Review Article

The role of copeptin as a novel cardiovascular biomarker

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ABSTRAK

Kopeptin adalah peptida ujung C dari provasopresin, prekursor arginin vasopresin (AVP), suatu hormon antidiuretik hipotalamus. Fungsi AVP diketahui sebagai pengatur kadar air, volume darah, dan homeostasis elektrolit, tapi fungsi fisiologis kopeptin sendiri belum diketahui. Kopeptin disekresikan bersama AVP dalam jumlah ekuimolar sebagai respons terhadap stimulasi pelepasan AVP, sehingga pelepasan kopeptin dapat mewakili pelepasan AVP. Kadar AVP, kopeptin, dan neuropeptida lain dalam sistem vasopresinergik meningkat pada kondisi stres akut suatu penyakit. Penggunaan klinis AVP memiliki kekurangan sehingga keandalannya kurang. Sebagai penanda biologis pengganti, kopeptin ideal dalam penilaian klinis karena lebih stabil, pemeriksaan praktis, dan hasil cepat tersedia. Contohnya, kombinasi kopeptin dan troponin jantung memungkinkan penyingkiran infark miokard akut (IMA), dan kombinasinya dengan brain-type natriuretic peptide *(BNP) atau prekursornya dapat memprediksi luaran buruk pada gagal jantung kronik (GJK). Pada syok kardiovaskular, konsentrasi kopeptin meningkat. Disimpulkan bahwa kopeptin merupakan penanda biologis penting pada deteksi dini IMA dan prediktor morbiditas dan mortalitas GJK.*

ABSTRACT

Copeptin is a provasopressin-derived peptide, the precursor for arginine vasopressin (AVP), which is an antidiuretic hormone from the hypothalamus. Copeptin is secreted together with AVP equally as a response of AVP stimulation. While AVP's main function is water and blood volume regulation and maintaining electrolyte homeostasis, copeptin's function is still not fully understood. AVP, copeptin, and other vasopressinergic neuropeptides' levels are elevated in acute stress caused by pathological conditions. Clinical use of AVP levels has many weaknesses. Copeptin can act as a replacement because of its molecular stability, easier testing methods, and faster results. For example, combination of copeptin and cardiac troponins can eliminate myocardial infarction (MI) diagnosis faster, while combined with brain-type natriuretic peptide (BNP) or its precursor can predict heart failure (HF) outcome. In cardiovascular shock, copeptin levels are elevated. As such, copeptin is a potential biomarker for MI diagnosis and predictor for HF mortality and morbidity.

Keywords: biomarker, copeptin, cardiovascular shock, heart failure, myocardial infarction, vasopressin

pISSN: 0853-1773 • eISSN: 2252-8083 • http://dx.doi.org/10.13181/mji.v24i1.1208 • Med J Indones. 2015;24:59-66
• Received 17 Feb 2015 • Accepted 26 Mar 2015

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The introduction of biomarkers has brought improvement for both diagnostic and management of cardiac patients. Cardiac troponins, brain-type natriuretic peptide (BNP), and its precursor, N-terminal BNP (NT-proBNP), are important in evaluating, diagnosing, and stratifying the risk of acute coronary syndrome (ACS) and heart failure (HF) patients.[1] Both BNP and NT-proBNP's are influenced by age, which considered as one of their weakness. In addition BNP has great time-variability in HF patients. Luckily, novel biomarkers like procalcitonin and copeptin have been discovered to complement their predecessors.[1-3]

Copeptin at first was thought to be a novel neuroendocrine hormone in the vasopressinergic system. Copeptin, a precursor for arginine vasopressin (AVP), is a glycopeptide that belongs to the class of provasopressin. Since AVP is unstable and unfit to be used as a biomarker, copeptin instead used in the place of AVP. Copeptin is secreted from pituitary gland together with AVP after hemodynamic and osmotic stimuli.[1-5] Copeptin levels can be easily calculated in an hour, perfect for both HF and emergency setting. There is also proof that copeptin is possibly useful as a diagnostic and prognostic biomarker in various cardiovascular diseases. It has been studied and proven for years that copeptin is a prognostic biomarker for myocardial infarction (MI), HF, and acute decompensated HF.[1-3,5] This review article focuses on the profile and role of copeptin as a novel cardiovascular biomarker.

