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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.

Contents

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

stimulation in experimental animal settings exerts protective effects (Vanoli et al., 1991). Nonetheless, data in man are relatively scarce and available evidence originates from indirect information; for example, low serum potassium has been consistently found in patients with primary VF, considered a marker of catecholamine surge during acute MI, as circulating catecholamines shift potassium intracellularly through muscular β2-receptor stimulation of the sodium–potassium–ATPase (Gheeraert et al., 2006). Additional information stems from cross-sectional clinical reports, in which events causing extreme emotional stress triggered both, acute MI (Wilbert-Lampen et al., 2010) and ventricular tachyarrhythmias, often leading to sudden cardiac death (Leor et al., 1996).

ET-1 and sympathetic activation: a complex interplay

The relation between ET-1 and the sympathetic system and the resultant effects on arrhythmogenesis have attracted considerable research interest recently (Kolettis, 2013). A clinical study (Wilbert-Lampen et al., 2010), examining patients admitted with acute coronary syndrome induced by emotional stress, reported a two-fold increase in plasma ET-1 levels, as compared to similar patients without apparent sympathetic activation as a precipitating factor. In addition, several pieces of information derived from experimental data have demonstrated a complex interplay between ET-1 and sympathetic activation, with ETA and ETB receptors exerting opposing effects (Tawa et al., 2012). Importantly, this interplay appears to be exerted at the ventricular myocardial level, but also at the adrenal gland level, albeit much less information is available on the latter.

ETA and ETB receptors in the adrenal gland

The role of endogenous ET-1 in catecholamine secretion in response to electrical stimulation has been investigated in isolated, perfused rat adrenal glands (Nagayama et al., 2000); in these experiments, selective ETA receptor blockade inhibited epinephrine and norepinephrine output, whereas pre-treatment with selective ETB receptor blockade abolished this response. These findings indicate a complex interaction, during which activation of ETA receptors interferes with the endothelin ETB receptor-mediated inhibitory effects on the secretion of adrenal catecholamines (Nagayama et al., 2000).

ETA and ETB receptors in the ventricular myocardium

The opposing effects of ET receptors in norepinephrine release from sympathetic nerve endings were first shown in a pivotal study, performed in Langendorff-perfused rat hearts (Yamamoto et al., 2005); in these experiments, the protective role of ETB receptors was indirectly ascertained by pharmacological blockade or with the use of a previously characterized rat strain (Gariepy et al., 2000), deficient of functional ETB receptors in the cardiovascular system.

Isaka and co-workers (Isaka et al., 2007) subsequently demonstrated the presence of both endothelin receptors in cardiac sympathetic nerve varicosities of guinea pig hearts. In isolated, Langendorff-perfused beating preparations, selective ETA receptor blockade attenuated norepinephrine release, whereas a less potent effect was shown after dual ETA/ETB ET receptor; moreover, selective ETB receptor blockade markedly elevated local norepinephrine release (Isaka et al., 2007).

Current understanding on the modulation of norepinephrine overflow by ET-1 in cardiac sympathetic nerve endings was summarized in a recently published review by Tawa et al. (Tawa et al., 2012); as elegantly described in this work, myocardial ischaemia causes immediate norepinephrine release from sympathetic nerve endings and this effect is markedly potentiated by reversal of norepinephrine transporter in an outward direction at subsequent stages. ET-1 plays a prominent pathophysiologic role in this process, by stimulating neuronal Na^+/H^+ exchanger via activation of ETA receptors, thereby modulating norepinephrine release (Tawa et al., 2012); this is suggested by decreased norepinephrine release after pharmacological inhibition of the Na^+/H^+ exchanger by 5-(N-ethyl-N-isopropyl)-amiloride (Yamamoto et al., 2005; Isaka et al., 2007), but the second messengers mediating this response remain unclear (Tawa et al., 2012). In contrast to these effects, ETB receptors decrease norepinephrine overflow, possibly by enhancement of nitric oxide production in cells containing nitric oxide synthase.

Our group further addressed this issue in the in vivo rat model of MI, using wild-type and ETB receptor-deficient rats (Oikonomidis et al., 2010b). We found a marked temporal variation in VT/VF duration post-MI, consisting of higher arrhythmogenesis in ETB receptor-deficient rats during the early phase post-ligation, but lower during the delayed phase. This pattern was accompanied by corresponding changes in plasma catecholamines and non-invasive indices of sympathetic activation, whereas the observed differences in VT/VF episodes were abolished by β-blockade. These findings confirm the opposing effects of endothelin receptors, but also shed further light on the differences in arrhythmogenic mechanisms between acute ischaemia and evolving MI (Clements-Jewery et al., 2005).

