

# 70-Year-Old Woman With Sudden Onset of Chest Pain and Diaphoresis



Armando Villanueva, MD; Gaja Shaughnessy, MD; and Steven Ung, MD

**A** 70-year-old woman presented to the emergency department with sudden-onset chest pain of 3 hours duration. She described it as pressing, heavy, substernal with radiation to left shoulder, and associated with profound dyspnea, palpitations, and diaphoresis. Just before symptom onset, her dog had chased her cat, knocking over a birdcage, and causing her bird to escape. The discomfort began immediately after she attempted to corral her dog. She denied any change in her symptoms with exertion or rest. Her medical history was notable for a myocardial infarction requiring placement of right coronary artery drug-eluting stent. Her current pain differed from her previous ischemic event. Cardiac risk factors included age, hypertension, dyslipidemia, and a 45 pack-year smoking history. She denied any drug or alcohol use and attested to compliance with clopidogrel, statin, metoprolol, and aspirin.

Physical examination revealed an afebrile and anxious female with a heart rate of 80 beats per minute, a blood pressure of 124/76 mm Hg, breathing comfortably on room air. Cardiac examination disclosed warm extremities with trace symmetric peripheral edema and absent jugular venous distention. She had a regular rhythm, S1 and S2. A soft S3 was auscultated in the left lateral decubitus position and a II/VI early peaking systolic murmur at the left sternal border. Trace crackles were present at the lung bases. The rest of her examination was unremarkable.

Pertinent laboratory studies included a hemoglobin level of 11.6 g/dL (reference ranges provided parenthetically) (12.0-15.5 g/dL), white blood cell count  $6.1 \times 10^9/L$  ( $3.5-10.5 \times 10^9$ ), platelet count  $264 \times 10^9/L$  ( $150-450 \times 10^9$ ), creatinine 0.6 mg/dL (0.6-1.1 mg/dL), and troponin 0.29 ng/mL (0.0-0.1 ng/dL). Electrocardiogram (EKG) demonstrated a sinus rhythm with T-wave inversions in the precordial leads without any

ST-segment elevation or depression. During the evaluation, the patient expressed that the symptoms were constant and still present.

## 1. In this patient, which one of the following is the most appropriate next test?

- Serial EKGs and cardiac biomarkers
- Cardiac stress testing
- Computed tomography angiogram
- Cardiac catheterization with coronary angiography
- Echocardiography

Electrocardiograms and cardiac biomarkers are integral part of evaluation of a patient with chest pain. Electrocardiogram changes suggestive of ischemia are ST-segment elevation in 2 contiguous leads, new or downsloping ST depression in 2 contiguous leads, or T-wave inversion in 2 contiguous leads with prominent R. Electrocardiogram changes can, however, be a reflection of other processes as well, including pulmonary embolism, hypothermia, intracranial processes, electrolyte disturbances, and pericarditis/myocarditis. Cardiac biomarkers such as troponin and MB fraction of creatinine kinase are reflection of myocardial injury/ischemia. Cardiac biomarkers should be drawn at the first assessment and repeated at 3 to 6 hours because the values can be initially within normal limits and a rising pattern may aid in diagnosis of acute ischemia/injury. However, these biomarkers may be abnormal in other conditions as well, such as heart failure or renal disease.<sup>1</sup>

Stress testing is less useful in those with either a high or a low pretest probability because it is subject to more false negatives and false positives, respectively.<sup>2</sup> Previous studies have noted a 90% prevalence of angiographically confirmed coronary artery disease in patients who presented with typical angina.<sup>2</sup> A patient with significant

**See end of article for correct answers to questions.**

Resident in Internal Medicine, Mayo Clinic School of Graduate Medical Education (A.V., G.S.) and Advisor to residents and Consultant in Cardiovascular Diseases, Mayo Clinic (S.U.), Jacksonville, FL.

cardiovascular risk factors and typical angina may not be appropriate for stress testing, given the high pretest probability of obstructive coronary artery disease. In addition, for a patient who presents to the hospital with an acute coronary syndrome of chest pain and elevated biomarkers, stress testing is contraindicated.

The risk for a patient with a suspicion for pulmonary embolism is evaluated using the Well's score, which takes into account factors such as sedentary behavior, recent cancer and treatment, tachycardia, hemoptysis, and the likelihood of pulmonary embolus/deep venous thrombosis as the primary diagnosis among others to risk stratify the patients at the greatest risk for pulmonary embolus and in which further diagnostic studies such as a computed tomography angiogram should be performed. For those with very low risk, such as the case in our patient, no further diagnostic evaluation should be performed.

