Chapter 1
Coronary Artery Disease: From Mechanism to Clinical Practice

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Abstract In most developed countries, coronary artery disease (CAD), mostly caused by atherosclerosis of coronary arteries, is one of the primary causes of death. From 1990s to 2000s, mortality caused by acute MI declined up to 50%. The incidence of CAD is related with age, gender, economic, etc. Atherosclerosis contains some highly correlative processes such as lipid disturbances, thrombosis, inflammation, vascular smooth cell activation, remodeling, platelet activation, endothelial dysfunction, oxidative stress, altered matrix metabolism, and genetic factors. Risk factors of CAD exist among many individuals of the general population, which includes hypertension, lipids and lipoproteins metabolism disturbances, diabetes mellitus, chronic kidney disease, age, genders, lifestyle, cigarette smoking, diet, obesity, and family history. Angina pectoris is caused by myocardial ischemia in the main expression of pain in the chest or adjoining area, which is usually a result of exertion and related to myocardial function disorder. Typical angina pectoris would last for minutes with gradual exacerbation. Rest, sit, or stop walking are the usual preference for patients with angina, and reaching the maximum intensity in seconds is uncommon. Rest or nitroglycerin usage can relieve typical angina pectoris within minutes. So far, a widely accepted angina pectoris severity grading system included CCS (Canadian Cardiovascular Society) classification, Califf score, and Goldman scale. Patients with ST-segment elevated myocardial infarction (STEMI) may have different symptoms and signs of both severe angina pectoris and various complications. The combination of rising usage of sensitive MI biomarkers and precise imaging techniques, including electrocardiograph (ECG), computed tomography, and cardiac magnetic resonance imaging, made the new MI criteria necessary. Complications of acute myocardial infarction include left ventricular dysfunction, cardiogenic shock, structural complications, arrhythmia, recurrent chest discomfort, recurrent ischemia and infarction, pericardial effusion, pericarditis, post-myocardial infarction syndrome,

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venous thrombosis pulmonary embolism, left ventricular aneurysm, left ventricular thrombus, and arterial embolism.

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1.1 Epidemiology

In most developed countries, coronary artery disease (CAD) is one of the primary causes leading death. The primary cause of CAD is the atherosclerosis of coronary arteries. The word "atherosclerosis" is the combination of two Greek words, "athero" and "sclerosis", which mean "gruel" and "hardening", respectively. Though during the last 40 years, a decrease in the global coronary heart disease (CHD) mortality has been seen. From 1990s to 2000s, mortality caused by acute MI declined up to 50%. Of all the cardiovascular disease (CVD) cases, nearly one-third to 50% were caused by CHD (Rosamond et al. 2008; LloydJones et al. 2010; Nichols et al. 2014). Each year, more than four million people die of CHD in the 49 countries of Europe and Northern Asia. Also, about 1.5 million Americans suffer from heart attack or stroke yearly, which results in around 250,000 deaths.

1.1.1 Prevalence

From the report on The 2010 Heart Disease and Stroke Statistics update of the American Heart Association (LloydJones et al. 2010), despite the significant increase in CVD deaths since 1990, age-standardized death rate of the same period fell by 22% instead, which was mainly contributed by shifting age demographics and causes of death worldwide.

In a 2009 report, which made use of the NHANES data, MI prevalence of middle-aged individuals (35–54 years) was compared by sex from 1988 to 1994 and 1999 to 2004 (Towfighi et al. 2009). In this report, it showed a greater MI prevalence in both time periods (2.5 versus 0.7 and 2.2 versus 1.0, respectively) in men than women. Prevalence of anatomic CHD of both general population and military personnel has been documented to decrease *over time* according to autopsy data.

Based on the comparison of autopsy data between the periods 1979 to 1983 and 1990 to 1994, the prevalence of significant anatomic CHD fell in both male and female aged 20–59 subjects, 42%–32% and 29%–16%, respectively (Roger et al. 2001). Yet the prevalence showed no difference for those over 60.

An autopsy analysis including 3832 United States military personnel, who died of combat or unintentional injuries between October 2001 and August 2011, and of whom 98% were male, with a mean age of 26, showed a 8.5% prevalence of CHD (Webber et al. 2001). Compared with the autopsy-documented CHD prevalence

shown during the Korean War in the 1950s (77%) and the Vietnam War in the 1960s (45%), a significant decrease would be seen.

1.1.2 Incidence Demographics

The original Framingham Study cohort with 44 years' follow-up displayed that the lifetime risk of developing CHD was 49% and 32% for 40 years old men and women, respectively, For CHD free people who were at age 70, the nontrivial lifetime risk of developing CHD was 35% and 24% for men and women, respectively.

Both the longevity and age-specific mortality from CVD, CHD, and stroke have been improved since 1975. Yet still, high prevalence and treatment cost are the principal features of CVD and its related complications. One cohort study, which included over 1.9 million people, who were 30 or above, free of known baseline CVD, suggested that neither myocardial infarction nor stroke were the majority of initial CVD presentations (Kannel 1987). Angina, heart failure, peripheral arterial disease, transient ischemic attack, and abdominal aortic aneurysm, along with some less common manifestations, represented 66 percent of the initial CVD presentations based on a median of six years' follow-up.

Though for both genders, the incidence increases greatly with age, women apparently lag behind men, 10 years for total coronary events and 20 years when it comes to more serious manifestations of coronary disease, such as MI and sudden death, yet as people grow older, the incidence of sex ratio narrows progressively (LloydJones et al. 2010). The incidence of women aged 65–94 tripled compared to ages 35–64, and it doubled in men. For women who are menopausal, the rates of incidence and severity of coronary disease tripled of those the same age.

1.1.3 Temporal Trends

In developed countries, the incidence of CHD has declined with time. An epidemiologic follow-up study of 10,869 patients from 1971 to 1982 and the other one that consisted of 9774 patients from 1982 to 1992 were included in NHANES I (Ergin et al. 2004), according to which the CHD incidence descended to 1.14% cases from 1.33%.

1.1.4 International Trends

The decline of heart disease mortality that has been seen in America and regions with relatively advanced economies and health care systems does not apply to the whole world. Despite their counties' income level, the number one cause of death

of patients is ischemic heart disease. And between 1990 and 2020, nearly 29% and 48% increase in coronary heart disease mortality, respectively, for women and men from developed countries could be expected according to the report. For women and men in developing countries, the corresponding estimated rises were 120 and 137% (Yusuf et al. 2001).

Together with the mortality associated with initial CVD event improvement is the rapidly increased prevalence of CVD in developing countries. Also along with the growth of population worldwide, the global burden of CHD was estimated to rise by 29% due to the increases in therapy and longevity (Goyal and Yusuf 2006). Furthermore, markedly regional variation was showed in CHD mortality; according to the 2010 data, while South Asia possess the largest number of CHD death, Eastern Europe and Central Asia have the highest rate of CHD mortality.

In China, what comes along with economic development is an epidemiological transition. Every year more than 1 million people die of ischemic heart disease (IHD), which means the mortality caused by IHD has risen more than double during the past two decades (Yang et al. 2013; Omran 1971). Number of individuals with myocardial infarction will rise to 23 million by 2030 based on the estimation of World Bank (The World Bank 2013), with the trend to accelerate. Improvements of implementing policies have been executed with financial barriers reduced, numbers of hospitals and physicians increased to develop the Chinese medical care system, while the epidemiology's changing (Chen 2009; Ministry of Health of People's Republic of China 2012). Yet during the last ten years, no definition of clinical profiles, management, and outcome of patients with this disorder found in any national representative studies, even though acute myocardial infarction being such crucial in China, particularly ST-segment elevation myocardial infarction (STEMI) accounting for 80% of such events in the country. A retrospective analysis of hospital records named China PEACE-Retrospective AMI Study and lasted from 2006 to 2011 assessed the trends in STEMI management and outcomes in China during the past decade. For both 30-day acute MI hospital mortality and readmission rate of Medicare beneficiaries 65 years of age, important regional differences was found existing. Thus, performance may be improved with the reasons of such differences understood.

