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Article type: Review article

Received: September 19, 2019.

Accepted: September 19, 2019.

Published online: September 25, 2019.

ISSN: 0022-9032

e-ISSN: 1897-4279

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The role of arginine vasopressin in myocardial infarction and reperfusion

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Conflict of interest: none declared
ABSTRACT

Little attention is paid to the coronary microvasculature when treating acute myocardial infarction (MI). Microvascular obstruction (MVO) contributes to ischaemia-reperfusion (I-R) injury which hampers distal blood flow to the myocardium despite recanalisation 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 effect on the coronary microvessels. AVP levels are elevated as part of a stress response triggered by MI which can exert vasoconstrictive effects on coronary arteries in pre-clinical models, mainly in non-epicardial vessels of the microcirculation. Circulating AVP levels are up to 100-fold increased in MI and do not immediately decrease to baseline levels upon reperfusion. This would allow slow flow phenomenon and mediate I-R injury. Recently, the C-terminal fragment of pre-provasopressin, copeptin, has emerged to be 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 in 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 epicardial vessel but also to target 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.

Key words: acute myocardial infarction, STEMI, reperfusion, vasopressin, copeptin, reperfusion injury, microvascular obstruction
1.1 Introduction
Cardiovascular disease remains the top cause of mortality worldwide with estimated 17.9 million deaths in 2016, coronary artery disease (CAD) being the single largest contributor. CAD acutely manifests with plaque rupture as an acute coronary syndrome, with ST elevation myocardial infarction (STEMI) being the most serious due to complete coronary artery obstruction and extensive myocardial ischaemia as a result. Prolonged ischaemia 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 (PPCI) is the first line strategy, involving re-opening of the artery and placing a stent. PPCI is intentionally used to salvage viable myocardium, limit infarct size, and preserve systolic function. Yet, damage to the heart can still occur following reperfusion, known as ischaemia-reperfusion (I-R) injury. Therefore, myocardial reperfusion still comes at a cost despite restoration of blood flow. I-R injury is thought to be multi-factorial. Factors include distal embolization, endothelial damage, leukocyte infiltration & plugging, reactive oxygen species (ROS) production, sarcoplasmic reticulum dysfunction, the opening of the mitochondrial permeability transition pore, cell swelling, etc. Together with these factors, microvascular obstruction also plays a role in I-R injury. It involves impaired vasodilatation, thus increasing the likelihood of neutrophil plugging and micro-embolisation.

1.2 Microvascular obstruction in ischaemia-reperfusion injury
Coronary angiography allows visualisation of larger, conductive epicardial coronary arteries. However, the coronary arterial system not only consists of conductive vessels but also 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 visualise and is difficult to access (Diameter <300μm). In a considerable proportion (30-40%) of STEMI patients,
recanalization of the epicardial coronary artery does not necessarily correspond to reperfusion of myocardium. 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, in which sustained microvascular obstruction (MVO) is suggested to play a role in. Failure to completely reperfuse myocardium in STEMI patients is common yet often goes unnoticed due to the lack of sensitive microvascular evaluation method. Clinical presentations of this phenomenon include the lack of improvement in cardiac function post-reperfusion, chest pain following recanalization, and reduced re-flow (measured as thrombolysis in myocardial infarction (TIMI) grade <2 flow) after PCI.

MVO augments I-R injury by causing slow flow and is associated with larger infarct size and lower left ventricular ejection fraction (LVEF). Carrick and colleagues measured the index of microvascular resistance (IMR) at the end of PCI in 283 STEMI patients and found that an IMR >40 was closely associated with MVO. A normal value was generally considered to be <25. Furthermore, the level of IMR was a multivariate associate of deleterious left ventricular changes and poor long-term clinical outcomes following STEMI (i.e.: 4-fold increase in heart failure or all-cause mortality). The team also concluded that IMR is superior in risk stratifying myocardial reperfusion failure. In accordance to that, Fearon et al. also discovered that IMR at the time of STEMI could predict the extent of myocardial damage. Patients with an IMR >40 had a higher rate of death or heart failure at 1 year than patients with an IMR ≤ 40 (17.1% vs 6.6%; p=0.027). In patients with high IMR, the hazard ratio for death was 4.3 and 2.2 for heart failure. These findings strengthen the importance of assessing microvascular dysfunction in predicting the outcome after STEMI therapy. Therefore, the treatment of choice for 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 I-R injury subsequent to STEMI reperfusion. It had been postulated that reperfusion contributed to MVO through embolisation of debris (Khan MVO). However, Khan et al. examined MVO phenomenon using cardiac magnetic resonance in 94 STEMI patients with and without reperfusion therapies (i.e.: PPCI, thrombolysis, and rescue PCI). They found that the occurrence of MVO was comparable across all groups—irrespective of recanalisation mode—including the non-reperfused group. The authors concluded that MVO was primarily related to ischaemic time and is not exclusive to reperfusion therapy. 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 I-R injury.

