CHAPTER I

INTRODUCTION

Cardiovascular diseases account for approximately one quarter of all deaths worldwide.[1] The proportion of deaths due to cardiovascular disease is estimated to be 50% and 15% of all deaths in developed and developing countries, respectively.[1] World health statistics 2007 by World Health Organization (WHO) showed that, between 2002 and 2030, although age-specific death rates for most noncommunicable diseases are projected to decline, the aging of global population will result in significant increases in the total number of deaths caused by most noncommunicable diseases over the next 30 years.[2] Overall, noncommunicable conditions will account for almost 70% of deaths in 2030 and the four leading causes of death globally in 2030 are projected to be ischemic heart disease, cerebrovascular disease or stroke, HIV/AIDS and chronic obstructive pulmonary disease.[2] Regarding cardiovascular mortality, there are a significant number of patients who die of acute coronary syndromes before they appear in the hospital or shortly after arrival.[3] For the treatment strategy, biochemical markers play a pivotal role in the diagnosis and management of patients with acute coronary syndromes.[4] Moreover, for prognostic and risk stratification purposes, the information from multimarker approach may be needed in order to predict the future cardiovascular events.[5] Currently, there is no ideal marker for these purposes. Therefore, the need for novel cardiac markers will continue as the population and the death from heart disease increases. Recently, urocortins have been reported as a possible marker with cardioprotective effect in heart failure.[6]

Urocortins are peptides belonging to corticotrophin releasing factor peptide family. Growing number of evidence suggest that it may have cardioprotective effects. In the sheep hearts, exogenous urocortins increases heart rate and cardiac output and produces coronary vasodilatation.[7] Its beneficial effects on cardiovascular system were expressed both in the normal heart and in the diseased heart.[8;9] Some cardioprotective effects of urocortins were significantly enhanced in heart failure subjects, suggesting that this peptide may have protective compensatory actions in cardiovascular diseases.[10] Urocortins also enhanced cardiac function during ischemia/reperfusion (I/R). The cardioprotection was reflected in increasing the survival of cultured cardiac rat cells [11], reducing infarct size in the ischemia and reperfused rat hearts [12], improved contractile function in isolated working rat hearts [13], reduced arrhythmic incidences in anaesthetized mongrel dogs [14], and reduced creatine kinase (CK) and LDH levels in isolated rat hearts.[15] It has been showed that ischemia increased the expression of urocortin mRNAs in cultured rat cardiac myocytes which rapidly translated to the mature forms and then rapidly released and exerted protective effects through their receptor.[11] However, long-period ischemia induces apoptosis and necrosis of rat cardiac myocytes and leads to reduce urocortins levels.[16] Therefore, urocortins may act as an endogenous protective substance in the myocardium after triggered by ischemia and reperfusion.

Despite those findings on beneficial effects of urocortins, most studies were performed by using the exogenous urocortins in animal models. There are only a few studies that investigated the role of endogenous urocortins in human.[6;17] Since urocortins are endogenous cardiac peptides and its level was increased after stimulating ischemia of cardiac myocytes [11;16], basal level of urocortins may

determine the degree of cell loss and functional compromise in individual patients suffering from myocardial infarction.[18] Moreover, the raised basal level of urocortins may play a role in pathophysiological effects and may be useful for diagnostic as well as prognostic marker in the cardiac diseases.[6;19;20] Therefore, the present study was designed to investigate levels of plasma urocortins in acute myocardial infarction patients, compared with those in normal subjects. Although previous studies reported plasma urocortins level in human placenta, maternal plasma [21], and also in human systolic heart failure.[6] There is no study that investigates the urocortins level in acute myocardial infarction patients either soon after or remote from the onset. It remains to be seen whether plasma urocortins level is elevated in patients with acute myocardial infarction, how urocortins affects the left ventricular function in human with and without acute myocardial infarction and what are the related factors that involve changes of the urocortins level. Furthermore, since the predictive probabilities of urocortins are also still unknown, the relation of urocortins and the prognostic ability is needed to be proved.

This present study is the first study to investigate the plasma profile of urocortins in acute myocardial infarction patients. The information obtained from this study should provide the reference value, in order to compare with those in normal people, which may be used in diagnosis of acute myocardial infarction. Moreover, the levels of urocortins may be used as a prognostic marker for acute myocardial infarction patients in long term after discharge from the hospital.

