CHAPTER IV

DISCUSSION

Plasma urocortins level in normal and heart diseases

Biomarkers are one such tool to better identify high-risk individuals, to diagnose disease conditions promptly and accurately, and to effectively prognosticate and treat patients with disease.[99] This is the first study investigating the plasma urocortins levels as one possible putative biomarker for acute myocardial infarction patients. Plasma level of urocortins was significantly increased from the onset day to day 5 after the onset. Moreover, its level on the onset day was significantly predictive for the mortality from cardiac events. Acute myocardial infarction patients whose plasma urocortins levels were higher than 149.99 pmol/l on the onset day were significantly correlated with poorer survival. A previous study reported that the plasma urocortins level in healthy men and women were about 19.5 (3.9 – 68.8) pmol/l and 14.2 (3.9 – 53.5) pmol/l [values are median (range), age 60.9 (26 – 81) yr], measured by using ELISA technique which was different from the assay used in this study.[6] Compared to the present study, the discrepancy of plasma urocortins levels might be explained with the difference of type of the peptide assays. In our study, EIA assays were performed. There are a number of factors that could influence the exact level of urocortins such as methodological factors and assay performance.[100]

In chronic heart failure patients, Ng et al. reported that males had higher urocortins levels than females at the time they were admitted to hospital.[6] However, in acute myocardial infarction patients, the plasma urocortins level was not different between genders at the onset, but only greater in male than female when measured on

the follow-up day in month 6. This finding suggests that unlike chronic heart failure patients, gender did not have influence on the plasma urocortins level at the early state in acute myocardial infarction patients. Therefore, this could be an advantage to use plasma urocortins as an acute myocardial infarction diagnostic marker.

Increased plasma urocortins level in acute myocardial infarction patients

In the present study, the plasma urocortins level was significantly elevated in acute myocardial infarction patients, similar to that found in chronic heart failure patients. This significant increase was found in every experimental day while patients were admitted in the hospital. There are a number of possible reasons to explain why urocortins level was significantly increased in acute myocardial infarction patients. Myocardial ischemia and reperfusion caused not only cardiocytes apoptosis and necrosis, but also induced a marked endothelial dysfunction and reduction of coronary relaxation due to reduced nitric oxide releasing.[101] Increased levels of urocortins after acute myocardial infarction could be a part of cardioprotective response to ischemic/reperfusion injury in these patients. Urocortins has a marked coronary vasodilator and positive inotropic effect.[93;102;103] It has been shown to increased coronary blood flow and myocardial function via nitric-oxide releasing [93]. Moreover, urocortins could promote hemodynamic and bioenergetic recovery and improve cell survival in rat's hearts exposed to ischemia and reperfusion. It enhanced cardiac function by improved left ventricular pressure and reduced necrotic and apoptotic cell death.[18] It also restored tissue's ATP and creatine phosphate levels, resulting in the prevention of necrotic cell death and allowing ischemic cardiocytes to remain viable.[18] In rat hearts exposed to ischemic and reperfusion injury, urocortins could

protect the heart by decreasing the infarction size.[104] Ischemia might be an important trigger that induces the release of urocortins in order to protect and improve the cardiac function. Consistent with a previous study, urocortins level increased after 5-minute ischemia and fell with the occurrence of necrotic cardiac cell death.[16]

Plasma urocortins level in STEMI and NSTEMI

The plasma level of urocortins measured on day 1 was significantly higher in NSTEMI than STEMI group. This finding was similar to the study of plasma NT-proBNP level on admission day, which were significantly higher in NSTEMI than STEMI patients.[105] It has been suggested that factors other than infarct size or pump failure may have a fundamental influence on the elevation of NT-proBNP since they excluded patients with pump failure greater than Killip class II. The differences of urocortins levels in NSTEMI and STEMI may be due to the differences in their primary causes. STEMI is caused by ischemia secondary to acute obstruction of coronary flow, commonly by more stable occlusive thrombus and more frequent single-vessel involvement.[22;106;107] Although fatal acute cardiac damage is less, NSTEMI can be considered as already overburdened heart.[108] NSTEMI have more frequent multi-vessel involvement that may involve more area of myocardium.[106] Hence, the cardiac function of NSTEMI is less than those in STEMI, resulting in lower LVEF and higher LVESV when compared with STEMI. However, the greater amount of viable and reversible myocytes in NSTEMI could have caused higher level of urocortins as found in the present study. It has been reported that the expression of urocortins mRNA and protein level was significantly enhanced in the rat hearts exposed to short-period ischemia, but fell dramatically and proportionally to the

duration of ischemia.[16] Urocortin mRNA as well as urocortin protein were not found in myocytes undergoing apoptosis and necrosis. These findings suggest that urocortins expression and release are mainly sustained by ischemic triggered but still viable myocytes. Furthermore, tumor necrosis factor levels were significantly increased and in STEMI patients were higher than NSTEMI patients, suggesting that STEMI patients were affected by more severe ischemic damage.[109] Therefore, STEMI, which reflects transmural myocardial ischaemia and necrosis, could have post-triggered viable myocytes in lesser amount and also lesser functional recovery, resulting in lesser amount of syntheses and release of urocortins in STEMI patients, compared to NSTEMI patients.

