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Endocardial Endothelium and Cardiac Contractility

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Following the observation by Furchgott and Zawadski (1980) about the obligatory role of vascular endothelium in vasomotor tone, several *in vitro* and *in vivo* studies provided experimental evidences that cardiac endothelium plays a similar role in regulating cardiac function. Modulation of contractility by endothelial cells has first described for the endocardial endothelium (EE), and was then extended to vascular endothelium in the myocardial capillaries (VEMC). It has been shown that EE and VEMC release paracrine messangers such as nitric oxide (NO), endothelin and prostacyclin, both in basal conditions and under mechanical or chemical stimulation.

A large number of studies showed that these mediators exert important effects on myocardial contractility, rhythmiticity and growth both in physiological and pathophysiological conditions.

Besides to relax vascular smooth muscle by elevating intracellular cGMP, NO may be also involved in modulation of cardiac function. It has been shown that NO and cGMP induce a concentration-dependent biphasic contractile response in isolated cardiac preparations, i.e. a positive inotropic effect at very low doses, and a negative one at high concentrations (Mohan et al., 1996). Endothelins enhance the transmembrane calcium current and induce positive inotropic effect in both isolated cardiac myocyte and papillary muscle preparations. Furthermore, these peptides have also been demonstrated to induce hypertrophy of cardiac myocyte and may play an important role in ventricular processes that lead to chronic cardiac failure (Kramer et al., 1997). Prostacyclin (PGI_2) enhances both action potential duration and calcium current in isolated cardiac cells (Alloatti et al., 1991) and exerts modulatory effects on cardiac contractility.

Recent studies suggest that the actions of EE and VEMC on myocardial performance are additive and analogous, but no identical. The functional differences between EE and VEMC were explained in view of their different embryological origin and according the to fact that the EE surface is continuously exposed to all the circulating blood, whereas VEMC is in contact with about 3-5% of it. Therefore, EE may function both as a sensor device, receiving all the circulating blood, and as an autocrine or paracrine modulator of cardiac performance, rhythm and growth. Furthermore, it has been suggested that the action of EE present in the left and the right ventricle might be different, in view of the different composition of circulating blood. By contrast, the activity of VEMC seems to be mainly modulated by cardiac muscle cells, rather than by blood present inside capillary bed. In conclusion, both EE and VEMC are essential for the normal functioning of the heart; their major differences probably reside in the way and the extent by which EE and VEMC receive and transmit signals.

Recent studies performed in our laboratory suggest that EE cells are also involved in some myocardial response to growth hormone and related signaling mediators. We were in particular interested to the action of the synthetic growth hormone (GH) secretagogue hexarelin, which has been shown to reduce cardiac dysfunction in ischemic-reperfused heart. The effects exerted by hexarelin are at least in part, independent from GH and IGF-1 release. To investigate on the mechanisms of its cardioprotective activity, we studied the effects of hexarelin (1-10 μM) on contractility of rat papillary muscles and on intracellular calcium in isolated ventricular cardiomyocytes. Hexarelin induced both time- and frequency-dependent inotropic effects on the isolated papillary muscle. They included a transient increase in contractile force followed by a reduction at low (60-240/min), but not at high (400-600/min) beating frequencies. The typical negative force-frequency relationship present in rat papillary muscles was therefore modified, and a minor increase in diastolic tension occurred after a sudden increase in stimulus frequency (Fig. 1A). Pretreatment of papillary muscles with the beta adrenergic receptor antagonist propranolol (0.2 μM) abolished the positive inotropic effect, suggesting that the release of endogenous catecholamines is responsible for the initial response to hexarelin. The remaining effects of hexarelin were absent in papillary muscles pretreated with indomethacin (1 μM; Fig. 1B), or after removal of endocardial endothelium with 0.5% triton X-100 (Fig. 1C). In contrast to papillary muscle, we observed that hexarelin had no significant effect on calcium transients measured in isolated ventricular cells.

In conclusion, our study shows that hexarelin exerts important effect on cardiac tissue, inducing an improvement of calcium handling, as can be seen in particular in a multicellular preparation. The absence of a direct effect on isolated cells and in papillary muscles pre-treated with indomethacin or in which endothelium has been removed, suggests that the effects of hexarelin are mainly due to the release of endothelium-derived mediators produced via the cyclooxygenase-dependent pathway.

