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Review

The effects of nitroglycerin during cardiopulmonary resuscitation

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ABSTRACT

The outcome for both in-hospital and out-of hospital cardiac arrest remains dismal. Vasopressors are used to increase coronary perfusion pressure and thus facilitate return of spontaneous circulation during cardiopulmonary resuscitation. However, they are associated with a number of potential adverse effects and may decrease endocardial and cerebral organ blood flow. Nitroglycerin has a favourable haemodynamic profile which promotes forward blood flow. Several studies suggest that combined use of nitroglycerin with vasopressors during resuscitation, is associated with increased rates of resuscitation and improved post-resuscitation outcome. This article reviews the effects of nitroglycerin during cardiopulmonary resuscitation and postresuscitation period, as well as the beneficial outcomes of a combination regimen consisting of a vasopressor and a vasodilator, such as nitroglycerin.

Contents

1. Introduction

Hospital discharge rates for both in-hospital and out-of hospital cardiac arrest (CA) remain dismal (Bobrow et al., 2008). Vasopressors are used to increase diastolic aortic pressure (DAP) and coronary perfusion pressure (CPP) and thus facilitate return of spontaneous circulation (ROSC) during cardiopulmonary resuscitation (CPR). However, they are associated with a number of potential adverse effects and may decrease endocardial and cerebral organ blood flow (Mayr et al., 2001; Ristagno et al., 2007).

The current CPR research is oriented toward possible drug combinations for enhancing forward organ blood flow and optimizing vital organ perfusion pressures. Therefore, the use of a vasodilator agent with potential beneficial effects in CA, such as nitroglycerin (NTG), is currently investigated in the literature since NTG has a favourable haemodynamic profile which promotes forward blood flow (Mehta, 1995).

The purpose of this paper is to review the literature in order to assess the effects of NTG during cardiopulmonary resuscitation and postresuscitation period and to review the beneficial outcomes of a

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combination regimen consisting of a vasopressor and a vasodilator, such as NTG.

2. Vasopressors during CPR

Epinephrine is a naturally occurring catecholamine and a potent alpha- and beta-adrenergic agonist. Its alpha-adrenergic effects, cause peripheral arteriolar vasoconstriction (Varon et al., 1998) thus promoting coronary and cerebral pressures increase (Otto and Yakaitis, 1984). Through its beta-1 effects it increases myocardial contractility and heart rate which lead to increased myocardial oxygen consumption. Moreover its beta-2-agonist effects cause smooth muscle relaxation, peripheral vasodilatation, and bronchial dilatation (Xanthos et al., 2011).

Epinephrine, however, also causes adverse effects. Its beta-1 agonist effect may result in a critically decreased endocardial blood flow and ischaemic injury. Moreover, epinephrine, through its alpha-1 adrenergic action, causes intramyocardial coronary arteriolar vasoconstriction with the potential of further reductions in myocardial blood flow. Although alpha-1-adrenergic stimulation mediates vasoconstriction and increases cerebral perfusion pressure (Gedeborg et al., 2000), it increases cerebral ischaemia severity through the reduction of cerebral microcirculatory flows (Mayr et al., 2001; Wenzel et al., 2000). It may induce dissociation between macrovascular and microvascular blood flow (Foreman et al., 1991) and adversely affect neurological function (Berecek and Brody, 1982). At high doses epinephrine may also exert direct effects on the brain independently of cerebral perfusion pressure increase. It may stimulate the increase of cerebral oxygen consumption during severe hypertension (Bryan, 1990).

The aforementioned epinehrine disadvantages have led to the use of vasopressin. Arginine vasopressin is an endogenous hypothalamic hormone with osmoregulatory, vasoconstrictive, haemostatic, thermoregulatory and central nervous effects. Via the V_1 receptors, it stimulates the contraction of vascular smooth muscles, resulting in peripheral vasoconstriction and increased blood pressure. It also causes coronary vasoconstriction (Cooke et al., 2001) and can reduce blood flow to the myocardial tissue, thus, causing myocardial ischaemia. Vasopressin may have a biphasic action on coronary and vertebrobasilar circulations (Martínez et al., 1994). It is characterized by an initial potent vasoconstriction, mediated by stimulation of V_1 receptors which is then followed by vasodilation, which is mediated by V_2 receptor stimulation (Cooke et al., 2001). Moreover, studies have shown that vasopressin dilates the cerebral vasculature via the release of nitric oxide (Oyama et al., 1993).