LITERATURE REVIEW

Acute myocardial infarction

The ischemic heart disease or myocardial ischemia, otherwise known as coronary heart disease, is a disease characterized by reduced blood supply to the heart. These reductions of the oxygen supply and nutrients to the heart musculature, which are essential supply for proper functioning of the heart, may cause permanent heart muscle damage or acute myocardial infarction resulting in a heart attack.

Acute myocardial infarction is a type of acute coronary syndromes, which is most frequently a manifestation of coronary artery disease. The acute myocardial infarction includes ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI). STEMI is a unique category in which a coronary artery is completely occluded, by more stable occlusive thrombus.[22] NSTEMI infers the partial occlusion of coronary artery or the complete occlusion in the presence of good collateral flow of the related artery.[23] The blockade of coronary artery causes myocardial ischemia.[24] After ischemia, it takes a finite period (20 minutes or less) to develop myocardial cell death or necrosis.[24] The ischemic symptoms include various conditions of chest pain, discomfort of upper extremities or jaw with exertion or at rest.[24] These symptoms usually exert for at least 20 minute. Although there are many etiologies of acute myocardial infarction, the occlusion of a coronary artery by the erosion or rupture of an atherosclerotic lesion on a coronary artery is responsible for most cases.[25]

Epidemiology and risks of myocardial infarction

Myocardial infarction is one of the leading cause of death and disability worldwide.[24] In general, it can occur at any age, but its incidence increases with age. According to the American Heart Association 2004, approximately 64.4 million Americans have cardiovascular diseases, which 7.8 million have suffered an acute myocardial infarction.[26]

A high proportion of deaths from acute myocardial infarction were due to cardiac arrhythmias and approximately two-thirds of coronary heart disease deaths occurred within the first 28 days (median) and the deaths often occurred before the patients reached hospital.[3] Another study also reported that three quarters of deaths from acute myocardial infarction occurred outside the hospital.[27] Interestingly, an over 4000-patients with suspected acute myocardial infarction study reported that the majority of the coronary deaths occurred within the first 24 hours and most of these were not diagnosed as acute myocardial infarction at the time, resulting in patients not being treated properly. Moreover, silent acute myocardial infarction (i.e. acute myocardial infarction with atypical symptoms) occurs in 5-25 % of patients, thus there can be delays in diagnosis.[28] After discharge from the hospital, early risks are higher in patients with STEMI compared to NSTEMI. However, within six months the risk of death is similar with NSTEMI.[29] Rising cardiac biomarker (i.e. serum creatinine) in patients who survived were detected in lesser amount than those patients who died (35% vs. 53.2%, respectively). These findings indicate the benefits of cardiac biomarkers and the need for better markers that are more sensitive and specific as well as having better positive predictive value for the diagnosis, treatment and prognostic prediction in patients with acute myocardial infarction.

Diagnosis of myocardial infarction

Since 1979, according to the WHO, the diagnosis of myocardial infarction requires the presence of at least two of the following three criteria 1) a clinical history of ischemic-type chest discomfort, 2) typical changes in the electrocardiogram (ECG) and 3) a rise and fall in serum cardiac markers [30], which identify irreversibly damaged myocytes. With these WHO criteria, it is possible to diagnose acute myocardial infarction without finding an increase in cardiac biomarkers. The electrocardiogram itself is insufficient to diagnose acute myocardial infarction since ST deviation may be observed in other conditions such as acute pericarditis, left ventricular hypertrophy, left bundle branch block (LBBB), Brugada syndrome and early repolarization patterns.[31] Recently, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) redefined the criteria for acute myocardial infarction in 2000. In particular, the ESC/ACC definition for acute myocardial infarction relies heavily upon measurements of sensitive and specific markers of myocardial injury (primarily the cardiac troponins) together with other criteria.[4]

In 2007, there is a universal definition of myocardial infarction which was composed by a number of experts within related fields (i.e. the field of biomarkers, ECG, imaging, clinical investigations, interventions, global perspectives and implications) in order to refine the ESC/ACC criteria for the diagnosis of myocardial infarction.[24] Currently, more specific biomarkers of myocardial necrosis became available. The accuracy of detecting myocardial infarction has changed to be more specific and sensitive. The criteria for acute myocardial infarction should be explained

by detection of rise and/or fall of cardiac biomarkers, preferably cardiac troponins, together with evidence of myocardial ischemia with at least one of the following:[24]

