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# Atypical Presentation in Patients with Acute Coronary Syndrome

Hyun Kuk Kim and Myung Ho Jeong

*The Heart Center of Chonnam National University Hospital, Gwangju, Korea*

## 1. Introduction

Chest pain has been reported as a cardinal clinical feature among the patients with acute coronary syndrome (ACS). However, several patients exhibit the atypical or no symptom on initial evaluation. Atypical symptom was defined as the absence of chest pain before or during admission, and may have included gastrointestinal or respiratory symptoms such as dyspnea, nausea, vomiting, and abdominal discomfort.

Patients who present without chest pain are frequently misdiagnosed, and less likely to receive optimal treatment for ACS. Consequently, greater in-hospital morbidity, and mortality are noted. Therefore, understanding the factor associated with atypical presentations may help in the earlier detection and treatments in patients with ACS.

Prior to discussing the risk factor, clarifying the concept of symptom in patients with ACS is needed to figure out this theme. In this manuscript, atypical presentation is used interchangeably 1 or 1+2 in figure 1 according to each reference (Fig.1).

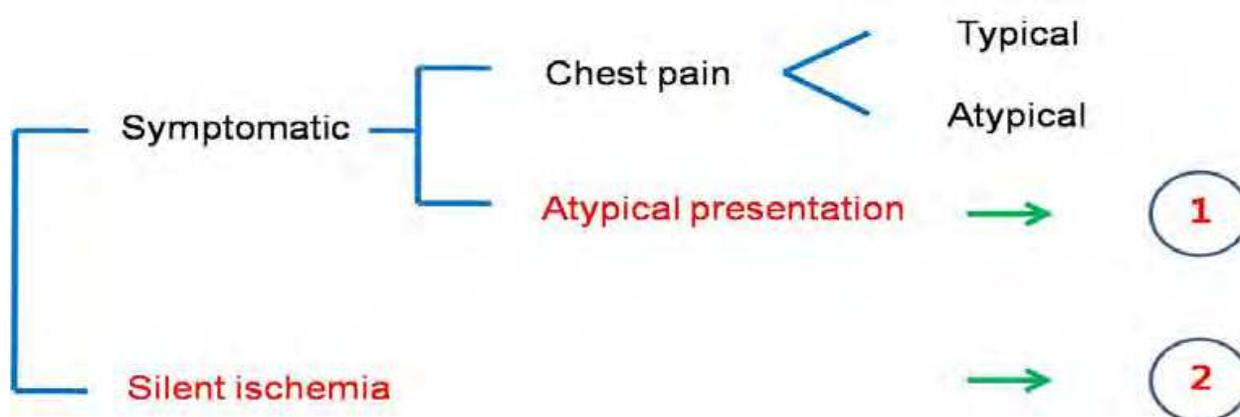


Fig. 1. Definition of atypical presentation; 1 or 1+2

## 2. Definition of clinical presentation

### 2.1 Ischemic chest pain

There are several features that tend to distinguish ischemic chest pain from non-cardiac pain.

- **Quality** – patients with ischemic pain often describe more as a discomfort than pain. Typical pain is expressed by terms include squeezing, tightness, pressure, constriction, strangling, burning, heavy weight on chest. It is not generally described as sharp, knife-like, stabbing, and pins.
- **Site** – ischemic pain is a diffuse discomfort that may be difficult to localize. The sensation is often located in the retro-sternal area but may be felt in the epigastrium, back, arms, or jaw. Pain radiating to the upper extremities is highly suggestive of ischemic pain.
- **Onset** – ischemic pain is described as having a crescendo pattern (wax and wane), and is typically gradual in onset.
- **Provocation and relieving factors** – ischemic pain is usually developed by situations such as exercise, emotional stress which increases cardiac oxygen demands. Chest pain that is reproduced on respiration, coughing, position change, palpation is often associated with not-ACS disease. Relief of pain after administration of nitroglycerin or gastro-intestinal cocktails (GI cocktails; viscous lidocaine and antacid) could not guarantee the cardiac or gastric origin pain.

### 2.2 Atypical chest pain and presentation

The following characteristics were considered as more non-ischemic chest discomfort.

- Sharp or knife like pain related to respiration, coughing
- Reproduced pain by movement or palpation
- Localized pain with one finger
- Radiating pain into the lower extremities or above the mandible
- Pain lasting for days or a few seconds

Atypical presentation was defined as the absence of chest pain before or during admission, and may have included gastrointestinal or respiratory symptoms such as dyspnea, nausea, vomiting, and abdominal discomfort. The prevalence of this presentation was 8.4% in the Global Registry of Acute Coronary Events (GRACE), 33% in the National Registry of Myocardial Infarction 2 (NRMI-2) and the dominant symptoms in these patients were dyspnea, nausea, syncope (Fig.2).

