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Review article

Ventricular tachyarrhythmias during acute myocardial infarction: The role of endothelin-1

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ABSTRACT

Ventricular arrhythmogenesis during acute coronary syndromes is a common cause of sudden cardiac death, but the underlying mechanisms remain incompletely understood. Recent evidence indicates an emerging pathophysiologic role of endothelin-1 during myocardial ischaemia and evolving infarction. At the early stages post-coronary occlusion, endothelin-1 enhances sympathetic activation, an effect mediated via the ETA receptor, whereas the ETB receptor exerts protective actions. The importance of this interaction is clearly decreased during subsequent stages, during which endothelin-1 may participate in the genesis of ventricular tachycardia or fibrillation via other mechanisms; of these, the effects of endothelin-1 on repolarizing potassium currents and electrical conduction via gap junctions merit further research. The relative roles of ETA and ETB receptors during this phase are unclear. Evaluation of the arrhythmogenic effects of endothelin-1 during acute coronary syndromes may provide the tools towards lowering sudden cardiac death rates.

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Ischaemia-related arrhythmias: the main cause of sudden death

Sudden cardiac death comprises over 10% of all deaths from natural causes and constitutes a major health-related problem worldwide (Rubart and Zipes, 2005). In approximately 80% of cases, sudden cardiac death is caused by sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) secondary to acute myocardial infarction (MI) (Rubart and Zipes, 2005). Due to the high prevalence of coronary artery disease, the annual number of sudden cardiac deaths in the general population is estimated at 250/million, with rates remaining stable during the past decade (Kolettis, 2013). Arrhythmogenesis after acute coronary occlusion often displays a biphasic pattern (Di Diego and Antzelevitch, 2011), with early clustering of VT/VF accounting for most of the mortality, due to its common occurrence prior to medical attendance (Rubart and Zipes, 2005; Kolettis, 2013).

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Pathophysiology of ischaemia-related arrhythmias

Myocardial ischaemia induces profound changes in cardiac electrophysiology that affect both, the ischaemic and the normal myocardium (Luqman et al., 2007). Shortly after acute coronary occlusion, extracellular concentration of potassium ions rises, generating injury currents towards normal myocardial areas that lead to myocardial cell depolarization. Sodium-ion conductance diminishes, decreasing the amplitude and slope of phase 0, and eventually slows conduction and alters refractoriness (Luqman et al., 2007). Moreover, acute coronary occlusion induces pronounced changes in the action potential duration in the ischaemic zone, resulting in heterogeneous repolarization across the myocardium (Carmeliet, 1999). As a result of these changes, abnormal automaticity and triggered activity can initiate polymorphic VT or VF that are sustained by multiple re-entrant circuits across the ischaemic and normal myocardium.

Factors associated with early arrhythmogenesis

The identification of factors predisposing to primary VF during acute MI has attracted multifaceted research efforts for decades (Kolettis, 2013). Positive family history of sudden cardiac death is common in these patients (Piccini et al., 2008), indicating genetic predisposition, a finding corroborated by genome-wide association studies (Aouizerat et al., 2011). The incidence of primary VT/VF appears to be higher in patients with larger infarct size (Gheeraert et al., 2006), as suggested by angiographic studies showing that patients presenting with cardiac arrest caused by acute MI are more likely to have proximal than distal coronary lesions (Hreybe et al., 2007). However, wide variation exists, with primary VF associated with small ischaemic myocardial areas not uncommonly encountered in clinical practice; this observation is supported by the lack of clear-cut association between the extent of myocardial ischaemia and VT/VF in other clinical reports (Gheeraert et al., 2000). Thus, the correlation between the size of ischaemic myocardium and arrhythmogenesis is relatively weak, signifying the presence of additional contributing factors.

Endothelin-1 during acute myocardial infarction

Shortly after its discovery in 1988 (Yanagisawa et al., 1988), marked rises in endothelin-1 (ET-1) plasma levels were demonstrated in patients presenting with acute MI (Miyauchi et al., 1989). In the porcine model of myocardial ischaemia, it was shown that even short periods of coronary flow obstruction increase the production of ET-1, which originates mainly from the ischaemic ventricular myocardium (Tonnessen et al., 1993). Plasma ET-1 levels usually peak 6 h after coronary occlusion and return to normal values within 24 h, but they can remain elevated for substantially longer periods in patients with continuing ischaemia or acute left ventricular failure (Kolettis et al., 2013a). ET-1 plays an active role in the pathophysiology of the entire spectrum of coronary artery disease, ranging from the formation of atherosclerotic plaque, acute coronary syndromes to post-MI heart failure (Kolettis et al., 2013a); amidst this array, the effects of ET-1 on ventricular arrhythmogenesis during acute MI may have important clinical ramifications.