1. Symptoms of ischemia;
2. ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)];
3. Development of pathological Q waves in the ECG;
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Cardiac markers of myocardial infarction

The courses of acute myocardial infarction are complex and dynamic, involving not only myocardium, but also vascular smooth muscle cells, endothelial cells and leukocytes.[32] In clinical settings, myocardial infarction is diagnosed when alteration of cardiac markers were detected.[24] The use of cardiac biomarkers can be divided into two categories, diagnosis and risk stratification. The existing biomarkers for acute myocardial infarction are different in their qualifications. The ideal biochemical marker for cardiac ischemia should meet the following clinical needs (table 1).[4]

Table 1 Requirements of an ideal marker for cardiac ischemia.[4]

Attributes of an ideal biochemical marker for cardiac ischemia
• Detection of myocardial ischemia whether or not necrosis is present
• No elevation during ischemic injury of other organs
• Rapid rise and fall after ischemia
• Reliable pre-analytical and analytical performance
• Simple to measure with a turnaround time of <60 minutes

Several known cardiac biomarkers for acute myocardial infarction are 1) unbound free fatty acid (FFAu) and Ischemia-Modified Albumin (IMA), 2) Myeloperoxidase (MPO), 3) Creatine kinase (CK), 4) Myoglobin, 5) Cardiac troponins and 6) Brain (B-type) natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP).

Unbound free fatty acid (FFAu) and Ischemia-Modified Albumin (IMA): FFAu is useful in testing for the early identification of cardiac injury.[33] Its elevation occurs well before other, more traditional, markers of cardiac necrosis.[4] The causes and mechanisms of FFAu increasing are not clear. It was found that increased levels of FFAu resulted from adipose lipolysis. Although cardiac lipid hydrolysis was activated by ischemia, the increased levels of serum FFAu seems to originate from non-cardiac tissues.[34] It has been shown that FFAu concentrations were significantly higher in STEMI group vs. NSTEMI group.[34] However, the measurement technology is not yet suitable for routine use and exact potential validation is required in more representative patient groups.[35]

Albumin in serum of patients with myocardial ischemia exhibited lower metal binding capacity for cobalt than the albumin in serum of normal subjects.[36] Based on these observations, an assay was recently developed in which cobalt not sequestered at albumin is detected using a colorimetric indicator.[37] In sera of normal subjects, more cobalt is sequestered by albumin, leaving less cobalt to react with indicator. Conversely, in sera from patients with ischemia, less cobalt is bound by the ischemia-modified albumin (IMA), leaving more free cobalt to react with indicator. Significant changes in IMA have been documented to occur minutes after transient ischemia and

to return toward baseline within 12 hours.[38] However, IMA was not used as a marker in clinical setting because increased IMA values may be found in patients with cancer, infections, end-stage renal disease, liver disease, and brain ischemia.[34] It is not clear about the exact mechanisms of IMA formation and its relationship to pathophysiology of ischemia.[39] Another reason is that the commercially available test's specificity of IMA is relatively poor.[40] Moreover, IMA assay performances and samples analysis need to be analyzed rapidly.[41] Recently, IMA measurement is used in combination with other conformational tests to identify acute myocardial infarction.

Myeloperoxidase (MPO): MPO is a mediator enzyme secreted by a variety of inflammatory cells.[42] It possesses pro-inflammatory properties and may contribute directly to tissue injury.[43] MPO level was increased in plasma after acute myocardial infarction and above-median levels of MPO were significantly associated with a nearly 2-fold increase in mortality.[44] High MPO concentrations remained predictive for increased cardiac risk.[45] The studies in populations with acute coronary syndromes showed that the plasma MPO at hospital admission predicted the risk of major adverse cardiac events in the ensuring 30-day and six-month periods.[45;46] However, it is unclear as yet whether MPO should be routinely used in clinical practice for acute myocardial infarction identification. Increased level of MPO may not be specifically caused by ischemic cardiac disease, as its level was correlated with neutrophil activation but it was not significantly changed after stress-induced ischemia.[47] It is more likely to be a marker for plaque instability. Further validation studies on MPO to determine its sensitivity, specificity, positive predictive value, and negative predictive value are still needed.[48]

