Acute chest pain is a major complaint quite commonly presented at emergency departments. A differential diagnosis of acute chest pain includes various disease entities, including some life-threatening disorders. Of these, acute coronary syndrome garners much clinical attention and forms a specific disease that includes a critical ST-segment elevation myocardial infarction and a less severe form of non-ST-segment elevation myocardial infarction and unstable angina. As an urgent and life-threatening disease leading to a high morbidity and mortality, accurate diagnosis of acute coronary syndrome remains a clinical challenge. Efficient management of this syndrome may rely on a quick yet accurate diagnosis. A high misdiagnosis rate and inappropriate discharge rate for acute coronary syndrome are still observed, especially in the elderly population, owing to a higher prevalence of atypical symptoms presented in this group. Moreover, the existence of high comorbidities in the elderly population makes effective clinical approach complicated. A delay in the identification and treatment may lead to worse outcomes in this patient population. The underlying pathophysiology and exact mechanisms are various. Patient evaluation strategies are currently being developed, as are new diagnostic facilities aimed at preparing physicians for urgent intervention in a more cost-effective manner. [International Journal of Gerontology 2010; 4(1): 1–8]
chest pain, Canto et al.\textsuperscript{8} found that in 434,877 patients diagnosed with MI, up to 33% did not present with typical chest pain. Therefore, early and accurate diagnosis of ACS is fundamental for subsequent effective therapy. A recent multinational, prospective, observational study suggested that there is a higher rate of atypical presentation in the elderly population leading to a worse prognosis\textsuperscript{9}. Patients with ACS discharged from the ED without an accurate diagnosis had a mortality rate nearly twice the mortality rate of those admitted to a hospital\textsuperscript{10}. In fact, dyspnea has been identified as the most frequent symptom of myocardial ischemia in patients older than 85 years\textsuperscript{11}. Age itself, together with sex and a family history of early coronary artery disease, is an important risk factor for ACS\textsuperscript{12}. In addition, both the prevalence and severity of coronary artery disease increases with the aging process, as well as morbidity and mortality\textsuperscript{13,14}. It remains very difficult to decide whether patients should stay longer in the ED or if more extensive investigations are warranted, especially for the elderly with multiple potential comorbidities. According to previous studies, patients with ACS inappropriately discharged from the ED generally have a worse prognosis owing to a possible delay in the implementation of effective therapeutics and the risk of sudden death\textsuperscript{8,15,16}.

In this article, we sought to review the prevalence and prognosis of atypical chest pain in the elderly population. In addition, we discussed the possible underlying mechanisms and recent advances in diagnostic tools and strategies that may help early identification of the higher risk groups. These innovations should help minimize the potential for misdiagnosis and inappropriate discharge of elderly patients with ACS who present with atypical symptoms.

**Differential Diagnosis of Acute Chest Pain in the ED**

Common causes of chest pain include those stemming from cardiac or noncardiac causes. Simple history taking, including gathering information about lifestyle, smoking and past medical history, provides important hints to discern possible acute coronary events during the preliminary assessment. Disorders related to the pulmonary, gastrointestinal and musculoskeletal systems and cardiac origins are all possible causes of chest pain symptoms. A cost-effectiveness analysis revealed that esophageal sources especially gastroesophageal reflux diseases were identified most frequently in patients presenting with acute chest pain in EDs\textsuperscript{17}. Chest pain suggestive of cardiac origin may refer to those with a sensation of chest compression, squeezing, or a penetrating sensation in the internal side or localized behind the sternum. Panju et al.\textsuperscript{18} reported the likelihood ratios for ACS based on clinical features including location, past medical history, associated symptoms, and hemodynamic findings (Table). In addition, pain radiating to the left shoulder, neck, jaws, teeth or arm regions with aggravated intensity or accompanied with sweating over a period of time may indicate an ischemic nature\textsuperscript{7,19}. Swap and Nagurney\textsuperscript{20} reported that pain that radiated to both arms/shoulders or exacerbated by exertion or physical efforts may show a likelihood ratio of ischemic coronary events of 2.3–4.7. Conversely, atypical chest pain may refer to a sharp, tingling, “burning” sensation or may be associated with meals, localized to a small point or area or pain that can be elicited by direct pressure, touch or postural changes. Pain accompanied by fever or a history of past chest pain not originating from a cardiac source may help identify noncardiac causes. Recent guidelines from the American College of Cardiology and American Heart Association provide some useful information on identifying noncardiac origin ischemic episodes\textsuperscript{21}.

