Mechanisms Responsible for Coronary Vasospasm

JOHN T. SHEPHERD, MD, DSc, FACC, PAUL M. VANHOUTTE, MD, PhD

Rochester, Minnesota

Studies have been conducted on isolated segments of the left circumflex coronary artery of the dog to gain information on the mechanism or mechanisms of vasospasm. Coronary arteries contain both postjunctional alpha$_1$- and beta$_1$-adrenoceptors, and both are accessible to norepinephrine released from the sympathetic nerves. However, owing to the dominance of the beta$_1$-adrenoceptors, sympathetic stimulation causes relaxation of the vascular smooth muscle. In the primary branches of the circumflex artery, only beta$_1$-adrenoceptors are present. In patients with spasm of the coronary arteries, blockade of the beta$_1$-adrenoceptors may aggravate the spasm by permitting the unopposed constrictor action of the sympathetic nerves on the alpha$_1$-adrenoceptors on these vessels.

The blood platelets contain substances, including 5-hydroxytryptamine (serotonin) and thromboxane A$_2$, which can cause constriction of vascular smooth muscle. These substances are released whenever platelets aggregate. The normal endothelium, by forming and releasing prostacyclin, inhibits platelet aggregation. In addition, in response to platelet products, the normal endothelium forms one or more inhibitory substances that cause relaxation of the underlying smooth muscle. Also, if any thrombin is formed, this also causes an endothelium-mediated relaxation of the artery. Patients with coronary artery spasm usually have morphologic changes in the artery at the site of the spasm. Thus, platelets can aggregate at the site and the resultant release of serotonin and thromboxane A$_2$, acting directly on the smooth muscle, causes constriction of the artery. Hypoxia of the myocardium follows and this augments the constriction.

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Mechanisms responsible for coronary spasm. The demonstration by Furchgott (1) that acetylcholine can cause an endothelium-dependent relaxation of vascular smooth muscle has focused attention on the importance of the vascular endothelium in the normal control of the blood vessels and on the relation of endothelial damage to spasm of human cerebral, coronary and digital arteries. The present report summarizes studies conducted on the main coronary arteries of the dog that have relevance to the causation of variant angina (2). The term variant angina was coined by Prinzmetal et al. (3) to describe anginal pain that, unlike classic angina of effort, develops at rest, often in the early morning hours. Because the work of the heart is not increased, the pain must be due to a metabolic deficit caused by a reduction in coronary blood flow. Prinzmetal et al. suggested that the angina was caused by a spasm of a major coronary artery because it was relieved quickly by administration of nitroglycerin. Since then, many additional observations have confirmed that the angina is caused by spasm of the main coronary artery or arteries. Coronary angiography reveals that many patients have varying degrees of vascular obstruction in one main artery, but in a few patients no abnormality is detected (4–6). Even in those patients with little evidence from the angiogram of any vascular abnormality, the intravenous administration of ergonovine maleate, a naturally occurring ergot alkaloid, can cause a prolonged isolated contraction of a main coronary artery, thus revealing a region especially susceptible to vasoconstriction (6,7). Thus, although the clinical manifestations are well defined, the mechanism or mechanisms responsible for the episodes of spasm are not.

Various theories have been advanced including: 1) Asymmetric stimulation of the sympathetic nerves to the heart, leading to alpha-adrenergically mediated constriction of the coronary artery (8,9). However, more recent studies (10) have shown that activation of the sympathetic nerves causes dilation of the main coronary arteries due to the predominance of beta$_1$- over alpha$_1$-adrenoceptors. 2) A decrease in the numbers of alpha-adrenoceptors or the sympathetic nerve terminals or in their affinity (11). These receptors, if activated, can reduce the output of norepinephrine from the nerve endings. However, if they no longer provide this negative feedback on neurotransmitter release, more
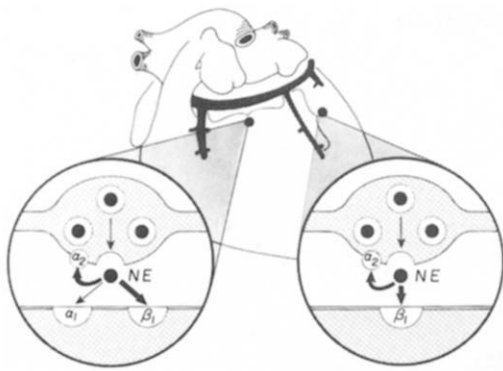
Figure 1. Adrenoceptors in canine coronary artery neuroeffector junction. In large vessels, such as the left circumflex artery, both postjunctional alpha₁- and beta₁-adrenoceptors (α_1 and β_1) are present, but the latter predominate functionally. When the adrenoceptors are activated, the former cause contraction and the latter cause relaxation of smooth muscle. In branch arteries, only beta₁-adrenoceptors are present. As in all blood vessels that have been examined, alpha₂-adrenoceptors (α_2) are present on the sympathetic nerve terminals. When activated, these adrenoceptors reduce the output of the neurotransmitter. NE = norepinephrine. (Reprinted with permission from Vanhoutte PM. Autonomic nerves, aggregating platelets and contraction of coronary arterial smooth muscle. In: Abel FL, Newman WH, eds. Functional Aspects of the Normal, Hypertrophied and Failing Heart. Boston: Martinus Nijhoff, 1984:125–48.)