## 3. Clinical characteristics and prognosis with atypical symptom

In NRMI-2 report, patients with atypical presentation had a longer delay before hospital seek (mean, 7.9 vs. 5.3 hours), were less likely to be diagnosed with a myocardial infarction on admission (22% vs. 50%), and were less likely to be treated with optimal medical therapy [aspirin (60% vs. 85%),  $\beta$ -blocker (28% vs. 48%), heparin (53% vs. 83%)] and to receive thrombolytic therapy or primary percutaneous coronary intervention (25% vs. 74%).<sup>6</sup> Its results were similar with GRACE report. Not surprisingly, in-hospital mortality rates were much higher in patients with atypical presentation in both registry data (NRMI-2, 23% vs. 9%; GRACE 13% vs. 4%). Moreover, in-hospital complications were developed more in atypical presentation group.

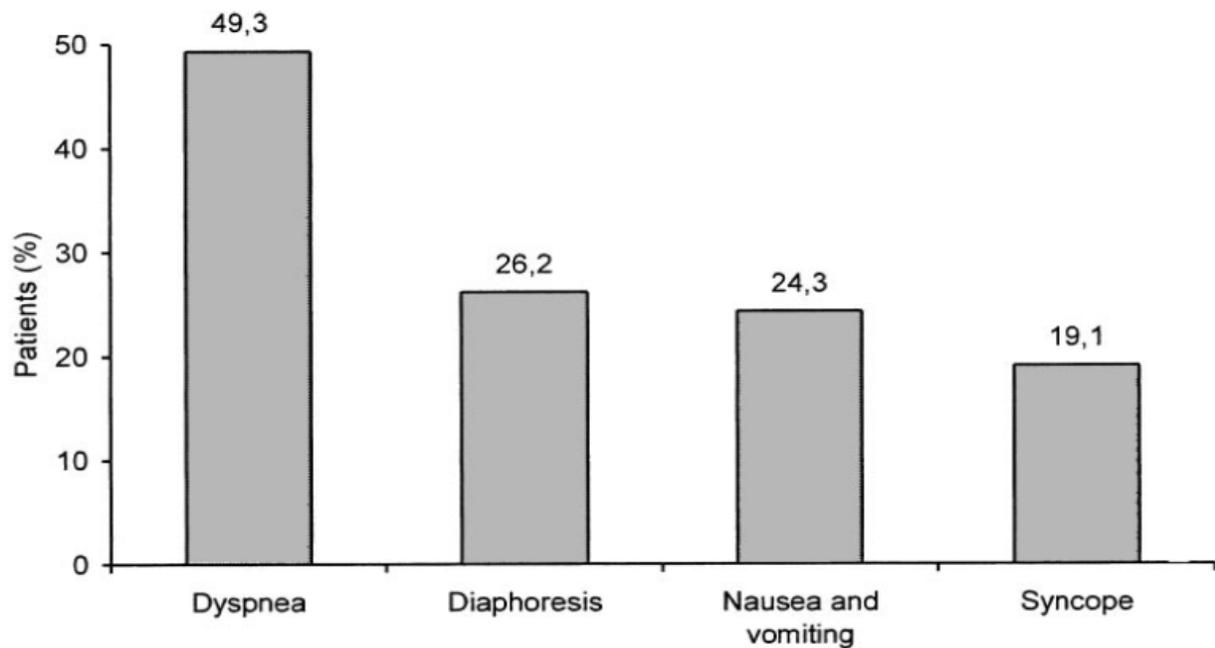


Fig. 2. Dominant symptom among patients with atypical presentation (Adopted from Brieger D, et al. *Chest*. 2004;126: 461-9)

#### 4. Risk factors of atypical presentation

In NRMI-2 registry, Variables such as older age, gender, race, and co-morbidities (diabetes, stroke, heart failure) were considered as a risk factor for atypical symptom (Table.1), and many studies have described the association of aging, gender, and diabetes mellitus.

Variables	Odds Ratio (95% confidential interval)
Nonwhite	1.05 (1.03-1.07)
Women	1.06 (1.04-1.08)
Diabetes mellitus	1.21 (1.19-1.23)
Age (10-year interval)	1.28 (1.26-1.28)
Prior stroke	1.43 (1.40-1.47)
Prior heart failure	1.77 (1.74-1.81)

Table 1. Independent risk factor for atypical presentation (Adopted from Canto J.G, et al. *JAMA*. 2000;283:3223-9)

#### 4.1 Women

Atypical presentation in ACS was observed more commonly in women than men in large cohort studies (Table 2). Women with coronary heart disease are older by 10 years and have more risk factors than men. It might be due to lack of early recognition and management.

There are several differences between men and women in presentation. Women were less likely to have typical angina, rated their pain as more intense, used different words to describe it (more burning, sharp), and reported more non-pain-related symptoms than men. They experienced pain and other sensations in the neck area more frequently. Another feature of chest pain in women is that angina being induced by rest, sleep, mental stress instead of or addition to physical exertion. Psychosocial factors might also affect symptom presentation and diagnostic approach in women. For example, a history of anxiety disorders is associated with a lower probability of significant angiographic disease among women with chest pain symptoms. As women underestimate their own risk of coronary artery disease, diagnostic approach by physician could be altered less aggressively than men. Compared with men, women are less likely to perform cardiac monitoring, cardiac enzyme measurement, electrocardiogram, cardiac consultation, admission to a coronary care unit, undergo less coronary angiography, angioplasty, and bypass surgery.

