

The role of arginine vasopressin in myocardial infarction and reperfusion

Andre Nobian¹, Ashfaq Mohammed², Ioakim Spyridopoulos^{1,2}

¹ Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom

² Department of Cardiology, Freeman Hospital, Newcastle upon Tyne, United Kingdom

KEY WORDS

acute myocardial infarction, copeptin, microvascular obstruction, reperfusion injury, vasopressin

ABSTRACT

Little attention is paid to the coronary microvasculature when treating acute myocardial infarction (MI). Microvascular obstruction (MVO) contributes to ischemia–reperfusion injury, which hampers distal blood flow to the myocardium despite recanalization of the culprit epicardial vessel. One of the mechanisms behind reperfusion injury is MVO due to persistent vasoconstrictor tone during reperfusion. Arginine vasopressin (AVP) is a hormone with prominent vasoactive effects on the coronary microvessels. Its levels are elevated as part of a stress response triggered by MI, which was shown to exert vasoconstrictive effects on the coronary arteries in preclinical models, mainly in the nonepicardial vessels of the microcirculation. Circulating AVP levels are up to 100-fold higher in MI and do not immediately decrease to baseline levels on reperfusion. This results in the so called coronary slow flow phenomenon and mediates ischemia–reperfusion injury. Recently, the C-terminal fragment of preprovasopressin, copeptin, has emerged as a surrogate biomarker for AVP, as it is more stable in the circulation. Multiple studies have shown the predictive value of both AVP and copeptin with regards to long-term prognoses of MI patients. We propose that both AVP and copeptin have more than just a predictive value but also play a role in the pathophysiology of adverse outcome post-MI. Therefore, the treatment of choice for MI should not only focus on the epicardial vessel but also on targeting MVO that might pre-exist or might directly follow reperfusion. This mandates a clinical trial with an AVP-receptor antagonist in patients with acute MI undergoing reperfusion therapy.

Introduction Cardiovascular disease remains the top cause of mortality worldwide with estimated 17.9 million deaths in 2016,¹ coronary artery disease being the single largest contributor. Acute coronary artery disease manifests with plaque rupture as an acute coronary syndrome, with ST-segment elevation myocardial infarction (STEMI) being the most serious manifestation due to complete coronary artery obstruction and extensive myocardial ischemia as a result. Prolonged ischemia may result in irreversible myocardial damage; thus, the treatment of choice is aimed at reopening the occluded coronary artery to achieve myocardial reperfusion. Primary percutaneous coronary intervention (PCI) is the first-line strategy, involving reopening of the artery and placing a stent.² Primary PCI is intentionally used

to salvage a viable myocardium, limit an infarct size, and preserve systolic function. Yet, damage to the heart can still occur following reperfusion, which is known as ischemia–reperfusion injury.³ Therefore, myocardial reperfusion still comes at a cost despite restoration of blood flow.

The pathogenesis of ischemia–reperfusion injury is thought to be multifactorial. Factors include distal embolization, endothelial damage, leukocyte infiltration and plugging, reactive oxygen species production, sarcoplasmic reticulum dysfunction, the opening of the mitochondrial permeability transition pore, cell swelling, and others.^{3,4} Together with these factors, microvascular obstruction (MVO) also plays a role in ischemia–reperfusion injury. It involves impaired vasodilation, thus

Correspondence to:

Prof. Ioakim Spyridopoulos,
MD, FRCP, FESC,
Cardiovascular Research Centre,
Institute of Genetic Medicine,
Newcastle University,
Central Parkway,
Newcastle upon Tyne,
NE1 3BZ, United Kingdom,
phone: +44 191 2418675, email:
ioakim.spyridopoulos@newcastle.ac.uk

Received: September 19, 2019.

Accepted: September 20, 2019.

Published online:

September 25, 2019.

Kardiologia Pol. 2019; 77 (10): 908–917

doi:10.33963/KP.14986

Copyright by the Author(s), 2019

increasing the likelihood of neutrophil plugging and microembolization.³

Microvascular obstruction in ischemia-reperfusion injury

Coronary angiography allows a visualization of larger conductive epicardial coronary arteries. However, the coronary arterial system not only consists of conductive vessels but also of smaller microvessels, which get little attention and are often neglected in daily practice. This is most likely because the microvasculature of the heart is not easy to visualize and is difficult to access (diameter <300 µm).^{5,6} In a considerable proportion of patients with STEMI (30%–40%), recanalization of the epicardial coronary artery does not necessarily correspond to reperfusion of the myocardium.^{7,8} This condition is known as slow flow (with its extreme form called no-reflow) and is defined as inadequate myocardial perfusion without evident angiographic obstruction, with a possible involvement of sustained MVO.^{8–10} Failure to completely reperfuse the myocardium in patients with STEMI is common yet often goes unnoticed due to the lack of a sensitive microvascular evaluation method.¹¹ Clinical presentations of this phenomenon include the lack of improvement in cardiac function postreperfusion, chest pain following recanalization, and reduced reflow (measured as thrombolysis in myocardial infarction grade <2 flow) after primary PCI.^{8,9,12}

Microvascular obstruction augments ischemia–reperfusion injury by causing slow flow and is associated with a larger infarct size and lower left ventricular ejection fraction.^{3,8} Carrick et al¹¹ measured the index of microvascular resistance (IMR) at the end of primary PCI in 283 patients with STEMI and found that an IMR higher than 40 was closely associated with MVO. A normal value was generally considered to be less than 25. Furthermore, in a multivariate analysis, the level of IMR was associated with deleterious left ventricular changes and poor long-term clinical outcomes following STEMI (ie, a 4-fold increase in heart failure or all-cause mortality rates).¹¹ The authors also concluded that IMR was superior for risk stratifying patients with myocardial reperfusion failure.¹¹ In line with that, Fearon et al¹³ also discovered that IMR at the time of STEMI could predict the extent of myocardial damage. Patients with an IMR of more than 40 had a higher rate of death or heart failure at 1 year than those with an IMR of 40 or lower (17.1% vs 6.6%; $P = 0.027$). In patients with high IMR, the hazard ratio for death and heart failure was 4.3 and 2.2, respectively.¹³ These findings strengthen the importance of assessing microvascular dysfunction in predicting the outcome after STEMI therapy. Therefore, the treatment of choice for myocardial infarction (MI) should not only aim to restore epicardial blood flow but also to target

MVO that might pre-exist or might directly follow reperfusion.

Initially, MVO was widely considered as a manifestation of ischemia–reperfusion injury subsequent to STEMI reperfusion. It had been postulated that reperfusion contributed to MVO through embolization of debris.¹⁴ However, Khan et al¹⁴ examined the MVO phenomenon using cardiac magnetic resonance in 94 patients with STEMI with and without reperfusion therapies (ie, primary PCI, thrombolysis, and rescue PCI). They found that the occurrence of MVO was comparable across all groups—irrespective of a recanalization mode—including the nonreperfused group. The authors concluded that MVO was primarily related to ischemic time and was not exclusive to reperfusion therapy.¹⁴ This clearly demonstrates that MVO may develop during MI independent of reperfusion therapy and is rather a sign of extensive microvascular and myocardial damage, eventually promoting even further ischemia–reperfusion injury.

Understanding the mechanisms of slow flow is pertinent to the management of this condition. One factor that is proposed to contribute to MVO is a persistent vasoconstrictor tone after revascularization. The ability to dilate (ie, the percentage of diameter expansion) was found to be inversely related to the initial diameter: coronary arterioles were able to dilate to a greater magnitude—percentagewise—compared with the smaller arteries.¹⁵ Also in that study, small coronary arterioles did not dilate maximally during hypoperfusion. Therefore, these vessels are the site of persistent vasomotor tone in the subepicardial microcirculation during coronary insufficiency.¹⁵ In other words, microvessels are stiffer and more prone to be under the influence of a vasoconstrictor. This finding is in accordance with that of Quillen et al,¹⁶ who reported that an ischemic condition brings about mild alterations of coronary microvascular reactivity, and, if followed by reperfusion, progresses to a more marked impairment of coronary microvessel responses. In contrast, the ability of larger epicardial coronary arteries to dilate is relatively refractory after exposition to ischemia with or without reperfusion.¹⁶

Studies have shown that arginine vasopressin (AVP) has a constrictive effect on the coronary artery microvasculature.^{17,18} A multitude of studies have indicated that AVP is a potent coronary vasoconstrictor able to produce an MI-like state characterized by coronary venous oxygen desaturation, myocardial lactate production and accumulation, and, finally, reduced cardiac function.¹⁹ This ability of AVP appears to be dose dependent. Ischemic electrocardiographic changes post-AVP treatment have also been reported, which further supports the coronary vasoconstrictive effect of AVP.¹⁹

Arginine vasopressin Arginine vasopressin is a hormone that is produced in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary gland or neurohypophysis.²⁰ It is a potent vasoconstrictor,²¹ but it is more widely known as the main regulator of overall water balance, keeping blood osmolality in the normal range of 275 to 290 mOsm/kg.²² Thus, a rise in plasma osmolality is the main stimulus for the release of this hormone, already at a level above ~280 mOsm/kg.²³ The magnocellular neurons in the supraoptic nucleus become directly depolarized by hypertonic conditions (hence releasing more AVP) and vice versa in hypotonicity.²⁴ Arginine vasopressin then migrates to the posterior pituitary, along the supraoptic–hypophyseal tract, where it finally enters the systemic circulation.²⁴

In addition, AVP is also involved in stress response.²¹ Stress is defined as a nonspecific body response to any factor that disturbs homeostasis. A stress response is assimilated by the hypothalamus and manifests as an integrated neurohormonal activation.²¹ The major neural response to a stressful situation involves sympathetic nervous system activation. The predominant hormonal response during stress involves adrenocorticotropic hormone (ACTH), which is released from the anterior pituitary gland in response to stimulation by corticotropin-releasing hormone. Almost any

type of a stressful situation (eg, physical stress, neurogenic stress, tissue damage, pain) results in a marked and immediate increase of ACTH levels.²⁵ Thus, ACTH is a well-known stress hormone. Another hormone that is simultaneously released during stress response is AVP. Together with catecholamines, AVP helps sustain blood pressure (BP) during stress. In acute conditions such as hemorrhage, circulatory arrest, sepsis, and surgery, circulating AVP levels increase.²⁶

The third signal for AVP release is a change in extracellular fluid volume. Input signals are sent by low-pressure sensing atrial volume receptors located in the left atrium and pulmonary arteries, which respond to pressure-induced stretch.^{21,25} Atrial volume receptor firing to the nucleus tractus solitarius (and then to the hypothalamus) inhibits AVP release. The firing decreases during a reduction of extracellular fluid volume (eg, during major hemorrhage).²⁷ In cases of hypovolemia, BP drops significantly in the atrium. This causes AVP release, which leads to water retention in the kidneys in order to preserve blood volume. The release of AVP is also affected by hypotension-sensitive arterial baroreceptors (eg, in congestive heart failure) (FIGURE 1).^{28,29}

Arginine vasopressin in the circulation The physiologic concentration of AVP ranges from 1 to 5 pg/ml.³⁰ At this level, it achieves the ability to maintain body fluid homeostasis. This level of AVP is below its vasoactive range (it only has a minor

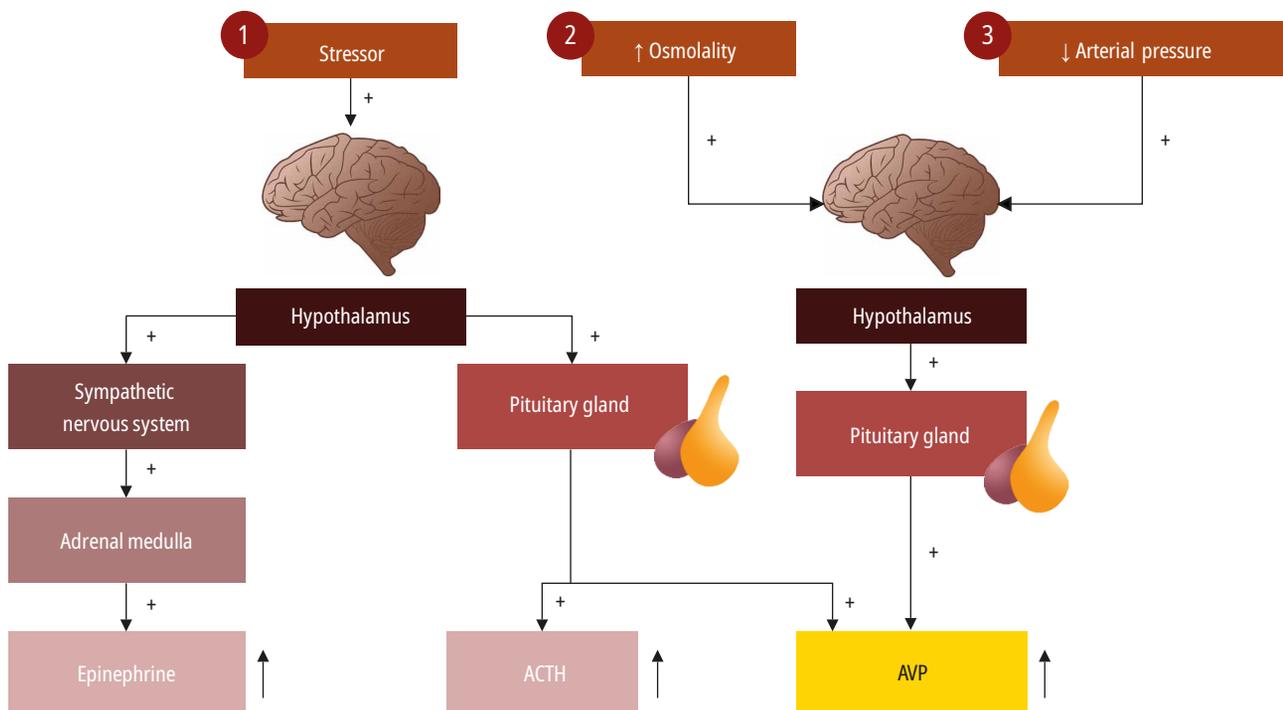


FIGURE 1 The 3 pathways to stimulate arginine vasopressin (AVP) secretion from the posterior pituitary gland, including stress response, elevated blood osmolality, and major blood pressure drop; ↑, increased levels; ↓, reduced levels; +, positive stimulation

Abbreviations: ACTH, adrenocorticotropic hormone

role in BP maintenance despite its vasoconstrictive properties).^{25,31} Higher plasma concentrations (>50 pg/ml) are required to bring about its vasoconstrictive effect and raise BP in healthy individuals.³² Under normal conditions, AVP is of minor importance for the maintenance of BP.³³ It can increase peripheral vascular resistance, but BP would not be raised because the pressor effect of AVP would be buffered by a normal baroreceptor reflex.^{34,35} Therefore, it serves as a backup mechanism in the setting of impaired autonomic nervous system (such as vasovagal syncope, pure autonomic failure) or impaired baroreceptor reflex (such as during septic shock).^{33,35}

Due to the vasopressor effect of AVP, the use of this agent as a potentially interesting alternative therapy for vasodilatory shock states is starting to emerge.^{24,35} Studies have shown that infusion of low-dose AVP in patients with vasodilatory shock reduces the need for norepinephrine administration, sustains BP and cardiac output, and also decreases pulmonary resistance.³⁶ A combined infusion of AVP (4 units per hour) and norepinephrine (adjusted to maintain a mean arterial pressure of 70 mm Hg or higher) was able to restore vascular tone in vasodilatory shock treatment.³⁷ Vasodilatory shock states include septic shock, postcardiopulmonary bypass shock, phosphodiesterase inhibition shock, hemodynamic instability in organ donors, and an irreversible phase of volume-treated hemorrhagic shock.³⁶

In acute conditions, AVP levels can rise dramatically (ie, up to >500 pg/ml in severe hemorrhage and >450 pg/ml in cardiac arrest).^{26,32} As MI disturbs homeostasis, it may act as a stressor that may be one of the stimuli for AVP release, because this hormone is involved in stress response. Thus, AVP levels are very likely to be elevated during MI. Recently, Roy et al³⁸ demonstrated an increase in the activity of cardiac sympathetic nerves and AVP-secreting neurons induced by MI in an animal model. Notably elevated plasma AVP levels have also been documented in patients with evolving MI.¹⁹ As mentioned previously, at high concentrations, AVP shows its vasoconstrictor effects. It was reported that coronary vasoconstriction can occur when serum AVP levels range between 10 and 1000 pg/ml.¹⁹

Arginine vasopressin and coronary vasculature in myocardial infarction

In the post-MI period, AVP may have some detrimental effects. Although the systemic vasoconstriction by AVP can appear to be important in BP maintenance, the resulting coronary vasoconstriction would offer no homeostatic advantage.¹⁹

Increased blood levels of AVP in dogs (from a mean [SD] 3.9 [0.9] pg/ml to 14.7 [4.6] pg/ml) were found to impair ventricular contraction and decrease stroke volume.³⁹ This negative inotropic

effect may correlate with the finding that AVP has the ability to produce coronary vasoconstriction.⁴⁰⁻⁴² This can exacerbate the already compromised coronary perfusion, thus increasing the infarct size and disturbing cardiac function. Arginine vasopressin was found to selectively have more effect on the microvasculature of the coronary arteries than on larger vessels in both healthy and ischemic settings.^{17,18} Moreover, AVP was demonstrated to have a stronger constricting effect in parts where the ratio of oxygen supply to oxygen demand was relatively high (resembling postreperfusion *in vivo*).¹⁹ Moreover, AVP administration in a normoxic rat heart was shown to constrict the coronary arteries, reduce coronary perfusion, depress cardiac function via a reduction of oxygen supply, and increase lactate production. This constricting effect was weakened during hypoxia. However, when hypoxia was discontinued—thus resembling reperfusion—a significant reduction in coronary flow was observed.¹⁹ If one would translate this effect to human patients with MI, it is conceivable that AVP release in response to myocardial ischemia would cause vasoconstriction in the coronary microvasculature distal to the recanalized occlusion of the epicardial vessel. This, in turn, could enhance or trigger ischemia–reperfusion injury.

However, there is some ambiguity in predicting the effect of AVP under ischemic conditions in humans. Both coronary vasoconstriction and vasodilation have been demonstrated post-AVP treatment in experimental models. One study described an increase of myocardial blood flow under a low dose of AVP due to increased systemic perfusion pressure and selective coronary vasodilation.³⁷ Another study assessed the effect of a bolus AVP injection into the left descending artery in pigs, and AVP was shown to significantly increase the vessel diameter.³⁶ Preclinical studies evaluated the effect of low-dose AVP in animal models of cardiac arrest.³⁶ They found an improvement in cardiac contractility, yet they concluded that this positive inotropic effect may probably be mediated by increased coronary perfusion pressure as opposed to vessel dilation. This contradictory feature not shared by other vasoconstrictor agents might be explained if we looked into the different receptors of AVP, as explained below. The net effect of vasoconstriction or vasodilation produced by AVP depends on the density of different AVP receptors in the vascular bed studied in the experimental models, and most likely also on the dose of AVP.³⁶

Since the effect of AVP on coronary vessels is dose dependent, progressive vasoconstriction was observed with increasing AVP concentrations.³⁶ At low dose, this hormone may seem to exert a “net positive inotropic effect.”³⁶ However, Forrest et al²⁶ found that AVP levels that cause

minimal effects in healthy individuals may generate a marked pressor action in acute conditions. Indrambarya et al⁴³ observed that low-dose AVP administration (0.04 U/min) in mice after MI and reperfusion had adverse effects, which included depressed cardiac contractility and increased mortality. Again, this heightened sensitivity can be explained by receptor changes that occur during different heart conditions. The net effect of AVP on cardiac function in a stress condition will depend on the AVP concentration as well as on the coronary perfusion pressure, coronary vascular tone, and selective activation of certain receptor types.

Although animal and in vitro studies suggest that AVP may promote a negative inotropic effect and coronary vasoconstriction, clinical studies of low-dose AVP administration have not reported any adverse cardiac effects so far.³⁶ All in all, AVP levels, sensitivity, and its effect on coronary vasculature in MI and reperfusion are yet to be discovered. Increased AVP levels, when coupled with heightened sensitivity of coronary artery microcirculation, may result in MVO in MI and reperfusion.

Copeptin In the blood circulation, AVP is unstable and mainly bound to platelets. It is rapidly cleared, making its measurement difficult and seldom accurate.⁴⁴⁻⁴⁸ Arginine vasopressin originates from a large precursor called preprovasopressin, which is produced in the hypothalamus^{31,45} and axonally transported to the neurohypophysis.⁴⁴ Copeptin, a 39-amino acid glycopeptide, is the C-terminal fragment of

preprovasopressin,^{45,49} which is cosecreted—in an equimolar amount—with AVP into the circulation following cleavage in the neurohypophysis.⁴⁷ Thus, copeptin can act as a surrogate biomarker for AVP and its levels reflect AVP production. The secretion of copeptin and AVP is similar to that of C-peptide and insulin (FIGURE 2).

Unlike AVP with its short half-life of 5 to 20 minutes,⁵⁰ copeptin is much more stable in the circulation, with its half-life of 82 minutes.⁵¹ This was also confirmed by our own finding of copeptin's half-life of 90 minutes (unpublished data). Copeptin can remain stable ex vivo even for days after blood withdrawal at room temperature,^{23,46,47,49} making it readily measurable in plasma or serum.²³ As reliable plasma AVP quantification is technically challenging and time consuming, valid AVP assays are uncommon.²³ More than 90% of circulating AVP is bound to platelets, resulting in either under- or overestimation of AVP levels.²³ Another advantage of copeptin measurement is that its concentrations remain unaltered by exogenous AVP therapy, thus enabling the assessment of its endogenous production.⁵² Therefore, the measurement of copeptin is likely to be more accurate than that of AVP.

Normal AVP levels vary between 1 and 5 pg/ml (equivalent to 0.9–4.6 pmol/l), and copeptin levels in healthy individuals range between 1.0 and 4.4 pmol/l.^{45,53} It was reported that both AVP and copeptin correlated with plasma osmolality in healthy individuals ($r = 0.77$ and $r = 0.49$, respectively). The same study also revealed a close correlation of AVP and copeptin

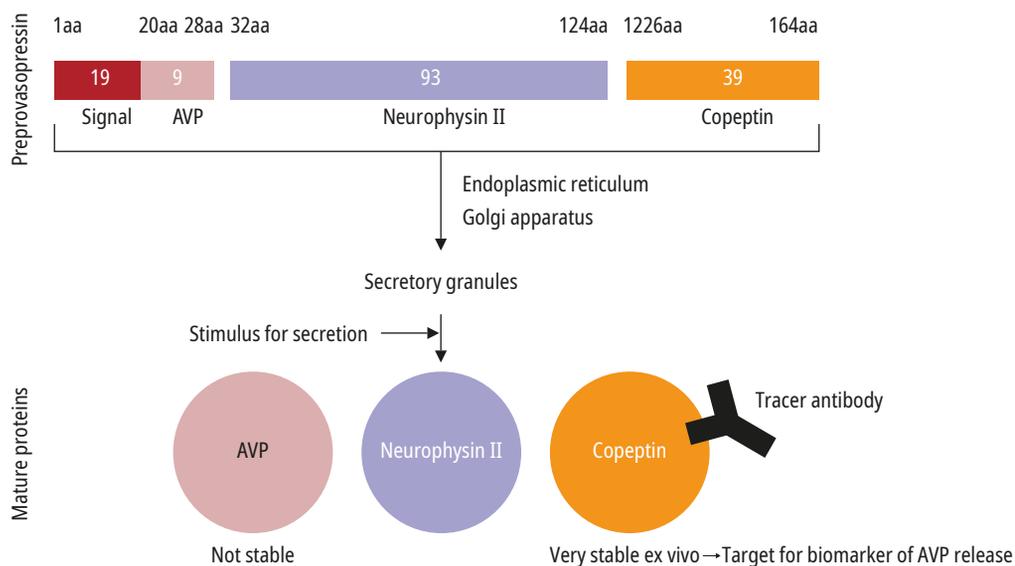


FIGURE 2 Schematic presentation of the peptide precursor of arginine vasopressin (AVP) that undergoes several processes through endoplasmic reticulum and golgi apparatus prior to becoming mature proteins that are stored in secretory granules. Upon stimulation, the granules release the contents into the circulation. Copeptin, which is coreleased with AVP, is more stable following blood withdrawal. Thus, it is more favorable to measure AVP through copeptin. Numbers denote the number of amino acids (aa) present in each part.

concentrations ($r = 0.8$).²³ Apart from the hyperosmolar states, increased copeptin levels were also found on nonosmotic stimulation that increases AVP levels (ie, 79.5 pmol/l in sepsis, 171.5 pmol/l in septic shock, 269 pmol/l in hemorrhagic shock, 88 pmol/l in systemic inflammatory response syndrome, etc).^{45,54,55} After MI, plasma copeptin levels were the highest on admission and reached a plateau at days 3 to 5.⁴⁴ Slagman et al⁵⁶ showed that copeptin levels increased right after spontaneous MI (highest at admission) and decreased gradually within 12 to 36 hours. In a different study, the copeptin concentration was found to be highest within 4 hours of symptom onset.⁵⁷ In patients undergoing transcatheter ablation of septal hypertrophy as the equivalent of MI induction, the median copeptin concentration was significantly elevated at 30 minutes postablation (16.0 pmol/l; interquartile range [IQR], 13.4–20.2 pmol/l), peaked at 90 minutes (31.9 pmol/l; IQR, 16.4–117.1 pmol/l), and returned to baseline after 24 hours (8.2 pmol/l; IQR, 6.3–10.1 pmol/l).⁵⁸ The cutoff value for copeptin to exclude MI was proposed at 14 pmol/l.⁵⁷

When combined with cardiac troponins, copeptin has shown to provide additional diagnostic sensitivity for early discrimination of acute MI.⁵⁰ The median copeptin levels in patients with acute coronary syndrome without infarction was lower compared with those with MI.⁵⁶ Due to the distinct temporal pattern of copeptin release, it provides a diagnostic aid especially in the first 3 hours of symptom onset, when cardiac troponin levels have not yet increased.^{56,57,59} In an experimental study on pigs, increased circulating copeptin levels were related to changes in mean arterial pressure, that is, animals with high values showed a reduction in mean arterial pressure as a consequence of MI.⁶⁰

In the post-MI period (days 2–5), copeptin levels were found to be associated with myocardial remodeling and heart failure in survivors of MI.^{44,49} High circulating copeptin levels had a predictive value for the outcome of advanced heart failure after MI.²³ Copeptin levels were higher in patients who died or were readmitted with heart failure in comparison with MI survivors (median, 18.5 pmol/l vs 6.5 pmol/l; $P < 0.0005$).⁵² The predictive value of copeptin was found superior to that of clinical variables, left ventricular ejection fraction, and major cardiovascular risk factors.⁵⁶ Patients with MI with copeptin values above the median level (10.4 pmol/l) demonstrated a larger infarct area ($r = 0.388$, $P = 0.004$ at baseline and $r = 0.385$, $P = 0.011$ at 4-month follow-up) and lower left ventricular ejection fraction ($r = -0.484$, $P < 0.001$ at baseline and $r = -0.461$, $P < 0.001$ at 4-month follow-up).⁶¹ This is supported by another study that found a positive correlation between plasma copeptin concentrations and the infarct size ($r = 0.96$, $P < 0.0001$).⁵⁸

Furthermore, copeptin levels on admission were found to independently predict the final infarct size in a multivariate analysis.⁵⁹ Copeptin levels were also assessed in other populations, including 1195 stable ambulatory patients with type 2 diabetes.⁶² In a 10-year follow-up, copeptin levels were associated with cardiovascular death (hazard ratio, 1.17; 95% CI, 0.99–1.39; $P = 0.068$) and all-cause mortality (hazard ratio, 1.22; 95% CI, 1.09–1.36; $P = 0.001$). This association was found to be independent after adjustment for various confounders. The median baseline copeptin levels in survivors were lower compared with those who had died of cardiovascular causes and of all causes (4.9 pmol/l [IQR, 3.0–8.5 pmol/l] vs 7.9 pmol/l [IQR, 3.9–13.8 pmol/l] vs 7.3 pmol/l [IQR, 3.7–13.0 pmol/l], $P < 0.0001$).⁶²

Given the similarities between copeptin and AVP and the stability of copeptin, it is more favorable to measure AVP concentrations from this surrogate biomarker. A sensitive sandwich immunoassay for the measurement of copeptin in human serum or plasma has been developed.²³ The assay utilizes 2 polyclonal antibodies to the amino acid sequence 132–164 of preprovasopressin in the C-terminal region of the precursor: one antibody is bound to polystyrene tubes and the other is labeled with acridinium ester for chemiluminescence detection.⁵²

Cardiac synthesis of arginine vasopressin

Initially, AVP was thought to be exclusively produced in the hypothalamus. However, in one animal study, Hupf et al⁶³ discovered AVP production in the rat heart after left ventricular pressure overload. Arginine vasopressin mRNA and peptide were detectable following 60 minutes of elevated wall stress. Thus, AVP can be expressed by the heart independent of central production in response to an insult to the heart. Boeckel et al⁵⁰ analyzed local cardiac copeptin release by using a transcatheter gradient model in patients with acute MI. Transcatheter gradient model data were calculated by comparing blood samples withdrawn from the aortic bulb and the coronary venous sinus. Although they discovered a significant increase of copeptin levels in the systemic circulation, they did not obtain a positive gradient for copeptin, suggesting no significant production of copeptin in the heart. However, further studies are needed to confirm this finding.

Arginine vasopressin receptor Arginine vasopressin exerts its actions through several AVP G-protein-coupled receptors^{24,31}: receptor 1a (AVPR1a), receptor 1b (AVPR1b, also known as receptor 3), receptor 2 (AVPR2), oxytocin subtypes (OTR), and P_2 purinergic receptors (P_2R). The AVPR1a receptor is located predominantly in vascular smooth muscle cells^{31,64,65}; AVPR1b, in the anterior pituitary; and AVPR2, in the distal

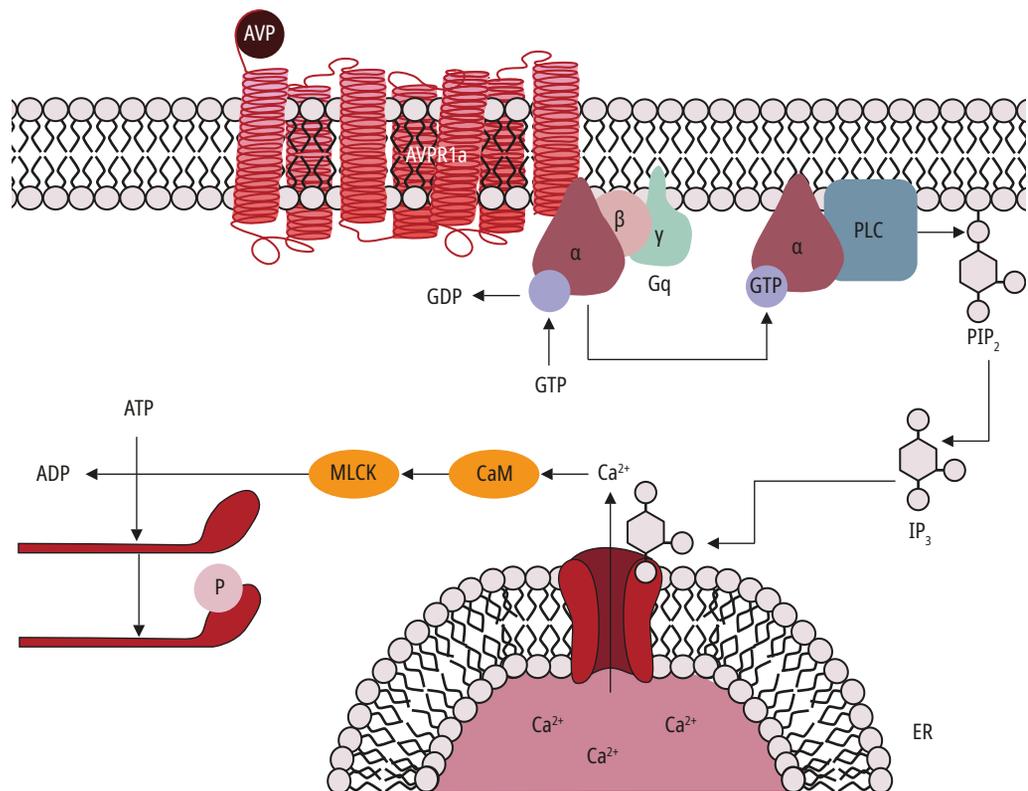


FIGURE 3 Arginine vasopressin receptor 1a (AVPR1a) is a G-protein coupled receptor. Upon activation by arginine vasopressin (AVP), Gq protein α subunit (Gq α) stimulates phospholipase C (PLC) to hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP₂), thereby increasing cytosolic calcium ion (Ca²⁺) levels and mediating cell contraction.

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CaM, calmodulin; ER, endoplasmic reticulum; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IP₃, inositol triphosphate; MLCK, myosin light-chain kinase; P, phosphate

tubules and collecting ducts of the kidneys.³¹ Oxytocin subtypes are present in high density in the vascular endothelium,²⁴ while P₂Rs are expressed on the cardiac endothelium.²⁴

Upon binding to AVPR1a, the peripheral and coronary vessels undergo vasoconstriction.⁶⁶ In arteriolar smooth muscle cells, stimulation of AVPR1a leads to an increase in ionized calcium in the cytoplasm via the phosphatidylinositol-bisphosphonate cascade.^{24,38} In addition to smooth muscle cells, AVP can also increase intracellular calcium levels in cardiac myocytes through AVPR1a (FIGURE 3).⁶⁶

The pressor effect of AVP was eliminated in AVPR1a^{-/-} mice,^{31,67} indicating that AVP-induced vasoconstriction is mediated through AVPR1a. As mentioned previously, the vasoconstrictive action of AVP is more marked in acute conditions.²⁶ This heightened sensitivity was found in patients with MI, whose coronary arteries, especially the arterial microvessels, were shown to have an increased vasoconstrictive response to AVP after ischemia in comparison with the control group.²⁶ Indrambarya et al⁴³ also observed that low-dose AVP administration (0.04 U/min) had minimal effects on baseline mice hearts but exerted adverse effects on mice hearts after reperfusion of MI. This ischemia-induced cardiac

sensitization to AVP might be caused by upregulation of AVPR1a. Human platelets also seem to express AVPR1a, which upon stimulation promotes aggregation by increasing intracellular calcium,²⁴ thus favoring ischemia-reperfusion injury. However, the thrombotic response appears to vary among individuals due to the heterogeneity and polymorphism among AVPR1a receptors of human platelets.²⁴

The most abundant AVP receptor in the heart appears to be AVPR1a.⁴³ However, P₂Rs have also been shown recently to be expressed on the cardiac endothelium, where AVP can exert its cardiac effects.²⁴ An intracoronary infusion of AVP in combination with dextran produced coronary vasoconstriction and negative inotropy in isolated perfused guinea pig hearts. These outcomes were inhibited by AVPR1a and P₂R antagonists.²⁴ Therefore, the vasopressor effect of AVP on the heart can be mediated by more than 1 receptor type.

Another AVP receptor of interest is the OTR. It has equal affinity for both AVP and oxytocin; thus, it is considered to be nonselective.²⁴ These receptors abound on the vascular endothelium to mediate nitric oxide-dependent vasodilation.^{24,68} This finding might explain the seemingly contradictory actions of AVP in

the heart: coronary vasoconstriction vs vasodilation as well as a positive vs negative inotropic effect. A discrepancy in response to AVP between the “normal” and stressed heart has been reported (ie, vasoconstriction in the normoxic state and vasodilation during hypoxia, as mentioned earlier).³⁶ Thus, the activity and density of OTR vs AVPR1a and P₂R in MI and reperfusion are yet to be elucidated. Recently, OTR has been discovered in the heart, and, upon stimulation, it facilitated the release of atrial natriuretic peptide (ANP).²⁴ The release of ANP by AVP seems to be affected by hemodynamic changes, as only pressor doses of AVP generated an immediate increase in plasma ANP levels.⁶⁹

Arginine vasopressin in cardiovascular diseases Rohla et al⁷⁰ revealed a predictive value of osmolality on admission for death outcome in patients with acute coronary syndrome undergoing PCI. They found that patients with osmolality greater than 292 mOsm/kg on admission had a 2.8-fold increased risk of in-hospital mortality. The same level of osmolality on admission was also associated with higher death rates after 30 days and 1 year. They also reported a study which found that the mean osmolality on admission and maximum osmolality levels were significantly higher among MI patients who died after 3 months in comparison with survivors.⁷⁰ At first, the rationale for their hypothesis was that osmolality would be directly affected by blood glucose and blood urea nitrogen levels. Later, they concluded that this parameter was independent of the presence of diabetes and renal impairment.⁷⁰ This may suggest the role of AVP—activated by high osmolality—in bringing about detrimental effects. The AVP level approximately 1 month after MI was also independently associated with adverse long-term cardiovascular outcomes, including heart failure, recurrent MI, and death.⁶⁶

Francis et al⁶⁶ observed elevated AVP levels in patients with heart failure and left ventricular dysfunction after MI, suggesting some association with adverse cardiovascular outcomes. They also reported elevated AVP levels in patients with asymptomatic left ventricular dysfunction when compared with controls, whereas patients with symptomatic mild-to-moderate heart failure had even higher AVP levels.⁶⁶ On the other hand, elevated levels of AVP might lead to an increase in ANP levels in heart failure.⁶⁹ Moreover, AVP levels were not shown to correlate with serum sodium levels or cardiac index.⁷¹ This lack of correlation indicates the possibility of an impaired osmotic regulatory mechanism in cardiovascular diseases.⁷¹

Arginine vasopressin antagonist Currently there are 2 AVP antagonists: conivaptan and tolvaptan. Conivaptan is a combined AVPR1a

and AVPR2 antagonist, whereas tolvaptan is an AVPR2 antagonist. Therapy with AVP receptor antagonists has been recommended to reduce cardiac afterload in patients with congestive heart failure.³⁶ Creager et al (as quoted in Udelson et al⁶⁶) studied patients with heart failure undergoing short-term therapy with an AVPR1a antagonist and found a reduction in systemic vascular resistance and an increase in cardiac output. In a randomized placebo-controlled trial, Udelson et al⁶⁶ found that conivaptan had favorable hemodynamic and renal effects in patients with heart failure: a reduction in systemic vascular resistance with an increase in cardiac output as well as an increase in diuresis. Hemodynamic effects of conivaptan were also evaluated in a study of patients with heart failure in New York Heart Association functional class III or IV.⁷² Conivaptan administration was associated with a significant reduction in pulmonary capillary wedge pressure and right atrial pressure as well as an increase in urine output. No serious adverse outcomes or drug-related deaths occurred. Administration of the AVP antagonist in rat hearts after hypoxia and AVP infusion resulted in a significant increase in coronary flow, eliminating the AVP-mediated cardiac effects of contractile function.¹⁹ Pretreatment with a specific AVPR1a antagonist abolished the coronary vasoconstrictor effect and contractility responses.³⁶ Furthermore, Zeynalov et al⁷³ evaluated the effect of an AVP receptor antagonist in an experimental mice model of stroke. They found that continuous infusion of conivaptan, but not tolvaptan, resulted in a favorable hemodynamic outcome as it reduced brain edema and blood-brain barrier disruption. The AVPR1a inhibition after subarachnoid hemorrhage led to improvements in regional cerebral blood flow.⁷³

Looking at the above results, the hemodynamically altering agent—which is the point of interest in MI—is conivaptan. As a dual AVPR1a and AVPR2 blocker, conivaptan is able to regulate both vascular tone and urine output at the same time. Conivaptan is a nonpeptide combined AVPR1a and AVPR2 antagonist.⁷² It is the first AVP receptor antagonist to be approved in the United States, and it is currently indicated for the treatment of euvolemic hyponatremia (<135 mEq/L).⁷² For that condition, conivaptan is administered as a 20 mg intravenous bolus over 30 minutes (loading dose), followed by a continuous infusion of 20 mg over 24 hours for up to 4 days.⁷² However, Udelson et al⁶⁶ administered a single intravenous dose of 20 to 40 mg in patients with heart failure. Apart from its intravenous preparation, Ghali et al⁷⁴ found that oral conivaptan (40 and 80 mg/dl) was well tolerated and efficacious in correcting serum sodium levels in hyponatremia.

Conclusions Arginine vasopressin is released into the circulation as part of stress response

triggered by MI. This is most likely attributable to increased hypothalamic AVP expression, in contrast to the local cardiac AVP system. Arginine vasopressin, most likely at higher (nonphysiologic) concentrations, can exert vasoconstrictive effects on the coronary arteries in preclinical models, mainly in the nonepicardial vessels of the microcirculation. Circulating AVP levels are up to 100-fold higher in MI and do not immediately return to baseline levels upon reperfusion. This may contribute to the slow flow phenomenon and mediate ischemia–reperfusion injury. Ischemia-induced cardiac sensitization to AVP from the upregulation of AVPR1a or P₂R expression needs to be evaluated in future studies. We suggest that both AVP and copeptin have more than just a predictive value and that they are involved in the pathophysiology of adverse outcome post

MI. This mandates a clinical trial with conivaptan, an AVP-receptor antagonist, in patients with acute myocardial infarction undergoing reperfusion therapy (FIGURE 4).

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0), allowing third parties to download articles and share them with others, provided the original work is properly cited, not changed in any way, distributed under the same license, and used for non-commercial purposes only. For commercial use, please contact the journal office at kardiologiapolska@ptkardio.pl.

HOW TO CITE Nobian A, Mohammed A, Spyridopoulos I. The role of arginine vasopressin in myocardial infarction and reperfusion. *Kardiol Pol.* 2019; 77: 908-917. doi:10.33963/KP.14986

REFERENCES

- Cardiovascular diseases (CVDs). World Health Organization. <http://www.who.int/mediacentre/factsheets/fs317/en/>. Accessed August 1, 2019.
- Silber S, Albertsson P, Avilés FF, et al. Guidelines for percutaneous coronary interventions. *Eur Heart J.* 2005; 26: 804-847.
- Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. *J Clin Invest.* 2013; 123: 92-100.
- Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. *J Am Coll Cardiol.* 2009; 54: 281-292.
- Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med.* 2007; 356: 830-840.
- Carlo Dal L, Francesco T, Elena O. Coronary microvascular function and beyond: the crosstalk between hormones, cytokines, and neurotransmitters. *J Endocrinol.* 2015; 2015: 312848.
- Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *Eur Heart J.* 2014; 35: 1101-1111.
- Eckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J.* 2001; 22: 729-739.
- Tanaka A, Kawarabayashi T, Nishibori Y, et al. No-reflow phenomenon and lesion morphology in patients with acute myocardial infarction. *Circulation.* 2002; 105: 2148-2152.
- Zavala-Alarcon E, Cecena F, Little R, et al. The no-flow phenomenon during diagnostic coronary angiography. *Cardiovasc Revasc Med.* 2005; 6: 126-132.
- Carrick D, Haig C, Ahmed N, et al. Comparative prognostic utility of indexes of microvascular function alone or in combination in patients with an acute ST-segment-elevation myocardial infarction. *Circulation.* 2016; 134: 1833-1847.
- Rezkalla SH, Kloner RA. No-reflow phenomenon. *Circulation.* 2002; 105: 656-662.
- Fearon WF, Low AF, Yong AS, et al. Prognostic value of the index of microcirculatory resistance measured after primary percutaneous coronary intervention. *Circulation.* 2013; 127: 2436-2441.
- Khan JN, Razvi N, Nazir SA, et al. Prevalence and extent of infarct and microvascular obstruction following different reperfusion therapies in ST-elevation myocardial infarction. *J Cardiovasc Magn Reson.* 2014; 16: 38.
- Chilian WM, Layne SM. Coronary microvascular response to reductions in perfusion pressure. *Circ Res.* 1990; 66: 1227-1238.
- Quillen JE, Sellke FW. Ischemia-reperfusion impairs endothelium-dependent relaxation of coronary microvessels but does not affect large arteries. *Circulation.* 1990; 82: 588-594.
- Sellke FW, Quillen JE. Altered effects of vasopressin on the coronary circulation after ischemia. *J Thorac Cardiovasc Surg.* 1992; 104: 357-363.
- Maturi MF, Martin SE, Markle D, et al. Coronary vasoconstriction induced by vasopressin. Production of myocardial ischemia in dogs by constriction of nondiseased small vessels. *Circulation.* 1991; 83: 2111.
- Boyle WA, Segel LD. Attenuation of vasopressin-mediated coronary constriction and myocardial depression in the hypoxic heart. *Circ Res.* 1990; 66: 710-721.
- Koshimizu T, Nakamura K, Egashira N, et al. Vasopressin V1a and V1b receptors: from molecules to physiological systems. *Physiol Rev.* 2012; 92: 1813-1864.
- Sherwood L. *Human physiology: from cells to systems.* 7th International student ed. Belmont, CA: Brooks/Cole Cengage Learning; 2010.
- Sharman A, Low J. Vasopressin and its role in critical care. *Cont Educ Anaesth Crit Care Pain.* 2008; 8: 134-137.
- Balanescu S, Kopp P, Gaskill MB, et al. Correlation of plasma copeptin and vasopressin concentrations in hypo-, iso-, and hyperosmolar states. *J Clin Endocrinol Metab.* 2001; 96: 1046-1052.
- Holmes CL, Landry DW, Granton JT. Science review: vasopressin and the cardiovascular system part 1 – receptor physiology. *Crit Care.* 2003; 7: 427-434.

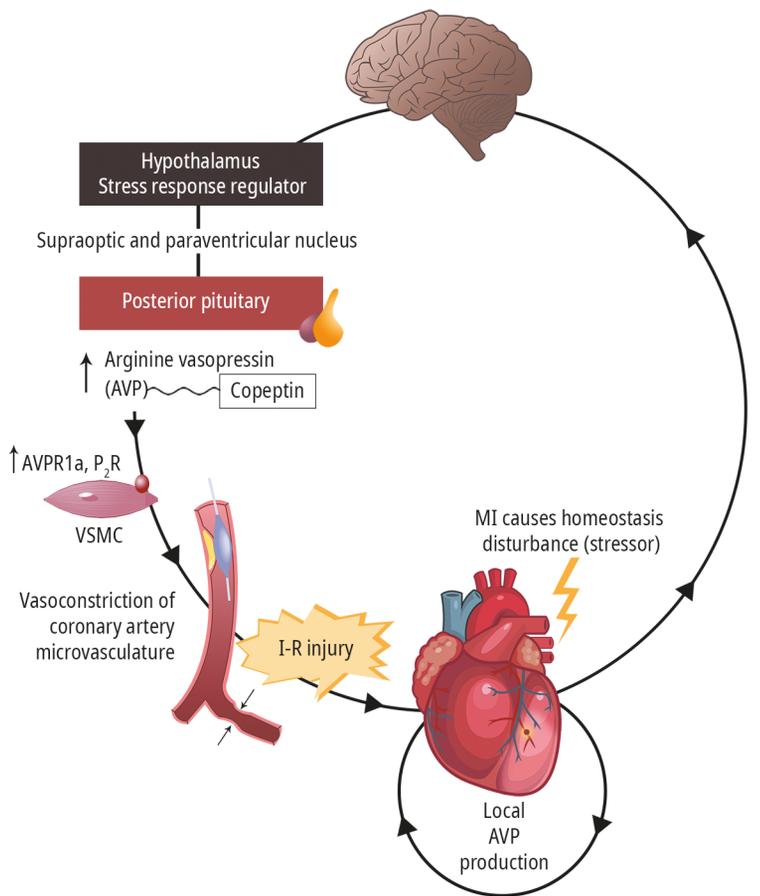


FIGURE 4 Hypothesis summary. Myocardial infarction (MI) acts as a stressor, which is sensed by the brain. The hypothalamus serves as a stress response regulator. In response to stress, the supraoptic and paraventricular nuclei of the hypothalamus increase the expression of arginine vasopressin (AVP), with a subsequent release from the posterior pituitary gland. AVP is cosecreted with copeptin. In turn, AVP brings about a detrimental effect to the coronary artery microvasculature by binding to AVP receptor 1a (AVPR1a) or P₂ purinergic receptors (P₂R), which get upregulated during MI. This mediates further ischemia-reperfusion (I-R) injury despite recanalization. Furthermore, we hypothesize that MI could activate local AVP production, which results in additional vasoconstrictive effect in the coronary artery microvasculature. The resulting injury can cause further disturbance.

