AKI.

Type 2 CRS is also known as chronic CRS. It is a chronic state of heart failure that eventually causes chronic kidney disease (CKD) that results in the slow increase of creatinine over time. Type 2 CRS is unlikely to have been the cause of the acute creatinine rise in our patient because his creatinine level on admission was within normal limits. Given the acuity seen in our patient, type 1 CRS is more likely.

Type 3 CRS is also known as acute renal-cardiac syndrome. In this case, an AKI results in substantial volume overload resulting in an acute heart failure exacerbation. It is multifactorial, involving inflammatory markers and metabolic abnormalities with uremia. Because our patient’s symptoms of heart failure preceded his initial increase in creatinine, type 3 CRS is unlikely.

Type 4 CRS is also known as chronic renocardiac syndrome. It results from CKD leading to chronic heart failure. Over time, CKD will lead to left ventricular hypertrophy and cardiomyopathy. Our patient did not have baseline CKD, making type 4 CRS an unlikely cause of his increase in creatinine.

Type 5 CRS is also known as secondary cardiorenal syndrome. Secondary cardiorenal syndrome is caused by a systemic condition leading to reduction in cardiac and kidney function. Examples include sepsis, hypovolemic shock, or vasculitis. Our patient had no signs of another underlying systemic condition that would explain his kidney findings.

The patient’s diuretics were withheld, and dobutamine was administered for inotropic support to assist with increased renal perfusion. Once his AKI improved, he underwent cardiac catheterization, which identified nonobstructive coronary disease. Cardiac CT displayed normal coronary heights compatible for a valve-in-valve (ViV) procedure. His TEE was negative for signs of vegetations or paravalvular leak. On day 8 of hospitalization, he underwent the ViV replacement without complications.

4. Compared with this patient’s original valve replacement, which one of the following complications poses the highest risk following the ViV procedure?
   - a. Complete heart block leading to pacemaker implantation
   - b. Paravalvular leak
   - c. Annulus rupture
   - d. Coronary artery obstruction
   - e. Prosthetic valve endocarditis

The use of bioprosthetic valves has increased in the past few decades, resulting in an increased rate of valve degeneration and the need for reintervention. The ViV procedure has become one of the most preferably used methods since it was first performed in 2007. It is less invasive and safer than open heart surgery. The long-term outcomes have not been studied extensively.

The rigid stented valves protect the conduction system from compression with valve expansion leading to fewer heart blocks and the need for a pacemaker. The valves used in ViV procedures are more rigid and rounder in structure compared with the valves used in transcatheter aortic valve replacement. The rigid and round structure of the valve allows better fit and an appropriately positioned valve causing less paravalvular leak. It also provides more consistent anchoring; the risk of annulus rupture is less likely.

One of the most reported ViV procedural concerns compared with initial transcatheter aortic valve replacement is coronary obstruction. The obstruction is due to the bioprosthetic leaflets being pushed outward by the newly placed transcatheter heart valve. The outward push is caused by the grossly oversized transcatheter heart valve compared with the true internal diameter of the previously placed valve. It yields direct contact...
with coronary ostia or the sinotubular junction. This potential complication can likewise be due to patient-dependent anatomic factors such as low-lying coronary ostia or narrow sinotubular junction. To determine preprocedural risks for coronary obstruction, patients undergo coronary angiography before ViV procedures.

Prosthetic valve endocarditis is always a possible concern. However, the reported rates for ViV complications are not as well studied or documented as for coronary artery obstruction.

Postprocedural TTE identified a decline in the left ventricular ejection fraction to 40% with worsened anterior and septal wall motion abnormalities but improvement in the patient’s aortic insufficiency and the replacement valve in the correct location. Subjectively, he felt considerably better than on admission, and he was discharged to home with the addition of lisinopril (2.5 mg daily) and warfarin for 6 months.

5. Which one of the following procedures would warrant empirical antibiotic prophylaxis for this patient?
   a. Cardiac catheterization
   b. Colonoscopy with biopsy
   c. Endoscopic retrograde cholangiopancreatography
   d. Bone marrow biopsy
   e. Bronchoscopy with biopsy

Prosthetic heart valves confer one of the highest risks of complications if infective endocarditis occurs. Cardiac surgery, but not cardiac catheterization, would require antibiotic prophylaxis.

Colonoscopies with or without biopsy would not require antibiotic prophylaxis because the risk of bacterial translocation to the prosthetic heart valves is considered low. Endoscopic retrograde cholangiopancreatography is also considered a low-risk procedure that would not necessitate prophylaxis.