Structure, synthesis, secretion and function

Copeptin is a 39-amino acid, glycosylated peptide, and the C-terminal part of provasopressin. It has molecular weight of 5000 dalton.[4,6,8] Copeptin, along with AVP and neurophysin-II (NP-II), is derived from pre-provasopressin, which is encoded from chromosome 20p13. It is encoded from the third exon alongside the latter part of NP-II, while the first two exons are encoded into AVP and NP-II. AVP, an antidiuretic hormone, is a peptide produced in the hypothalamus and functions as water conservation signal for the kidney, also as osmotic and homeostatic regulator of the cardiovascular system. Meanwhile, NP-II is thought to be associated with AVP in its maturation and transportation.[6,8]

Synthesis of AVP, NP-II, and copeptin from its precursor occurs along the axonal pathway in the paraventricular and supraoptical nucleus, after which all three will be transported to the posterior pituitary and stored inside vesicles. AVP is also synthesized in parvocellular neurons in hypothalamus, and stored in the median eminence, ready to be secreted when there is stimulus.[4] Copeptin is also secreted equally alongside AVP in response to the stimulus, in essence reflecting the amount of AVP secreted and correlates with plasma osmolarity.[4,6-7,9-10]

As a vasoactive pituitary hormone, AVP functions as regulator for water, blood, and electrolytes homeostasis after hyperosmolar state. AVP couples with 3 receptors, AV1a, AV1b, and AV2, with AV1a serving as the main, most expressed receptor.[4,11] AV1a is expressed in, among others, endothelial smooth muscle, adrenal gland, myometrium, urinary tract, adipocytes, and the nervous system. Coupling of this receptor with AVP causes arterioles vasoconstriction, platelet aggregation, positive inotropic action, steroid hormones synthesis, gluconeogenesis, cardiomyocyte, smooth muscle myocyte and hepatocyte proliferation, and also central regulation of the (blood pressures, heart rates, body temperatures) and emotional signs.[4,11] In the other hand, AV1b receptors stimulate adrenocorticotropic hormone (ACTH), and AV2 receptors that increases water permeability collecting ducts of the kidney, causing water reabsorptions. AV2 receptors can also be found in endothelial cells, and it plays a role in blood clotting.[4,11]

AVP is a major part in hypothalamic-pituitary-adrenal (HPA) axis, and any stimulus activating the axis will end in AVP release, along with corticotropin-releasing hormone (CRH). The two hormones will, in turn, activate the corticotrophic cells in anterior pituitary and trigger the release of ACTH. The end result is the release of cortisol from the adrenal glands.[4,12] AVP and CRH also regulate autonomic limbic response to stress condition, both acute and chronic, such as in obesity and diabetes mellitus.[4]

Meanwhile, copeptin's function is still not fully understood. Recent hypothesis suggests that copeptin acts in provasopressin processing, specifically on the proteolytical maturation,

correct folding, and structural stabilization of provasopressin.[4,6,7] Those processes are thought be stimulated by interaction of copeptin and calnexin-calreticulin system. This hypothesis was found to be significant in the pathogenesis of diabetes type I, where the lack of copeptin causes defective provasopressin folding.[4]

Copeptin levels as a biomarker and comparison to other biomarker

As mentioned before, because of its equal secretion rate, copeptin levels reflect the AVP levels in the aforementioned AVP-CRH system. Several other studies have proven that copeptin levels are increased in acute phase of a disease. For example, Katan, et al[12] concluded that there is a positive correlation between plasma copeptin levels and individual stress degree including insulin resistance, diabetes, obesity, metabolic syndrome, and diabetic nephropathy.[4,13] Copeptin levels also increase in critical conditions like sepsis, hemorrhagic shock, and stroke, insulin-induced hypoglycemia in diabetes type 1 patients, and in pituitary adenoma after trans-sphenoidal surgery. In the cardiovascular system, serum copeptin levels immediately increase after an acute episode of myocardial infarction (MI). No significant change in copeptin levels has been suggested as a negative predictor for MI especially in atypical chest pain patients. In conclusion, copeptin has potential as a biomarker for stress conditions.[4,13,14]