Although laboratory investigations demonstrated that vasopressin caused an increase in vital organ blood flow when compared to epinephrine (Lindner et al., 1995; Wenzel et al., 1999), as well as improved neurological recovery (Miller and Wadsworth, 2009; Wenzel et al., 2000), other studies show controversial results. Animal studies in which vital organ blood flow has been evaluated, have indicated that vasopressin results in suboptimal endocardial perfusion during CPR (Cooke et al., 2001) and contributes to hypoperfusion of the myocardium (Foreman et al., 1991).

Due to the V_2 mediated vasodilatory effect of vasopressin it was hypothesized that the combination of epinephrine and vasopressin would improve the end-organ hypoperfusion caused by epinephrine. Experimental studies (Mayr et al., 2001) showed that the addition of vasopressin to epinephrine improves the impaired cerebral microcirculatory blood flow caused by epinephrine. Vasopressin's vasodilating effect counterbalanced the vasoconstriction induced by epinephrine. Moreover, experimental models indicated that an epinephrine–vasopressin combination increases survival (Stadlebauer et al., 2003) and improves the histopathologic outcomes when compared with epinephrine alone (Wenzel et al., 1998a, 1998b). However, other studies have shown different results. The combination of vasopressin plus epinephrine was associated with a decrease in cerebral and endocardial blood flow CPR when compared with vasopressin alone (Mulligan et al., 1997). In another study by Wenzel et al., epinephrine significantly diminished the vasodilating effect of vasopressin on the cerebral vasculature (Wenzel et al., 1998a, 1998b).

3. Nitroglycerin

NTG as well as other nitrates function as prodrugs that, when bioactivated, release nitric oxide (NO) in the vascular smooth muscle and endothelial cells (Kleschyov et al., 2003). NO activates soluble guanylyl cyclase (sGC) (Munzel et al., 2003) in the vascular smooth muscle, an intracellular NO receptor, subsequently stimulating the synthesis of the intracellular second messenger cyclic-guanosine monophosphate (cGMP). cGMP exerts its effects by interacting with cGMP-dependent protein kinases (PKC), leading to smooth muscle relaxation. It has been shown that PKC mediates vasorelaxation through phosphorylation of proteins that regulate intracellular calcium levels (Fullerton and McIntyre, 1996) (Fig. 1).

NTG is a powerful venodilator and reduces venous return and cardiac preload (Hollenberg, 2007). The reduction in preload is manifested by a decrease in ventricular filling pressure, and wall stress (Brazzamono et al., 1988; Groszmann et al., 1982; Wenzel et al., 1998a, 1998b). The reduction in wall tension decreases the subendocardial resistance to blood flow (Mehta, 1995).

At high plasma nitrate concentrations, it has a mild arteriolar vasodilatory effect, leading to increased arterial conductance and decreased peripheral vascular resistance with consequent reduction in the left ventricular afterload. The reduction in preload and afterload lowers myocardial oxygen requirements and provides unique therapeutic benefit in cardiac ischaemia (Abrams, 1996). NTG is known to increase cardiac output in animal models (Brazzamono et al., 1988) and in humans (Groszmann et al., 1982). Moreover, studies have shown that NTG has a positive inotropic effect. This NTG induced positive inotropic effect is based on the fact that elevated amounts of intracellular cGMP increase myocardial contractility (Kojda et al., 1996).

NTG potently dilates the larger coronary arteries thus improving the subendocardial/subepicardial blood flow ratio (Klemenska and Berȩsewicz, 2009). It also dilates coronary collateral vessels and improves collateral subendocardial blood flow (Mehta, 1995). For this reason, NTG has clear benefits for the treatment of angina pectoris, congestive heart failure, unstable angina, non-ST-segment myocardial infarction and acute myocardial infarction (Brunton et al., 2006).

Due to the beneficial effects of NTG, its use in conjunction with vasopressors has been evaluated in several studies. Bache studied the effect of the combination of nitroglycerin with a vasopressor phenylephrine in a laboratory model with acute occlusion of the left circumflex coronary artery. The combination significantly improved myocardial blood flow in both injured and non-injured areas (Bache, 1978). The approach of combining a vasodilator with vasopressin has been used successfully for the management of patients with bleeding esophageal varices (D'Amico et al., 1994). Moreover, Spronk et al. (2002) showed that impaired microcirculatory perfusion from septic shock was treated with NTG.

4. NTG during cardiopulmonary resuscitation

4.1. Animal studies

The combined use of NTG with vasopressors was also evaluated in critical conditions such as cardiac arrest. Wenzel et al.