A patient who presents to the hospital with signs and symptoms concerning for acute coronary syndrome with associated elevated cardiac enzymes and ST-segment changes should be evaluated for coronary artery disease via cardiac catheterization with coronary angiography for assessment of critical stenosis or blockage. This also allows for early revascularization with percutaneous coronary intervention if indicated.<sup>1</sup>

The strength of echocardiography is the assessment of cardiac structure and function; in particular, myocardial thickness and motion. However, positive predictive value of echocardiogram in acute myocardial infarction is not high because wall motion abnormality can be caused by many other conditions including but not limited to old myocardial infarction, stunning, inflammatory, and infiltrative diseases, as well as cardiomyopathy. However, it may assess for other causes of chest pain such as pericarditis, valvular disease, and Takotsubo cardiomyopathy (TC), aortic dissection, or pulmonary embolism.<sup>1</sup>

Our patient had percutaneous coronary angiography, which demonstrated a patent stent in the right coronary artery, and a 20% stenosis of the left anterior descending artery. Otherwise, the left heart catheterization showed no significant stenosis or occlusion. The transthoracic echocardiogram noted an ejection fraction of 35% with new apical akinesis and hypokinesis of the anterior and

posterior midventricular segments without valvular abnormalities or a pericardial effusion.

**2. Which one of the following is the most likely cause of this patient's chest pain?**

- a. Acute coronary syndrome (ACS)
- b. Takotsubo cardiomyopathy
- c. Pericarditis
- d. Cocaine intoxication
- e. Spontaneous coronary artery dissection

Myocardial ischemia may present with substernal chest, upper extremity, mandibular, or epigastric discomfort, or an ischemic equivalent such as dyspnea. The chest pain typically worsens with exertion and improves with rest and nitroglycerin.<sup>1</sup> The chest pain can be associated with diaphoresis and shortness of breath. The ACS can be divided into 3 entities: unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Unstable angina is a new chest pain or a change in symptoms of stable angina without elevation in cardiac biomarkers. Typically, the pain occurs at rest and is more severe or can last longer than the typical exertional chest pain associated with stable angina. The hallmark of NSTEMI is elevation in cardiac biomarkers, indicating release of myocardial protein or enzymes without ST-segment elevation in EKG. STEMI is defined as myocardial ischemia with EKG changes notable for ST-segment elevation in 2 contiguous leads of at least 1 mm of vertical elevation from baseline and elevation in cardiac biomarkers.<sup>3</sup>

Takotsubo cardiomyopathy may present with chest pain or dyspnea, although nausea, vomiting, syncope, and palpitations have also been reported. Less frequently the initial presentations have been hypotension, shock, ventricular fibrillation, and cardiac arrest.<sup>4</sup>

The pain associated with pericarditis is generally pleuritic and positional, improved by sitting up or leaning forward. Patients may have a history of a recent viral infection. A triphasic pericardial friction rub is often present. Early EKG findings include diffuse concave ST elevation with PR-segment depression.<sup>5</sup>

Sympathomimetic drugs such as cocaine may cause a hyperadrenergic state, resulting

in chest pain due to arterial vasoconstriction and demand ischemia or stress cardiomyopathy.<sup>6</sup>

Spontaneous coronary artery dissection is a clinical entity that can be included in the ACS category. Although infrequent, this entity typically affects young healthy women. These patients typically present with acute chest pain and a STEMI on EKG, for which the mainstay of diagnosis is coronary angiography. Patients are treated either conservatively, with percutaneous coronary intervention, or with coronary artery bypass grafting.<sup>7</sup>

Considering our patient's symptoms, demographic characteristics, patent coronary arteries on coronary angiography, and echocardiographic findings, transient left ventricular apical ballooning syndrome was the most likely diagnosis.

The morning after admission to the cardiology service, our patient developed sinus tachycardia and symptomatic orthostatic hypotension with a sitting blood pressure (BP) of 130/80 mm Hg and standing BP of 110/70 mm Hg.