1.1.5 STEMI or Non-STEMI

Over the past decade, incidence rate of STEMI has dropped whereas the rate of non-ST-elevation ACS ascended in the United States Community. MI presentations contribute approximately 25–40% STEMI so far. The non-ST elevation MI compared with ST elevation MI relatively increased over time (Furman et al. 1975; Rogers et al. 1990; Roger et al. 2010). A report including 2.5 million MIs from 1990–2006 from The National Registry of Myocardial Infarction (Rogers et al. 1990) showed that the proportion of NESTEMI, accounted for 59% of MIs, and that was 19% in 1994. And this variation was related to the incidence of STEMI's certain decline and rate of NSTEMI's increase or remain unchanged (Roger et al. 2010). The

mortality rates from STEMI, in-hospital (nearly 5–6%) and 1-year (nearly 7–18%), have declined remarkably in association with a significant raise in the frequency of care, which consist of guideline directed medical therapy (GDMT) and interventions ("defect-free" care).

1.2 Risk Factors

Risk factors of CHD exist among many individuals of the general population; for individuals with one or more risk factors, over 90% of CHD events would eventually happen (Yusuf et al. 2004; Vasan et al. 2005; Stamler et al. 1999). According to the report from three observational studies, systolic blood pressure ≥140 mmHg/diastolic blood pressure ≥90 mmHg, total cholesterol ≥240 mg/dL (≥6.22 mmol/L), diabetes, obesity, and smoking were defined as the five major CHD risk factors, which caused approximately an over 50% of cardiovascular mortality (Patel et al. 2015) 0.87% (men aged 40–59 in the MRFIT trial) to 100% (women aged 18–39 in the Framingham Heart Study) subjects dying of CHD exposed to at least one risk factor.

Meanwhile, a much lower incident rate of CHD can be predicted among people without major risk factors. In Framingham Heart Study and the Third National Health and Nutrition Examination Survey (NHANES III), the frequency and predictive value of the five major risk factors were evaluated. The percentage of patients having one to two elevated risk factors is nearly 60% for men and 50% for women, and for those with at least one borderline risk factor (defined as low density lipoprotein cholesterol (LDL-C) 100–159 mg/dL [2.6–4.1 mmol/L], high density lipoprotein cholesterol (HDL-C) 40–59 mg/dL [1.0–1.5 mmol/L], blood pressure 120–139/80–89 mmHg, smoking history and impaired fasting glucose without overt diabetes), is 26% and 41%, respectively. Apart from women aged 35–40 (8.9%) or 45–54 (3.7%), only 0–0.4% had none of elevated or borderline risk factor. This cohort also evaluates the frequency of "borderline" risk factors (Vasan et al. 2005). The incidence of CHD events is nearly 8% for patients with multiple borderline risk factors, while it rarely happens to patients with none.

Studies of both Western and Asian population display a rise in the risk when multiple risk factors exist (Vasan et al. 2005; Jackson et al. 2005; Lowe et al. 1998; Asia Pacific Cohort Studies Collaboration 2005). Take the general principles in ESTABLISHED RISK FACTORS FOR ATHEROSCLEROTIC CVD as example. Almost all cases of CHD are caused by atherosclerosis, which processes as follows: fatty streaks in adolescence, plaques in early adulthood, thrombotic occlusions, and coronary events in middle age and after. For coronary arteries and other arterial beds, when various factors take concerted actions, the risk of atherosclerotic plaques rises (Wilson 1994). Adult patients with dyslipidemia, hypertension, and diabetes can use risk factor assessment as therapy guidance, while risk of coronary disease events can be helpfully estimated by using multivariate formulations (Wilson et al. 1998; Ridker 1999).

1.2.1 Risk Factor Prevalence

It has been a long time that in emerging nations, the prevalence of risk factors remains strange and/or neglected in the literature. A national representative cohort of Chinese showed a low overall prevalence of CVD (1.8% and 1.1% in males and females, respectively) (Yang et al. 2012). Traditional CVD risk factors showed a much higher prevalence; followings are the prevalence of risk factors for male and female, respectively: overweight or obese—36.7 and 29.8%, hypertension—30.1 and 24.8%, dyslipidemia—64 and 67.4%, and hyperglycemia—26.7 and 23.6%. With the presentation of risk factors, the odds of CVD increased (odds ratio 2.4, 4.2, 4.9, and 7.2 for 1, 2, 3, and 4 or more risk factors, respectively, compared with no risk factors) (Yang et al. 2012). The result indicated that without medical intervention and effective lifestyle, the incidence and prevalence of CVD in China may rise significantly.

Despite the abstruseness of CVD risk factors prevalence, as the improvement of awareness and diet and lifestyle, prevalence of established risk factors has changed. Reports from NHANES show that from 1960 to 2000, the prevalence of obesity (body mass index $\geq$ 30 kg/m^2) rises to 30% from 15%. Meanwhile, the diagnosed diabetes increased to 5% from 1.8%, especially obvious in obese population. On the contrary, there are other cardiovascular risk factors declined significantly, with smoking 39–26%, hypertension (blood pressure $\geq$140/$\geq$90 mmHg) 31–15%, and serum total cholesterol $\geq$240 mg/dL (6.2 mmol/L) drop from 34 to 17%. These changes were associated with the improved usage of lipid-lowering drugs and antihypertensive medications, occurring among all weight groups. Also, seven ideal cardiovascular health metrics have been promoted by AHA, which includes physical activeness, no smoking, normal blood pressure, normal blood glucose level, normal total cholesterol level, normal weight, and healthy diet.

Among participations in NHANES (1988–1994), all seven metrics were achieved by only 2%. Compared to those achieving none or one metric, people with six or seven metrics had lower cardiovascular mortality (adjusted harzard ratio [HR] 0.24, 95% confidence interval [CI] 0.13–0.47) and overall mortality (adjusted HR 0.49, 95% CI 0.33–0.74). In NHANES (1999–2002), people with five or more metrics had lower cardiovascular mortality (adjusted HR 0.12, 95% CI 0.03–0.57) compared to people with none.

1.2.2 Hypertension

A well-established risk factor for adverse cardiovascular outcomes (mortality from CHD and stroke) is hypertension (Miura et al. 2001; Lewington et al. 2002). Patients with hypertension have higher lifetime risk of developing CVD. The INTERHEART study showed that of the population-attributable risk of first MI, hypertension contributed 18% (Yusuf et al. 2004). Both duration and degree of hypertension are risk factors.

1.2.3 Lipids and Lipoproteins

Lipids (mainly cholesterol and triglycerides) are compounds that involve in water. They need apolipoproteins or apoproteins to transport in blood. Also in the INTERHEART, 49% of the population-attributable risk of a first MI was contributed by dyslipidemia,which was defined as a raised apo B to apo A-1 ratio) (Yusuf et al. 2004). Lipoprotein metabolism Disturbances are usually familial, with Lp (a) excess (alone or with other dyslipidemia), combined hyperlipidemia, and hypertriglyceridemia with hypoalphalipoproteinemia being the most common ones. With the given of primary and secondary prevention, coronary events and mortality can be reduced as the total and LDL-cholesterol levels decrease (mainly all with statins) based on randomized trials (Shepherd et al. 1995; Downs et al. 1998; Sacks et al. 1996). Statins therapy contributes to LDL-cholesterol lowering may as well as other factors improvement.

1.2.4 Diabetes Mellitus

Atherosclerotic cardiovascular disease is related to all of insulin resistance, hyperinsulinemia, and elevated blood glucose (Kannel and McGee 1979a, b; Almdal et al. 2004; Reaven 1988; Zavaroni et al. 1989; Singer et al. 1992; Gerstein et al. 1999; Al-Delaimy et al. 2004). In the INTERHEART, of the population-attributable risk of a first MI, 10% was contributed by diabetes ((Yusuf et al. 2004). Other than being a risk factor, compared to nondiabetic, diabetics have a greater burden of hypertension, obesity, increased total-to-HDL-cholesterol ratio, hypertriglyceridemia, and elevated plasma fibrinogen. It has been elevated to the maximum risk kinds since it was pointed out in the 2002 National Cholesterol Education Program, specific diabetes was reported a CHD risk equivalent. According to the guidelines published by the National Cholesterol Education Program and the sixth Joint National Committee, coronary risk factors in diabetics should be treated aggressively (Miura et al. 2001; National Cholesterol Education Program (NCEP) 2002). Strong evidence shows the value of treating serum cholesterol and hypertension in patients with diabetes aggressively.

