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Letters to the Editor

Adrenergic Receptors: the Key Therapeutic Target

To the editors:

Ahlquist first hypothesised the existence of a dynamic molecular entity called receptor in 1948 [1]. He postulated that the excitatory and inhibitory pressor responses to catecholamines must be mediated by distinct adrenergic receptors (ARs), then designated α (for excitatory) and β (for inhibitory) [1].

The extensive research that followed not only improved our understanding of receptors physiology and cellular mechanisms that underlay ARs control of cardiomyocyte function, but allowed to underscore the enormous therapeutic potential of agonists and antagonists.

ARs are virtually expressed on the surface of any type of cells, ready to bind to chemicals and, on the other side, regulating cellular physiology [2]. Receptors, after binding to circulating or diffusing molecules, internalise inside the cell, give rise to a specific effect, and finally, are recycled, surfacing again on the cell membrane [2]. Myocardial ischaemia, chronic heart failure (CHF), paramount and long lasting adrenergic stimulation of cardiomyocytes, drug therapy, and genetic mutations have been shown to modify receptor homeostasis. Indeed, in the presence of irreversible ischaemia or CHF, the β 1-adrenergic receptors decrease on ischaemic or stretched cardiomyocytes, whereas, at difference, α -adrenoceptors increase and externalise [3]. This altered ARs homeostasis plays a detrimental role in the mechanical performance of the cardiomyocytes. In normal myocardium the α -adrenergic tone is low [4], allowing an appropriate vasodilatation status. The α 1-adrenoceptors up-regulation that occurs in ischaemia [3] decreases coronary arteries cross sectional area [for details on ARs see ref. 5-15].

The Paradox of Post-Ischaemic Coronary Vasoconstriction Myocardial ischaemia brings, by definition, to a reduction of blood supply in the territories supplied by the stenotic or "spastic" artery, but a diffuse "compensatory" vasodilatation was hypothesised to occur in collateral circulation. At difference, and amazingly, this vasodilatation does not occur [14, 15].

Background

At the early beginning of angioplasty procedures it became evident that successful balloon dilation was followed by a long lasting vasoconstriction of the dilated segment. This phenomenon was called in the clinical setting "elastic recoil" [16] to emphasise a possible passive reaction to balloon overinflation and to coronary stretching. Moreover, in this condition [16], the intracoronary injection of nitrates had no dilator effect. At the time some studies were done in the aim to find a correlation between the balloon size or stenosis morphology and immediate or delayed elastic recoil [17], while other authors postulated a mediator role to thromboxane A_2 and to serotonin released by local platelet activation in coronary arteries constriction [18].

The mechanisms of "elastic recoil" have been investigated by El Tamimi et al. who performed the cold pressure test [19] to patients 30 min. after PTCA, to study the potential role of the sympathetic nervous system (SNS) in eliciting the constriction of the dilated artery. Amazingly, no further vasoconstriction was observed along the culprit lesion artery, making the authors conclude that the SNS had no role in this phenomenon [19].

To obtain further understanding of the mechanisms underlying post-ischaemic vasoconstriction in 5 different groups of patients we selectively injected into the dilated coronary artery of the α non-selective blocker phentolamine (Regitin 1 mg), the α_2 -selective blocker yohimbine (2 mg), the neurolytic agent bretylium (20 mg ic), and the combination of phentolamine 1 mg and 2 mg propranolol ic [20]. In this study we have observed that after balloon dilatation the dilated segment had a 31 ± 2 % diameter reduction (as shown by the other authors) [16-19] and that the coronary constriction occurred also along apparently normal remote vessels (-17 ± 2 %), making us hypothesise that neural cardio-cardiac and cardio-sympathetic reflexes were responsible for "elastic recoil" [20, 21]. The α-non-selective adrenergic blockers phentolamine counteracted the -31 ± 2 % vasoconstriction and induced an additional 22 ± 6 % vasodilatation. Moreover the balloon inflation elicited a 60 % increase in coronary resistance. Phentolamine decreased resistance by 90 %, whereas the combined use of α - and β -blockers attenuated the vasodilator effect of α alone [20]. Later it was shown that the vasoconstriction occurring at the coronary tree affects the whole arterial tree, being present also along limb arteries [22].