norepinephrine will be released, and this should cause a further dilation rather than constriction of the major coronary arteries. 3) Incorporation of cholesterol into the membranes of the smooth muscle cells of the arteries, thus facilitating their constriction when the sympathetic nerves are activated

Figure 2. Interaction of cholinergic with adrenergic nerves at the coronary neuroeffector junction. Acetylcholine (ACh), released when cholinergic nerves are activated, acts on muscarinic receptors (M) on the sympathetic nerves to reduce the output of norepinephrine (NE). Because less norepinephrine is then available to activate the beta-adrenoceptors (β), the degree of smooth muscle relaxation is reduced. α_2 = alpha₂-adrenoceptors. (Reprinted from Shepherd JT. The heart as a sensory organ. J Am Coll Cardiol 1985;5:83–7B.)
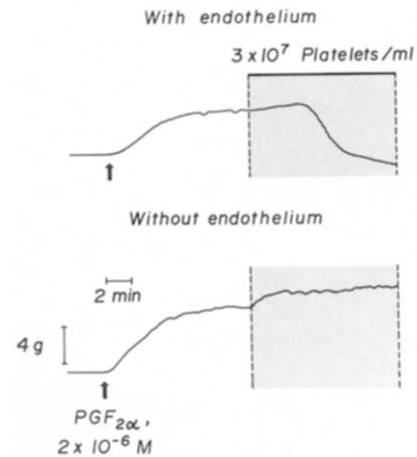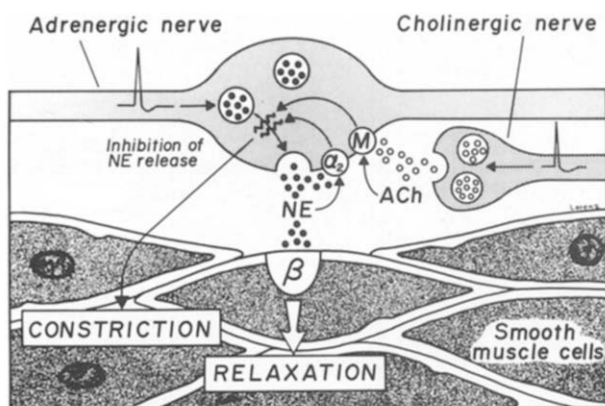

Figure 3. When coronary artery rings are exposed to aggregating platelets, they relax if the endothelium is intact (**top**) but contract if it is removed (**bottom**). PGF₂α = prostaglandin F₂α. (Reprinted with permission from Cohen RA. Inhibitory role of the endothelium in the response of isolated coronary arteries to platelets. Science 1983;221:273–4.

(12). 4) Platelet aggregation with release of vasoconstrictor agents (13–15). These various ideas illustrate the necessity of understanding the function of the autonomic nerves to the coronary vessels, the types of receptors on their smooth muscle cells and autonomic nerve endings, and the reaction of the smooth muscle and the endothelium to substances formed in the heart or released from the blood elements, or both.

The nature of the receptors at the neuroeffector junction of the main coronary arteries. Adrenergic receptors are classified as alpha₁, alpha₂, beta₁ and beta₂. In the canine left circumflex coronary artery, beta₁-adrenoceptors predominate over alpha₁-adrenoceptors and in the first branches