Understanding the mechanisms of slow flow is pertinent for the management of this condition. One factor that is proposed to contribute to MVO is a persistent vasoconstrictor tone post-revascularization. The ability to dilate (i.e., 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 to the smaller arteries. Also in that study, coronary small arterioles did not dilate maximally during hypoperfusion. Therefore, these vessels are the site of persistent vasomotor tone in the subepicardial microcirculation during coronary insufficiency. In other words, microvessels are stiffer, more prone to be under the influence of vasoconstrictor. This finding is in accordance with the finding of Quillen et al., that is: ischaemic condition brings about mild alterations of coronary microvascular reactivity, and if followed by reperfusion, get heightened into more marked impairment of coronary microvessel responses. In contrast, the ability of larger epicardial coronary arteries to dilate is relatively refractory after exposition to ischaemia with or without reperfusion. Studies have shown that arginine vasopressin (AVP) has a constrictive effect on the coronary artery microvasculature. A multitude of studies indicate 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. This ability of AVP appears to be dose-dependent. Ischaemic ECG changes post-AVP treatment are also reported, which would further verify the coronary vasoconstriction ability of AVP.

1.3 Arginine vasopressin

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

In addition, AVP is also a part of the stress response. Stress is defined as a non-specific body response to any factor that disturbs the equilibrium of homoeostasis. A stress response is assimilated by the hypothalamus and manifests in an integrated neurohormonal activation. The major neural response to a stressful situation involves sympathetic nervous activation. The predominant hormonal response during stress involves adrenocorticotropic hormone (ACTH) that is released from the anterior pituitary gland in response to stimulation by corticotropin-releasing hormone (CRH). Almost any type of stressful situations (e.g.: physical stress, neurogenic, tissue damage, pain) increase ACTH immediately and markedly; thus ACTH is a well-known stress hormone. Another hormone that is
simultaneously released during stress response is AVP. Together with catecholamines, AVP helps to sustain blood pressure during stress. In acute conditions such as haemorrhage, circulatory arrest, sepsis, and surgery, circulating AVP levels rise.  

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. Atrial volume receptor firing to the nucleus tractus solitarius (and then to hypothalamus) is inhibitory to AVP release. The firing decreases during a reduction of extracellular fluid volume (e.g.: during major haemorrhage). In cases of hypovolaemia, blood pressure drops significantly in the atrium. This causes the release of AVP, which leads to water retention in the kidneys in order to preserve blood volume. AVP release is also affected by hypotension-sensitive arterial baroreceptors (i.e.: in congestive heart failure). (FIGURE 1)

1.3.1 Arginine vasopressin in circulation

The physiological concentration of AVP ranges between 1-5 pg/ml in which it achieves the ability to maintain body fluid homoeostasis. This level of AVP is below its vasoactive range (it only has a minor role in blood pressure maintenance role despite its vasoconstrictive capability). Higher plasma levels (>50 pg/ml) are required to bring about its vasoconstrictive effect and raise blood pressure in healthy human subjects. Under normal conditions AVP is of minor importance for the maintenance of blood pressure. AVP can increase peripheral vascular resistance but blood pressure would not be raised as the pressor effect of AVP would be buffered by a normal baroreceptor reflex. Therefore, it serves as a back-up mechanism in the setting of impaired autonomic nervous system (such as vasovagal syncope, pure autonomic failure) or in impaired baroreceptor reflex (such as
during septic shock). 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. Studies show that infusion of low-dose AVP in patients with vasodilatory shock reduces the need of norepinephrine (NE) administration, sustains blood pressure and cardiac output, and also decreases pulmonary resistance. Combined infusion of 4 units of AVP per hour and NE (adjusted to maintain MAP ≥70 mmHg) was able to restore vascular tone in treating vasodilatory shock. Vasodilatory shock states include septic shock, post-cardiopulmonary bypass shock, phosphodiesterase inhibition shock, haemodynamically unstable organ donors, and ‘irreversible’ phase of volume treated haemorrhagic shock.

