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Role of levosimendan in the management of subarachnoid hemorrhage☆

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ABSTRACT

Aneurysmal subarachnoid hemorrhage (aSAH) is one of the leading causes of neurologic disability accounting for dismal long term survival rates. aSAH leads to a sudden increase in intracranial pressure and a massive sympathetic discharge. Excessive sympathetic stimulation leads to catecholamine mediated myocardial dysfunction and hemodynamic instability which may critically hamper brain perfusion and oxygenation. In the setting of acute aSAH, administration of vasoactive drugs aims at stabilizing impaired hemodynamics. However, studies have shown that conventional treatment with vasoactive drugs that lead to Ca^{+2} overload and increase myocardial oxygen consumption, fail to restore hemodynamics and decrease cerebral blood flow. Levosimendan is a non-adrenergic inotropic Ca^{+2} sensitizer with not only beneficial hemodynamic properties but also pleiotropic effects, contributing to its cardioprotective and neuroprotective role. Although there have been limited data available regarding the use of levosimendan in patients with aSAH, current evidence suggests that levosimendan may have a role in the setting of post-aSAH cardiomyopathy and decreased cerebral blood flow both in the emergency departments and in intensive care units. The purpose of this review is to provide an overview of studies of levosimendan therapy for aSAH, and describe current knowledge about the effects of levosimendan in the management of aSAH.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is one of the leading causes of neurologic disability accounting for permanent neurological deficits of survivors [1]. The prognosis of aSAH remains poor, with mortality rates as high as 33% [2].

aSAH leads to a sudden increase in intracranial pressure (ICP) and a massive sympathetic discharge. Excessive sympathetic stimulation leads to catecholamine mediated myocardial dysfunction and hemodynamic instability which may critically hamper brain perfusion and oxygenation [3]. In the setting of acute aSAH, administration of vasoactive drugs aims at stabilizing impaired hemodynamics. However, several studies [4,5] have shown that conventional treatment with vasoactive drugs [6] that lead to Ca^{+2} overload and increase myocardial oxygen consumption, fail to restore hemodynamics and decrease cerebral blood flow [7]. Although there has been limited data available regarding the use of levosimendan in patients with aSAH, levosimendan appears to be an emerging tool for the treatment of post –aSAH cardiomyopathy and decreased cerebral blood flow both in the emergency departments (EDs) and in intensive care units [8–11]. It is a non-adrenergic inotropic Ca^{+2} sensitizer that allows rapid restoration of cardiac output without increasing myocardial oxygen consumption and also optimizes cerebral perfusion [9]. Moreover, its antioxidant and anti-inflammatory effects contribute to its cardioprotective and neuroprotective role [10].

The purpose of this review is to provide evidence of levosimendan therapy for aSAH, and describe current knowledge about the effects of levosimendan in the management of aSAH.

2. Post-aSAH neurogenic stunned myocardium

Approximately 20–30% of aSAH patients manifest neurogenic stunned myocardium, which is associated with high mortality. Its onset occurs within 72 hours after aSAH and its prognosis depends on the degree of neurological rather than cardiac damage [12]. Neurogenic-stunned myocardium is a reversible myocardial injury with a severely depressed left ventricular (LV) systolic function which leads to a decreased cardiac output during the acute stage of aSAH [13]. The classic triad of clinical findings includes transient LV wall motion abnormality, electrocardiographic abnormalities, such as QT prolongation, T-wave and ST-segment changes, and elevation in

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myocardial enzymes in the absence of coronary artery disease [14]. LV wall motion abnormality is characterized by either hypokinesis of the basal and mid-ventricular segments with sparing of the apex or global LV hypokinesis [14]. In the neurogenic stunned myocardium, myocyte injury results in nonvascular territory patterns of abnormality, specifically contraction band necrosis, coupled with normal coronary arteries. Myocardial contraction band necrosis is characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory response [15]. The range of myocardiac dysfunction in the early phase after aSAH extends from asymptomatic minor elevations in cardiac enzymes to severe complications such as pulmonary edema, malignant arrhythmias, and cardiogenic shock [16]. Therefore, it requires prompt recognition and proper intervention both in the ED and in the intensive care unit.

aSAH leads to a sudden increase of ICP, a decrease in cerebral perfusion pressure (CPP) and consequently to a reduction in cerebral blood flow [3]. The compensatory mechanism in order to increase cardiac output and mean arterial pressure (MAP) and therefore to restore CPP includes an intense neuronal sympathetic activation. The sympathetic stimulation of adrenoceptors in the ventricular myocardium is achieved through a local release of catecholamines by sympathetic nerve terminals directly innervating the myocardium [17]. This leads to an interaction with stimulatory G proteins (Gs), which in turn activates adenylyl cyclase to enhance cyclic adenosine monophosphate (cAMP) formation. Elevated cAMP concentrations activate protein kinase A (PKA) [18], which phosphorylates several downstream intracellular targets, resulting in an increased contractile response [19]. However, an excessive release of catecholamines from sympathetic nerve terminals triggered by aSAH leads to Ca^{+2} overload of the myocyte and prolonged contraction and structural damage to the myocardium [20]. All the above result in a depletion of high-energy phosphates, mitochondrial dysfunction, and myocardial stunning [21]. Grad et al have shown that increased levels of catecholamines and their metabolites have been noted in the urine and serum of patients with aSAH and were associated with direct myocardial toxicity [22]. Moreover, Melville et al reported that ablation of cardiac sympathetic nerves in animal models of SAH prevented early myocardial dysfunction [23].