Relationship of plasma urocortins level and echocardiographic parameters

In the present study, plasma urocortins were not correlated with echocardiographic parameters. This finding was different from a previous report in heart failure patients in which urocortins level was positively correlated with LVEF.[6] However, in the study of urocortin-1 infusion in human with heart failure, it was found that urocortin-1 did not alter hemodynamic and echocardiographic parameters such as heart rate, cardiac output, blood pressure, LVEF, LVEDV, LVESV, as well as renal indices.[9] Since previous reports demonstrated that urocortins exert its effects in a dose-related manner, it is possible that the raised urocortins level triggered by ischemia was insufficient to affect the myocardial performance.[10;110;111]

Urocortins is produced in human hearts and found in the highest level in left ventricular chamber and may exert its cardiac effects in autocrine/paracrine manner.[82] In the present study, plasma urocortins level was not significantly correlated with the

areas of myocardial infarction or occluded vessels. This may suggest that urocortins could be produced and then released in endocrine manner to exert its actions. A previous study has shown that plasma BNP level was significantly correlated with size of myocardial infarction.[112] Similar to the present study, the plasma NT-proBNP level was also significantly correlated with occluded vessels and level of severity. These findings could reflect the relationship between NT-proBNP level and post-ischemic myocardial performances. There was a study reported that urocortins could induced BNP secretion from rat neonatal cardiocytes and involved in cardiac hypertrophy.[86] However, in present study, the relationship between plasma NT-proBNP and urocortins level was not found.

Plasma urocortins level and mortality

When measured within 24 hours after the onset (day 0) of acute myocardial infarction, the plasma urocortins levels were significantly higher in patients incurring endpoint of death than patients who had adverse events and who was alive. This may be explained by the fact that according to the cardioprotective benefits of urocortins, it is released after the heart is triggered by ischemia in order to produce transient regulation for cardiac function. If the greater numbers of cardiac myocytes are triggered, the greater amounts of urocortins will be released as in more vulnerable patients. The major cause of death in acute myocardial infarction is sudden cardiac death due to cardiac arrhythmia or ventricular fibrillation.[3] In the study of the hearts of men who died suddenly from coronary disease, the mortality is correlated with vulnerable plaque rupture.[113] The inflammatory process plays an important role in plaque rupture.[114;115] In acute coronary syndrome patients, the proinflammation

agent, named lipopolysaccharide (LPS), is increased.[116] Moreover, acute myocardial infarction patients who experienced ventricular fibrillation had increased proinflammatory response after receiving LPS.[117] LPS increases the expression and secretion of ventricular endothelial growth factor which is involved in the formation of collateral vessels in ischemic myocardium.[118] However, LPS and urocortins can cause a marked decrease in CRH-R2 mRNA expression.[119] It has been reported that urocortins exerted its coronary vasodilation and inotropic effects mainly via CRH-R2.[103] Therefore, in patients who had more vulnerable plague and/or patients who died after myocardial infarction, it is possible that they may have less urocortins receptor level. Furthermore, an increased urocortins level in those acute myocardial infarction patients could be due to their attempt to balance the decreased level of its receptors. As in the present study, the higher level of plasma urocortins was significantly correlated with poorer prognosis.

Prognostic probability of plasma urocortins level

The present study is the first study to discover that plasma urocortins level is an effective predictor for mortality in acute myocardial infarction patients. This similar scenario has been reported with BNP level.[71] A previous study reported that plasma NT-proBNP measured 2 to 4 days after myocardial infarction independently predicted left ventricular function and 2-year survival, and that high plasma NT-proBNP levels at above median was significantly correlated with lesser survival rate.[71] In the present study, the prognostic probabilities of plasma urocortins and NT-proBNP levels were examined. Plasma urocortins levels within 24 hours after the onset were significantly predictive for mortality. Furthermore, the urocortins levels at above the cutoff value

were significantly associated with poorer survival. Plasma NT-proBNP levels at above the cutoff value were also significantly correlated with poorer survival, a consistent finding with a previous study.[71] Moreover, when using the combined-cutoff values of urocortins and NT-proBNP, the specificity and predictive value of mortality prediction was stronger than using urocortins alone. These findings suggest the additional advantage point of using multiple-markers to evaluate the prognostic prediction of acute myocardial infarction patients.

Study limitations

In this study, it is possible that the therapeutic management in these patients may alter the exact plasma urocortins and NT-proBNP level. Future large clinical trials are needed to warrant these findings and to investigate whether the absolute value of plasma urocortins and NT-proBNP levels are affected by biological or therapeutic factors.

Clinical Implications

The elevated plasma urocortins level can help to identify acute myocardial infarction patients at high risk of mortality, in order to avoid aggressive treatment, and unnecessary tests. It can be used by clinicians to plan treatment strategies with additional caution. Together with high negative predictive value, it is helpful to use plasma urocortins level to identify the patients who are likely to have certainly satisfied outcome and not at intermediate risk for cardiovascular mortality.