Platelets and cardiac arrhythmia

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Sudden cardiac death (SCD) remains one of the most prevalent modes of death in industrialized countries, and myocardial ischemia due to thrombotic coronary occlusion is its primary cause. The role of platelets in the occurrence of SCD extends beyond coronary flow impairment by clot formation. Here we review the substances released by platelets during clot formation and their arrhythmic properties. Platelet products are released from three types of platelet granules: dense core granules, alpha-granules, and platelet lysosomes. The physiologic properties of dense granule products are of special interest as a potential source of arrhythmic substances. They are released readily upon activation and contain high concentrations of serotonin, histamine, purines, pyrimidines, and ions such as calcium and magnesium. Potential arrhythmic mechanisms of these substances, e.g., serotonin and high energy phosphates, include induction of coronary constriction, calcium overloading, and induction of delayed after-depolarizations. Alpha-granules produce thromboxanes and other arachidonic-acid products with many potential arrhythmic effects mediated by interference with cardiac sodium, calcium, and potassium channels. Alpha-granules also contain hundreds of proteins that could potentially serve as ligands to receptors on cardiomyocytes. Lysosomal products probably do not have an important arrhythmic effect. Platelet products and ischemia can induce coronary permeability, thereby enhancing interaction with surrounding cardiomyocytes. Antiplatelet therapy is known to improve survival after myocardial infarction. Although an important part of this effect results from prevention of coronary clot formation, there is evidence to suggest that antiplatelet therapy also induces anti-arrhythmic effects during ischemia by preventing the release of platelet activation products.

Keywords: platelets, arrhythmias, cardiac, sudden death, ventricular fibrillation
de Jong and Dekker

Platelets and cardiac arrhythmia

PLATELET ADHESION AND ACTIVATION

Platelets are small anuclear cells (2–3 μm, 7.5–1.5 fL), which are derived from defragmentation of megakaryocytes. Platelets have a life-span of 8–12 days, and the blood of healthy individuals has a platelet concentration of 150–400 × 10^9/L (Greer, 2008). Coronary plaque rupture results in exposure of subendothelium—containing collagen, collagen-bound-von Willebrand factor (vWF), fibronectin, and laminin. Platelet membranes expose an array of adherence proteins waiting to adhere with these exposed molecules. Upon adhesion, intracellular signal transduction pathways are activated. Granules fuse with the platelet membrane leading to a platelet-shape change, expulsion of granule contents and exposure of formerly intragranular membrane molecules on the outside of the platelet. Amongst these are glycoprotein 1b/V/IX and glycoprotein αIIbβ3 receptors which mediate platelet aggregation and finally clot formation.

Three types of platelet granules are morphologically distinct (Figure 2; Table 1): dense core granules (δ-granules), alpha-granules, and platelet lysosomes (λ-granules; Rendu and Brohard-Bohn, 2001).

About three to eight dense granules are present per platelet. They are inherently electron dense when viewed in electron microscopy. Dense granules are acidic (pH 6.1) and contain platelet agonists...
that serve to amplify platelet activation. They are the most rapidly secreted granules and release, amongst others, adenosine diphosphate (ADP), ATP, guanosine 5′-triphosphate (GTP), guanosine diphosphate (GDP), Ca++-triphosphate (GTP), Ca++-triphosphate (GTP), Ca++, magnesium pyrophosphate, and amines such as serotonin and histamine. After exocytosis, ADP acts as a platelet agonist and is important in the activation of additional circulating platelets (McNicol and Israels, 1999).

Alpha-granules release various proteins involved in platelet interaction. Proteomic studies of the platelet secretome have yielded a list of more than 2000 of such proteins (Coppinger et al., 2004; McRedmond et al., 2004). These proteins are involved in platelet interactions (glycoprotein αIb-β3 receptor, fibrinogen, vWF, thrombospondin-I, fibronectin, vitronectin, GAS6), coagulation and fibrinolysis (plasminogen, plasminogen activator inhibitor-1, protein S), and chemotaxis and cell signaling (transforming growth factor-β, platelet-derived growth factor; Gresele et al., 2002).