b-Adrenoreceptors couple predominantly to Gs proteins but also couple to G-inhibitory (Gi) proteins [24]. High levels of circulating catecholamines trigger a switch in intracellular signal trafficking in ventricular cardiomyocytes, from Gs protein to Gi protein signalling via the b2-adrenoreceptors [25]. b2-AR-Gi mediated signalling in ventricular myocytes leads to a negative inotropic effect through inhibition of Gs-cAMP production [26] and alters myofilament sensitivity to Ca^{+2}. In this way, the myocardium is protected from the effects of Gs–cAMP–PKA overstimulation [27]. Moreover, this effect is greatest at the basal myocardium than in the apical, in which the b-adrenoreceptor density is greatest [26]. Furthermore, increased catecholamine levels may result in desensitization and down-regulation of b1-adrenoreceptors. The above leads to a reduced contractile response to the activation of b1-adrenoreceptors and to aSAH related myocardial dysfunction [28].

Acute aSAH is accompanied by neurometabolic cardiac abnormalities which may lead to metabolic stunning [29]. Studies have shown that depression of myocardial lipid and glucose metabolism may be involved in the pathogenesis of neurogenic stunned myocardium. Catecholamine-mediated increased output of glucose from the liver leads to lactate production and hyperglycemia [30]. Moreover, sympathetic stimulation leads to insulin resistance and inhibition of insulin release. The above lead to reduced glucose uptake by the myocardium, depression of glucose metabolism, and intramyocardial lipid accumulation [31]. Hyperglycemia may be associated with denudation of the endothelial glycocalyx and deleterious effects on the microcirculation [32]. Moreover, hyperglycemia and lipid accumulation exacerbates aSAH-induced myocardial and brain injury by enhancing the mitochondrial dynamic imbalance, apoptosis and inflammation [33]. Dilsizian et al showed a direct correlation between catecholamine-induced segmental dysfunction, lipid accumulation and glycogen exhaustion as well as a reduced uptake of lipid and glucose in the akinetic segments of the myocardium in aSAH patients during the acute phase [34].

In the acute phase of aSAH auto-oxidation of catecholamines results in the generation of highly toxic cytotoxic free radicals [35]. An exposure of the normal myocardium to reactive oxygen species (ROS) induces oxidative damage [36]. Free radicals initiate the peroxidation of membrane-bound fatty acids, damaging the membrane integrity leading to both functional and structural myocardial injury [36]. Moreover, the excessive production of ROS directly inhibits the respiratory chain complexes activities and thus may lead to mitochondrial dysfunction and myocardial cell death [37]. There is also accumulating evidence that a sympathetic overstimulation in the setting of aSAH induces cytokine expression. Studies have shown increased circulating levels of pro-inflammatory cytokines, such as tumor necrosis factor–α (TNF-α) and interleukines 6 and 8 to 10 [38] in cerebrospinal fluid and serum of patients with aSAH. In addition, the activation of various cytokine cascades not only triggers proapoptotic signalling pathways and therefore aggravates cardiovascular injury but also contributes to the refractoriness to inotropic drugs and to high mortality [15].

Rhythm and conduction disturbances are common during the first 48 hours after aSAH. Repolarization abnormalities after SAH include T-wave inversions, ST depression, and QT prolongation [39]. Excessive sympathetic stimulation triggered by aSAH elevates intracellular Ca^{+2} concentration, leads to arrhythmiogenesis, and may exacerbate myocardial ischemic injury [40]. Moreover, in the setting of aSAH, vagal nerve reflexes are disturbed due to the ischemic insult, which may lead to heart rhythm irregularities [41]. Early assessment of electrocardiographic abnormalities in the ED is important as they are independently associated with the in-hospital mortality of patients with aSAH [42].

Sympathetic over-stimulation induces pulmonary venous constriction and microembolus formation and leads to increases in pulmonary capillary pressure [43]. Furthermore, sympathetic activation aggravates myocardial dysfunction due to peripheral vasoconstriction and increased left ventricular afterload. Papanikolaou et al have shown that in aSAH, aortic stiffness may further increase left ventricular afterload, reduce diastolic coronary blood flow and induce subendocardial ischemia [44]. Aortic stiffness and associated LV dysfunction might play a role in the pathogenesis of neurologic sequelae in aSAH because they may affect cerebral blood flow adversely [44] (Fig. 1).

3. Levosimendan and post-aSAH neurogenic stunned myocardium

Neurogenic stunned myocardium in the setting of aSAH commonly results in hemodynamic instability and decreased cerebral blood flow [2]. The treatment of post-aSAH neurogenic stunned myocardium warrants the use of inotropic drugs, aiming at increasing organ perfusion and tissue oxygen delivery [45]. Although data regarding the optimal vasoactive drug therapy of neurogenic stunned myocardium in aSAH patients is limited, treatment includes primarily cAMP-mediated Ca^{2} increase by either b1-adrenergic stimulation or phosphodiesterase inhibition. However, in the setting of acute aSAH in which adrenergic stimulation is already maximal, further increase in intracellular Ca^{+2} and myocardial oxygen consumption with conventional inotropes would no longer be beneficial [46]. Several studies have shown that neurogenic stunned myocardium may be refractory to conventional treatment [4,9]. cAMP-dependent inotropes may have a negative inotropic effect in the already compromised myocardium and increase mortality [47], despite their rapid onset of action. They may not only aggravate the vicious cycle of catecholamine-induced cardiotoxicity by augmenting the already increased circulating catecholamine levels but also induce themselves stress cardiomyopathy in the late period post-aSAH [48,49].

Levosimendan is a non-adrenergic inotropic calcium sensitizer [8] that exerts its inotropic effect principally via binding to the Ca^{+2}