Role of the α -Adrenergic Receptors Blockers in Ischaemia-Reperfusion and Left Ventricular Dysfunction

Heyndrickx et al. [23] have shown in animal studies that short and transient periods of myocardial ischaemia are followed by a durable reduction (hours and days) in LV function. Moreover, Vatner [24] demonstrated in the dog model, that a strict correlation exists between myocardial shortening and blood flow. Accordingly, to study if also in humans post-ischaemic vasoconstriction blood flow reduction correlated with LV function we investigated regional LV shortening in patients after successful coronary stenting. The changes in LV function were assessed by transesophageal echocardiography (TEE) during the whole angioplasty procedure in 50 patients with effort angina [25] and in 40 patients who had an acute myocardial infarction treated within 90 min. with successful thrombolysis (TIMI) [26]. The AMI patients underwent coronary angiography 24 hours after TIMI and were revascularised by PCI 72 hours later [26]. In brief, first we documented by TEE baseline LV function. LV function was measured soon after PCI (3 minutes, reperfusion) and 15 minutes after PCI (15 min. LV dysfunction). In our TEE study we have observed that LV dysfunction involved myocardial region subtended both by the dilated artery (thickening -42 ± 4 % versus before dilation, p < 0.005; see Fig. 1) and by remote apparently normal arteries (thickening -25 ± 3 %). In the presence of LV dysfunction we injected intracoronary 10 mg urapidil (α_1 -blocker) [25, 26]. This dose elicited only a transient (3/5 min.) and minor (-5 mmHg MAP) blood pressure reduction, with no changes in HR [25-28]. The negligible blood pressure decrease was, 5 min. after IC injection, followed by a significant and diffuse improvement in thickening that reached a 80 % improvement versus "15 min. after PCI" condition (stunning [29]; Fig. 1). The injection of α_1 -blockers in patients receiving β_1 -blockers pretreatment underscored the vasoconstrictor effect of β -blockers alone [30]. As previously shown [20], also in the two studies focusing the LV function [25, 26] urapidil and

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phentolamine decreased coronary resistance. Accordingly, we hypothesised that the injection of α_1 - and α_2 -adrenergic blockers superimposed on top of, or combined with adenosine infusion might improve coronary flow reserve [31].

In this recent study we have observed that both α_1 - and α_2 -adrenergic blockers exert an additional vasodilatation of the microcirculation, improving coronary flow reserve [31]. Coronary flow reserve was calculated as the ratio between hyperaemic coronary flow velocity (or flow in ml/min.) and baseline flow. In particular we have confirmed a previous observation [32–34] that in all patients baseline flow velocity was increased after angioplasty [31]. This increase in baseline velocity is not due to the dilation of the plaque, but rather to distal embolisation that occurs after plaque fracture [35].

Hori et al. [36, 37] have previously described that in dogs acute microspheres embolisation of small coronary vessels elicits subsequent release of adenosine from the nearby non-embolised vessels and that this adenosine secretion is responsible for hyperaemia. The recent use of intracoronary filters underscored that a considerable amount of plaque debris can be retrieved in the basket [38]. It is rational to assume that also in thrombolysis the slow flow or no-reflow or the lack of ECG normalisation might be due to distal particles embolisation.

The reduction of baseline flow velocity observed 5 min. after urapidil injection might be ascribed both to vasodilatation and to the fact that the α_1 -adrenergic blocker urapidil may share with prazosin the capacity of inhibiting adenosine release [36]. Kern et al. [39] had previously described that α -adrenergic blockers exert a significant vasodilatation and decrease in resistance in humans.

Nevertheless, we still have much to learn about the effects of ARs blockers in the pathophysiology of coronary syndromes. Bypass surgery and angioplasty restore blood flow in epicardial vessels, effectively relieve angina pectoris but do not prevent inflammation, atherosclerotic plaques progression and plaque rupture, platelet activation, matrix degradation and endothelial dysfunction. The effects of α -blockers alone are inferior to diuretics to prevent heart failure, but the interaction of these drugs with the other drugs that are commonly used to treat CAD or CHF [40], need to be elucidated [41].