1.2.5 Chronic Kidney Disease

Mild to moderate renal dysfunction are now proved to be associated with substantial increase in CHD risk as well as end-stage renal disease (Gansevoort et al. 2013). According to the ACC/AHA 2004 practice guidelines, chronic kidney disease was a CHD risk equivalent (National Kidney Foundation 2002; Antman et al. 2006a). The annual cardiac death rate of patients with no chronic kidney disease (CKD) and ischemia was 4.5, 11% for those who had both.

1.2.6 Age and Genders

The contributions of CVD development appear to include age, and each additional decade of life was associated with an approximate doubling of the risk of vascular disease: 51–60 years 3.5%, 61–70 years 7.15, 71–80 years 13%, 81–90 years 22.3%, and 91–100 years 32.5%.

Male gender alone may contribute to the risk of CHD, although the potential mechanisms for such risk are not well understood. Several population studies have identified male gender as a risk factor for higher rates of CHD and CHD-related mortality. from the ONTARGET and TRANSCEND study populations, females had approximately 20% lower risk than males for all major cardiovascular endpoints including cardiovascular death, myocardial infarction (MI) and a combined endpoint of death, MI, stroke, and heart failure hospitalization (adjusted relative risk [RR] 0.81, 95% CI 0.76–0.87) (Kappert et al. 2012).

1.2.7 Family History

Family history alone also could contribute to CHD, especially for the young who have the family history of premature disease (Sesso et al. 2001; Andresdottir et al. 2002; Roncaglioni et al. 1992; Lloyd-Jones et al. 2004; Murabito et al. 2005; Sivapalaratnam et al. 2010; Otaki et al. 2013). It is generally agreed that first-degree relative such as parent or sibling suffering from atherosclerotic CVD or dead from CVD indicates a remarkable family history, even prior to age 55 (males) or 65 (females) (Patel et al. 2018). For people who have two or more first-degree relatives die of premature cardiovascular disease, the incidence of CVD increased 3 times before 50. The Framingham Offspring Study started an analysis to explore the reliability of self-reported family history of CHD and risk factors for CHD (Sivapalaratnam et al. 2010), and the findings were noted as follows: For family histories of hypertension, diabetes, and hypercholesterolemia, the positive statement's value for prediction was over 75%, while for cardiac death, it was 66% and 47%, respectively, for fathers and mothers. When it came to a negative statement, for family history of cardiac death or diabetes, the predictive value was over 90%, yet for family history of hypertension or hypercholesterolemia, less than 60%.

1.2.8 Risk Factors in Childhood

Cardiovascular risk factors in childhood can be recognized and used to predict the subsequent development of CHD (Li et al. 2003; Raitakari et al. 2003; Davis et al. 2001).

1.2.9 Lifestyle Factors—Cigarette Smoking

Cigarette smoking is an important and reversible risk factor for CHD. Compared with nonsmokers, subjects who smoke no less than 20 cigarettes every day have a higher incidence of myocardial infarction, six times increased for women while 3 times for men (Njølstad et al. 1996; Prescott et al. 1998). Of the population-attributable risk of a first MI, 36% was led by smoking in the INTERHEART (Yusuf et al. 2004). On the other hand, a study of smokers who had MI showed that the risk of recurrent infarction decreased by 50% for those with one year's smoking cessation; for those with two years, the risk was normalized to that of nonsmokers (Wilhelmsson et al. 1975). Patients benefit from smoking cessation no matter how long or how much they smoked previously.

1.2.10 Diet

The risk of CHD may also be contributed by high glycemic index (GI) or glycemic load (GL) diets. Increasing evidence points out that the risk of CHD and stroke and the consumption of fruit and vegetable have an inverse correlation. According to the meta-analysis of seven prospective cohorts, every additional daily portion of fruit could decrease the risk of stroke by 11%; yet no similar effect found in vegetable (Dauchet et al. 2005). While according to the INTERHEART study, 14% of population-attributed risk of first MI was caused by lacking of daily fruit and vegetables consumption (Yusuf et al. 2004). Significant controversy exists regarding the types of dietary fat and the associated risks of CHD (Chowdhury et al. 2014; de Souza et al. 2015). In a 2014 meta-analysis, no significant association was identified between types of dietary fat (i.e., saturated, monounsaturated, or polyunsaturated) and risk of CHD (Chowdhury et al. 2014). Higher risks of CHD have been associated with higher red meat and high-fat dairy products' consumption. Compared to low fiber consumption, the reduced risk of CHD and stroke is associated with high intake of fiber. The reduction in risk for MI was associated to an additional 10 g fiber intake per day (relative risk 0.81, 95% CI 0.66–0.99) (Rimm et al. 1996; Wolk et al. 1999). A neutral effect on the development of CVD was found in both caffeinated and non-caffeinated coffee intake (Floegel et al. 2012). Both risk of acute coronary events and CHD mortality have an inverse correlation with high serum concentrations of enterolactone and high diet putative biomarker of fiber and vegetables.

1.2.11 Obesity

It is reported that obesity is the risk factor for atherosclerosis, CHD, hypertension, insulin resistance and glucose intolerance, hypertriglyceridemia, and lower levels of

HDL-C (Eckel et al. 2004; Calle et al. 1999; Wolk et al. 2007; Tirosh et al. 2011). After adjusting for traditional risk factors, the occurrence of CHD and cerebrovascular disease can be predicted by obesity (measured by body mass index [BMI]) significantly and independently (Wilson et al. 2008). In addition to that, the risk of CVD increases along with the BMI linearly (Jensen et al. 2014; Twig et al. 2016). All atherogenic risk factors can be intensified or worsened by obesity, while only some can be aggravated by physical inactivity. Yet both obesity and physical inactivity would make patients of all ages more vulnerable to CHD events.

1.2.12 Exercise

Exercise was suggested that coronary heart disease and all-cause mortality can be effectively protected by exercise, even it is moderate degree (Yusuf et al. 2004). Exercise benefits variously–serum HDL-cholesterol elevated, blood pressure reduced, insulin resistance decreased, and weight loss. Besides the exercise amount, the decrease of coronary heart disease risk and overall cardiovascular mortality is also related to the degree of cardiovascular fitness, which is a measure of physical activity and determined by the exercise duration and the Maximal Oxygen Consumption on treadmill (Barlow et al. 2012; Mandsager et al. 2018). The INTERHEART study also found that 12% of the population-attributable risk of a first MI was contributed by lacking of regular physical activity (Yusuf et al. 2004).

1.2.13 Psychosocial Factors

All of sudden cardiac death, acute precipitation of MI and the early development of atherosclerosis may be promoted by psychosocial factors, including depression, anger, stress, and other factors, and all the above have a relationship with cardiovascular outcomes.

1.2.14 Inflammatory Markers

It has been reported that the increased risk of CVD is related to various numerous inflammatory markers (Emerging Risk Factors Collaboration et al. 2010), such as C-reactive protein (CRP), interleukin-6, myeloperoxidase, and other inflammatory markers. What else has been reported to be the markers of increased CHD risk are elevated levels of white blood cells, erythrocyte sedimentation rates, interleukin-18, tumor necrosis factor alpha, transforming growth factor beta, soluble intercellular adhesion molecule-1, P-selectin, cathepsin S, and lipoprotein-associated phospholipase A2.