Arrhythmogenesis during evolving myocardial infarction

After the initial stages of ischaemia, prolonged coronary artery occlusion produces a progressive necrosis wavefront (Reimer and Jennings, 1979). Evolving myocardial infarction results in a second arrhythmogenic period that has been clearly described in animal models (Kolettis et al., 2013b), and a similar pattern is also believed to be present in man (Kolettis, 2013; Di Diego and Antzelevitch, 2011). Delayed ventricular tachyarrhythmias during acute MI are important not only in patients with late presentation, but also in hospitalized patients, due to the associated increase in short-term morbidity and mortality (Kolettis, 2013; Piccini et al., 2008). Thus, VT/VF during evolving MI constitute an important—and often neglected—therapeutic target (Clements-Jewery et al., 2005).

The mechanisms underlying delayed arrhythmogenesis in the course of acute MI are still under investigation, but sympathetic activation appears to play a less important role, when compared to early stages. This conclusion is supported by experimental data in Langendorff-perfused preparations, which are devoid of sympathetic activation and, as such, do not exhibit delayed-phase VT/VF (Ravingerova et al., 1995); however, the addition of catecholamines in the perfusion solution in this experimental setting did not restore delayed-phase VT/VF, indicating the presence of factors (other than catecholamines) mediating VT/VF during evolving MI (Clements-Jewery et al., 2002). These factors remain poorly defined, but current evidence suggests ET-1 as a possible candidate, based on its effects on ion channels and gap junctions.

Effects of ET-1 on ion channels

The regulatory action of ET-1 on ion currents has been demonstrated by cellular studies long ago (Yorikane et al., 1991), and more recent findings have fuelled further research interest. In isolated human ventricular cardiomyocytes, ET-1 decreased the rapid component of the delayed rectifier potassium channel (Magyar et al., 2000); likewise, a marked inhibition of the main repolarizing potassium current *IK1* was noted in isolated human atrial cardiomyocytes (Kiesecker et al., 2006). The latter action of ET-1 was exerted via phosphorylation of Kir2.2 channel subunits and additional regulatory effects on Kir2.3 channels (both mediated by protein kinase-C) (Kiesecker et al., 2006); this effect was time-dependent, raising the possibility that a similar action on ventricular cardiomyocytes may be (at least partly) responsible for arrhythmogenesis during the time-frame of evolving MI.

Another potential mechanism involved in the genesis of delayed VT/VF lies in the action of ET-1 on the transient outward current (*Ito*). This calcium-independent current is activated immediately

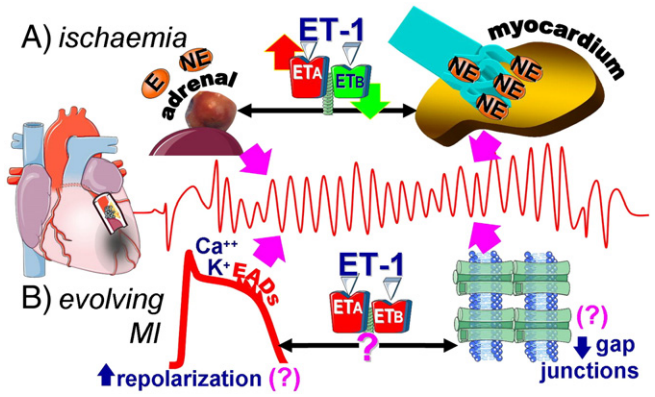

Fig. 1. ET-1 and arrhythmias during acute MI. Effects of endothelin-1 (ET-1) during the early ischaemic phase (upper panel) and evolving myocardial infarction (MI, lower panel). During ischaemia (A), activation of ETA receptors increases arrhythmogenesis by enhancing sympathetic response (red arrow) in the adrenal gland and the myocardium; ETB receptors exert protective effects (green arrow). E: epinephrine, NE: norepinephrine. During evolving necrosis (B), the arrhythmogenic actions of ET-1 appear to be exerted by increased action potential duration (leading to early afterdepolarizations, EADs); another possible mechanism is lower conductance mediated by decreased gap junction density. The relative role of ETA and ETB receptors during this phase is unclear.