Role of ARs Blockers

Apparently ARs play a key role in modulating the puzzle of excitatory and inhibitory mechanisms involved in cell homeostasis, both in normal and in pathological conditions [42–46]. Cell homeostasis goes through adaptive changes of the receptors dynamic, i.e. through receptors' up- or down-regulation, and, at short term, internalisation or externalisation of receptors' mol-



Figure 1. Percent thickening changes induced by PCI and $\alpha/\beta\mbox{-block};$ mod. from [26]

ecules [2–15]. Extensive research was in the last decades performed on β -adrenergic receptors. Less is known on α -ARs pathophysiology. In fact, from recent studies we know that β blockers reduce immune activation, coagulation activation, inhibit platelet aggregation as well as thromboxane-B2 formation, exert antiendothelin effects, and reduce cardiomyocytes apoptosis. Chronic β_1 -adrenergic receptor signaling may be the dominant cardiotoxic pathway in the failing heart, and may trigger β receptors down-regulation, whereas α_1 -receptors increase in nonviable myocardium. Further research is needed to understand the receptor behavior after a long-term α_1 -adrenergic blockade.

Chronic Effects of α -Adrenergic Receptors Blockers on Post-Ischaemia Reperfusion LV Function

In a limited number of patients (n = 32), revascularised with coronary stenting for a single vessel stenosis, in a double blind study we have investigated the effects of urapidil on LV function 3 months after angioplasty [43]. After 3 months of administration of the non-hypotensive dose of 30 mg/day urapidil patients showed a 10 % increase in ejection fraction, versus placebo. Multicenter trials are needed to give the final answer.

The Potential Role of the α -Adrenergic Receptors Blockers in Distal Embolisation Damage

The no-reflow phenomenon is likely due to distal embolisation [44-45]. The lack of angiographic reflow occurs after thrombolysis, and is followed by the absence of ECG normalisation [46-48]. The 10 % of the no-reflow cases occur in primary PCI [47]. The increase in resistance, the abrupt microvascular constriction, platelet plugging, serotonin release, oxy-radical production, and inflammation are the reactive reactions to debris plugging which interrupts flow in the subtended territories [45]. The lack of microvascular reperfusion correlates with survival and major cardiac events [48]. Many therapeutic attempts have been made to restore flow including the injection of verapamil, nitroprusside, adenosine, papaverine, GPIIb/IIIa inhibitors or high velocity boluses of patient's blood [49-55]. These drugs are, some time, able to induce reflow. Nevertheless the best therapeutic choice at short and long term is still unknown. At present, the use of intracoronary filters device does not improve versus PCI alone the no-reflow phenomenon [56]. The reason for this lack of success might be the fact that both infarct related arteries and unstable plaques may embolise before TIMI or primary PCI, or filters, per se, may dislodge some thrombus. In the aim of restoring flow we injected ic the combination of adenosine and urapidil in 20 AMI patients who showed the phenomenon of noreflow. Five minutes after the injection we observed the angiographic reflow in all cases. A multicenter study comparing different treatments to restore flow and ST normalisation after primary PCI is ongoing. All the patients were treated with heparin, clopidogrel (450 mg orally), and with a bolus of abciximab and nitrates. We do not have an explanation for this effect. Nitrates alone nor saline did not restore the angiographic flow. We hypothesise that urapidil might have exponentiated the effects of nitrates [45] or of adenosine [42-44] or that it might have added to the anticoagulant and anti-platelet treatment given to AMI patients undergoing primary PCI. In fact among other effects, urapidil possesses an antiserotoninergic action [57]. The potential beneficial effect in the no-reflow phenomenon and in the long term improvement in LV function need further investigation.

Conclusions

The α_1 -adrenergic blocker urapidil acutely

- a) counteracts elastic recoil and diffuse coronary constriction after ischaemia,
- b) decreases coronary resistance,
- c) counteracts post-ischaemic stunning and LV dysfunction, and
- d) improves coronary flow reserve.
- e) The LV function improvement seems to persist 3 months after coronary stenting.

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