In acute conditions, AVP levels can rise dramatically (i.e.: up to >500 pg/ml in severe haemorrhage, >450 pg/ml in cardiac arrest). As MI disturbs homoeostasis, it may act as a stressor that may be one of the stimuli for AVP release as that hormone is part of a stress response. Thus, AVP levels are very likely to be elevated during MI. Recently, Roy et al. demonstrated an increase in cardiac sympathetic nerve activity and AVP-secreting neurons activity that are induced by MI in an animal model. Noticeably elevated plasma AVP levels have also been documented in patients with evolving MI. As mentioned previously, when AVP levels are considerably high, its vasoconstrictor effects are present. It is thought that coronary vasoconstriction can occur during AVP serum levels between 10–1,000 pg/ml.

1.3.2 Arginine vasopressin and coronary vasculature in MI

In the post-MI period, AVP may have some detrimental effects. Although the systemic vasoconstriction by AVP can appear to be important in blood pressure sustenance, the resulting coronary vasoconstriction would offer no homeostatic advantage. Increased blood levels of AVP in dogs (from 3.9 ± 0.9 pg/ml to 14.7 ± 4.6 pg/ml) were found to impair ventricular contraction and decreases stroke volume. This negative inotropic
effect may correlate with the finding that AVP has the ability to produce coronary
vasoconstriction.\textsuperscript{40-42} This can potentially exacerbate the already compromised coronary
perfusion, thus increasing infarct size and disturbing cardiac function. AVP was found to
selectively have more effect on the microvasculature of coronary arteries than larger vessels
in both healthy and ischaemic setting.\textsuperscript{17,18} Moreover, AVP would be expected to have a
stronger constricting effect in parts where the oxygen supply/demand ratio is relatively high
(remarking post-reperfusion in vivo).\textsuperscript{19} This was demonstrated by a study in which AVP
administration in a normoxic rat heart was able to constrict coronary arteries, reduce coronary
perfusion, depress cardiac function via reduction of oxygen supply, and increase lactate
production.\textsuperscript{19} This constricting effect was weakened during hypoxia.\textsuperscript{19} However, when
hypoxia was discontinued — thus, resembling reperfusion — significant coronary flow
reduction was observed.\textsuperscript{19} If one would translate this effect to human MI patients, it is
conceivable that AVP release in response to myocardial ischaemia would cause
vasoconstriction in the coronary microvasculature distal to the recanalized occlusion of the
epicardial vessel. This in turn could enhance or trigger I-R injury.

There is some ambiguity though predicting the effect of AVP under ischaemic conditions in
the patient. Both, coronary vasoconstriction and vasodilation have been demonstrated post-
AVP treatment in experimental models. One study describes an increase of myocardial blood
flow under a low dose of AVP due to increased systemic perfusion pressure and selective
coronary vasodilation.\textsuperscript{37} Another study assessed the effect of bolus AVP injection into the left
descending artery in pigs and AVP was shown to significantly increased the vessel
diameter.\textsuperscript{36} Preclinical studies have evaluated the effect of low-dose AVP in animal models
of cardiac arrest.\textsuperscript{36} They found 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.\textsuperscript{36} This contradictory feature not shared by other
vasoconstrictor agents might be explained if we look into the different receptors of AVP that will be 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 experimental models, and most likely also on the dose of AVP. At low dose, this hormone may seem to exert a ‘net positive inotropic effect’. However, Forrest et al. found that AVP levels that cause minimal effects in normal subjects may generate marked pressor action in acute conditions. A study from Indrambarya and colleagues observed that low-dose AVP administration (0.04 Units/minute) in mice after MI/R had adverse effects, which include depressed cardiac contractility and increased mortality. Again, this heightened sensitivity can be explained by receptor changes that take place during different heart conditions. The net effect of AVP on cardiac function in a stressed 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 negative inotropic effect and coronary vasoconstriction, clinical studies of low-dose AVP administration thus far do not exhibit any adverse cardiac effects. All in all, AVP levels, sensitivity, and its effect on coronary vasculature in MI/R are yet to be discovered. Increased AVP levels when coupled with heightened sensitivity on coronary artery microcirculation may result in MVO in MI/R.

1.4 Copeptin

In the blood circulation AVP is unstable and mainly bound to platelets. It is rapidly cleared, making its measurement difficult and seldom accurate. AVP originates from a large precursor called pre-provasopressin that is produced in the hypothalamus and axonally
transported to the neurohypophysis. Copeptin, a 39-amino acid glycopeptide, is the C-terminal fragment of pre-provasopressin that is co-secreted—in equimolar amount—with AVP into the circulation following cleavage in the neurohypophysis. 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 5–20 min, copeptin is much more stable in the circulation with its half-life of 82 minutes. 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, making it readily measurable in plasma or serum. Reliable plasma AVP quantification is technically challenging and time-consuming, thus valid AVP assays are uncommon. More than 90% of circulating AVP is bound to platelets, resulting in either under- or overestimation of AVP levels during measurement. Another advantage of copeptin measurement is that its concentrations remain unaltered by exogenous AVP therapy, thus would enable assessment of endogenous production. Therefore, measurement of copeptin is likely to be more accurate than AVP measurement.

Normal AVP levels vary between 1.5 pg/ml (equivalent to 0.9 – 4.6 pmol/l) and copeptin levels in healthy individuals range between 1.0 – 4.4 pmol/l. A study presented that both AVP and copeptin correlated with plasma osmolality in healthy subjects (r=0.77 and 0.49, respectively). Furthermore, a close correlation of AVP and copeptin concentrations (r=0.8) was also obtained. Aside from the hyperosmolar states, increased copeptin levels were also found upon nonosmotic stimuli that increase AVP (i.e.: 79.5 pmol/l in sepsis, 171.5 pmol/l in septic shock, 269 pmol/l in haemorrhagic shock, 88 pmol/l in systemic inflammatory response syndrome, etc.). Post-MI, plasma copeptin was highest on admission and
reached a plateau at day 3–5. Another study by Slagman et al. showed that copeptin increased right after spontaneous MI (highest at admission) and decreased gradually within 12–36 hours. In a different study, copeptin concentration was found to be highest within 4 hours of symptom onset. In patients undergoing transcoronary ablation of septal hypertrophy as the equivalent of MI induction, the median copeptin concentration was significantly elevated at 30 min post (16.0 pmol/L; IQR 13.4–20.2), peaked 90 minutes post (31.9 pmol/L; IQR 16.4–117.1) and finally restored to baseline after 24 hours (8.2 pmol/L; IQR 6.3–10.1). The cut-off value for copeptin to exclude MI has been proposed at 14 pmol/L. Copeptin, when combined with cardiac troponins, has shown to provide additional diagnostic sensitivity for early discrimination of acute MI. The median copeptin levels in acute coronary syndrome patients without infarction was lower compared to those with MI. Due to the distinct temporal pattern of copeptin release, it provides a diagnostic aid especially in the first 3 hours of symptom onset, whereby cardiac troponin levels have not raised. In an experimental study conducted in pigs, increased circulating copeptin was related to mean arterial pressure (MAP) changes, i.e.: animals with high values showed a drop of MAP as a consequence of MI.

Post-MI (day 2–5) copeptin levels were found to have a relationship with myocardial remodelling and heart failure in survivors of MI. High circulating copeptin levels were found to have predictive values for the outcome of advanced heart failure after MI. Copeptin was 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). The predictive value of copeptin was found superior to clinical variables, LVEF, and major cardiovascular risk factors. MI patients with copeptin values above median level (10.4 pmol/L) demonstrated 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 ejection fraction (r= –0.484, p<0.001 at baseline and r= –0.461, p<0.001 at 4-
month follow-up). This is supported by another study that found a significant positive correlation between plasma copeptin concentrations and infarct size \((r=0.96; p<0.0001)\). Furthermore, admission levels of copeptin was found to independently predict final infarct size after multivariate analysis. Not only in MI, copeptin levels measured in 1,195 stable, ambulatory patients with type 2 diabetes was 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 [1.09–1.36]; \(p=0.001\)) after a 10-year follow-up. This association was found to be independent after adjustment for various confounders. The median baseline copeptin levels in survivors were significantly lower compared to those who had died of cardiovascular causes and of all causes (4.9 [IQR 3.0–8.5] pmol/l vs 7.9 [3.9–13.8] pmol/l vs 7.3 [3.7–13.0] pmol/l; \(p<0.0001\)).

Given the similarities and the stability of copeptin, it is more favourable to measure AVP concentration from its surrogate biomarker: copeptin. A sensitive sandwich immunoassay for the quantification of copeptin in human serum or plasma has been developed. The assay utilizes two polyclonal antibodies to the amino acid sequence 132–164 of pre-provasopressin 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.

### 1.5 Cardiac synthesis of arginine vasopressin

Initially, AVP was thought to be exclusively produced in the hypothalamus. However, in one animal study, Hupf et al. discovered AVP production in the rat heart after left ventricular pressure overload. AVP 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. One study analysed local cardiac copeptin release by using a transcoronary gradient model (TCG) in patients with acute MI. TCG data
was calculated by comparing blood samples withdrawn from the aortic bulb and the coronary venous sinus. Although they discovered a significant increase of copeptin in the systemic circulation, they did not obtain a positive gradient for copeptin, suggesting no significant production of copeptin in the heart. Further studies are needed to confirm this finding.

1.6 Arginine vasopressin receptor
AVP exerts its actions through several AVP G-protein-coupled receptors: receptor 1a (AVPR1a), receptor 1b (AVPR1b) or also known as receptor 3, receptor 2 (AVPR2), oxytocin subtypes (OTR), and P2 purinergic receptors (P2R). AVPR1a is located predominantly in vascular smooth muscle cells (VSMCs). Meanwhile, AVPR1b is located in anterior pituitary and AVPR2 is located in distal tubules and collecting ducts of the kidneys. OTRs are present in high density on vascular endothelium. P2Rs are expressed on cardiac endothelium.

Upon binding to the AVPR1a, the peripheral and coronary vessels undergo vasoconstriction. In arteriolar smooth muscle cells, stimulation of AVPR1a leads to an increase in ionized calcium in the cytoplasm via the phosphatidyl-inositol-bisphosphonate cascade. In addition to smooth muscle cells, AVP can also increase intracellular calcium levels in cardiac myocytes through AVPR1a.

(Figure 3)

The pressor effect of AVP was eliminated in AVPR1a−/− mice, indicating that AVP-induced vasoconstriction is mediated through AVPR1a. As mentioned previously, the vasoconstrictive action of AVP is more marked in acute conditions. This heightened sensitivity was also found in MI. Coronary arteries, especially the arterial microvessels, were found to have an increased vasoconstrictive response to AVP after ischaemia in comparison to the control group. Indrambarya and colleagues also observed that low-dose AVP
administration (0.04 Units/minute) had minimal effects on baseline mice hearts, but adverse effects on MI-reperfused mice hearts. This ischaemia-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—thus favouring I-R injury. However, the thrombotic response appears to vary among individuals due to the heterogeneity and polymorphism among AVPR1a of human platelet.

The most abundant AVP receptor in the heart appears to be AVPR1a. However, P2Rs were recently shown to be expressed as well on cardiac endothelium, from which AVP is able to exert its cardiac effects. Intracoronary infusion of AVP-dextran produced coronary vasoconstriction and negative inotropy in isolated perfused guinea pig hearts. These outcomes were inhibited by AVPR1a antagonist and P2R antagonist. Therefore, vasopressor effect of AVP on the heart can be mediated by more than one receptor type.

Another AVP receptor of interest is the OTR. It has equal affinity for both AVP and oxytocin, thus is considered to be a ‘nonselective’. OTRs exist abundantly on vascular endothelium to mediate nitric oxide-dependent vasodilation. This finding might explain the seemingly contradictory actions of AVP in the heart: coronary vasoconstriction vs vasodilation, positive vs negative inotropic effect. A response discrepancy between the ‘normal’ and stressed heart to AVP has been reported (i.e.: vasoconstriction in normoxic state and vasodilation during hypoxia, as mentioned earlier). Thus, the activity and density of OTR vs AVPR1a and P2R in MI/R are yet to be elucidated. Recently, OTR has been discovered in the heart and, upon its stimulation, facilitated the release of atrial natriuretic peptide (ANP). ANP release by AVP seems to be affected by haemodynamic changes, as only pressor doses of AVP generated an immediate increase in plasma ANP.
1.7 Arginine vasopressin in cardiovascular diseases