1.3 Clinical Presentation

1.3.1 Characteristics of Angina

Angina pectoris is caused by myocardial ischemia in the main expression of pain in the chest or adjoining area, which is usually a result of exertion and related to myocardial function disorder. Angina is firstly described as a sense of "strangling and anxiety" in Heberden, and that is still *prominently* relevant. The sense is also described in the manner of heavy, squeezing, tight, suffocating, constricting, and crushing. The sensation for some patients is more vague including a mild pressure-like discomfort, a numb or burning sensation. Generally, the discomfort area is substernal, with the ulnar surface of left arm as a common radiant area, the outer of both arms and right arm sometimes. Patients may also have discomfort in Epigastric area alone or along with chest pressure. It is rare to find anginal discomfort above the mandible or below the epigastrium. Except angina, dyspnea, eructations, fatigue, and faintness are also the common symptoms of myocardial ischemia, defined as anginal equivalents, especially for older patients. For patients without angina or ECG (electrocardiogram)-proved CAD, abnormal exertional dyspnea history may be useful in indicating IHD. Severe ischemia may present dyspnea (at rest or with exertion), which results in increased left ventricular (LV) filling pressure (Abidov et al. 2005). In the case of nocturnal angina, sleep apnea should remain on high alert. Another possible marker of severe CAD is postprandial angina, which may be occur when the coronary blood supplied by the severely stenotic vessels is redistributed. Typical angina pectoris would lasts for minutes with gradual *exacerbation*. Rest, sit or stop walking are the usual preference for patients with angina, and reaching the maximum intensity in seconds is uncommon.

Angina can be indicated with a discomfort in the chest while walking uphill or in the cold. Manifestations like pleuritic pain, fingertip pain, pain that lasts for hours or only seconds, pain caused by movement, pain caused by chest wall, or arms palpation are not markers of angina pectoris. Another highly unusual angina pectoris expression is pain that radiated to the lower extremities.

Rest or nitroglycerin usage can relieve typical angina pectoris within minutes. Though nitroglycerin may cause esophageal pain and other syndromes, it can be used to diagnose angina pectoris. When the symptoms are not brought on by ischemia, or caused by severe ischemia as well as unstable angina or acute MI, with rest and nitroglycerin, relief would be delayed for more than 5–10 min. The ability of continuing same or greater level exertion without symptoms of exertion-led patients can be described using the symptom of first effort angina. With repetitive exertion, attenuation was observed in myocardial ischemia presumably for ischemic preconditioning; and it seems that the warm-up phenomenon could be induced with ischemia greater or equal to medium intensity.

1.3.2 Grading of Angina Pectoris

So far, a widely accepted angina pectoris severity grading system was proposed by CCS (Canadian Cardiovascular Society) (Kaul et al. 2009). And this system, which was modified by NYHA (New York Heart Association) functional classification, makes a more specific classification of patients possible. In addition to the above, there is also an angina score and a specific scale of activity, developed by Califf and Goldman with their associates, respectively.

Yet all these grading system would be limited without precise observation of patients or their diverse symptoms' tolerance. The reproducibility shown on the CCS was only 73%, and no positive correlation was found between that and objective measures of exercise performance. The indicator in the Goldman scale is the metabolic cost of particular activity, and it seems to be effective for both physicians and nonphysicians. While in the anginal score of Califf and coworkers, both ST and T wave changes on the ECG and clinical manifestations are combined, which becomes an independent prognostic factor except LV function, age, coronary angiographic anatomy, and gender.

1.3.3 AMI General Appearance

Anxiety and major distress are common clinical features of STEMI patients, who usually have anguished facial expression, with fist clenched and held against their sternums during description. While any activity was believed to aggravate their discomfort for severe angina pectoris patients, whose preferences are sitting, lying or standing still.

Clinical manifestations of typical LV failure and sympathetic patients include chest discomfort and suffocation. Their sputum is usually pink, frothy or blood-streaked. Thus sitting or propped up in bed are their typical position. And skin pallor and cold perspiration also may be obvious.

Features of cardiogenic shock are as follows: listless lying, pallor face, cold and humid skin, few or no autonomous movements, bluey or mottled extremities, and cyanosed nail beds and lips. Both normal conversation or confusion and disorientation could happen for patients in shock based on their cerebral perfusion level.

1.3.3.1 Heart Rate

Different degrees of LV failure and underlying rhythm make heart rate various, including bradycardia, rapid regular or irregular tachycardia. Premature ventricular beats are also ordinary. Rapid and regular pulse in these patients usually means sinus tachycardia at 100–110 beats/min. Relief of anxiety and pain would slow down the heartbeat.

1.3.3.2 Blood Pressure

Though the systolic and pulse pressure decreased and diastolic pressure elevated for tachycardia accompanied stroke volume reduction, the blood pressure for most patients with noncomplex STEMI is normal. For patients whose previous blood pressure is normal, probably due to the release of adrenergic, which is secondary to agitation, pain, and anxiety, occasional hypertension would be observed in the first few hours, and arterial pressure over 160/90 mmHg. Although 3–6 months postinfarction, elevated blood pressure would be recovered for many of those who have a history of hypertension, without post-STEMI therapy, the blood pressure of some often get normalized.

For patients with massive infarction, LV dysfunction and venous pooling resulted from morphine and/or nitrates administration would cause acute fall in arterial pressure, which inclines to back to preinfarction levels once they recover.

According to the definition of cardiogenic shock, the systolic pressure should be lower than 90 mmHg with proved end-organ hypoperfusion. Since for some inferior infarction patients who have activated Bezold–Jarisch reflex, a transient under 90 mmHg systolic pressure is also possible, hypotension is not a independent indicator for cardiogenic shock. For patients with slight hypotension, cardiogenic shock results from infarction extension and ischemia increasing. Their blood pressure may decline gradually and cardiac output reduce progressively in hours or days.

Hypertension, tachycardia, or both occur in half of both inferior and anterior STEMI patients, with excess parasympathetic stimulation occurring in former, sympathetic excess in the latter.

1.3.3.3 Temperature and Respiration

Within 24–48 h starting from onset, fever and nonspecific response to necrosis occur in most extensive STEMI patients. Following the development of STEMI may be mildly increased respiratory rate. Based on the fact that with therapy for physical and psychological discomfort, respiratory rate of non-HF patients was back to normal, its elevation was brought on by pain and anxiety, while respiratory rate in LV failure patients has correlation with the serious degree of failure. And the respiratory rate in pulmonary edema patients may over 40/min.

1.3.3.4 Chest

For STEMI patients who also have LV failure and/or LV reduction, moist rales are audible. For severe LV failure patients, diffuse wheezing exists. The occurrence of hemoptysis can also indicate pulmonary embolism with infarction. In 1967, based on STEMI patients' presence and severity of rales, a prognostic classification plan was suggested by Killip and Kimball (Barter et al. 2007). No rales or third heart sound was detected in Class I patients. A mild to medium rales (<50% of lung fields) and

a possible S3 in Class II patients. Rales in over 50% of each lung field and continual pulmonary edema in Class III patients, while cardiogenic shock occurs in Class IV patients.

1.3.3.5 Cardiac Examination

Auscultation

Murmurs
For patients with mitral valve regurgitation or tricuspid regurgitation or interventricular septum rupture, systolic murmurs usually are audible.

Friction Rubs
Pericardial friction rubs, most of which would be noticed in two or three days since infarction onset, are usually audible either along the border of left sternal or just inside the apical impulse for STEMI patients.

Laboratory Findings

Serum Markers of Cardiac Damage
The combination of rising usage of sensitive MI biomarkers and precise imaging techniques made the new MI criteria necessary. Compared to unstable angina (UA), more patients are diagnosed with MI when discharged.

For STEMI patients, who is urgent for reperfusion, the 12-lead ECG are recommended than biomarker assay for clinicians to start the treatment for STEMI. Serum creatine kinase (CK) concentration, which could be tested in most hospitals, is a sensitive indicator of STEMI. Yet a false-positive MI could be diagnosed in patients with alcohol intoxication, skeletal muscle trauma, convulsions, thoracic outlet syndrome, muscle disease, diabetes mellitus, after vigorous exercise, intramuscular injections, and pulmonary embolism, which could all result in an elevated serum CK concentration (Marcus et al. 2006).