Creatine kinase (CK): CK and its MB isoenzyme (CK-MB) is a highly specific marker for the diagnosis of myocardial infarction.[49] CK is found in heart (CK-MB), striated and smooth muscle (CK-MM) and brain (CK-BB). One major advantage of CK-MB as a marker of myocardial infarction is its ability to detect reinfarction.[50]. The CK-MB measurement should be recorded at the time of the first assessment of the patient and 6-9 hours later.[24]

Although most CK-MB assays are reliable and extremely sensitive to early detection of myocardial infarction, CK-MB is not the ideal cardiac marker in all clinical situations. Owing to the fact that it rises within 3-8 hours and returns to normal levels within 36-48 hours after an initial myocardial infarction [50;50;51], if the patients arrive at the hospital later than 36 hours after the onset, the CK-MB peaking pattern will be missed because the level has returned to normal by that time. Also, according to the lack of specificity of this enzyme, CK-MB levels may be falsely elevated in a number of noncardiac conditions such as patients with severe skeletal muscle injury, chronic renal failure and cocaine use.[52;53]

Myoglobin: Myoglobin is an oxygen-binding protein. It is rapidly released after myocardial injury.[54] Myoglobin achieves maximal sensitivity 3 to 4 hours after symptom onset, however, it is only marginally more sensitive than creatine kinase early after the onset of symptoms, and it is less sensitive 6 to 8 hours after symptom onset. Because of rapid clearance from the blood, myoglobin may "miss" late-presenting patients, and it is less cardiospecific than creatine kinase.[54] It is less cardiospecific than CK-MB because it is falsely increased in patients with skeletal disease and renal failure.[55;56]

Cardiac troponins: The cardiac troponins are more specific than other cardiac biomarkers for myocardial injury. It is the preferred biomarker for myocardial necrosis, reflecting even more microscopic zones of myocardial necrosis.[57] Cardiac troponins are found in higher concentrations in the heart than CK [52] and the testing of cardiac troponins has various advantages over CK-MB testing.[52;58] Patients with a normal CK-MB level but raised cardiac troponins level are considered to have minor myocardial damage or microinfarction.[59] Troponins are not normally present in serum unless cardiac cell necrosis has occurred. Thus, these markers are more specific than isoenzyme markers.[50] Moreover, elevated cardiac troponin levels are predictive of poor outcome. Patients with high troponin have a higher risk for acute myocardial infarction and cardiac death within the immediate future (4 to 6 weeks).[60] Cardiac troponins need 4-10 hours after symptom onset to appear on serum, at about the same time as CK-MB elevations become detectable, and peak at 12-48 hours, remaining elevated for 7-14 days.[61;62]

Despite their benefits, cardiac troponins have two main drawbacks that prevent them from being an ideal cardiac marker. First, an advantage of cardiac troponins, their ability to detect cardiac damage up to several days after myocardial infarction, is also a disadvantage in detection of reinfarction if a second or third cardiac event occurs soon after the initial infarction.[50] Second, cardiac troponin is less sensitive than myoglobin in the early stage of infarction.[63] Although cardiac troponin is more sensitive in patients who presented at least 24 hours after symptom onset [52], it has a clinical sensitivity of only 63% in first 6 hours after onset, which is insufficient for effectively early diagnosis.[64]

Brain (B-type) natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP): B-type natriuretic peptide is a 32 amino acid protein, synthesized as a pro peptide and then cleaved to the active moiety by a protease.[62] BNP and the N-terminal fragment of its prohormone (NT-proBNP) are released from cardiac myocytes in response to increases in ventricular wall stress. Its levels are elevated in a majority of patients with acute congestive heart failure.[65] BNP are used for diagnosis of heart failure and prediction of sudden death.[66] However, it was found that gender, age, obesity and renal failure could influence BNP level.[62;67;68] The study of plasma sample from patients with non-traumatic chest pain who presented at emergency department reported that BNP showed increased sensitivity at the cost of decreased specificity for acute myocardial infarction.[69] Because of this tradeoff, BNP cannot be recommended for use among all emergency-department visited chest pain patients. Although plasma BNP is not a good marker for diagnosing acute myocardial infarction, it may be a good marker for prognosis. The plasma levels of BNP measured within a few days (approximately two days) after the onset of myocardial infarction were predictive of an increased risk of death.[70] Plasma BNP levels at above median values were significantly associated with mortality and adverse outcome after myocardial infarction. Plasma BNP and NT-proBNP measured 2 to 4 days after myocardial infarction also independently predicted left ventricular function and 2-year survival.[71] It was higher in patients who were dead and had left ventricular failure. Both plasma BNP and NT-proBNP above median levels were significantly associated with the lesser survival rate.[71]

