Clinical research

Alpha-adrenergic receptor blockade and hyperaemic response in patients with intermediate coronary stenoses

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Background Maximal hyperaemia is paramount in the diagnosis of patients with coronary artery disease. However in these patients, enhanced \(\alpha\)-adrenergic microvascular vasoconstriction may preclude adenosine to induce maximal hyperaemia.

Aim To assess the presence and the clinical relevance of residual microvascular resistance after administration of adenosine.

Methods and results Fractional flow reserve (FFR, calculated by coronary pressure measurements during adenosine-induced hyperaemia) was assessed in 85 patients with an intermediate coronary stenosis (mean diameter stenosis of 50 ± 1%) and normal left ventricular function which were divided into the following three groups: (a) 33 patients before and after IC bolus of phentolamine, an \(\alpha_1,\alpha_2\)-adrenergic blocker; (b) 32 patients before and after IC bolus of urapidil, a selective \(\alpha_1\)-adrenergic blocker; (c) 20 patients before and after IC bolus of saline.

Since minimal luminal diameter remained unchanged before and after phentolamine (1.46 ± 0.06 vs. 1.47 ± 0.06 mm, ns), urapidil (1.46 ± 0.06 vs. 1.39 ± 0.08, ns), and saline (1.56 ± 0.08 vs. 1.55 ± 0.08, ns), changes in FFR reflects changes in microvascular resistance.

Overall, phentolamine and urapidil induced a slight but significant decrease in FFR (phentolamine: 0.79 ± 0.02 vs. 0.77 ± 0.02, \(p < 0.05\); urapidil: 0.78 ± 0.02 vs. 0.75 ± 0.02, \(p < 0.05\)). However, only 6 patients showed a change in FFR from \(\geq 0.75\) to <0.75 and no patients showed a change in FFR from \(\geq 0.80\) to <0.75 that could have influence clinical decision making. Saline did not induce any change in FFR. Phentolamine and urapidil induced only transient and negligible haemodynamic changes in heart rate and blood pressure.

KEYWORDS Fractional Flow Reserve; Alpha-blockers; