Cardiac complications of influenza infection in 3 adults

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A 57-year-old man was admitted to the coronary intensive care unit with severe pulmonary edema after a 5-day history of influenza-like illness. His medical history included previous tobacco use and a family history of early myocardial infarction. He had received the seasonal influenza vaccine in the fall before presentation.

On examination, he was in marked respiratory distress. His temperature was 38.4 °C, respiratory rate was 33 breaths/min, and oxygen saturation was 86% on 100% nonrebreather mask. His blood pressure and heart rate were within normal limits. Respiratory examination revealed diffuse bilateral crackles. An electrocardiogram (ECG) taken on admission showed left bundle branch block, and his cardiac troponin I level was 0.77 (normal < 0.07) µg/L. There was no previous ECG available for comparison. Echocardiography showed left ventricular dilatation, moderate hypokinesis with regional variability and an ejection fraction of about 30% (Figure 1). A radiograph of his chest showed left ventricular dilatation with air-space opacification consistent with moderate pulmonary edema. The differential diagnosis was viral myocarditis with heart failure, acute coronary syndrome with heart failure or community-acquired pneumonia with acute respiratory distress syndrome.

Despite supplemental oxygen and diuresis therapy, the patient’s hypoxemia worsened and intubation was required; high-frequency oscillatory support and norepinephrine for blood pressure support were also required. He was given empirical treatment with oseltamivir, ceftriaxone and azithromycin, and dual antiplatelet therapy (acetylsalicylic acid and clopidogrel).

On repeat testing, the patient’s cardiac troponin I level was 0.48 µg/L, and his creatine kinase level was 2561 (normal < 240) U/L. Influenza A (pH1N1) was detected in bronchoalveolar lavage samples by polymerase chain reaction. All other culture samples were negative. Repeat echocardiography showed no improvement in left ventricular function. His course in hospital was complicated by dyspnea, and magnetic resonance imaging showed a small lacunar infarct. He was discharged to a stroke rehabilitation centre 40 days after admission. A persantine cardiolite study performed on an outpatient basis did not show any cardiac ischemia but suggested possible prior myocardial infarction. Diagnostic coronary angiography showed mild to moderate plaque in several small branch vessels but no hemodynamically important atherosclerotic coronary artery disease.

In the second case, a 67-year-old woman presented to the emergency department with a 1-week history of cough and pleuritic chest pain. Her medical history included hypertension, dyslipidemia, diabetes, obesity and smoking, and she had a family history of coronary artery disease. She had not previously received influenza vaccine. In the emergency department, she had cardiac arrest with pulseless electrical activity that required intubation, mechanical ventilation and 10 minutes of cardiopulmonary resuscitation. An ECG obtained after the arrest showed 0.5 mm of ST-segment elevation in leads V1–V3 and ST-segment depression in the inferolateral lead distribution. Her cardiac troponin I level was elevated (0.51 µg/L). The patient was transferred to our facility for possible emergent percutaneous coronary intervention. Diagnostic coronary angiography showed normal coronary arteries, and left ventricular angiography showed an ejection fraction of about 40%, with anteropapical dyskinesis suggestive of apical ballooning. Her left ventricular function improved and she was discharged to a stroke rehabilitation centre 40 days after admission.

In the third case, a 57-year-old man was admitted to the coronary intensive care unit with marked respiratory distress. His temperature was 38.4 °C, respiratory rate was 33 breaths/min, and oxygen saturation was 86% on 100% nonrebreather mask. His blood pressure and heart rate were within normal limits. Respiratory examination revealed diffuse bilateral crackles. An electrocardiogram (ECG) taken on admission showed left bundle branch block, and his cardiac troponin I level was 0.48 µg/L, and his creatine kinase level was 2561 (normal < 240) U/L. Influenza A (pH1N1) was detected in bronchoalveolar lavage samples by polymerase chain reaction. All other culture samples were negative. Repeat echocardiography showed no improvement in left ventricular function. His course in hospital was complicated by dyspnea, and magnetic resonance imaging showed a small lacunar infarct. He was discharged to a stroke rehabilitation centre 40 days after admission. A persantine cardiolite study performed on an outpatient basis did not show any cardiac ischemia but suggested possible prior myocardial infarction. Diagnostic coronary angiography showed mild to moderate plaque in several small branch vessels but no hemodynamically important atherosclerotic coronary artery disease.

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Key points

- Cardiac conditions associated with influenza include myocarditis, pericarditis, myocardial infarction, congestive heart failure and sudden death
- Influenza-associated cardiac conditions are typically short-lived and reversible.
- During influenza season, nasopharyngeal swabs for influenza should be obtained from patients with cardiac illness if they have fever or any symptoms compatible with acute respiratory illness.
- Influenza vaccination may be associated with a reduction in the risk of cardiac events, but definitive studies are needed.
end-diastolic pressure was 17 mm Hg. The patient was thought to have moderate cardiomyopathy secondary to acute catecholamine-mediated injury (Takotsubo cardiomyopathy). The peak troponin I level was 2.36 µg/L, and the creatine kinase level was 1193 U/L. The patient’s ECG results normalized on day 2, and an echocardiogram obtained on day 5 showed normal left ventricular function, without evidence of apical ballooning.

A nasopharyngeal swab obtained on admission contained influenza A (pH1N1), as revealed by polymerase chain reaction. There was no other evidence of infection. A metabolic workup, including renal, liver and thyroid function, was within normal limits, and the patient reported no stressful emotional events before presentation. The patient remained hemodynamically stable in hospital, but she required treatment for acute respiratory distress syndrome. She was given oseltamivir for 10 days, transferred back to the referring facility on day 11, and discharged to a rehabilitation facility on day 32 without further cardiac complications.

In the third case, a previously healthy 25-year-old woman, who had not been vaccinated against influenza, presented to hospital with syncope and back pain on day 5 of an influenza-like illness. Physical examination was normal except for sinus tachycardia and dehydration. Chest radiographs and ECG were normal, her troponin T level was 0.04 (normal < 0.01) µg/L, and her creatine kinase level was 35 U/L. In the emergency department, she was given about 7 L of intravenous fluid for rehydration. Computed tomographic pulmonary angiography performed 18 hours after admission to rule out pulmonary embolism showed large bilateral pleural effusions and moderate pericardial effusion. Subsequent echocardiography showed a moderate-to-large circumferential pericardial effusion (maximum width 2 cm), without definite evidence of tamponade. A nasopharyngeal swab yielded influenza A (H3N2) by polymerase chain reaction and culture. The patient was given oseltamivir and discharged on day 5. Repeat chest radiography and echocardiography 7 days after discharge showed small residual pleural effusions and a substantial reduction in the size of the pericardial effusion.

### Discussion

The relation between cardiac disease and influenza is complex. Although infection due to human influenza is usually confined to the respiratory tract, myocarditis and pericarditis are well-recognized complications.1 The identification of influenza ribonucleic acid in endomyocardial biopsies suggests that myocarditis (including fulminant cardiomyopathy) complicating influenza is caused by disseminated influenza infection.2 The finding that influenza RNA has been identified in the myocardium in cases of sudden death,2 and a recent study reporting that 15.4% of deaths due to pH1N1 in the United States occurred at home,3 suggest that influenza infection may trigger arrhythmias and cardiac arrest. However, the incidence of myocardial involvement in influenza is not known. Older case series with results based on symptoms, ECGs, and measurements of creatine kinase and creatine kinase–muscle and brain (CK-MB) suggested that about 10% of infected individuals have some cardiac abnormalities.4 More recently, Greaves and colleagues5 found that creatine kinase was elevated in 8% of ambulatory young adults with laboratory-confirmed influenza (n = 152), but CK-MB was elevated in only 2%, and no patients had elevated levels of cardiac troponins. Similar data are not available for older adults or patients with influenza that required admission to hospital.

Many observational studies have reported consistent associations between influenza and acute myocardial infarction.6 A recent analysis by Warren-Gash and colleagues estimated that 3.1%–3.4% of deaths associated with myocardial infarction in England and Wales from 1998–2008 were attributable to influenza.7 In addition, randomized controlled trials provide some evidence that influenza vaccination may reduce the risk of myocardial infarction and cardiovascular death.8 The pathophysiology of this effect is not understood. Both clinically defined influenza-like illness and community-acquired pneumonia
are associated with significant rates of cardiac complications,8 and the association with influenza may be specific to infection, or some types of infection, rather than influenza itself.

Clinical course
As in the cases described in this report, symptoms associated with cardiac complications of influenza are typically (although not invariably) preceded by a 2- to 7-day history of influenza-like or upper respiratory illness. Most cases in Canada occur during a 10- to 18-week period of increased influenza activity (“influenza season”) each winter.10 Otherwise, the presentations are indistinguishable from cardiac presentations unassociated with influenza. In individual cases, it is not possible to distinguish complications of influenza from cardiac events temporally associated with incidental influenza infection. In myocarditis, common ECG findings include sinus tachycardia, heart block, ST elevation and T-wave inversion; typical echocardiographic findings include globally reduced left ventricular function and pericardial effusion with or without tamponade.

In most cases — as with the second and third patients in our report — cardiac involvement is relatively short-lived and reversible.11,12 In our first patient, left ventricular dysfunction persisted for 4 weeks after presentation, and echocardiography showed evidence of regional variability rather than global dysfunction, suggesting that the cardiac abnormality may have resulted from exacerbation of pre-existing coronary disease rather than myocarditis. However, data on the distribution of time to recovery from influenza myocarditis are sparse, and observational data have failed to identify prognostic indicators of time to recovery of left ventricular function after myocarditis.13

Prevention
In this series, 1 of the 3 patients had been vaccinated against influenza. Influenza vaccine prevents about 60% of uncomplicated symptomatic influenza in healthy younger adults (18–64 yr) and is more effective in preventing severe disease and complications than in preventing uncomplicated disease.14 Vaccination is less effective in high-risk and older adults ( 65 yr).15 Although vaccination prevents enough illness and death to be cost-saving to the health care system, many older or chronically ill adults who are vaccinated still require admission to hospital for influenza and its complications. A Cochrane review concluded that there are insufficient data to draw firm conclusions on the effect of vaccination in preventing cardiac complications.8

Management
All of the patients in this report were given antiviral treatment. Whether such treatment is of benefit in preventing or improving the outcome of influenza-associated cardiac dysfunction has not been established. In randomized controlled trials, early treatment of influenza in young healthy adults significantly reduced both viral shedding and the duration and severity of symptoms.16 In more severely ill patients with influenza, recent cohort studies have suggested that early antiviral therapy improves clinical outcomes and shortens hospital stay but that late therapy may still provide a treatment benefit.17,18 For these reasons, expert guidelines recommend that adults admitted to hospital with suspected or confirmed influenza — either seasonal or pH1N1 — receive antiviral treatment. Moderately ill outpatients, especially those with risk factors for severe illness, and those whose condition is deteriorating may also benefit from antiviral therapy.19,20

Conclusion
There are many presentations of influenza-associated cardiac dysfunction. During influenza season, complications of influenza may be difficult or impossible to distinguish from primary cardiac disease with incidental influenza. Recognizing the community level of influenza activity and the presence of prodromal symptoms of upper respiratory illness may help clinicians determine which patients require influenza testing. Identifying influenza may be of benefit, both because antiviral therapy may improve patient outcomes and because additional infection-control precautions may prevent transmission of influenza to other patients and staff.

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