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

Furthermore, elevated AVP levels are often observed in patients with heart failure and left ventricular dysfunction after MI; and that high quantity seems to have a degree of association with adverse cardiovascular outcomes. In accordance to that, Francis et al. also reported elevated AVP levels in patients with asymptomatic left ventricular dysfunction when compared to control patients, whereas patients with symptomatic mild-to-moderate heart failure had even higher AVP levels. In turn, this elevated levels of AVP might play a role in the increased levels of ANP seen in heart failure. Moreover, AVP levels failed to correlate with serum sodium nor cardiac index. This lack of correlation indicates the possibility of impaired osmotic regulatory mechanism in cardiovascular diseases.
1.8 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. Antagonism of AVP receptors has been advocated as a therapy to reduce cardiac afterload for congestive heart failure patients. Creager et al. studied patients with heart failure undergoing short-term AVPR1a antagonism and found reductions in systemic vascular resistance and increases in cardiac output. In a randomized, placebo-controlled trial, Udelson et al. found that the combined AVPR1a and AVPR2 antagonism via conivaptan resulted in a favourable haemodynamic and renal effects in heart failure patients: reductions in systemic vascular resistance with increases in cardiac output, as well as increases in diuresis. Haemodynamic effects of conivaptan were also evaluated in a study of NYHA Class III/IV heart failure patients and conivaptan administration was associated with a significant reduction in pulmonary capillary wedge pressure, right atrial pressure, and an increase in urine output. No serious adverse outcomes or drug-related deaths occurred. Administration of the AVP antagonist in post-hypoxic, post-AVP infusion rat hearts resulted in significant increases in coronary flow, eliminating the AVP-mediated cardiac effects of contractile function. Pretreatment with a specific AVPR1a antagonist totally abolished the coronary vasoconstrictor effect and contractility responses. Furthermore, Zeynalov et al. conducted a study to evaluate the effect of AVP receptor antagonism after experimental stroke in mice. They found that continuous infusion of conivaptan, but not tolvaptan, resulted in a favourable haemodynamic outcome as it reduced brain edema and blood-brain barrier disruption. AVPR1a inhibition after subarachnoid hemorrhage leads to improvements in regional cerebral blood flow. Looking at the results above, the haemodynamically 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/AVPR2 antagonist.\textsuperscript{72} It is the first AVP receptor antagonist to be approved in the U.S. and is currently indicated for the treatment of euvolemic hyponatremia <135 mEq/L.\textsuperscript{72} For that condition, conivaptan is administered as a 20 mg IV bolus over 30 minutes (loading dose) followed by a continuous infusion of 20 mg over 24 hours for up to 4 days.\textsuperscript{72} However, Udelson et al. administered a single IV dose of 20 mg–40 mg in heart failure patients.\textsuperscript{66} Aside from its intravenous preparation, Ghali et al. found that oral conivaptan (40 and 80 mg/dl) was well-tolerated and efficacious in correcting serum sodium in hyponatremia.\textsuperscript{74}

**Conclusion**

AVP is released into the circulation as part of a stress response triggered by MI. Increased hypothalamic AVP expression is the most likely to be responsible for this in contrast to local cardiac AVP system. AVP, most likely at higher (non-physiological) concentrations, can exert vasoconstrictive effects on coronary arteries in pre-clinical models, mainly in non-epicardial vessels of the microcirculation. Circulating AVP levels are up to 100-fold increased in MI and do not immediately decrease to baseline levels upon reperfusion. This may contribute to slow flow phenomenon and mediate I-R injury. Ischaemia-induced cardiac sensitisation to AVP from the upregulation of AVPR1a or P\textsubscript{2}R expression needs to be evaluated in future studies. 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. This mandates a clinical trial with conivaptan, an AVP-receptor antagonist, in patients with acute myocardial infarction undergoing reperfusion therapy.

(FIGURE 4)

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Figure 1. Pathways to induce AVP release

The three pathways to stimulate AVP secretion from posterior pituitary gland include stress response, elevated blood osmolality, and major blood pressure drop.

Figure 2. Schematic of the peptide precursor of AVP.

AVPR1a is a G-protein coupled receptor. Upon activation by AVP, Gq stimulates phospholipase C to hydrolyse phosphatidylinositol, thereby increasing cytosolic Ca\textsuperscript{2+} level and mediating cell contraction. PLC= phospholipase C; PIP\textsubscript{2}= phosphatidylinositol 4,5-biphosphate; IP\textsubscript{3}= inositol triphosphate; ER= endoplasmic reticulum; CaM= calmodulin; MLCK= myosin light-chain kinase.
Figure 4. Hypothesis summary.

MI acts as a stressor, which is sensed by the brain. Hypothalamus serves as stress response regulator. In response to stress, supraoptic and paraventricular nucleus of hypothalamus increase the expression of AVP, with subsequent release from posterior pituitary gland; AVP is co-secreted with copeptin. In turn, AVP brings about detrimental effect to the coronary artery microvasculature by binding to AVPR1a or P2R, which gets upregulated during MI. This mediates further injury despite of recanalization. Furthermore, we hypothesise that MI could activate local AVP production that adds more vasoconstrictive effect in the coronary artery microvasculature. The resulting injury can cause further disturbance.