Creatine Kinase Isoenzymes
CK has three isoenzymes: MM, BB, and MB. The BB isoenzyme mainly exists in brain and kidney extracts; major MM and some MB (1–3%) in skeletal muscle, while both MM and MB isoenzymes exist in cardiac muscle. There is also small amount of MB found in the following: tongue, uterus, small intestine, diaphragm, and prostate. For a given laboratory, several units over the reference limit above would generally be set as the cutoff value for abnormal elevated CK-MB.

Electrocardiography

Serial electrocardiographic changes occur in most of STEMI patients. Yet ECG has been limited with age of the infarct, presence of conduction defects, changes in electrolyte concentrations, extent of myocardial injury, its location, presence of previous infarcts or acute pericarditis, and administration of cardioactive drugs in the diagnosis and location of MI. ST segment and T wave changes, which are nonspecific, may be caused in the following cases: stable and unstable angina pectoris, acute and chronic pericarditis, early repolarization, shock, following the administration of digitalis, ventricular hypertrophy, myocarditis, electrolyte imbalance, and metabolic disorders; all the cases above could be differentiated from STEMI with the help of Serial ECG. With shock, persistent metabolic disorders and administration of digitalis eliminated, persistent changes prove infarction while transient changes support electrolyte disturbances or angina.

The electrocardiographic leads suggest that the infarction location, all of QRS duration and the extent of ST-segment elevation are related to poor prognosis. For most STEMI patients, electrocardiographic changes occur from the onset of infarction and last lifelong especially when they develop into Q waves. While for substantial minority, after several years, Q waves and even ECG are back to normal.

The Q wave patterns that may mimic MI in the following conditions: ventricular hypertrophy, preexcitation, pneumothorax, amyloid heart disease, traumatic heart disease, hyperkalemia, early repolarization, myocardial disease, conduction disorders, pulmonary embolus, heart tumors, pericarditis, intracranial hemorrhage, and cardiac sarcoidosis.

1.3.4 Right Ventricular Infarction

A fairly sensitive and specific evidence of infarction in right ventricular is the ST-segment elevation in the right precordial leads (V1, V3R to V6R) (Bhatt et al. 2007; Bangalore et al. 2007). Anterior ST-segment elevation caused by right ventricular injury usually would be inhibited by concurrent inferior wall injury. Likewise, the anterior ST-segment depression seems to be wakened by right ventricular infarction.

1.3.5 Imaging

Echocardiography

The fairly portable facility provides an ideal evaluation solution for coronary care unit (CCU) or even emergency patients with MI. Echocardiography, which favors myocardial ischemia, can also help with the diagnosis for MI patients with chest pain and nondiagnostic ECG based on the distinct area of disordered contraction. Similarly, it also help with the diagnosis of aortic dissection.

The echocardiograms' estimation in LV function is consistent with that of angiograms and it can be used in the post-MI prognosis establishment (Sipahi et al. 2007). Moreover, in the early diagnosis of congestive heart failure post-MI, MI mechanical complications, residual provocable ischemia, and stunned myocardium yet may still viable; echocardiography can also be helpful.

The blood flow across the cardiac valves and in the chambers can be evaluated with Doppler, whose combination with echocardiography can be used in the detection and assessment of post-STEMI mitral or tricuspid regurgitation. It can also possibly used to identify the position of acute ventricular septal rupture, calculate the shunt flow through the defect and assess the acute cardiac tamponade (Lee and Johnson 2009).

1.3.6 Other Imaging Modalities

Computed Tomography
Despite its relative inconvenience, compared to echocardiography, computed tomography is more sensitive in thrombus detection. Various applications of computed tomography include detection of LV aneurysms, assessment of cavity dimensions, and wall thickness and intracardiac thrombi in STEMI patients. Except that, MI patients' cross-sectional information can also be obtained.

Cardiac Magnetic Resonance Imaging
Compared to its narrow usage in acute phase, cardiac magnetic resonance imaging is widely used in subacute and chronic phases of MI, such as to localize and size the infarction area, to recognize early MI, and to assess the ischemic insult. Other than the above, it provides the assessments of infarcted and noninfarcted tissue perfusion, myocardium reperfusion, ventricular segmental wall motion and chamber size, also the identification of harmed but not infarcted myocardium, myocardial fibrosis, edema, hypertrophy, wall thinning, and the temporal transition between ischemia and infarction (Al-Mallah et al. 2006).

1.3.7 Estimation of Infarct Size

Electrocardiography
With the recognition that the infarcted myocardium volume implicate prognosis, interest has been concentrated on the accurate measurement of MI. However, the mortality rate is related to the number of electrocardiographic leads that display ST-segment elevation; for anterior MI patients, quantity of ST-segment elevations obtained from multiple precordial leads has a relationship with the myocardial injury extent. Compared to patients with only 2 or 3 leads with ST-segment elevation, the mortality rate of those with 8 or 9 are 2–3 times higher. A relationship also exists between the ischemia duration, which could be estimated by monitoring ST-segment

continuously, and IS (infarcted size), IS/AAR (area at risk) ratio, and subsequent abnormality in partial wall motion extent (Bonaa et al. 2006).

Serum Cardiac Markers
With its release ratio, volume of distribution, and amount of lost marker, the infarcted size can be estimated with the usage of serum cardiac markers. The measurement of MI size can use the help of serial calculations of proteins discharged from necrotic myocardium. Besides that, it can be estimated approximately with the crest value of CK or CK-MB, which has wide prognostic applications. Yet the washout kinetics of CK and other markers could be remarkably altered by the coronary artery reperfusion, which leads to overstated and premature peak levels and less the useful of the curves. Infarcted size may be responsibly determined with post-STEMI cardiac-specific troponin level test even after a successful reperfusion (Levonen et al. 2008).

Noninvasive Imaging Techniques
The infarct size can be assessed both experimentally and clinically with the help of the imaging modalities above. For patients whose arteries are occluded persistently, partial heterogeneity of infarction patterns can be displayed clearly in contrast-enhanced cardiac magnetic resonance.

1.3.8 The Presentations of Anginal Pain in NSTE-ACS Patients Are as Follows

Post-MI angina; new-onset (de novo) angina (class II or III of the Canadian Cardiovascular Society classification); prolonged (0.20 min) angina at rest; or previous stable angina become unstable in recent with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina).

80 and 20% patients are found to have prolonged and de novo/crescendo angina, respectively. The elderly, female and patients with diabetes, chronic renal disease or dementia found are more likely to get anginal pain. One of the characters of typical chest pain refers to the retrosternal sensation of pressure or heaviness radiating to the left arm, sometimes to both arms or to the right arm, neck or jaw. A typical chest pain usually lasts for several minutes or persistent. What else possibly come along are sweating, nausea, abdominal pain, dyspnoea, and syncope. Epigastric pain, indigestion-like symptoms, and isolated dyspnoea are all included in the typical presentations. Intense physical activity and its relief afterword would aggravate the symptoms, which possibly lead to a higher the chance of myocardial ischaemia. Nitrites can relieve the symptoms, which according to a report of acute chest pain's other causes is not specific for angina.

There is very limited performance of chest pain characteristics to diagnose MI. The incidence of NSTE-ACS is possibly to be increased by many factors, including male gender, older age, diabetes, hypertension, hyperlipidaemia, renal insufficiency, and family history of CAD, previous manifestation of CAD as well as carotid artery

disease or peripheral. All of infection, fever, anemia, inflammation, and metabolic or endocrine (in particular thyroid) disorders may aggravate or facilitate NSTE-ACS.

1.3.8.1 Clinical Examination

The physical examination may be unremarkable or may support the diagnosis of cardiac ischemia. Signs suggesting that ischemia involves a large proportion of the left ventricle include sinus tachycardia, diaphoresis, pale cool skin, a third or fourth heart sound. In some patients, ischemia of a large area of myocardium reduces left ventricular dysfunction and causes hypotension.