Bone marrow biopsies are considered low-risk procedures. However, if there are signs of infected skin or soft tissue above the biopsy site, then antibiotics against *Staphylococcus aureus* and β-hemolytic streptococci should be administered.

Antibiotic prophylaxis is recommended in patients undergoing bronchoscopy with planned biopsy. Patients who have a known respiratory tract infection undergoing this procedure should have empirical treatment guided toward viridans group streptococci.

Repeated TTE 6 months after discharge revealed substantial improvement in the left ventricular systolic function with a left ventricular ejection fraction of 53%.

**DISCUSSION**

Bioprosthetic valves are starting to be preferred over mechanical valves because they do not require lifelong anticoagulation, although the traditional recommendations favor the use of mechanical valves in younger patients (<55 years) because they can last longer. Bioprosthetic valves are prone to structural degeneration and can result in regurgitation, stenosis, or both. Prosthetic valve regurgitation can be symptomatic or asymptomatic depending on the severity, hemodynamics, and provoking factors. The typical auscultatory finding is early diastolic decrescendo murmur with a blowing character that can be heard well on the second right intercostal space and left sternum. Symptomatic patients can present with unexplained or new-onset heart failure or severe hemolysis. In those symptomatic patients, infective endocarditis should be kept in mind and excluded first. If it is suspected, antibiotic treatment should be initiated to avoid delay in surgical or transcatheter intervention. In symptomatic patients with prosthetic valve regurgitation, the appropriate management is correction of the underlying valve failure. Even in asymptomatic patients, replacement may be considered because of rapid disease progression. The backward flow of AR can cause systolic dysfunction and decrease in cardiac output. Type 1 CRS is associated with diminished end-organ perfusion secondary to acute decompensated heart failure. Management with inotropic agents can increase kidney perfusion and help improve this condition. In cases of AKI secondary to acute
valvular disease, kidney function improves after correction of the underlying structural abnormality.

For a long period of time, the standard practice of valvular reintervention was surgery. Given the drastic increase in the use of bioprosthetic valves and concomitant increase in the requirement of reoperation, less invasive procedures were developed. The transcatheter ViV procedure was first performed in Germany in 2007 for aortic valve replacement. Since then, it has become an attractive alternative for patients who are not candidates for surgery. The updated 2020 ACC/AHA guideline helped elucidate the choice of intervention between surgery or a ViV procedure. It was recommended to begin the evaluation with either TTE or TEE. If the patient is asymptomatic but has severe regurgitation, surgery is recommended (class 2a). In symptomatic patients, the surgical risk should be evaluated to decide the intervention modality. If there is low risk, surgical replacement is strongly recommended (class 1). In patients with high surgical risk or with paravalvular regurgitation, percutaneous repair is reasonable (class 2a). A ViV procedure can be chosen for patients with bioprosthetic valve regurgitation (class 2a). However, the final decision is based on shared decision making between the patient and the medical care team.

Valve-in-valve is a relatively new procedure, and its comprehensive long-term consequences are not fully understood. Nonetheless, the outcomes of current multicenter studies are promising, showing less risk of mortality and morbidity compared with reoperation. It is also associated with lower rates of paravalvular leak, need for a pacemaker, and annulus rupture compared with transcatheter aortic valve implantation for native aortic valves. Conversely, coronary artery obstruction is the most worrisome concern with aortic ViV procedures. The common mechanism behind it is the previously placed tissue valve leaflets being pushed outward by the new one. This leads to direct contact with coronary ostia or the sinotubular junction. In addition to procedure-dependent factors, patients might have anatomic differences that make them more prone to coronary artery obstruction after a ViV procedure. In order to evaluate for low-lying coronary ostia or narrow sinotubular junction, angiography is performed prior to ViV procedures, although it is not part of routine practice yet.

The follow-up of patients with prosthetic heart valves is defined in AHA/ACC guidelines. The first outpatient visit should be 6 weeks to 3 months after the procedure. Assessment of the valve function, whether there are signs of infection, conduction abnormalities, and myocardial ischemia/infarction should be the main focus in the first visit. The recommended imaging modality is TTE, which provides information regarding valvular structure and hemodynamics, possible leaks, the size of the ventricles, and systolic function. Afterward, routine follow-up visits should be scheduled annually. If patients have any auscultatory changes on examination or if they become symptomatic (ie, with symptoms of anemia or new-onset heart failure), a diagnostic work-up should be undertaken without waiting for the next appointment. The severity of regurgitation should be evaluated by looking at transvalvular velocities, valve areas, and pressure gradients.

POTENTIAL COMPETING INTERESTS
The authors report no competing interests.

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with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography.


CORRECT ANSWERS: 1. b. 2. b. 3. a. 4. d. 5. e