Currently, there are several cardiac biomarkers used routinely in a clinical setting for acute myocardial infarction diagnosis and morbidity/mortality prediction. The pattern of traditional cardiac biomarkers release after the onset of infarction is shown in figure 1. However, none is clinically ideal due to its sensitivity and specificity. Therefore, using of multibiomarkers would provide complementary information and enable clinicians to stratify risk more effectively among patients with acute coronary syndromes.[5]

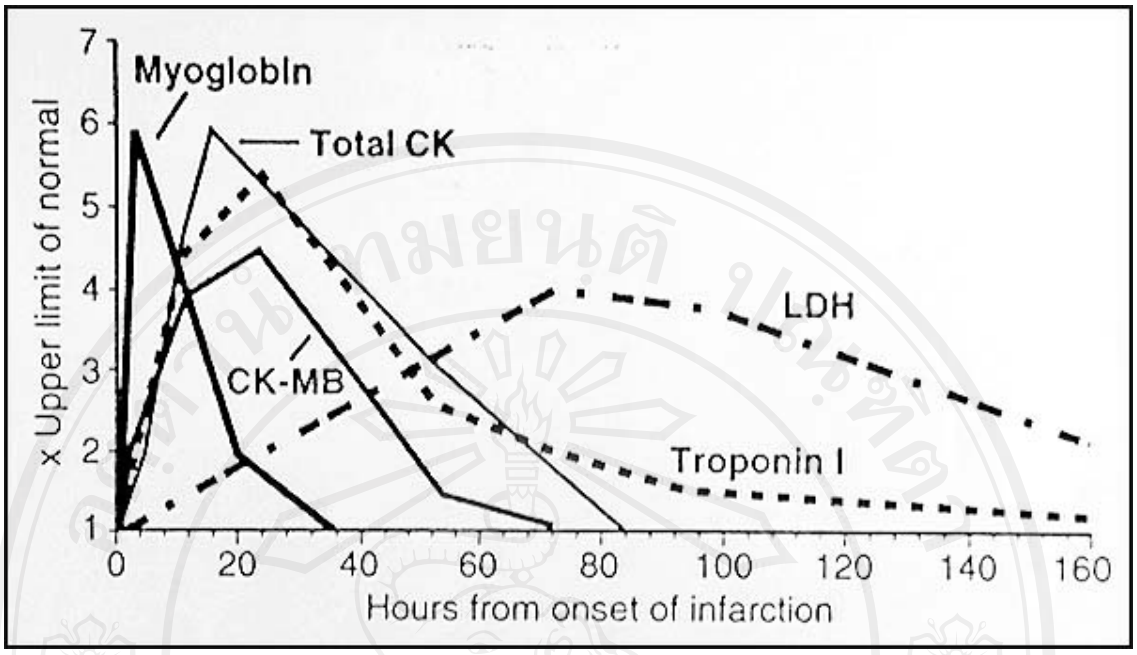

Figure 1 The pattern of cardiac markers released after onset of myocardial infarction.[72]

Table 2 Sensitivities and specificities of cardiac biomarkers for the diagnosis of acute coronary syndrome.

Cardiac markers	sensitivity	specificity
1) Unbound free fatty acid (FFAu) [39]	91%	-
2) Ischemia-Modified Albumin (IMA) [73]	70%	24%
3) Myeloperoxidase (MPO)	-	-
4) Creatine kinase (CK) [74]	95.5%	89.1%
5) Myoglobin [74]	81.8%	100%
6) Cardiac troponins [75]	100%	78-82%
7) BNP and NT-proBNP [69]	87-97%	48-62%