Some of the proteins are known as markers of platelet activation (P-selectin, β-thromboglobulin, platelet factor 4). Alpha-granules also contain plasma proteins such as albumin, vWF antigen II, immunoglobulins, plasma protease inhibitors, and histidine-rich glycoprotein.

Finally, lysosomes release clearing factors such as cathepsins, proteases, and glycohydrolases. Lysosome-release requires a stronger type of stimulus, such as thrombin or high doses of collagen, whereas alpha- and dense-granules are readily released with weaker types of stimulation, such as platelet exposure to ADP (Gresele et al., 2002).

**ELECTROPHYSIOLOGICAL EFFECTS OF ACTIVATED PLATELET PRODUCTS**

Many of the substances released by platelets can alter the electrophysiological properties of the heart in various animal species (Flores et al., 1999).

**Amines**

Serotonin or 5-hydroxytryptamine (5-HT) is not synthesized in platelets but is actively taken up from the plasma and accumulated in dense granules where it is likely complexed with ATP and potentially with calcium (De Clerck et al., 1984). The serotonin released by exocytosis is relatively stable and functions as a weak platelet agonist on 5HT receptors (De Clerck et al., 1984), although it is probably less important in this respect than ADP. The positive feedback effect of serotonin may be of secondary importance to its vasoconstrictive action, which reduces flow at the site of injury and thereby limits blood loss (De Clerck, 1986). Dense granular concentration of serotonin was calculated to be 65 mM (Holmsen and Weiss, 1979), whereas (platelet-rich) plasma serotonin concentration was 842 ± 38 nmol/L in healthy individuals (Vikenes et al., 1999). Serotonin can be used to assess the platelet release reaction: it locally increased 18- to 27-fold from normal levels in tissue surrounding a coronary thrombus in a dog model (Ashton et al., 1986).

Human atrial and ventricular cardiomyocytes express 5-HT receptors (Kaumann et al., 1990; Bach et al., 2001), and exposure to serotonin results in tachycardia, increased atrial contractility, and atrial arrhythmias (Kaumann and Levy, 2006). 5-HT causes an up to sixfold increase in L-type Ca2+ channel current through 5-HT receptors, in atrial myocytes from patients in sinus rhythm (Ouadid et al., 1992; Pau et al., 2003). Likewise, serotonin has positive inotropic and lusitropic effects on ventricular cardiomyocytes (Brattelid et al., 2004). Arrhythmic effects have also been observed and are probably mainly related to Ca2+-overload mediated by an increase in L-type Ca2+ current (Kaumann, 1994). Antidepressants from the selective serotonin reuptake inhibitor class (SSRI) have QT prolonging effects in patients with SSRI intoxications. The major clinical interaction with cardiovascular disease is likely its platelet inhibiting effect, which may reduce incidence of MI (Sauer et al., 2003).

Like, serotonin, histamine is another amine present in dense granules. Resting human platelets contain 25 ng histamine/10^8 platelets, which can increase toward 47 ng/10^8 platelets upon platelet activation (Jancinová and Nosál, 1998). The major arrhythmic effects of histamine consist of H1-receptor mediated slowing of AV nodal conduction and H2-receptor mediated increase in sinus rate and ventricular automaticity (Wolff and Levi, 1986). Histamine also has a positive inotropic effect on ventricular cardiomyocytes (Ginsburg et al., 1980).

In addition to serotonin, histamine can also cause vasoconstriction as further discussed below.

**Nucleotide derivatives**

Extracellular purines (adenosines, ADP, and ATP) and pyrimidines [uridine diphosphate (UDP) and uridine triphosphate (UTP)] can initiate a wide range of intracellular signaling cascades through purinergic receptors (Ralevic and Burnstock, 1998). Platelet-dense granules contain a high concentration of ATP (436 mM) and ADP (653 mM; Holmsen and Weiss, 1979), which can accelerate platelet activation binding to ADP receptors upon release. Normal extracellular ATP concentration is about 2 μM (Born and Kratzer, 1984) and may increase to 100 μM under pathological conditions (Coade and Pearson, 1989). Under normal conditions, ATP is rapidly converted to adenosine (Flores et al., 1999).