Copeptin also have a positive correlation with diseases' severity and prognosis, where it can predict the outcome of a patient. The accuracy of this has been studied in several conditions, such as sepsis, pneumonia, lower respiratory tract infections, stroke, and other acute conditions with positive results. Copeptin provides additional prognostic information to clinical outcomes, and can support clinical judgement. Thus, copeptin is deemed to be potentially useful as a diagnostic and prognostic tool in acute conditions.[4,12]

Copeptin has advantages over other biomarkers. Compared to AVP, copeptin is superior. AVP has several weaknesses as a biomarker. AVP has a very short half-life (5-15 minutes), with very high affinity to thrombocytes (more than 90%). AVP's very small size also makes the test hard to validate. AVP is also unstable *in vitro*, even in -20°C because of its quick biodegradation. Another weakness is that AVP analysis takes a long time (12-24 hours), with complex procedures and meticulous sample management, which makes it impractical.[4] In the other hand, copeptin is stable both *in vivo* and *in vitro*, residing in blood plasma and serum for 7-10 days in room temperature, and up until 14 days in 4°C. Sample extraction and management is also easier in copeptin, and it also applies to its test procedures. Minimal amount of blood is required for the test (50 µL), unlike AVP (1 mL). Lastly, copeptin levels are available faster for analysis (1-5.5 hours from extraction).[4]

Currently, cardiac troponins I and T are the standards for MI diagnosis in clinical laboratories. Both biomarkers are specific in myocardial tissue alongside good sensitivity for diagnosing and stratifying the risk of MI and acute coronary syndrome (ACS) patients. The main drawback of troponins is its delayed accumulation in plasma, resulting in a negative result in some early examination. Consequently, it will need serial sample extraction and testing to determine MI diagnosis. Also, even though it has good sensitivity, troponin does not have good specificity.[15] Because of that drawback, examination of high-sensitivity troponins needs to be coupled with copeptin. Several studies has combined those biomarkers with promising results, where with an additional copeptin cut-off levels, MI diagnosis specificity is higher compared to high-sensitivity troponin alone, with comparably good sensitivity.[15]

Although MI prognosis has improved with time, HF still causes high rates of cardiovascular morbidity and mortality, especially after MI. Clinical symptoms alone could not accurately predict which patient has a risk of post-MI complications. As such, biomarkers have been used as a tool to predict the outcome of these patients. BNP and NT-proBNP (more stable compared to BNP) are biomarkers with promising results in this aspect, especially in patients with ACS history.[15] Recent studies have shown that copeptin can also predict negative outcomes in HF patients, especially among those with elevated NT-proBNP. In unstable HF patients, copeptin can also accurately predict mortality. Copeptin is also elevated in deceased acute MI patients compared to surviving ones. This is why copeptin is considered as a significant and independent predictor for mortality or negative outcomes.[15]

Copeptin as a myocardial infarction biomarker

In acute MI cases, especially in ST-segment elevation MI (STEMI), it is important to applies pharmacological reperfusion therapy administration as soon as possible, either by percutaneous coronary intervention (PCI) or fibrinolytic medications, to reduce morbidity and mortality rates.[4,16,17] Patients with non-ST-segment elevation MI (NSTEMI) or unstable angina pectoris (UAP) are also in indication for early catheterization, in addition to an intensive antiplatelet therapy. Revascularization of unstable coronary lesion is important to prevent future ischemic complications.[18]