Arrhythmogenic effects of ET-1

Early studies have demonstrated direct electrophysiologic effects of ET-l, exerted via activation of L-type calcium channels (Yorikane et al., 1991). It was subsequently shown that ET-1 infusion increased the frequency of spontaneous diastolic calcium transients in isolated ventricular cardiomyocytes, through activation of inositol triphosphate receptors in the sarcoplasmic reticulum membrane (Proven et al., 2006). Via this mechanism, ET-1 enhanced the occurrence of afterdepolarizations, an action further supported by the regulation of repolarizing potassium currents (Kiesecker et al., 2006), responsible for changes in action potential duration.

The importance of direct electrophysiologic actions of ET-1 during acute coronary syndromes was initially debated, relative to those elicited due to aggravation of myocardial ischaemia (Szabo et al., 2000). However, subsequent studies have demonstrated distinct arrhythmogenic effects of ET-1, independently of its vasoconstrictive properties. In the in vivo canine model, low-dose ET-1 administration precipitated severe ventricular arrhythmias, without signs of reduced coronary blood flow or myocardial ischaemia (Szabo et al., 2000). Furthermore, low-dose ET-l administered via the intracoronary (Toth et al., 1995) or intrapericardial (Szokodi et al., 1998) routes in in vivo large animal models resulted in polymorphic VT and VF, triggered by afterdepolarizations following prolongation of the action potential. Lastly, disparate features of ventricular arrhythmogenesis were demonstrated after ET-1 administration and after the induction of myocardial ischaemia, characterized by prominent differences in activation patterns in the ischaemic and normal myocardium (Becker et al., 2000).

Endothelin receptor blockade during myocardial ischaemia

Given the documented rise of ET-1 production during MI (deteriorating myocardial ischaemia), along with its direct arrhythmogenic effects, the hypothesis has been put forward that endothelin receptor blockade may exert antiarrhythmic actions during acute MI (Duru et al., 2001). This issue has been examined in a number of studies (reviewed in Oikonomidis et al. (2010a)), but the results were contradictory, due to the diversity in ischaemia protocols and experimental settings, and to the nature of ET-1 examined (i.e., endogenous versus exogenous origin). More importantly, these studies (Oikonomidis et al., 2010a) included relatively short recording periods, despite the need for longer observation, directed by the biphasic pattern of VT/VF occurrence in the post-MI setting.

To overcome these limitations, our group (Baltogiannis et al., 2005) previously evaluated the effects of selective ETA receptor blockade in the in vivo rat model; this model is suitable for the study of ischaemia-related arrhythmias, as the rat displays a large number of episodes in response to coronary artery ligation. We used miniature telemetry transmitters, which permit long-term recording in conscious, unrestricted animals, without the confounding effects of anaesthesia (Baltogiannis et al., 2005). We reported prominent reduction in the total duration of VT/VF episodes during both, early and delayed phases post-ligation, confirming the important pathophysiologic role of the ETA receptor. To examine the role of the ETB receptor, we subsequently evaluated the effects of dual ETA/ETB endothelin receptor blockade in the same experimental setting (Kolettis et al., 2008); in this study, the reduction in the duration of VT/VF episodes was mainly confined to the delayed phase post-ligation, indicating a beneficial effect of functioning ETB receptors during the early phase (Kolettis et al., 2008). Monophasic action potential measurements suggested improved repolarization homogeneity as a candidate mechanism in both studies (Baltogiannis et al., 2005; Kolettis et al., 2008), thereby attributing this action to ETA receptor blockade. Another interesting finding in these experiments (Kolettis et al., 2008) was the diverse effect of pre-treatment with dual ETA/ETB endothelin receptor blockade on plasma catecholamines, measured 24 h post-ligation; specifically, plasma norepinephrine decreased, but epinephrine levels increased in treated rats (Kolettis et al., 2008). These findings highlight the complex interaction between the endothelin system and sympathetic activation, exerted at the myocardial and adrenal gland levels.

Sympathetic activation: an important arrhythmogenic mechanism

Acute coronary occlusion increases sympathetic activation and constitutes an essential mechanism underlying ischaemia-related ventricular tachyarrhythmias (Schomig et al., 1991); by contrast, vagal