In rat and mouse ventricular cardiomyocytes, exposure to ATP induces a cytosolic Ca2+ rise and has positive inotropic effects (Danziger et al., 1988; Pucéat et al., 1991; Mei and Liang, 2001). By activation of purinergic receptors, ATP induces sustained increases in diastolic Ca2+ and triggers multiple Ca2+ waves, leading to DADs in current clamped mouse hearts (Gurung et al., 2009).

**Ions**

The dense granular concentration of calcium was calculated to be 2.2 M (Holmsen and Weiss, 1979). The total amount of calcium in human platelets is 10.1 μmol/10^8 platelets (Meyers et al., 1982). In
humans, arrhythmias related to high calcium and magnesium levels are rare (Diercks et al., 2004). The normal plasma concentration of Ca$^{2+}$ ranges from 1.03 to 1.23 mmol/L (Larsson and Ohman, 1978). The Ca$^{2+}$ concentration in dense granules is very high, but the amount of released Ca$^{2+}$ relative to the plasma concentration is small. The platelets in 1 mL blood (about 250 × 10$^9$) contain about 25.3 nmol of Ca$^{2+}$, and upon release would increase the local Ca$^{2+}$ concentration by about 2% (assuming a volume of dispersion of 1 mL). This raw estimate does not take into account the high concentration of platelets in an actual thrombus and the washout of Ca$^{2+}$ during the non-occlusive phase of thrombus formation.

The platelet content of Mg$^{2+}$, the second most abundant ion, is much smaller that the Ca$^{2+}$ content. Platelets contain about 0.4 μmol/10$^{11}$ platelets of releasable magnesium (Meyers et al., 1982). Normal plasma concentrations of Mg$^{2+}$ range between 0.6 and 0.7 mmol/L. A large influence of platelet Mg$^{2+}$ release during platelet aggregation is therefore less likely than it is for Ca$^{2+}$.

### Thromboxane, arachidonic acid, and other alpha-granule contents

During platelet activation, arachidonic acid is liberated by phospholipase-A2 from membrane phospholipids and is converted enzymatically to epoxyeicosatrienoic acids (EETs) via the cyclooxygenase and lipooxygenase pathways. EETs have several effects on cardiac tissues (Flores and Sheridan, 1990; Xiao, 2007). EETs inhibit cardiac Na$^+$ channels (Lee et al., 1999), significantly increase intracellular Ca$^{2+}$ concentrations in isolated guinea pig cardiomyocytes (Moffat et al., 1993), and significantly modulate the activities of cardiac Ca$^{2+}$ channels (Chen et al., 1999) and K$^+$ ATP channels (Lee et al., 1999). Furthermore EETs can uncouple neonatal rat cardiac myocytes by reducing gap-junction conductance (Massey et al., 1992).

Thromboxane is an arachidonic-acid derivative that is prothrombotic and released by platelets. Thromboxane is produced by cyclooxygenase from prostanoids, a process that is inhibited by aspirin. Thromboxane is chemically unstable in blood, but its stable analog, U41669, has been shown to increase automaticity and to increase both resting and peak intracellular Ca$^{2+}$ concentrations and induce irregular Ca$^{2+}$ transients in isolated neonatal rat ventricular myocytes (Hoffmann et al., 1993). This is supported by the fact that these effects can be reversed in rabbit cardiomyocytes by blockade of U41669 (Wacker et al., 2009).

Chien et al. examined the effects of platelet products of rabbit platelets on cytosolic calcium in chick embryonic heart cells. They identified the arrhythmic platelet product(s) as small trypsin-sensitive peptide(s) (Chien et al., 1990). Examples of such small peptides, found in alpha-granules, are substance P, calcitonin, vasoactive intestinal peptide, and angiotensinogen. Of the latter three no direct cardiac effects have been described. Substance P has only recently been found to be present in relatively high concentrations in platelets (Jones et al., 2008). It is primarily known as a neurotransmitter of pain sensation, but also has cardiovascular effects which are primarily mediated through vasodilatation. However, direct cardiac effects have been described: induction of bradycardia and hypotension in denervated and anesthetized rats (Tompkins et al., 1999).