In MI cases, cardiac troponins levels, alongside electrocardiography (ECG) findings, are a key element and gold standard for diagnosing MI in emergency care. Cardiac troponins are myocardial structural proteins and its appearance in plasma signals myocardial necrosis. Unfortunately, troponins cannot differentiate between ischemic and non-ischemic causes of necrosis.[4,19-21] Troponins also have a delayed increase in plasma concentration (6-9 hours from onset of symptoms), which is why its sensitivity are low in the early phase of MI.[4,22,23] Thus, biomarkers that are not dependent on myocardial necrosis, such as copeptin, can provide more information on whether there is myocardial ischemia, plaque rupture, or other early MI symptoms to help an early diagnosis.[4,23]

Several studies have been conducted on the usefulness of copeptin as a cardiac biomarker. Reichlin, et al[24] conducted a cohort study in emergency patients with symptoms suggesting acute MI with onset ≤ 12 hours, where copeptin and other biomarkers (cardiac troponin-T (cTnT), creatine kinase myocardial band (CKMB), myoglobin) are serially evaluated in 3, 6, and 9 hours.[24] The result was that copeptin levels were significantly higher in MI patients. When compared to cTnT, copeptin levels were elevated earlier after onset (as soon as 4 hours after onset of symptoms).[24] Copeptin, with a cutoff level of 14.0 pmol/L, combined with other biomarkers, especially cTnT, had a high rate of sensitivity (98.8%) with good specificity (77.1%) when compared with cTnT alone or with combination of other biomarkers without copeptin. It can be concluded that copeptin is a viable additional biomarker to diagnose acute MI in early presentation without the need for a serial cTnT testing.[24]

Keller, et al.[23] conducted a similar study in patients admitted to emergency with acute chest pain complaint, where copeptin, cTnT, CKMB, and myoglobin levels were analyzed at admission, three hours, and six hours after. It was found that while plasma concentration of cTnT increase over time, copeptin levels decrease over the same time, with plasma copeptin in MI patients being five times higher than those with non-cardiac chest pain or unstable angina in the first three hours of onset and declined subsequently. It was concluded that copeptin and cTnT combination had the best accuracy compared to other biomarkers to diagnose MI in the early hours afer onset.[23]

Another study by Ray, et al[25] in patients with ACS history ≤ 6 hours of onset and no ECG or cardiac troponins (cTn) findings on admission examined copeptin levels once on admission and cTnT levels after 3, 6, and 9 hours. The results showed that mean copeptin levels were significantly higher in MI patients compared to non-ischemic patients, with no difference between STEMI and NSTEMI patients. Concurrent with the other studies, copeptin combined with cTnT had the best accuracy in predicting MI. With a copeptin cutoff level of 10.7 pmol/L, the negative predictive value (NPV) was 98%.[25]

Potocki, et al[26] further strengthen the aforementioned studies in their study. In their study, ACS patients with symptoms of acute MI were examined of their copeptin, cTnT, or high-sensitivity cTnT (hs-cTnT) to evaluate its diagnostic and prognostic value. MI patients with prior ACS history can possibly have chronically elevated cTn levels, alongside with permanent ECG changes. Copeptin levels were significantly higher in MI patients compare to non-MI patients, with higher accuracy when combined with cTnT or hs-cTnT, with NPV of 99.5%. From the prognostic side, copeptin was found to be an independent factor for 1-year mortality. They concluded that in patients with ACS history, copeptin significantly enhances the diagnostic accuracy combined with cTnT, and it can act as an independent prognostic predictor for survival.[26]

A study by Chenevier-Gobeaux, et al[27] compared cardiac troponin I (cTnI) with copeptin in early

MI diagnosis in patients with MI symptoms, where cTnI and copeptin levels were compared at admission, after three hours, and after nine hours. Plasma copeptin levels were found to be significantly higher in MI patients compared to other group of biomarkers. Combined with cTnI, copeptin had a very high sensitivity and NPV. It was concluded that copeptin combined with cTnI can provide faster and more reliable diagnosis of MI.[27]