Common causes of chest pain emanating from cardiac causes other than coronary events include pericardial or valvular heart diseases. Patients with pericarditis accompanying pleuritis may experience sharp

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Likelihood ratio (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>Pain in chest or left arm</td>
<td>2.7\textsuperscript{1}</td>
</tr>
<tr>
<td>Chest pain radiation</td>
<td>2.8 (1.7–3.1)</td>
</tr>
<tr>
<td>Left arm</td>
<td>2.8 (1.7–3.1)</td>
</tr>
<tr>
<td>Both left and right arms</td>
<td>7.1 (3.6–14.2)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>1.5–3.0\textsuperscript{8}</td>
</tr>
<tr>
<td>Association with nausea or vomiting</td>
<td>1.9 (1.7–2.3)</td>
</tr>
<tr>
<td>Association with diaphoresis</td>
<td>2.0 (1.9–2.2)</td>
</tr>
<tr>
<td>Hypotension (systolic blood pressure &lt; 80 mmHg)</td>
<td>3.1 (1.8–5.2)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Adapted from reference 18; \textsuperscript{1} data not available to calculate confidence interval; \textsuperscript{2} in heterogeneous studies, the likelihood ranges are reported as ranges.
pain during breathing and coughing. Valvular heart diseases such as severe aortic valve stenosis or subaortic stenosis may also induce chest pain in the elderly, whereas a young subject suffering atypical chest pain with palpitations may have mitral valve prolapse disease. Common noncardiac causes of chest pain include pulmonary, vascular and gastrointestinal disorders. Of all noncardiac causes presenting with acute chest pain, pulmonary embolism, aortic dissection and pneumothorax are common life-threatening emergencies seen in the ED. By differentiating the location of the pain, a physician can identify the underlying disease easily. For example, lateralizing pain may be associated with a pulmonary embolism or pneumothorax. Precordial chest pain location can be associated with ACS, ascending aortic dissection and interscapular back pain, which is typical of aortic dissections of the descending aorta.

Gastrointestinal system disorders with a “burning sensation” linked to meal behavior may indicate a lesion arising from the esophagus or stomach, such as gastroesophageal reflux disease, ulcers or even Mallory-Weiss tears. Furthermore, chest pain arising from musculoskeletal causes, cervical disc diseases or even skin lesions may be easily diagnosed by the pain characteristics and physical examination.

Prevalence, Risk Factors and Prognosis of Atypical Chest Pain in the Elderly

Previously published studies on the prevalence, risk factors and prognosis of atypical chest pain in the elderly showed a 20–60% rate of unrecognized MI reflecting possible differences in race, population, study design and the definition used for MI diagnosis. Specific subgroups, including the elderly, persons with diabetes, women and the very young, have been found to have a higher misdiagnosis rate. In the first three subgroups, atypical symptoms are common, whereas the final group is not usually considered owing to a generalized low prevalence. In a large, prospective, population-based cohort study with 4- to 20-year follow-up focusing on males in the Reykjavik area in Iceland, nearly 30% of MIs were unrecognized. The prevalence increased steeply with age by up to 47% in the group aged 75–79 years. Although there were no significant differences in the risk profiles in the Reykjavik study, increasing age (odds ratios, OR, 1.08; 95% confidence interval, CI, 1.05–1.10), serum cholesterol level (OR, 1.06; 95% CI, 1.01–1.10), heavy smoking behavior (OR, 5.2; 95% CI, 1.6–15.2), cardiomegaly (OR, 2.0; 95% CI, 1.1–3.8), baseline angina symptoms (OR, 4.7; 95% CI, 2.8–7.7) and diuretics usage (OR, 6.2; 95% CI, 2.6–14.9) were associated with a higher probability of unrecognized MI incidence. For those with unrecognized MI, nearly one quarter of patients experienced sudden death in the subsequent clinical course. In the Honolulu, Hawaii, Heart Program published in 1989, patients with unrecognized MI were associated with a history of hypertension, diabetes or impaired glucose tolerance, and higher levels of smoking behavior.