Electrocardiography
ST-T changes occur in about half of the patients with UA/NSTEMI. Newly (or presumably new) ST-segment deviation ($\geq$0.1 mV) is a relatively reliable measure of ischemia and prognosis. When electrocardiograms preceding the acute event are available, further ST depression of only 0.05 mV is a sensitive although nonspecific finding of UA/NSTEMI. Transient (i.e., <20 min) ST elevation, which occurs in approximately 10% of patients with UA/NSTEMI, portends a high risk of future cardiac events. T wave changes are sensitive but not specific for acute ischemia unless they are marked (>0.3 mV).

1.3.8.2 Continuous Electrocardiographic Monitoring

Continuous electrocardiographic monitoring serves two purposes in UA/NSTEMI: (1) to identify arrhythmias and (2) to identify recurrent ST-segment deviation indicative of ischemia. Recurrent ST-segment deviation is a strong independent marker of adverse outcome, even in the presence of troponin release.

1.3.8.3 Markers of Cardiac Necrosis

Among patients presenting with symptoms consistent with UA/NSTEMI, elevations of markers of myocardial necrosis (i.e., CK-MB, troponin T or I) identify patients with the diagnosis of NSTEMI. With the use of troponins, which are more sensitive than CK-MB, a greater percentage of patients are classified as having NSTEMI, which is associated with a worse prognosis. Persistent elevation of troponin after an acute event also associates with worse clinical outcomes.

1.3.8.4 Laboratory Tests

The chest radiograph may be helpful to identify pulmonary congestion or edema, which occurs more frequently in patients with UA/NSTEMI in whom ischemia

involves a significant proportion of the left ventricle or in those with antecedent left ventricular dysfunction. The presence of congestion confers an adverse prognosis.

Transthoracic echocardiography (UCG) should be routinely available in emergency rooms, which is performed/interpreted by trained physicians in all patients during hospitalization for NSTE-ACS. It is useful to identify abnormalities suggestive of myocardial ischaemia or necrosis. Besides, UCG is helpful in other which is related with chest pain, such as aortic valve stenosis, pericardial effusion, acute aortic dissection, hypertrophic cardiomyopathy or acute pulmonary embolism. Moreover, UCG is the diagnostic tool for patients with hemodynamics instability of suspected cardiac origin. Evaluation of left ventricular (LV) systolic function is important to estimate prognosis.

1.3.8.5 Clinical Classification

Because UA/NSTEMI comprises such a heterogeneous group of patients, classification schemes based on clinical features are useful. Some clinical classifications or scores of UA/NSTEMI provide a useful means to stratify risk. *In NSTE-ACS*, it is superior to make quantitative assessment of ischaemic risk by means of scores that the clinical assessment alone. *The GRACE* risk score provides the most accurate stratification of risk both on admission and at discharge.

The TIMI risk score uses seven variables in an additive scoring system: age $\geq$ 65 years, three or more CAD risk factors, known CAD, aspirin use in the past 7 days, severe, angina, ST change $\geq$0.5 mm and positive cardiac marker. It is easy to use, but more accurate in discriminating risk levels than GRACE risk score.

1.3.8.6 Coronary Arteriographic Findings

The extent of epicardial CAD among patients with UA/NSTEMI randomized to the invasive arm of the TACTICS–TIMI 18 trial, who systematically underwent angiography, was as follows: 34% had significant obstruction (>50% luminal diameter stenosis) of three vessels; 28% had two-vessel disease; 26% had single-vessel disease; and 13% had no coronary stenosis >50%.

Approximately 10% had left main stem stenosis >50%. Women and nonwhites with UA/NSTEMI have less extensive coronary disease than their counterparts do, whereas patients with NSTEMI have more extensive disease on coronary angiography than do those who present with unstable angina alone.

1.3.9 Woman: Clinical Presentation

Compared to male's presentation time, it would generally be ten years later for female to get coronary heart disease (CHD), and burden of risk factors for women are greater

(Rutledge et al. 2009). Symptoms at the beginning would not be considered as the presentation of heart disease by women, which results in not prompt medical advice; they also will not be used in evaluating myocardial ischemia as early in women. Women under 45 years also have CHD and the prognosis is worse compared to men. CHD first presentation can be various, including sudden cardiac death (SCD), myocardial infarction (MI), heart failure (HF) or chest pain. The Reynolds risk score as alternative was developed for female patients since risk in women with early heart disease family history was underestimated.

1.4 Complications of Acute Myocardial Infarction

1.4.1 Left Ventricular Dysfunction

Left ventricular dysfunction is the most significant predictor of post-AMI mortality. Systolic dysfunction may happen alone or together with diastolic dysfunction (Pitt 2003; White et al. 2005). The diastolic dysfunction of LV causes pulmonary congestion and pulmonary venous hypertension, while systolic dysfunction mainly leads to cardiac output depression and ejection fraction depression. For these patients, except the necessity of hypoxemia improvement, ACEI/ARB, beta-adrenergic agonists, and diuretics are also significant. Afterload can be induced with the usage of nitroglycerin and other oral vasodilators, and systolic dysfunction can be improved by digitalis (Udelson et al. 2003).

1.4.2 Cardiogenic Shock

Cardiogenic shock, which is the most serious clinical manifestation of LV failure, contributes nearly 60% of total deaths after fibrinolysis for AMI. AMI patients who are older and have history of congestive heart failure or prior MI, sustained an anterior infarction, are more likely to have cardiogenic shock (Palmeri et al. 2005; Babaev et al. 2005).

1.4.3 Rupture of the Free Wall

Hemopericardium and death from cardiac tamponade are often caused by rupture of the free wall of the left ventricle (Antman et al. 2006b). There are mainly three types of rupture, including the catastrophic (an acute tear leading to immediate death), the subacute (nausea, hypotension), and the pericardial (discomfort) (Birnbaum et al. 2002a).

1.4.4 Rupture of the Interventricular Septum

The 30-day mortality of patients who had acute myocardial infarction and subsequent rupture of interventricular septum is high (Birnbaum et al. 2002b). The character of a ruptured interventricular septum is a new harsh, loud holosystolic murmur, which is usually together with a thrill and can be heard best at the lower left sternal border (Antman et al. 2006b). It has been reported that for critical patients with acute septal rupture after AMI, their conditions can be stabilized by catheter placing an umbrella-shaped device within the ruptured septum.

1.4.5 Rupture of a Papillary Muscle

Transmural MI is rarely complicated with partial or total rupture of a papillary muscle, which is often fatal. Severe (not immediately fatal) and sudden massive (rare, fatal) mitral regurgitation can be caused (Birnbaum et al. 2002b).

Surgical Treatment
For AMI and circulatory collapse patients, operative intervention for identifiable and repairable mechanical lesion, which is surgically correctable (ventricular septal defect or mitral regurgitation, for example), is most successful. And coronary revascularization is often in company with surgical reparations include prosthetic mitral valve insertion, ventricular septal defect closure, or mitral regurgitation correction (Antman et al. 2006b).

1.4.6 Ventricular Arrhythmias

1.4.6.1 Ventricular Premature Complexes

Frequent ventricular premature complexes (VPCs) are assumed to be over 5 per min, before reperfusion therapy, beta-blockers, intravenous nitrates, and aspirin were wildly used for STEMI management. Now it's been found out that patients who do and do not develop fibrillation have the same incidence of this "warning arrhythmias". For STEMI patients who have VPCs, instead of routine prescription of antiarrhythmic drugs, conservative course should be carried out and determine the presence of recurrent ischemia or electrolyte or metabolic disturbances (Antman et al. 2006b).

1.4.6.2 Accelerated Idioventricular Rhythm

As many as 20% STEMI patients have accelerated idioventricular rhythm, and in the first two days, it has frequent occurrence, which is the same for anterior and

inferior infarctions. Routine treatment for accelerated idioventricular rhythms is not necessary since it is believed not to influence the prognosis, unlike rapid ventricular tachycardia (Antman et al. 2006b).

1.4.6.3 Ventricular Tachycardia

It appears that for either during hospitalization or over the first year and non-sustained runs of ventricular tachycardia has no relationship with increased mortality risk. STEMI patients who have transmural infarction and left ventricular dysfunction usually have late yet maybe sustained ventricular tachycardia, which often causes significant hemodynamic deterioration and is related to both hospital and long-term mortality rates.