Besides these, alpha-granules contain a long list of substances (Table 1) which can be subdivided in proteoglycans, adhesive glycoproteins, hemostatic factors, cellular mitogens, protease inhibitors, and miscellaneous other molecules (Rendu and Brohard-Bohn, 2001). Platelet proteomic approaches have tried to assess all proteins present in platelets (Maguire and Fitzgerald, 2003; McRedmond et al., 2004). Proteomics of the products of activated platelets have

### Table 1 | Platelet granules and their contents.

<table>
<thead>
<tr>
<th>Dense granules</th>
<th>Alpha-granules</th>
<th>Lysosomal granules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>Albumin</td>
<td>Cathepsin D</td>
</tr>
<tr>
<td>Histamine</td>
<td>Fibrinogen</td>
<td>Cathepsin E</td>
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<tr>
<td>ATP</td>
<td>Fibronectin</td>
<td>Carboxypeptidase A</td>
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<tr>
<td>ADP</td>
<td>Vitronectin</td>
<td>Carboxypeptidase B</td>
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<td>Calcium</td>
<td>Osteonectin</td>
<td>Prolincarboxypeptidase</td>
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<td>Magnesium</td>
<td>Calcitonin</td>
<td>D-N-acetyll-hexosaminidase</td>
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<tr>
<td>Pyrophosphate</td>
<td>Von Willebrand Factor</td>
<td>β-D-glucuronidase</td>
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<td>Von Willebrand antigen II</td>
<td>β-D-galactosidase</td>
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<td>Thrombospordin</td>
<td>α-D-mannosidase</td>
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<td></td>
<td>Platelet factor 4</td>
<td>α-D-arabinofuranosidase</td>
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<tr>
<td></td>
<td>IgG, IgA, IgM</td>
<td>α-D-fucosidase</td>
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<td></td>
<td>α$_2$ inhibitor</td>
<td>α-D-fucosidase</td>
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<td></td>
<td>Plasminogen</td>
<td>β-D-fucosidase</td>
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<td></td>
<td>Plasminogen activator</td>
<td>β-D-gucosidase</td>
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<td></td>
<td>Platelet-derived</td>
<td>α-D-glucosidase</td>
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<td></td>
<td>collagenase inhibitor</td>
<td>Acid phosphatase</td>
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<td>High molecular weight kininogen</td>
<td>Arylsulfatase</td>
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<td>Angiotensinogen</td>
<td>Arylsulfatase</td>
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<td>Protein S</td>
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<td>α$_2$-Antitrypsin</td>
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<td>α$_2$-Macroglobulin</td>
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<td>α$_2$-Antiplasmin</td>
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<td></td>
<td>Multimerin</td>
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<td>Platelet basic protein</td>
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<td></td>
<td>β-Thromboglobulin</td>
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<td>Histidine-rich glycoprotein</td>
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<td>Connective tissue-activating protein III</td>
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<td>Neutrophil-activating protein II</td>
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<td>Platelet-derived growth factor</td>
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<td>Coagulation factor V</td>
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<td></td>
<td>Coagulation factor VIII</td>
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<td></td>
<td>Substance P</td>
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<td>Vasoactive intestinal peptide</td>
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<td></td>
<td>&gt;300 other proteins</td>
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</table>

Table adapted from McNicol and Israels (1999).

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revealed more than 300 proteins (Maguire et al., 2002; Coppinger et al., 2004) which are mostly secreted in alpha-granules. Most of these proteins are present in only small quantities. Large electrophysiologic effects would therefore likely be mediated through membrane channels on cardiomyocytes.

**Lysoasomal products**
Platelet lysosomes contain “clearing factors” that breakdown the platelet clot: acid proteases and glycohydrolases. These lysosomal products have no known effect on cardiomyocytes. Breakdown products of platelet clots could potentially be arrhythmogenic, however a review on the incidence of early ventricular arrhythmias after thrombolytic therapy did not show evidence for increased early arrhythmias (Solomon et al., 1993).