Figure 4. Tension recording of canine coronary arteries with intact endothelium, contracted with prostaglandin F₂α (PGF₂α). Adenosine diphosphate (ADP) caused marked relaxation, which was maximal by 10^{-4} M (**top**). In some rings there was a partial recovery of tension in the presence of ADP; when platelets (9.8×10^7/ml) were added at this time, they did not cause relaxation, whereas in the paired ring without ADP, the relaxation to platelets was typical (**bottom**). Acetylcholine (ACh), even in the presence of ADP and platelets, was still able to induce relaxation. (Reprinted with permission from Houston DS, et al. [18].)
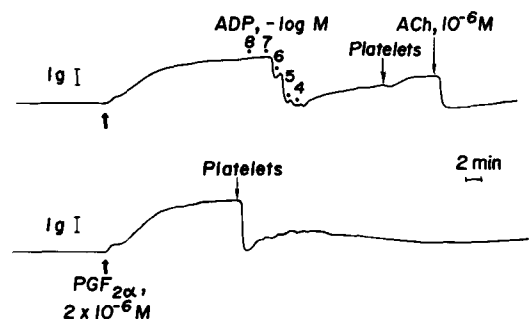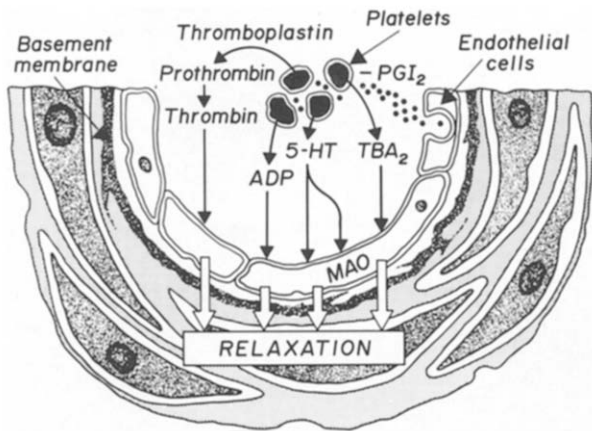
Figure 5. Importance of endothelium in generating inhibitory signals to smooth muscle when exposed to elements involved in blood coagulation. Prostacyclin (PGI$_2$), formed in the endothelial cells, inhibits platelet aggregation. If some platelets aggregate and release 5-hydroxytryptamine (5-HT), thromboxane A$_2$ (TBA$_2$) and adenosine diphosphate (ADP), the endothelium forms as yet unknown substances that relax the smooth muscle. In addition, the enzyme monoamine oxidase (MAO) in the endothelial cells degrades 5-hydroxytryptamine. Furthermore, any thrombin that is formed also leads to relaxation of the smooth muscle by formation of an inhibitory substance in the endothelium. (Reprinted with permission from Shepherd JT and Vanhoutte PM [2].)

of this vessel there are only beta$_1$-adrenoceptors. When the beta$_1$-adrenoceptors are stimulated, the cell membrane becomes hyperpolarized, the production of cyclic adenosine monophosphate (AMP) is accelerated, the concentration of Ca^{2+} in the cytoplasm of the smooth muscle cells is reduced and the muscle relaxes. Thus, stimulation of the sympathetic

Figure 6. When the endothelium is damaged, platelets aggregate because of the absence of prostacyclin. Substances released from the platelets, including 5-hydroxytryptamine (5-HT), thromboxane A$_2$ (TBA$_2$) and adenosine diphosphate (ADP), cause contraction of the smooth muscle. Formation of thrombin may enhance the contraction. (Reprinted with permission from Shepherd JT and Vanhoutte PM [2].)
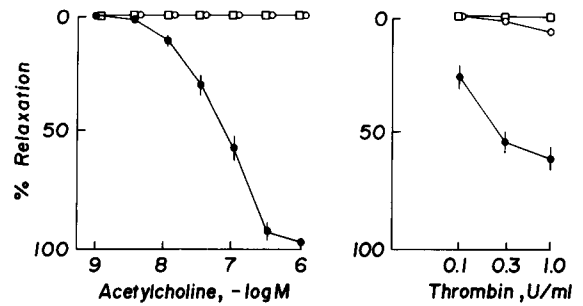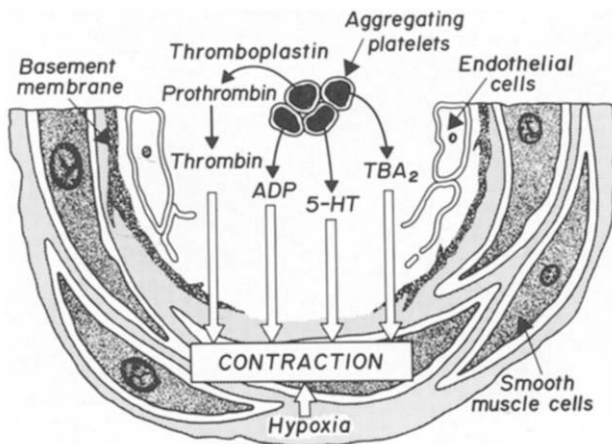

Figure 7. Effect of anoxia on endothelium-mediated relaxation of an isolated femoral artery of the dog. **Left,** In a ring of the artery in the presence of 95% oxygen and contracted with norepinephrine, acetylcholine causes a dose-dependent relaxation. This response is mediated by endothelial cells because no relaxation occurs in their absence. In the presence of endothelial cells, anoxia (95% nitrogen) also prevents the relaxation attributable to acetylcholine. **Right,** Results of similar studies show that anoxia presents the endothelium-mediated relaxation caused by thrombin. ● = Endothelium intact; ○ = endothelium intact, anoxic; □ = endothelium removed. (Reprinted with permission from Shepherd JT and Vanhoutte PM [2].)