Study name	Study years	Sample size	Atypical symptom (%)	
			Men	Women
GRACE	1999-2002	20881	7.3	10.6
NRMI-2	1994-1998	434877	28.6	38.6
Alabama UA registry	1993-1999	4167	50.2	53.0
United kingdom	1995	2096	17.6	24.6
Worcester MI study	1986-1988	1360	18.0	23.0
Worcester MI study	1997-1999	2073	30.9	45.8
26 hospitals, CCU Israel	2000	2113	18.7	29.7
Croatia	1990-1995	1996	12.4	20.3
Olmsted County	1985-1992	2271	25.0	19.0
<b>Cumulative</b>			<b>27.4</b>	<b>37.5</b>

Table 2. Prevalence of atypical presentation in large cohort

#### 4.2 Diabetes mellitus

Some patients with diabetes mellitus (DM) have a blunted perception of ischemic chest pain, which could result in atypical presentation. The suggested mechanisms of this phenomenon are as follows; 1) autonomic neuropathy, 2) prolongation of the anginal perceptual threshold.

Sympathetic denervation diabetic patients have evidence of a significant reduction in MIBG uptake, most likely on the basis of autonomic dysfunction. Furthermore, diabetic patients with silent myocardial ischemia have evidence of a diffuse abnormality in metaiodobenzylguanidine (MIBG) uptake, suggesting that abnormalities in pain perception may be linked to sympathetic denervation. Similar finding has also been observed with positron emission tomography. Moreover, regional heterogeneity in sympathetic denervation could result in potentially life-threatening myocardial electrical instability that may lead to life-threatening arrhythmias.

Another mechanism of abnormal perception is prolongation of the angina perceptual threshold during exercise. Anginal perceptual threshold (the time from onset of 0.1 mV of ST segment depression to onset of angina during treadmill exercise) is prolonged in diabetic patients with coronary artery disease. The permissive effect of a prolonged anginal perceptual threshold on exercise capacity is undesirable as reflected by its correlation with ischemia at peak exercise ( $r = 0.6$ ,  $p$  less than 0.001): the longer the threshold, the greater the exercise capacity and the more severe the ischemia.

#### 4.3 Age and atypical presentation

Advanced age is an important predictor of atypical presentation and poor prognosis. Recent study in Korea examined and compared the risk factor associated with atypical presentation according to the age parameter. In this study, diabetes and hyperlipidemia significantly predicted atypical symptom in relatively young (<70 years) age group. Otherwise, co-morbid conditions such as stroke or chronic obstructive pulmonary disease were the positive predictors in relatively old age group (>70 years) (Table 3).

	Younger (n=49) Adjust OR (95% CI)	P	Older (n=41) Adjust OR (95% CI)	P
Female gender	0.861 (0.576-1.769)	0.069	0.721 (0.780-2.599)	0.385
Hypertension	0.740 (0.712-1.875)	0.352	0.628 (0.780-2.599)	0.208
Diabetes	2.494 (1.108-4.014)	0.023	0.841 (0.416-1.515)	0.719
Hyperlipidemia	0.486 (0.285-0.828)	0.006	0.840 (0.438-1.611)	0.465
Co-morbidity	2.029 (0.889-4.633)	0.093	3.315 (1.357-8.729)	0.001
Smoking	0.595 (0.345-1.025)	0.061	0.575 (0.255-1.297)	0.157
ACS type	1.243 (0.675-1.235)	0.883	1.041 (0.744-1.417)	0.877
Constant	0.162	<0.001	0.258	0.001

Table 3. Predicting factors on atypical presentation in younger and older patients (Adopted from Hwang S.Y, et al. J Korean Med Sci. 2009;24:789-94)

### 5. Conclusions

ACS patients with atypical presentation are under-diagnosed and under-treated high risk group. Several clinical risk factors could be helpful in prediction of ACS in this group.

Health care providers should have more concerns about the presence of ACS in patients who have these risk factors.

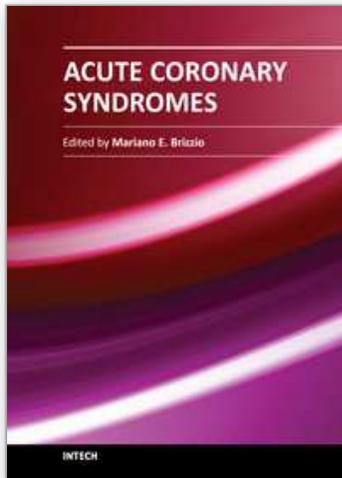
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This book has been written with the intention of providing an up-to-the minute review of acute coronary syndromes. Atherosclerotic coronary disease is still a leading cause of death within developed countries and not surprisingly, is significantly rising in others. Over the past decade the treatment of these syndromes has changed dramatically. The introduction of novel therapies has impacted the outcomes and surviving rates in such a way that the medical community need to be up to date almost on a "daily bases". It is hoped that this book will provide a timely update on acute coronary syndromes and prove to be an invaluable resource for practitioners seeking new and innovative ways to deliver the best possible care to their patients.

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