**Vasoconstriction**
Several dense granule products have been shown to have effects on coronary smooth muscle cells that mediate coronary constriction. ATP, UTP, and ADP can mediate prostacyclin and nitric-oxide release by interaction with the P2Y receptors on endothelial cells (da Silva et al., 2009). Serotonin injected in coronary arteries of angina patients leads to intense coronary constriction (McFadden et al., 1991), probably mediated by vascular 5-HT\textsubscript{1a} and 5-HT\textsubscript{1b} receptors (Kaumann and Levy, 2006). Like serotonin, histamine is another strong vasoconstrictor. In patients with variant angina, histamine could induce coronary spasm in 47% of subjects in one study (Kaski et al., 1986). Thrombus-released vasoconstrictive substances could reduce coronary perfusion and thereby increase local ischemia and reduce blood supply by collateral vessels. Ischemia due to coronary spasm in the absence of severe atherosclerosis has been described as a cause of VF (Seniuk et al., 2002; Al-Sayegh et al., 2007; Hung et al., 2007; Hendriks et al., 2008; Sanna et al., 2009; Sansone et al., 2009).

**Endothelial permeability**
Increased endothelial permeability during myocardial infarction can facilitate leakage of platelet products from the coronary lumen to epicardial myocytes. Increased endothelial permeability could be induced by platelet products or by ischemia. Indeed in a rat model of cerebral ischemia, thrombin injection induced vascular disruption, and increased permeability (Chen et al., 2010). In another study, platelet activating factor (PAF) greatly increased coronary permeability by the inhibition of endogenous NO synthesis (Filep et al., 1993). And, in a hamster model, PAF increased permeability of the microvasculature of the cheek pouch (Ramirez et al., 1995). Also, serotonin has been shown to increase vascular permeability in different animal models (Clerck et al., 1984).

Ischemia also induces coronary permeability as animal studies have shown. In a dog model, 15 min of coronary occlusion could increase protein leakage by 50% (Dauber et al., 1990). And, in a rat model, 20 min of severe ischemia increased transcapillary albumin flux by 100% (Sunnergren and Rottevo, 1980, 1987). Both the direct ischemic effects and the effects induced by platelet products promote interaction of platelet products and the myocardial tissue surrounding the ischemic coronary.

**Effects on myocardial contractility**
Both increases and decreases in myocardial contractility have been found in experiments with substances released by platelets. ATP has strong positive inotropic effects in rats. ATP stimulates a large increase in cytosolic Ca\textsuperscript{2+} transients (Danziger et al., 1988; Christie et al., 1992). ATP also increases the L-type Ca\textsuperscript{2+} current in rats, and both mechanisms can induce positive inotropic effects (Scamps and Vassort, 1990). Further upstream in rats and mice, activation of P\textsubscript{2} purinergic receptors exerts a positive inotropic effect on cardiomyocytes and intact hearts by increasing intracellular ATP levels (Mei and Liang, 2001). Thrombin promotes Ca\textsuperscript{2+} entry and release in cardiomyocytes (Chien et al., 1990). Serotonin has positive inotropic effects on the human atrium through the HT\textsubscript{1a} receptor, but such a receptor is absent in human ventricular cardiomyocytes (Kaumann, 1994).

Negative inotropic effects have been described for tumor necrosis factor-\alpha in rats (Edmunds et al., 1999; Tabrizchi, 2001). It’s likely that these effects leverage toward a positive inotropic effect of platelet products, as was confirmed by a study that added aggregating platelets to a bath of cat papillary muscles resulting in positive inotropic effects (Shah et al., 1989). Also, injection of low-dosed PAF into coronary arteries resulted in strong positive inotropic effects in isolated rabbit hearts (Alloatti et al., 1990).