Urocortins

Besides the innovation in cardiac markers studies in the last two decades, several bioactive peptides secreted by the cardiovascular organs were discovered. Since the isolation of the corticotrophin-releasing factor (CRF) in 1981, the mammalian CRF-like peptides have been identified.[76] One of these was urocortin, a 40 amino acid peptide, which was first identified in rat brain in 1995 [77], and later in human.[78] Urocortin is structurally related to CRF, exhibiting 45% homology and also shows homology with urotensin-1 (63%) and frog sauvagine (35%).[79] The urocortin family consists of three peptides; urocortin-1, urocortin-2 (stresscopin-related peptide [SRP] and urocortin-3 (stresscopin [SCP]). In the rat heart, urocortin mRNAs are expressed in vascular smooth muscle cells of cardiac blood vessels as well as in cardiomyocytes, but whether there are the primary source of urocortins is not known.[80] Urocortins exerts their effects through interaction with CRF peptide receptors on target cells. There are two types of urocortin receptors, CRF type 1 (CRF-R1) and CRF type 2 (CRF-R2), both are G protein-coupled receptors.[81] Urocortin-1 mRNA is expressed in all four chambers of human heart [82], and human urocortin-1 was shown to be expressed in various areas such as brain, pituitary, gastrointestinal tract, ovary, endometrium, placenta, synovial tissue, lymphocytes, skin.[83;84] Urocortin-1 binds to both CRF-R1 and CRF-R2 whereas urocortin-2 and urocortin-3 are specific agonists for CRF-R2 receptor which is expressed in the brain, peripheral tissues and cardiovascular organs.[85]

Physiological effects of urocortins

There is accumulated evidence indicating that urocortins has important pathophysiological effects. Vaughan et al., 1995 reported that urocortins lowered blood pressure in rats lasting for almost two hours and were associated with an increase in heart rate.[77] Similar with the study in anesthetized rats, intravenous infusion of urocortins led to a fall in arterial pressure, aortic flow, stroke volume and aortic resistance as well as to increased heart rate and aortic conductance, suggesting a peripheral vasodilator and positive inotropic actions in rats.[80] However, urocortins produced a slowly developing increase in mean arterial blood pressure, cardiac output and heart rate in conscious sheep.[7] Urocortins also induced a rapid and extremely potent increase in cardiac contractility, coronary blood flow, coronary conductance and all of the changes were dose dependent. In a comparison of urocortin effects between normal and experimental heart failure sheep, it has been shown that urocortins have profound and sustained hemodynamic, hormonal and renal effects in experimental heart failure.[10]

Urocortins reduced plasma potassium levels, attenuated vasopressin release and induced natriuresis or diuresis when administered to heart failure sheep [10], indicating that urocortins may play an inhibitory role in the osmotic control of vasopressin release. Another urocortins action that may play an important role in the cardioprotection is stimulating the secretion of natriuretic peptides. Ikeda et al., investigated the effect of urocortins in the regulation of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) release in cultured neonatal rat.[86] They found a significant increase in ANP and BNP secretions. These potent inotropic, chronotropic and hormonal and renal effects of urocortins may prove the useful of

urocortins as cardioprotective effects in cardiovascular diseases such as acute myocardial infarction and heart failure. Urocortins had beneficial effects on cardiovascular system and was expressed both in normal heart and was significantly higher in the left ventricle of failing hearts of dilated cardiomyopathic patients.[20] In systolic heart failure patients, plasma urocortin was elevated particularly in the early state and declined with increasing severity of heart failure and age.[6] Urocortins may have beneficial effects in preventing disease progression. Previous studies demonstrated anti-inflammatory actions of urocortins by down-regulation of the production of inflammatory mediators.[87] Since inflammation has been shown to play a role in the progression of coronary heart disease and heart failure, the anti-inflammatory effects of urocortins may be useful as cardioprotective peptides in these conditions.

Urocortins in myocardial infarction and ischemic/reperfusion injury

Reperfusion of ischemic cardiac myocytes is essential for restoring normal function. However, this return of blood flow can paradoxically produce a progressive destruction of reversibly damaged cardiocytes, necrosis and apoptosis. It leads to coronary endothelial dysfunction and reduction of coronary relaxation.[88] Apoptosis is a contributor to human myocardial infarction and occurs within 24 hours after ischemia.[89] Evidently, the cardioprotective ability of urocortins against the damaging effects of ischemia/reperfusion (I/R) injury could be of considerable medical importance.