It's significant that the levels of serum potassium and magnesium be maintained above 4.5 mEq/l and 2 mEq/l, respectively. And for STEMI patients, it is compulsive to abolish the sustained ventricular tachycardia rapidly. An index episode of ventricular tachycardia is usually followed with several days' maintenance infusions of antiarrhythmic drugs, which is a common clinical practice. Specialized methods like surgery or antitachycardia devices implantation should be considered for recurrent or refractory ventricular tachycardia.

1.4.6.4 Ventricular Fibrillation

For hospitalized STEMI patients, ventricular fibrillation happens in three settings. Those who has none or few signs or symptoms of left ventricular failure have sudden and unexpected primary ventricular fibrillation, while patients in the progressive downhill course with left ventricular failure and cardiogenic shock have the secondary ventricular fibrillation as final event. The late ventricular fibrillation usually occurs over 48 h post-STEMI and it has regular but not solely occurrence in large infarcts and ventricular dysfunction patients. Ventricular fibrillation can be treated with unsynchronized electrical countershock (at least 200–300 j), which should be performed as fast as possible. The administration of intravenous amiodarone also promotes effective prevention of refractory recurrent episodes or interruption of ventricular fibrillation (Volpi et al. 1998).

1.4.6.5 Bradyarrhythmias

Sinus Bradycardia

Sinus bradycardia usually happens at the early stage of STEMI, especially for patients who have inferior and posterior infarction (Antman et al. 2006b). For patients whose extremely slow sinus rate (<40–50 beats/min) is in association with hypotension,

atropine can raise the heart rate effectively without the company of hypotension or ventricular ectopy, sinus bradycardia alone should firstly be observed instead of treatment.

Atrioventricular and Intraventricular Block

Specific treatment for first-degree AV block usually is not necessary. First-degree AV block may be caused by beta-blockers and calcium antagonists (other than nifedipine), since they can prolong AV conduction. Type I second-degree AV blocks, which are most common in association with occlusion of the right coronary artery and resulted from ischemia of the AV node, seem do not influence prognosis. With the absence of heart failure, premature ventricular contractions, and bundle branch block and ventricular rate over 50 beats/min, specific treatment for patients with second-degree AV block of the type I variety is unnecessary. Either anterior or inferior infarction patients can have the occurrence of complete (third-degree) AV block.

Patients with inferior wall infarction and complete AV block, which usually is transient, do not require pacing. Atropine has little value in patients with the followings: slow ventricular rate (<40–50 beats/min), presence of ventricular arrhythmias or hypotension, or development of pump failure. The abolishment of AV block or acceleration of the escape rhythm is likely to be led by atropine only when complete heart block develops within 6 h of symptoms onset, in which cases, AV block is probably transient and related to growth of vagal tone. While persistent block, which is more observed in the course of STEMI, usually needs cardiac pacing.

Intraventricular Block

Blood of the right bundle branch and the left posterior division are supplied from both anterior descending and right coronary arteries, whereas that of the left anterior division is supplied only from septal perforators, whose origin is left anterior descending coronary artery. Since nearly half of conduction blocks observed in STEMI patients are already present on the first ECG, they can't all be considered to be the complications of infarcts, and they may stand for the antecedent disease of conduction system (Di Chiara 2006; Wong et al. 2006).

Right Bundle Branch Block

Right bundle branch block, which is usually new and related to anteroseptal infarction, alone can cause AV block. It appears that for anterior STEMI patients, with the company of congestive heart failure, isolated right bundle branch block is related to an elevated mortality risk, even without the occurrence of complete AV block.

1.4.7 Atrial Flutter and Fibrillation

Atrial flutter, which commonly is transient and is the typical consequence of augmented sympathetic stimulation of the atria in STEMI patients, usually occurs in LV failure and pulmonary emboli patients, who has hemodynamic deterioration that aggravated by arrhythmia, or atrial infarction (Kober et al. 2006).

Fibrillation is commonly transient and likely to happen in LV failure patients just like atrial premature complexes. Yet patients who have pericarditis and atria ischemic injury and right ventricular infarction can also have that. The treatments for atrial flutter and fibrillation in STEMI patients and these conditions in other settings are similar. Oral anticoagulants should be administered in patients with recurrent episodes of atrial fibrillation. Beta-blocker should also be used in patients after STEMI if no contraindications exist. And these agents can also help to decrease the ventricular rate, should atrial fibrillation recurrence, except other several beneficial effects.

1.4.8 Other Complications

1.4.8.1 Recurrent Chest Discomfort

Both previous abnormalities on the ECG and patients' blurry description of discomfort sometimes make the evaluation of postinfarction chest discomfort complicated. Patients may either be too sensitive to transient discomfort or negative a potential recrudescence of symptoms. Diagnostic strategies can be used are as follows: repeat ECG reading, assessment of the response to sublingual nitroglycerin, 0.4 mg and repeat physical examination.

1.4.8.2 Recurrent Ischemia and Infarction

With a repeat ST-segment elevation on ECG within the first 18–24 h after the primary infarction, and abnormal serum cardiac markers, recurrent infarction is worth of serious consideration (Keeley et al. 2003). After 24 h, either re-elevated cardiac markers or newly appeared Q wave on ECG can be used to diagnose recurrent infarction. Catheterization and percutaneous coronary intervention, or repeat fibrinolysis if PCIs unavailable, should be considered for patients who have re-elevated ST segment. During the arrangement of other procedures, patients may be stabilized with an intra-aortic balloon pump being inserted (Scirica et al. 2006; Antman et al. 2006c).

1.4.8.3 Pericardial Effusion

Effusions are usually detected with echocardiography. And the incidence changes along with criteria, laboratory expertise, and technique. Patients with the presence of congestive failure, larger infarcts, and anterior STEMI are more likely to have effusions. Most post-STEMI pericardial effusions do not lead to hemodynamic compromise; and with the occurrence of tamponade, ventricular rupture or hemorrhagic pericarditis often induces effusions (Hombach et al. 2005).

1.4.8.4 Pericarditis

Pain caused by pericarditis may start in the first day and last 6 weeks post-STEMI. A higher dose of aspirin (650 mg orally every 4–6 h) is necessary to treat the pericardial discomfort. And nonsteroidal antiinflammatory agents and steroids should be prevented from using since their interference with the formation of myocardial scar (Abildstrom et al. 2005; Birnbaum and Drew 2003).

1.4.8.5 Post-myocardial Infarction Syndrome

Presentations of post-myocardial infarction syndrome include malaise, pericardial discomfort, elevated sedimentation rate, fever, leukocytosis, and pericardial effusion. Since glucocorticosteroids and nonsteroidal anti-inflammatory agents have the potential to weaken the infarct recovery, increase coronary vascular resistance, and lead to ventricular rupture in Dressler syndrome patients within 4 weeks of STEMI, it is best not to use them in such cases. Large doses of aspirin would be effective (Reinecke et al. 1998).

1.4.8.6 Venous Thrombosis Pulmonary Embolism

The origin of mainly all peri-MI pulmonary emboli is thrombi in the veins of the lower extremities; mural thrombi overlying an area of right ventricular infarction as the origin is rather uncommon.

1.4.8.7 Left Ventricular Aneurysm

Left ventricular aneurysm, which is often termed as true aneurysm, usually means discrete, dyskinetic area of the left ventricular wall with a broad neck. Compared to true aneurysms after STEMI, it is more common to see dyskinetic or akinetic areas of the left ventricle, which are known as regional wall motion abnormalities. The wall of the true aneurysm, which generally consists of fibrous tissue, necrotic muscle, and sometimes viable myocardium, is thinner compared to the rest wall of the

left ventricle. In contrast to patients without aneurysms, the mortality of those who have is six times higher. Ventricular reconstruction surgery is worth of consideration (Cheitlin et al. 2003; Vargas et al. 1999).