nerves causes relaxation, due to the predominant action of the released norepinephrine on the beta$_1$-adrenoceptors and not, as previously thought, constriction of these vessels (Fig. 1). This explains the clinical observation that beta-adrenoceptor blocking agents may augment coronary vasospasm (16). Alpha$_2$-adrenoceptors and muscarinic receptors are present on the sympathetic nerve endings of the coronary arteries. Their activation by norepinephrine and acetylcholine, respectively, reduces the output of the sympathetic neurotransmitter which could lessen the dilation of these vessels. The vagal nerves to the coronary vessels may act primarily on these muscarinic receptors (Fig. 2). It has been shown that muscarinic agonists can precipitate coronary vasospasm in humans (17).

Figure 8. Contraction of a ring from a main coronary artery with 5-hydroxytryptamine and the effect of hypoxia. When the ring is made hypoxic, contraction is considerably augmented. (Reprinted with permission from Van Nueten JM and Vanhoutte PM. Serotonin and vascular function. Clin Anesth 1984;2:363.)
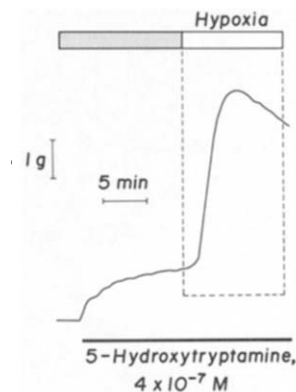
Role of the endothelium. The normal endothelium and the vascular smooth muscle cells produce prostacyclin, an endogenous vasodilator, which also inhibits platelet aggregation. The platelets contain thromboxane A_2 which facilitates platelet aggregation and causes constriction of vascular smooth muscle. Whenever platelets aggregate, other vasoactive substances, in addition to thromboxane A_2, are liberated. These include 5-hydroxytryptamine (serotonin) and adenosine diphosphate.

If segments of the circumflex coronary arteries of the dog are made to contract with prostaglandin $F_{2\alpha}$, they relax when exposed to aggregating platelets, provided the endothelium is intact. If the endothelium is removed, the segment undergoes a further contraction (Fig. 3). The relaxation is due mainly to the action of the released adenosine diphosphate on the endothelial cells (Fig. 4), and partly to the action of 5-hydroxytryptamine (Fig. 5). As a consequence of the exposure to these substances, the endothelial cells liberate one or more vasoactive substances that cause relaxation of the underlying smooth muscle (2,18). The presence of the enzyme monoamine oxidase in the endothelium also permits 5-hydroxytryptamine to be degraded (Fig. 5).

In miniature swine with selective atherosclerotic lesions in their coronary arteries and normal coronary angiograms, histamine and 5-hydroxytryptamine caused spasm of the artery only at the sites where the endothelium was denuded (19). In dogs, there is a close correlation between early atherosclerotic changes and enhanced segmental vasoconstriction to ergonovine and 5-hydroxytryptamine (20). Rings taken from human epicardial arteries that had atherosclerotic lesions had an enhanced contractile response to histamine (21). Patients who develop coronary artery spasm usually have atherosclerotic lesions at the site in the artery where spasm occurs (22). Thus, when the vascular endothelium is damaged there is diminished production of prostacyclin; this favors platelet aggregation and the release of adenosine diphosphate, 5-hydroxytryptamine and thromboxane A_2. In the absence of the protective role of the endothelium, constriction of the underlying smooth muscle ensues (Fig. 3 and 6). In the presence of normal endothelium, thrombin also causes an endothelium-dependent relaxation; in the presence of a damaged endothelium, the vasodilatory response to thrombin is lost (Fig. 5). As a consequence of the strong constriction of the vascular smooth muscle, the blood supply to the myocardium is reduced and hypoxia supervenes. When hypoxia occurs at the site of an atherosclerotic lesion, it prevents normal endothelium in the area from forming any substance that relaxes the underlying smooth muscle, and it also enhances the constrictor action of 5-hydroxytryptamine on the smooth muscle (Fig. 7 and 8). Those who smoke have an additional risk, because smoking can decrease the integrity of endothelial cells (23).

Conclusions. It seems that coronary vasospasm can be explained by the loss of the protective role of the endothelium and the resultant failure to produce one or more endothelium-dependent relaxing substances to counteract the direct vasoconstrictor action of substances released from platelets or formed by the blood elements. Similar factors may operate in the causation of spasm of cerebral and digital vessels (Raynaud's disease). The nature of these relaxing substances and the way in which the endothelium produces them offer an exciting challenge for future studies.

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