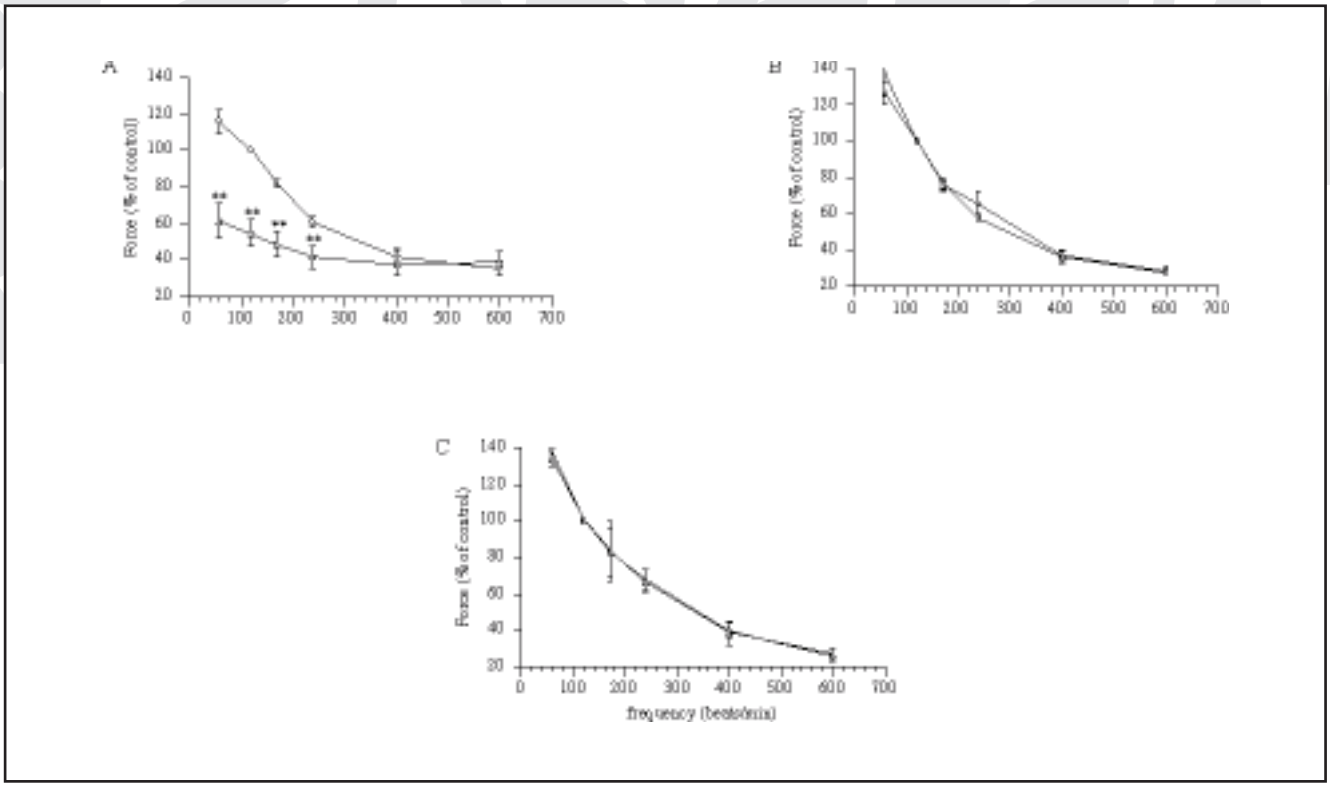

*Fig. 1. Effect of hexarelin (1 μM; triangles) on the force-frequency relationship measured from rat papillary muscles stimulated at different frequencies (60-600 beats/min) in control conditions (A, n = 5), after removal of endocardial endothelium (B, n = 4), or after tretment with 1 μM indomethacin (C, n = 5). Data are expressed as the mean ± S.E. percentage of the peak tension measured at 120/min before hexarelin (circles; statistical significance: ** p<0.01). Hexarelin had significant inotropic effect neither on triton X-100-, nor on indomethacin-treated papillary muscles.*

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