1.4.8.8 Left Ventricular Thrombus and Arterial Embolism

During the acute phase of infarction, a thrombogenic surface inside the left ventricle may be contributed by endocardial inflammation. Since the septum has been transmural-infarcted extensively, infarcted myocardium of both ventricles may be overlay with mural thrombi. When an embolic event has already occurred, or patient has a large anterior infarction with or without echocardiographically visualized thrombus, anticoagulation is recommended (intravenous heparin to increase the activated partial thromboplastin time to 1.5–2 times that of control, followed by at least 3–6 months of warfarin) (Rehan et al. 2006; Barbera and Hillis 1999).

1.5 Pathophysiology of Atherosclerosis

Atherosclerosis involves several highly interrelated processes, including platelet activation, thrombosis, lipid disturbances, endothelial dysfunction, oxidative stress, inflammation, altered matrix metabolism, vascular smooth cell activation, remodeling, and genetic factors (Libby 2002).

1.5.1 Platelet Activation and Thrombosis

Platelet activation and thrombosis are recognized as important components of atherosclerosis. Coronary thrombosis often occurs at sites of plaque rupture or erosion (Davies 1996). Subendothelial collagen, the lipid core, and procoagulants such as tissue factor and von Willebrand factor are exposed immediately to circulating blood after plaque rupture or erosion. Through the platelet glycoproteins (GP) Ia/IIa and GP Ib/IX20 (Rauch et al. 2001), platelets rapidly adhere to the vessel wall with subsequent aggregation to this initial monolayer through linkage with fibrinogen and the exposed GP IIb/IIIa on activated platelets. Platelets are a rich source of NO, which has been associated with thrombosis (Loscalzo 2001). Although thrombosis is an important process in ACS, it may have an even more critical role in modulating risk of acute ischemic events in peripheral arterial disease (PAD) (Makin et al. 2002). The findings of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial demonstrated that in reducing the number of cardiovascular events in patients with PAD than in those with coronary artery disease, inhibition

of the platelet adenosine diphosphate receptor with clopidogrel (versus aspirin) is more effective (A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) 1996).

1.5.2 Endothelial Dysfunction

The vascular endothelium is recognized as an important center of vascular control. The endothelium play an important role in regulation of nutrient delivery, vascular tone, inflammation, coagulation, and thrombosis.

Endothelial regulation of these processes stems primarily from production of autocrine and paracrine mediators including prostaglandins, NO, endothelin, endothelium-derived hyperpolarizing factors, and angiotensin II. These substances provide a balance between thrombosis and anticoagulation, vasodilation and vasoconstriction and modulation of inflammation. NO is the most potent vasodilator (Rees et al. 1989), which can be demonstrated by the wide variety of stimuli that modify its production and degradation. These activity modifiers differ from chemical to biomechanical stimuli and allow for the modulation of NO bioavailability (Luft 2002).

The decrease in the bioavailability of NO and the increase in production of vasoconstrictors such as angiotensin II can create a favorable environment for thrombosis and atherosclerosis (Loscalzo 2001). Besides to adversely affecting blood flow and nutrient delivery, another important aspect of endothelial dysfunction would likely be the increase in inflammation (Libby 2002). Endothelial cells are very important in the recruitment, adhesion, and diapedesis of leukocytes into the vascular wall through many chemokines and cytokines and intracellular transcription factors (Hawiger 2001; Berk et al. 2001; Rosenfeld 1996). Moreover, by enhancing vascular smooth muscle proliferation and migration, augmenting platelet activation and thrombosis, possibly participating in intravascular neovascularization, and favoring adverse lipid modification, decreased NO increases the tendency for lesion progression (Loscalzo 2001; Vallance and Chan 2001). After lesions have developed, endothelial dysfunction can exacerbate development of clinical events. Impaired endothelium may abnormally reduce vascular perfusion, produce factors that decrease plaque stability, and augment the thrombotic response to plaque rupture (Loscalzo 2001; Radomski et al. 1987; Diodati et al. 1998).

1.5.3 Inflammation

It is inflammation that plays a central role in atherosclerosis in a large body of experimental and clinical research studies (Libby et al. 2002). Inflammation and

accumulation of minimally oxidized LDL develop together in the arterial wall. Several adhesion molecules are expressed in the endothelial cell, including P- and E-selectins, intercellular adhesion molecule, and vascular cell adhesion molecule-1, which bind to circulating leukocytes (Hansson 2001). Chemoattractants such as monocyte chemotactic protein can mediate transmigration of leukocytes into the arterial wall, which leads to accumulation of inflammatory macrophages and T-cells within the arterial wall (Hansson 2001). Proteolytic enzymes and a variety of peptide growth factors and cytokines which can degrade matrix proteins and stimulate smooth muscle cells, endothelial cells, and macrophages are released by those activated leukocytes. Macrophage accumulation of oxidized LDL leads to foam cells aggregation. Several inflammatory cells, including macrophages, B and T lymphocytes, endothelial cells, vascular smooth muscle cells, and fibroblasts express CD40 receptor and CD40 ligand (Schonbeck and Libby 2001).

Plaque disruption and thrombosis can also be led to by the inflammatory process. A large lipid core, a thin fibrous cap, and inflammatory cells at the thinnest portion of the cap surface are characters of vulnerable plaques (Davies et al. 1993). Matrix metalloproteinases (MMPs) and other substances expressed by macrophages lead to degradation of the cap, resulting in an unstable plaque that is susceptible to rupture, which have been shown in several studies (Galis and Khatri 2002). Then, formation of a thrombus can be led to by exposure of the underlying atheroma and tissue factor to circulating platelets and thrombin. It is serum markers of inflammation such as high-sensitivity C-reactive protein that are elevated in patients with acute coronary syndromes and PAD, which independently predicts subsequent events (Ridker et al. 2001).

1.5.4 Oxidant Stress

Excess generation of reactive oxygen species (ROS) has been proved to be a critical pathological process in atherogenesis. Each component of the atherosclerotic blood vessel has been demonstrated to increase production of ROS, primarily superoxide anion (O_2) (Maytin et al. 1999). Important sources of ROS are endothelial cells, vascular smooth muscle cells fibroblasts, and infiltrating leukocytes (Zalba et al. 2000). The importance of oxidation can be seen by the presence of oxidized LDL in atherosclerotic lesions, although the mechanism of oxidative modification of LDL remains unknown. As measured by autoantibody titers, the amount of oxidized LDL is reflective of the atherosclerotic burden (Tsimikas et al. 2001). Oxidized LDL induces a series of atherogenic processes, including production of matrix metalloproteinases, transcription of proatherogenic genes and antagonism of endothelial cell production of NO, promotion of vascular smooth muscle cell apoptosis (Kita et al. 2001).

1.5.5 Smooth Muscle Cell Proliferation

The vascular smooth muscle cell (SMC) plays a critical role in atherosclerosis. The growth factor, the SMC undergoes a phenotypic change that leads to a migratory and secretory cell that migrates into the neointima after being activated by injury, (Rivard and Andres 2000). SMCs proliferate and secrete matrix proteins and enzymes through growth factor and cytokine stimulation.

The atherosclerotic plaque contains cellular elements and extracellular matrix. The constituents of the plaque's extracellular matrix include proteoglycans, glycosaminoglycans, collagen, elastin, fibronectin, vitronectin, laminin, and thrombospondin. Activated SMCs are closely related to the production of these matrix proteins (Raines 2000). Collagen provides the structural support and scaffold for the vessel wall, whose production and degradation are both increased in atherosclerosis (Rekhter 1999). Activated SMCs and macrophages secrete MMPs that degrade collagen and elastin, whereas SMCs produce collagen (Benjamin 2001). The entire vessel can enlarge or constrict in size during development of atherosclerosis. This is often referred to as geometric remodeling, which plays a critical role in determining luminal patency.

1.5.6 Genetic Factors

Genetic predisposition is an important risk factor for atherosclerosis. In some studies, up to 50% of the risk for atherosclerosis, which is attributable to genetic predisposition (Galis and Khatri 2002). It has been proved that this is a multifactorial disease. Over the next several years, atherosclerosis may be understood as a molecular disease. The challenge will be to identify better diagnostic and therapeutic strategies for these syndromes by using these findings (Ridker et al. 2001).

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