**Interaction of effects of platelet products and ischemic effects**
Arrhythmias are very common during cardiac ischemia and are the result of a multifactorial process. Ischemia is the most important factor in arrhythmia occurrence. This is evidenced by the fact that the absence of active platelets does not completely eliminate occurrence of VF in coronary ligation studies described above (Johnson et al., 1981; Chien et al., 1990; Coronel et al., 1997). Platelet products strongly increase the risk of arrhythmias in the setting of myocardial ischemia. It is tempting to speculate which platelet products have the strongest role in arrhythmia occurrence. From the clinical setting we know that ischemic VF often occurs within the first minutes after onset of chest pain, and it’s risk declines during the first hours. An arrhythmic mediator should therefore be released readily upon platelet activation and exert it’s effect within seconds as also has been observed in the animal models.

Amines from dense granules are readily released in high concentrations and after cardiomyocyte electrophysiology directly, which makes them likely candidates. On top of that serotonin-induced vasoconstriction could undermine collateral perfusion of the ischemic area. As a result of the findings of Chien et al., small trypsin-sensitive peptide(s) released by platelets, such as substance P, deserves further investigation. Increased endothelial permeability induced by ischemia promotes interaction between these substances and cardiomyocytes. An unstable thrombus with fragment embolization could lead to increased local heterogeneity.

**Platelet antagonists and arrhythmia prevention**
Antiplatelet therapy is known to improve survival after myocardial infarction (Lau et al., 1992), while patients with increased platelet aggregation have a worse prognosis postmyocardial infarction.
(Tripl et al., 1990). However, it is difficult to separate the beneficial effect of preventing thrombotic coronary occlusion from the potential anti-arrhythmic effects achieved during ischemia by preventing formation of platelet activation products. However, some evidence does exist for such an effect. Platelet antagonists effectively induced ventricular arrhythmias in models of ischemia by coronary ligation in rats (Ahn et al., 1999) and dogs (Moschos et al., 1978; Wainwright et al., 1989). In a dog model of regional ischemia, the threshold of epinephrine-induced VF was reduced after aspirin pre-treatment (Shelahdeh et al., 2000). In a rat model of coronary occlusion, sarpogrelate, a 5-hydroxytryptamine 2A receptor antagonist, but not cilostazol, a phosphodiesterase-III inhibitor, was able to prevent ventricular arrhythmias during ischemia (Barta et al., 2008). Sarpogrelate has multiple fields of action, including inhibition of serotonin-induced coronary spasm. However, administering aspirin after platelet activation had occurred did not block anti-arrhythmic effects of platelet products in isolated rabbit hearts (Alloatti et al., 1990).

**SUMMARY AND CONCLUSION**

The role of platelets in the occurrence of SCD extends beyond coronary flow impairment by clot formation. During clot formation, platelets release a plethora of substances, many with potent arrhythmic properties. Platelet products are released from three types of platelet granules: dense core granules, alpha-granules, and platelet lysosomes. The physiologic properties of dense granule products are of special interest as a potential source of arrhythmic substances. They are released readily upon activation and contain high concentrations of serotonin, histamine, purines (adenosines, ADP, and ATP), pyrimidines (UDP and UTP), and ions such as Ca\(^{2+}\) and Mg\(^{2+}\). The mode of action of these substances ranges from induction of coronary constriction (serotonin), Ca\(^{2+}\) overloading (serotonin), and the induction of DADs (ATP).

Alpha-granules contain thromboxanes and other arachidonic-acid products with many potential arrhythmogenic effects mediated by interference with cardiac K\(^+\) and Ca\(^{2+}\) channels. Alpha-granules also contain a large number of proteins in much lower concentrations that could potentially serve as a ligand to receptors on cardiomyocytes. Substance P is of particular interest. Lysosomal products are clearing factors that result in breakdown products of clots; but clinical studies do not suggest an important role of lysosomal products in arrhythmias, as evidenced by the absence of arrhythmia-induction during thrombolysis.

Antiplatelet therapy is known to improve survival after myocardial infarction. Although an important part of this effect results from the prevention of coronary clot formation, there is evidence to suggest that antiplatelet therapy also has anti-arrhythmic effects during ischemia by preventing the release of platelet activation products.


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