### 3. Which one of the following is the most common complication of TC?

- Congestive heart failure
- Left ventricular outflow obstruction
- Atrioventricular block
- Ventricular arrhythmias
- Atrial septal defect

Heart failure can occur with TC. Several studies have noted congestive heart failure as the most common complication from TC, with incidence ranging from 16% up to 20%.<sup>3,4</sup>

The transient hypokinesis or akinesis of the apical or midventricular segments of the heart, combined with an often hyperdynamic base, may lead to temporary dynamic left ventricular outflow tract obstruction in 18% of patients.<sup>3</sup> This may result in systolic anterior motion of the mitral valve and subsequent mitral regurgitation.

Electrical disturbances such as third-degree atrioventricular block, ventricular tachycardia, ventricular fibrillation, and cardiac arrest have been reported in about 14.6% of patients with TC. Although arrhythmias in general are rare occurrences in TC,

atrial arrhythmias such as atrial fibrillation and sinus node dysfunction can also be encountered.

Although atrial septal defects have not been reported as a complication of TC, rare but catastrophic cases of left ventricular free wall rupture have been encountered.<sup>3,4</sup>

Because of new symptoms our patient experienced, a repeat echocardiogram was performed and demonstrated a mild dynamic outflow tract obstruction with mild mitral regurgitation.

### 4. Which one of the following would be the next best step in managing this patient's condition?

- Dobutamine
- Metoprolol and intravenous fluids
- Intraaortic counterpulsation
- Phenylephrine
- Aspirin

Inotropic agents such as dobutamine can be considered in patients with hypotension and severe left ventricular dysfunction. However, if left ventricular outflow tract obstruction is present, the inotropic agents may worsen the obstruction and should not be used in patients with moderate to severe outflow tract obstruction.<sup>4</sup>

Similar to patients with hypertrophic cardiomyopathy, patients with dynamic left ventricular outflow obstruction benefit from beta blockade to slow the heart rate and increase diastolic filling. Despite a reduced ejection fraction from myocardial stunning, judicious fluid administration may be warranted in the absence of pulmonary edema. This may reduce the outflow obstruction by increasing cardiac filling and reducing the hypercontractility of the base of the left ventricle.<sup>3,8</sup>

In the absence of contraindications, cases of refractory cardiogenic shock may warrant temporary intraaortic counterpulsation.<sup>4</sup> However, aortic counterpulsation would not be the first-line treatment for orthostatic hypotension in an otherwise hemodynamically stable patient with transient left ventricular apical ballooning syndrome.

Severe hypotension in the setting of dynamic outflow obstruction may warrant phenylephrine administration to increase afterload and left ventricular cavity size and decrease the outflow

obstruction in a patient who is hemodynamically unstable. Phenylephrine can also be used as a second-line agent for patients with contraindications to beta-blockers and fluid administration.<sup>4</sup>

Although short-term anticoagulation with warfarin may be considered for patients with persistent systolic dysfunction to prevent ventricular thrombus formation and embolization, particularly in patients with persistent left ventricular dysfunction, no studies have actually evaluated the role of anticoagulation in TC.<sup>3</sup>

Our patient responded well to low-dose metoprolol and intravenous fluids. When starting a beta-blocker such as metoprolol, it is reasonable to start a low dose such as 12.5 mg twice a day and increase as tolerated by the BP. Our patient did well with the low-dose metoprolol and had resolution of tachycardia and hypotension.

**5. Which *one* of the following *best* describes the natural course and long-term prognosis of this patient's condition?**

- Recurrence is frequent
- Patients have a high in-hospital mortality rate
- Electrocardiogram findings during hospitalization predict long-term outcome
- Survival is similar to age-matched controls
- Myocardial function does not recover

Recurrence of TC is infrequent with a rate of only 2.9% per year in the first few years.<sup>9</sup>

In-hospital mortality rate was found to be only 2%, as compared with the reported 9% to 10% in-hospital mortality in patients with myocardial infarction.<sup>9</sup>

Neither troponin values, brain natriuretic peptide levels, nor EKG findings on admission predict 4-year survival of patients with TC.<sup>9</sup>

Mortality is not statistically different between age-matched controls and patients with TC.<sup>9</sup>

The time to recovery of left ventricular function averaged 2 weeks to 5 years in a meta-analysis.<sup>4</sup> In one series, the ejection fraction had returned to normal within 6 weeks after hospitalization.<sup>10</sup>

With supportive care, our patient's hemodynamic instability was short lived and she was discharged home. Repeat echocardiogram in 6 months showed return of her ejection fraction to her baseline.