In that study, the 10-year prognosis in terms of all-cause mortality and associated cardiovascular disease tended to be worse in the unrecognized group. Of all 9,509 healthy adults followed for 5 years in the Israeli Heart Attack study, age, left axis deviation by electrocardiography (ECG), left ventricular hypertrophy, smoking behavior, blood pressure, and the existence of peripheral vascular disease after multivariate analysis remained independent risk factors for the development of unrecognized MI with a subsequent higher mortality during 7-year follow-up. In the Framingham Heart study, nearly 53% of patients with unrecognized MI had had a silent infarction with 47% having some atypical symptoms with a 10-year mortality rate of up to 58%. Although the authors in that study failed to identify any major predisposing risk factors for the onset of unrecognized MI compared with those with recognized MI, they did notice that a history of diabetes, hypertension and abnormal electrocardiograms were associated with an increased incidence of unrecognized MI. In the National Registry of Myocardial Infarction 2, which enrolled 1,674 USA hospitals, 33% of patients who had suffered an MI did not have the typical presentation of chest pain. Similarly, those without chest pain tended to be older, and there was a higher proportion of women, diabetics and heart failure comorbidities. Furthermore, patients with atypical presentations were less likely to be treated with coronary angiography and percutaneous coronary intervention and had a lower chance of anticoagulants, aspirin and β-blocker usage in the same study. In a prospective, 8-year study focusing on the prevalence, incidence and prognosis of recognized and unrecognized MI in the aging population, about 34.7% of MI patients were older than 75 years. Around 7.9% of subjects had a history of MI without ECG changes (existence of Q wave), and 6.4% of subjects had ECG evidence without having a
clinical MI history. Authors in that study concluded that there was a higher prevalence of unrecognized Q-wave MI in the old-old population aged 75–94 years. During an average follow-up of 76.2 months, the total mortality rate was borderline higher for subjects with some evidence of MI at baseline than that of the control group (5.9/100 person-years vs. 3.9/100 person-years; \( p = 0.059 \)). Of all 20,881 participants in the recent, prospective Global Registry of Acute Coronary Events study involving 14 countries, atypical presentations of ACS (8.4% in the whole cohort) increased with age and with a higher female sex proportion. Similarly, a significantly higher prevalence of congestive heart failure and diabetes was observed in the atypical group in which the patients were also undertreated. Among all atypical presentations in that study, about 50% presented with dyspnea and approximately one-fourth presented with diaphoresis or gastrointestinal symptoms. In that study, painless presentations of unstable angina carried the highest incidence of developing subsequent in-hospital morbidity and mortality (OR, 2.2; 95% CI, 1.4–3.5). All hospital outcomes including congestive heart failure, pulmonary edema, major arrhythmias, acute renal failure and mortality were higher in the atypical group than the group with typical symptoms (13% vs. 4.3%; \( p < 0.0001 \)). In a population-based cohort, named the Rotterdam study, men and women aged 55 or older from 1990–1993 had an incidence rate of unrecognized MI of around 3.8 per 1,000 person years, compared with that of recognized MI at about 5.0 per 1,000 person years. In the Rotterdam study, the proportion of unrecognized MI was lower in men (33%) than in women (54%). However, age did not play a major role in the incidence of unrecognized MI in men compared with women.

**Mechanisms of Atypical Chest Pain**

The major underlying reasons why patients develop ACS without chest pain are not clear or heterogeneous, although several possible mechanisms may play a role. Different theories of such atypical chest pain in patients with ACS have been proposed; but to date, no single mechanism satisfactorily explains the full spectrum in this clinical phenomenon. Chest pain may arise from the stimulation of either visceral or somatic pain fibers. Visceral fibers originate from the heart, esophagus, blood vessels and visceral pleura, which enter the spinal cord at multiple levels. Stimulation of these fibers from any cause produces symptoms that are poorly localized and often difficult for patients to describe. In contrast, somatic pain fibers originate from musculoskeletal structures, the dermis and parietal pleura, which may produce pain following a dermatomal pattern that is well localized and easily described. It has been suggested that the lack of nerve innervations in a donor heart not linked to the host’s nerve system may be the main reason for developing silent ischemia. The repeated silent ischemic episodes after MI may be due to the deprivation of afferent innervations created by critically placed infarctions. The elderly appear to have a somewhat reduced pain perception and tend to have more comorbidities such as diabetes. Haro et al. reported that elderly patients may actually present more frequently with complaints of fatigue, worsening congestive heart failure or even altered mental status, lightheadedness and syncope. Diabetes itself, which is associated with autonomic nerve dysfunction, has been proven to be a predisposing factor for asymptomatic myocardial ischemic events. Moreover, diabetic patients are also more likely to present with exercise intolerance and severe fatigue, which may be confused with heart failure symptoms or lightheadedness.

The higher incidence of atypical chest pain in the female population is due to higher simultaneous symptoms such as neck and shoulder pain, nausea, fatigue, and dyspnea. In addition, the female population tends to have postmenopausal coronary artery disease, which may lead to higher comorbidities like diabetes or hypertension. The elderly may suffer from an altered threshold to pain perception or various noxious stimuli (such as electrical shock, pressure or cold) known as the “defective warning system” has been shown by Droste et al. to be related to silent infarcts. An increased incidence and link between silent MI or sudden death with diabetes has been suggested, although some epidemiologic studies failed to demonstrate this point very well. Psychologic factors have also been proposed as a possible mechanism in silent infarcts associated with diabetes. Furthermore, an excess of endogenous endorphins or possibly a particular biochemical inflammatory system activation pattern involving microenvironmental balance between proinflammatory and anti-inflammatory...
cytokines have also been reported to be possible causes of silent myocardial ischemia\textsuperscript{45,46}.