Lastly, a study from Folli, et al supports the superiority of Copeptins.[28] The study included patients who were admitted to emergency room with chest pain less than eight hours of onset, to whom dual biomarker examination of cTnT and copeptin were done. The result was that the combined examination provides a high accuracy to detect MI. The examination was more accurate in STEMI rather than NSTEMI.[28]

As described in above studies, copeptin and concurrently AVP significantly increases after acute MI. Unfortunately, the exact mechanism underlying these changes are not yet well understood. Several hypothesis have been proposed to explain this phenomenon, including the theory that AVP acts as an early stress response to life-threatening situations such as acute MI. In this response, AVP synergistically works with ACTH and cortisol as acute stress moderator. Another hypothesis is the hemodynamic hypothesis, where acute changes in cardiac dynamics, including underfilling, and the stimulation of cardiac baroreceptors after tissue injury resulted in AVP and copeptin release.[4]

Copeptin as a heart failure biomarker

In patients with heart failure and systolic dysfuction, individual prognosis can be hard to predict because of the varying clinical progression. The secretion of AVP in the pathogenesis of HF, and subsequently copeptin, has been evaluated in the condition. It was found by Uresky, et al. that plasma AVP concentration was elevated in chronic HF patients compared to non-chronic HF. In HF, AVP contributed to the progression of left ventricular (LV) dysfunction by stimulating ventricular hypertrophy and myocardial remodeling. Ebert, et al[32] also found that AVP has a big role in cardiovascular function and peripheral resistance mediated by cardiopulmonary baroreflex.[5,29-32]

Copeptin as a HF biomarker has recently been studied by several studies.[5,31] In one study, Khan, et al[8] analyzed the copeptin and NT-proBNP levels in post-MI patients to evaluate its prognostic value. Copeptin levels, alone or in combination with NT-proBNP, were found to be significantly higher in rehospitalized and deceased HF patients compared to surviving ones. Copeptin and NT-proBNP levels were also deemed as an independent predictors for 60-days HF mortality rate. These two biomarkers can help predict the prognosis of the patients, stratify their risk level, and evaluate the disease progression.[5,33]

Another study by Neuhold, et al[31] evaluated long-term predictive values of copeptin in all HF patients and compared it to BNP and NT-proBNP.[5,31] The study concluded that BNP, copeptin, and glomerular filtration rate (GFR) have an association with New York Heart Association (NYHA) functional class, a strong predictor for 24-months outcome of HF. Copeptin plasma levels also had a strong association with all-cause mortality, regardless of clinical signs and other predictors. Copeptin was then concluded to be superior to BNP and NT-proBNP as a predictor.[5,31] Similar results were found by Alehagen, et al where they evaluated, among others, concentrations of copeptin combined with NT-proBNP in predicting all-cause and cardiovascular mortality in geriatric patients with HF symptoms.[34] The study revealed that elevation in copeptin concentration, alone or combined with NT-proBNP, was related with both all-cause and cardiovascular mortality.[34] Balling, et al[35] also supported the evidence, where in HF patients with LV systolic dysfunction, copeptin was an independent predictor for hospitalization and mortality in those patients.

A different study by Marques, et al. analyzed the two year prognosis of symptomatic HF patients with varying degrees of systolic dysfunction. The study observed whether HF biomarkers, alongside clinical and echocardiographic results, can give additional prognostic information not provided by ejection fraction (EF) alone.[29] The results showed that copeptin was independently related with 2-year mortality outcome.[29] Khan, et al[8] also reported similar association between copeptin and LV dysfunction in early, post-acute MI stage and the association was remained during follow-up. Furthermore, copeptin was also associated with ventricle remodeling severity

after acute MI. This shows that AVP system could have progressive effects on LV dysfunction beyond the acute process of MI. AVP can cause cardiac remodeling, increase peripheral resistance and afterload ventricle stress, and cardiac fibroblast stimulation, the last one mentioned being the main target of AVP. Fan, et al[36] concluded in their study that myocardial fibrosis is possibly a result from contrasting balance effect between AVP and nitric oxide (NO).