Abbreviations: VSMC, vascular smooth muscle cell

- 25 Hall JE. Guyton and Hall textbook of medical physiology. 13th ed. Guyton AC, editor. Philadelphia, Pa: Saunders/Elsevier; 2016.
- 26 Forrest P. Vasopressin and Shock. *Anaesth Intensive Care*. 2001; 29: 463-472.
- 27 Klabunde RE. Cardiovascular physiology concepts. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
- 28 Den Ouden DT, Meinders AE. Vasopressin: physiology and clinical use in patients with vasodilatory shock: a review. *Neth J Med*. 2005; 63: 4-13.
- 29 Loscalzo J. Harrison's Cardiovascular Medicine. New York, NY: McGraw-Hill; 2015.
- 30 Antidiuretic hormone blood test. U.S. National Library of Medicine. MedlinePlus. <https://www.nlm.nih.gov/medlineplus/ency/article/003702.htm>. Accessed August 13, 2019.
- 31 Koshimizu TA, Nasa Y, Tanoue A, et al. V1a vasopressin receptors maintain normal blood pressure by regulating circulating blood volume and baroreflex sensitivity. *Proc Natl Acad Sci USA*. 2006; 103: 7807-7812.
- 32 Liard JF. Vasopressin in cardiovascular control: role of circulating vasopressin. *Clin Sci (Lond)*. 1984; 67: 473-481.
- 33 Jordan J, Tank J, Diedrich A, et al. Vasopressin and blood pressure in humans. *Hypertension*. 2000; 36: e3-e4.
- 34 Bussien JP, Waeber B, Nussberger J, et al. Does vasopressin sustain blood pressure of normally hydrated healthy volunteers? *Am J Physiol*. 1984; 246: H143-H147.
- 35 Patel BM, Chittock DR, Russel JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology*. 2002; 96: 576-582.
- 36 Holmes CL, Landry DW, Granton JT. Science review: vasopressin and the cardiovascular system part 2 – clinical physiology. *Crit Care*. 2004; 8: 15-23.
- 37 Dünser MW, Mayr AJ, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation*. 2003; 107: 2313-2319.
- 38 Roy RK, Augustine RA, Brown CH. Activation of oxytocin neurons in the paraventricular nucleus drives cardiac sympathetic nerve activation following myocardial infarction in rats. *Commun Biol*. 2018; 1: 1-11.
- 39 Cheng CP, Igarashi Y, Klopstein HS, et al. Effect of vasopressin on left ventricular performance. *Am J Physiol Heart Circ Physiol*. 1993; 264: 53-60.
- 40 Chan D, Ng LL. Biomarkers in acute myocardial infarction. *BMC medicine*. 2010; 8: 34.
- 41 Schäfer U, Kurz T, Jain D, et al. Impaired coronary flow and left ventricular dysfunction after mechanical recanalization in acute myocardial infarction: role of neurohumoral activation? *Basic Res Cardiol*. 2002; 97: 399-408.
- 42 Ali F, Raufi MA, Washington B, Ghali JK. Conivaptan: a dual vasopressin receptor v1a/v2 antagonist corrected. *Cardiovasc Drug Rev*. 2007; 25: 261.
- 43 Indrambarya T, Boyd JH, Wang Y, et al. Low-dose vasopressin infusion results in increased mortality and cardiac dysfunction following ischemia-reperfusion injury in mice. *Crit care (Lond)*. 2009; 13: R98.
- 44 Khan SQ, Dhillon OS, O'Brien RJ, et al. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) Study. *Circulation*. 2007; 115: 2103-2110.
- 45 Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem*. 2006; 52: 112-119.
- 46 Reichlin T, Hochholzer W, Stelzig C, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. *J Am Coll Cardiol*. 2009; 54: 60-68.
- 47 Reinstadler SJ, Klug G, Feistritz HJ, et al. Copeptin testing in acute myocardial infarction: ready for routine use? *Disease Markers*. 2015; 2015: 1-9.
- 48 Dobsa L, Edozien KC. Copeptin and its potential role in diagnosis and prognosis of various diseases. *Biochem Med*. 2013; 23: 172-190.
- 49 Kelly D, Squire IB, Khan SQ, et al. C-terminal provasopressin (copeptin) is associated with left ventricular dysfunction, remodeling, and clinical heart failure in survivors of myocardial infarction. *J Card Fail*. 2008; 14: 739-745.
- 50 Boeckel JN, Oppermann J, Anadol R, et al. Analyzing the release of copeptin from the heart in acute myocardial infarction using a transcoronary gradient model. *Sci Rep*. 2016; 6: 20812.
- 51 Schnyder I, Strauss K, Koch G, et al. Physiological area of normality of copeptin in normal-to-hyperosmolar states. Poster presented at: European Congress of Endocrinology 2015; May 16–20, 2015; Dublin, Ireland.
- 52 Morgenthaler NG, Struck J, Jochberger S, Dünser MW. Copeptin: clinical use of a new biomarker. *Trends Endocrinol Metab*. 2007; 19: 43-49.
- 53 Zweifel C, Katan M, Schuetz P, et al. Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage. *BMC Neurology*. 2010; 10: 34.
- 54 Morgenthaler NG, Müller B, Struck J, et al. Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. *Shock*. 2007; 28: 219-226.
- 55 Jochberger S, Morgenthaler NG, Mayr VD, et al. Copeptin and arginine vasopressin concentrations in critically ill patients. *J Clin Endocrinol Metab*. 2006; 91: 4381-4386.
- 56 Slagman A, Searle J, Müller C, Möckel M. Temporal release pattern of copeptin and troponin T in patients with suspected acute coronary syndrome and spontaneous acute myocardial infarction. *Clin Chem*. 2015; 61: 1273-1282.
- 57 von Haehling S, Papassotiropoulos J, Morgenthaler NG, et al. Copeptin as a prognostic factor for major adverse cardiovascular events in patients with coronary artery disease. *Int J Cardiol*. 2012; 162: 27-32.
- 58 Liebtreu C, Nef H, Szardien S, et al. Release kinetics of copeptin in patients undergoing transcatheter ablation of septal hypertrophy. *Clin Chem*. 2013; 59: 566-569.
- 59 Ananth V, Beig JR, Trambou NA, et al. Does plasma copeptin level at admission predict final infarct size in ST-elevation myocardial infarction. *Int J Cardiol*. 2016; 219: 326-330.
- 60 Jerichow T, Struck J, Vollert JO, et al. Elevation of plasma copeptin in acute myocardial infarction in pigs is related to changes in mean arterial blood pressure but not to myocardial ischemia. *J Am Coll Cardiol*. 2011; 57: E925.
- 61 Reinstadler SJ, Klug G, Feistritz HJ, et al. Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. *Heart*. 2013; 99: 1525-1529.
- 62 Riphagen IJ, Boertien WE, Alkhalaf A, et al. Copeptin, a surrogate marker for arginine vasopressin, is associated with cardiovascular and all-cause mortality in patients with type 2 diabetes (ZODIAC-31). *Diabetes Care*. 2013; 36: 3201-3207.
- 63 Hupf H, Grimm D, Riegger GA, Schunkert H. Evidence for a vasopressin system in the rat heart. *Circ Res*. 1999; 84: 365-370.
- 64 Cottet-Maire F, Avdonin PV, Roulet E, et al. Upregulation of vasopressin V1A receptor mRNA and protein in vascular smooth muscle cells following cyclosporin A treatment. *Br J Pharmacol*. 2001; 132: 909.
- 65 Wada K, Tahara A, Arai Y, et al. Effect of the vasopressin receptor antagonist conivaptan in rats with heart failure following myocardial infarction. *Eur J Pharmacol*. 2002; 450: 169-177.
- 66 Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effect of conivaptan, a dual V1A and V2 vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation*. 2001; 104: 2417-2423.
- 67 Aoyagi T, Tanoue A, Koshimizu TA. Vasopressin regulation of blood pressure and volume: findings from V1a receptor-deficient mice. *Kidney Int*. 2009; 76: 1035-1039.
- 68 Thibonnier M, Conarty DM, Preston JA, et al. Human vascular endothelial cells express oxytocin receptors. *Endocrinology*. 1999; 140: 1301-1308.
- 69 Gutkowska J, Jankowski M, Lambert C, et al. Oxytocin releases atrial natriuretic peptide by combining with oxytocin receptors in the heart. *Proc Natl Acad Sci USA*. 1997; 94: 11704-11709.
- 70 Rohla M, Freyhofner MK, Tentzeris J, et al. Plasma osmolality predicts clinical outcome in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Eur Heart J Acute Cardiovasc Care*. 2014; 3: 84-92.
- 71 Goldsmith SR, Francis GS, Cowley AW, et al. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol*. 1983; 1: 1385-1390.
- 72 National PBM Drug Monograph Conivaptan Hydrochloride Injection (Vaprisol®). VACO PBM-SHG; 2006. www.pbm.va.gov/PBM/clinicalguidance/drugmonographs/Conivaptan.pdf. Accessed August 13, 2019.
- 73 Zeynalov E, Jones SM, Seo JW, et al. Arginine-vasopressin receptor blocker conivaptan reduces brain edema and blood-brain barrier disruption after experimental stroke in mice. *PLoS ONE*. 2015; 10: e0136121.
- 74 Ghali JK, Koren MJ, Taylor JR, et al. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab*. 2006; 91: 2145-2152.