after the upstroke of the action potential and contributes to early-phase repolarization in many species including man, thereby influencing the shape and duration of the action potential (Sah et al., 2002); furthermore, the transient outward current regulates the transmural sequence of repolarization and contributes to the homogeneity of this process. Secondary to these effects, critical alterations of the transient outward current may promote the occurrence of early afterdepolarizations under certain conditions (Zhao et al., 2012). Data derived from isolated rat ventricular cardiomyocytes (Wagner et al., 2007) indicate a direct or indirect effect of ET-1 on the transient outward current, based on the responses after long-term selective ETA receptor blockade. These findings need to be confirmed under conditions of ischaemia and/or progressive necrosis, along with varying degrees of sympathetic activation.

Effects of ET-1 on gap junctions

The conduction of electrical impulse via the gap junctions is a fundamental element of cardiac electrophysiology; changes in their function induced by myocardial ischaemia decrease conduction velocity and set the stage for the formation of re-entrant circuits. An important in vitro study (Reisner et al., 2009), performed in cultures of neonatal rat ventricular cardiomyocytes, examined the impulse conduction after exposure to ET-1; after 3 h, a time-dependent decrease in conduction velocity was observed, accompanied by a redistribution of connexins from the membrane to cytosol, resulting in decreased density of gap junctions. These findings introduce an additional mechanism of ET-1-mediated arrhythmogenesis that needs to be confirmed in in vivo experiments.

Concluding comments

Sudden cardiac death, a major health-related problem, is caused mainly by sustained ventricular tachycardia (VT) and fibrillation (VF) secondary to acute MI. ET-1 rises markedly as a result of ischaemia and subsequent progressive myocardial necrosis and is involved in the genesis of ventricular tachyarrhythmias, both during the early (pre-hospital) and the delayed (in-hospital) phases. Current understanding and putative mechanisms underlying the involvement of ET-1 and its receptors in ventricular arrhythmogenesis during acute MI are depicted in Fig. 1.

In addition to its vasoconstrictive effects, ET-1 exerts complex direct electrophysiologic actions; cellular studies have demonstrated that ET-1 modulates the occurrence of afterdepolarizations by increasing the frequency of spontaneous diastolic calcium transients and by increasing the action potential duration. Likewise, low-dose ET-l administered via the intracoronary or intrapericardial route resulted in polymorphic VT and VF.

Based on the arrhythmogenic effects of ET-1, endothelin receptor blockade may exert antiarrhythmic effects. Indeed, selective ETA receptor blockade in the in vivo MI-rat model reduced the total duration of VT/VF episodes during the early and delayed phases; these findings suggest an important pathophysiologic role of the ETA receptor in the genesis of ischaemia-related VT/VF. By contrast, such reduction was mainly confined to the delayed phase after dual ETA/ETB endothelin receptor blockade, indicating a beneficial effect of functioning ETB receptors during the early stage post-acute coronary occlusion. Improved repolarization homogeneity and decreased sympathetic activation appear as likely mechanisms, underlying the beneficial actions of ETA receptor blockade in the setting of acute MI.

A complex interaction has been described between the endothelin system and sympathetic activation, with profound importance in the genesis of ischaemia-related VT/VF. This interaction appears to be exerted at the myocardial and adrenal gland levels; in both, opposing effects of ETA and ETB receptors have been demonstrated in ex vivo studies, further corroborated by in vivo experiments.

After the initial stages of ischaemia, evolving myocardial necrosis produces a second arrhythmogenic period, which is associated with increased short-term morbidity and mortality. The mechanisms underlying delayed arrhythmogenesis in the course of acute MI are still under investigation, but sympathetic activation appears to play a *less* prominent role, compared to early phase-VT/VF. By contrast, increased ET-1 production may mediate arrhythmogenesis during evolving myocardial necrosis, an effect that can be attributed to the possible alteration on repolarizing potassium currents and/or gap junction conductance. However, more data are needed from in vivo experiments before inferences can be made.

Deeper knowledge on the mechanisms underlying the arrhythmogenesis during myocardial ischaemia and MI may translate into lower morbidity and mortality during acute coronary syndromes.

Conflict of interest statement

No competing interests

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