**DISCUSSION**

Takotsubo cardiomyopathy is a reversible cardiomyopathy characterized by transient wall motion abnormalities of the apex and midventricular segments that extend beyond 1 coronary distribution. The name TC is derived from the traditional Japanese octopus trap, which resembles the left ventricular apical akinesis on echocardiography and left ventriculography. The syndrome is usually seen in postmenopausal females typically following a strong emotional or physical stressor.<sup>7</sup> As such, it has been nicknamed broken heart syndrome. About 38% of cases occur in the setting of acute medical illness or surgery.<sup>11</sup> Otherwise, preceding stressors vary wildly and include arguments, assaults, earthquakes, loss of loved ones, medical visits, and gambling losses.<sup>4,8</sup>

In patients presenting with ACS-like symptoms, the prevalence of TC was found to be 0.7% to 2.5%. Female predominance is 90.7% and the age of presentation ranges from 62 to 76 years.<sup>7</sup> Cases with patients aged 10 to 91 years have been described as well.<sup>11</sup>

The pathogenesis of this clinical entity remains unknown. Several mechanisms have been proposed, many focusing on the observed microvascular dysfunction and vasospasm associated with the surge in catecholamine release seen in other conditions such as cocaine intoxication and subarachnoid hemorrhage. Plasma catecholamine levels have been observed to be higher in TC than in cases of myocardial infarction.<sup>10</sup> The hypothesis is that circulating catecholamines cause either a sympathetically mediated microcirculatory dysfunction or direct myocardial injury through cyclic adenosine monophosphate mediated calcium overload, oxidative stress, or contraction band necrosis.<sup>4</sup> Hormonal changes in women, particularly decreased estrogen levels such as in postmenopausal women, have been hypothesized as to potentiate the catecholamine-mediated endothelial hypersensitivity and dysfunction.<sup>8</sup> However, the exact mechanism of myocardial stunning is yet to be elucidated.

Reports of myocardial biopsy in confirmed cases of apical ballooning syndrome

demonstrate nonspecific findings such as interstitial fibrosis and cellular infiltrates.<sup>6,10</sup>

A review of 28 case series of TC identified ST-segment elevation and T-wave inversion as the most common EKG findings (71%). T-wave inversion tends to occur in the subacute phase after initial ST elevation.<sup>12</sup> Another review of 17 patients found a transient prolongation of the QTc interval in all patients (median QTc interval of 500 ms).<sup>12</sup> Cardiac enzymes, including troponins, are mildly elevated in most cases.

Echocardiography and left ventriculogram during cardiac catheterization typically demonstrate apical and/or midventricular wall motion abnormalities that do not correlate with the distribution of a single major coronary distribution and hyperkinesis of the basal myocardial segments.<sup>11</sup>

Given the overlap in symptoms and diagnostic and laboratory findings between TC and ACS, most patients require coronary catheterization. Indeed the absence of significant atherosclerotic coronary disease is a defining characteristic of the syndrome. The Mayo Clinic Diagnostic criteria for TC require the presence of the 4 following criteria for diagnosis: transient hypokinesis or akinesis of the left ventricular midsegments or apex extending beyond a single coronary territory, new EKG abnormalities or modest elevation in cardiac enzymes, absence of pheochromocytoma or myocarditis, and absence of flow-limiting coronary disease or plaque rupture.<sup>3</sup>

Without concomitant complications or left ventricular outflow obstruction, care of patients with TC is mainly supportive. Although no randomized controlled trials have been performed, reports of this condition discuss treatments similar to heart failure with angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics. In a systematic review, it was noted that empirical use of angiotensin-converting enzyme inhibitors, calcium channel blockers, and beta-blockers was commonly associated with the idea of counteracting the presumed catecholamine-mediated myocardial stunning.<sup>4</sup>

In conclusion, most patients with TC have a good prognosis, with complete resolution of

transient myocardial stunning within a matter of days to weeks. Takotsubo cardiomyopathy should be considered in the differential diagnosis for episodes of chest pain associated with acute physical or emotional stressors when wall motion abnormalities do not correlate with anatomic findings on coronary angiography. Given the increasing frequency with which stress cardiomyopathy is being reported, it is imperative to be aware of TC.

**Potential Competing Interests:** The authors report no competing interests.

**Correspondence:** Address to Steven Ung, MD, Department of Cardiovascular Diseases, Mayo Clinic, 4500 San Pablo Rd S, Jacksonville, FL 32224 ([ung.steven@mayo.edu](mailto:ung.steven@mayo.edu)).

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