Beside its relations with LV dysfunction, copeptin can also predict other negative outcome in potential HF, for example in post-MI patients. The OPTIMAAL (Optimal Trial in Myocardial Infarction With the Angiotensin-II Antagonist Losartan) study by Voors, et al[2] analyzed these in a subset of their patients. They found that in post-MI patients with HF, copeptin levels were a strong biomarker for morbidity and mortality, even stronger than BNP and NT-proBNP. They also proved that serial copeptin examination had a better predictive value than one-time examination on admission.[5,37]

Another study by Tentzeris, et al[37] analyzed copeptin in conjunction with hs-cTnT levels in stable, high-risk HF patients. The patients were then followed to evaluate mortality and hospitalization caused by HF. Both copeptin and hs-cTnT independently predicts negative clinical outcomes. There was a stronger association when both copeptin and hs-cTnT were combined in predicting negative outcomes.[37] Evidence provided supported above proves the capability of copeptin as a predictor for morbidity and mortality in HF.[38]

Copeptin as a cardiovascular shock biomarker

In patients with shock, including cardiovascular, hemorrhagic, and septic shock, there is an increase of plasma AVP levels. This phenomenon was observed by Lindner, et al[40] in post-successful resuscitation patients after shock. AVP concentration, among other hormones, was increased compared to those with unsuccessful resuscitation. It was hypothesized that in those unsuccessful patients, the lower hormone levels might indicate neuroendocrine dysfunction response.[5,39-41] This study was further analyzed by Krismer, et al[41] to analyze the impact of AVP in cardiopulmonary resuscitation. The latter concluded that AVP administration was more effective than epinephrine in asystole patients. AVP followed by epinephrine administration was also more effective compared to epinephrine alone in recurrent cardiac arrest.[39,41]

Hemorrhagic shock's effect on copeptin was studied by Morgenthaler, et al where they found an increase in copeptin plasma concentration in hemorrhagic shock-induced experimental monkeys.[5,39] They observed the same phenomenon in humans with shock conditions. Copeptin levels drastically increased in 2 hours post-onset and reached its peak in the third hour. After reperfusion, copeptin levels decreased after an hour and steadily declined until reaching a plateau. In critical state, copeptin levels were even reach a higher level.[5,39] After eliminating other factors, copeptin levels were proven to be an independent and significant predictor for mortality in shock. Additionally, in deceased patients copeptin levels were higher than those surivived. Also, the severity of shock has an association with higher levels of copeptin, where it was found that in a severe sepsis, the level of copeptin was also increased.[39]

Prior studies also found that AVP is increased in hemorrhage, which causes a decrease in arterial pressure. A study by Arnauld, et al[42] in experimental monkeys analyzed the effect of hemorrhage on AVP secretion by taking different amounts of blood from the monkey and subsequently examining its blood pressure. AVP was secreted if there is a drop in blood pressure, and thus it was concluded that blood pressure decrease will lead to AVP release. As copeptin are released together with AVP, it was concluded that concentration of copeptin will follow AVP concentration in the plasma.[5,42]

In conclusion, copeptin, a C-terminal peptide derived from provasopressin, can indicate AVP levels in the body. AVP functions as awater and blood volume regulator and electrolytes' homeostasis, whereas copeptin's function is still not fully understood. The levels of AVP, copeptin and other neuropeptides in the vasopressinergic system increase in acute stress conditions.

Because of limitations in AVP, copeptin is thought and proven to be an alternative biomarker to AVP because of its superiority compared to AVP.

Copeptin alone or combined with other biomarker has been shown to be superior as biomarker in clinical settings. Copeptin can diagnose acute MI earlier when combined with cardiac troponins or predicts negative outcome in HF patients when combined with BNP or NT-proBNP. In shock conditions, there is also studies that showed an increase in copeptin levels. Thus, copeptin is an important biomarker in MI early detection and is a significant predictor for morbidity and mortality in HF.

Acknowledgment
I would like to thank to dr. Gusti Rizki who helped me to finish the paper.

Conflicts of Interest
The authors affirm no conflict of interest in this study.

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