There are a number of studies reporting that urocortins are potent cardioprotective peptides against myocardial infarction and I/R injury. In the study

using neonatal rat cardiac myocytes, it has been shown that administration of urocortins results in a significant reduction in infarct size when administered either 30 minutes prior to ischemia or from the moment of reperfusion.[12] Ischemic simulating of neonatal rat cardiocytes is also associated with increased expression of several diverse genes and urocortin mRNAs, which are rapidly translated to the mature form and then rapidly released into the medium, acted in an autocrine/paracrine manner to protect cardiac cells.[11] In the study of urocortins effects using isolated rat hearts exposed to I/R, it was shown that urocortins reduces necrotic and apoptotic cell death and enhances the ventricular function.[18] It was reported that urocortins reduced autophagy, a form of cardiac cell death induced by I/R, resulted in enhancing of cell survival.[90] Urocortins may have beneficial effects on coronary perfusion by protecting the endothelial function, as low concentration of urocortins improved the coronary relaxation in perfused rat hearts after I/R, suggesting that urocortins may have therapeutic potential in myocardial infarction management.[91]

Urocortins may protect endothelial functions via the protein kinase C (PKC) pathway activation because its vascular relaxation action was abolished by PKC blockers.[92] Moreover, when nitric oxide synthesis was blocked, coronary blood flow and myocardial function were also abolished. This suggested that the coronary and myocardial protective actions of urocortins are nitric-oxide dependent.[93] In Brar et al. study, using neonatal rat cardiac myocytes, they found that urocortins productions are increased during ischemia.[11] This peptide is rapidly released and acts as endogenous cardioprotective peptide during ischemic episode. Together with the data from the study using endomyocardial biopsy specimens obtained from the patients with heart

diseases, urocortins were expressed more abundantly in the diseased heart.[19] Cardiac synthesis and release of urocortins were increased when stimulated by short-period ischemia and cardiocytes still remained, without apoptosis.[16] But long-period ischemia induced cardiocytes apoptosis and decreased urocortins production. Therefore, urocortins level may be useful for the detection of sublethal myocardial ischemia.

Expression and plasma level of urocortins

Up to present, there are only few studies that measured plasma urocortins and related peptides in human. From the measurement of urocortins levels in human placenta and maternal plasma by specific radioimmunoassay, although plasma immunoreactive corticotropin-releasing factor levels were increased in pregnant women as compared to men and non-pregnant women, there was no difference of plasma immunoreactive urocortins levels among groups.[21] Urocortins were expressed more abundantly in the diseased heart i.e. hypertrophic cardiomyopathy, dilated cardiomyopathy.[19] It has been found to be raised in human systolic heart failure, especially in early states and declined with increasing heart failure severity. The relative increase was greater in male than female. Urocortins levels fell with increasing age and with increasing in New York Heart Association (NYHA) class in heart failure patients. There was a significant correlation between urocortins levels and ejection fraction in heart failure patients.[6] In the diagnosis of heart failure, incorporating N-terminal pro-brain natriuretic peptide (N-BNP) and urocortins were better than either peptide alone.[6] Plasma urocortins measurement may also complement N-BNP in the diagnosis of early heart failure. These findings have shown the potential of urocortins in heart failure patients.

Despite the potential benefits of urocortins in heart failure, plasma level of urocortins and its role in acute myocardial infarction patients are not yet available. The relationships of involved factors such as sex, age, severity, area of infarction, left ventricular function which may affect plasma urocortins level are also unknown. Moreover, plasma urocortins level may be useful as a prognostic indicator. Until present, it remains to be investigated 1) how plasma urocortins level of acute myocardial infarction patients is changed and 2) whether plasma urocortins level has any relationship with mortality and adverse events in those patients. The understanding of the plasma profile of urocortins and its relationship to the pathophysiological progression in acute myocardial infarction patients may enhance the utilization of urocortins for diagnosis, therapeutic proposes and predicting prognosis in acute myocardial infarction patients.

Hypotheses

1. Plasma urocortins level is increased in acute myocardial infarction patients.
2. Plasma urocortins level of acute myocardial infarction patients are related to the mortality prognostic.

Objectives

1. To investigate the plasma urocortins level in acute myocardial infarction patients comparing with those in healthy controls.
2. To investigate the relationship between plasma urocortins levels and echocardiographic parameters of acute myocardial infarction patients.
3. To investigate the prognostic probability of plasma urocortins level in prediction of mortality in acute myocardial infarction patients.