**Evolution of and Advances in Diagnostic Tools for ACS**

Although much effort has been made to assist the early detection of ACS, the misdiagnosis and inappropriate discharge rates remain high (up to 10\%) as shown in previous studies\textsuperscript{5,6,20}. It has been shown that elderly patients with ACS are less likely to have typical ECG findings than younger patients. Moreover, they are less likely than younger patients to present with ST segment elevations (31.4\% vs. 50.1\%; \( p < 0.05 \)) and are more likely to present with left bundle branch block (8.0\% vs. 0.6\%; \( p < 0.05 \))\textsuperscript{47}. Elderly patients are also more likely to have pacing rhythms from a previous pacemaker implant as well as a previous MI history, both of which may lead to more frequent non-diagnostic ECGs of acute myocardial injury. Comparison with previous ECGs is thus necessary\textsuperscript{48}. A flowchart based on a prospective protocol as a predictive model implemented on ECG and clinical variables further aids the decision strategy in cardiac care unit admission with a similar sensitivity compared with physicians and an even higher specificity\textsuperscript{49}. Chest radiography is a cost-effective diagnostic tool that may influence the management strategy in up to 23\% of patients presenting at the ED with chest pain\textsuperscript{50}. In patients with pneumothorax or pneumomediastinum, chest radiography may be conclusive and diagnostic, and may also provide a hint for the diagnosis of aortic dissection. Cardiac biochemical markers such as creatine kinase and creatine kinase MB are key in the establishment of MI, whereas a more sensitive marker, troponin I, provides a more sensitive and prognostic tool for ACS\textsuperscript{51,52}. The utility of the D-dimer marker test in elderly patients with acute chest pain has been shown to provide a high sensitivity and a negative predictive value in the diagnosis of pulmonary embolism\textsuperscript{53}. Systematic and well-designed diagnostic strategies combining serial cardiac markers and ECG may help identify patients suffering from ACS when compared with routine methods\textsuperscript{54}. In the detection of wall motion abnormalities related to a specific coronary artery territory, cardiac echography is also a useful and reliable tool in the diagnosis of acute myocardial ischemia\textsuperscript{55,56}. A triage algorithm, developed by Pelliccia et al.\textsuperscript{57}, based on a scoring system including serial cardiac enzymes follow-up, ECG, resting echocardiography and clinical features has further improved the accurate diagnostic rate and treatment in the elderly population, resulting in comparable outcomes with the younger age group. Using resting sestamibi perfusion images based on initial ECG and cardiac enzymes for the effective identification of initially unsuspected, high-risk patients who may require a prompt intervention from those who are truly at low risk has also been proposed\textsuperscript{58}. ECG is efficient as a rapid and convenient bedside test for the detection of wall motion abnormalities at rest or under stress test in the diagnosis of ACS\textsuperscript{55,59}. Recently, it has been shown that cardiac biomarkers, such as brain-type natriuretic peptide and N-terminal fragment of the prohormone brain natriuretic peptide, released from the ischemic myocardium as a clinical predictive value after ACS may actually reflect the severity of myocardial ischemia or be related to ventricular wall stress and systolic dysfunction after infarct\textsuperscript{60}. White et al.\textsuperscript{61} reported that in a study of 69 patients who underwent 16-slice computed tomography, in the patients with cardiac or non-cardiac chest pain presenting in the ED compared with those diagnosed by traditional methods, the sensitivity and specificity were high for the establishment of cardiac cause (83\% and 96\%, respectively) of chest pain and all (including cardiac and noncardiac) causes (87\% and 96\%, respectively). A recently developed “triple rule-out” strategy using a 64-slice computed tomography examination protocol for evaluation of acute MI, pulmonary embolism and aortic pathology on a single, 12-second study has also been proposed with acceptable diagnostic accuracy\textsuperscript{62–64}. The widespread application of such imaging modalities implemented on traditional diagnostics, however, poses its own disadvantages and shortcomings such as radiologic exposure and contrast load. However, White et al.\textsuperscript{63} have further expanded the current diagnostic and treatment triage leading to potentially better outcomes in the elderly population.

**Conclusion**

The incidence of atypical symptoms in the elderly population with ACS presenting at the ED is high, and accurate diagnosis and urgent therapeutic intervention remain a challenge. Comorbidities are common in this population who has a higher risk of being misdiagnosed or inappropriately discharged, leading to
worse outcomes. Efficient triage and further integration of clinical features, biomarkers and emerging diagnostic cardiovascular imaging in the future may help improve the accuracy of the diagnostic rate with subsequent better outcomes in this patient population.

References


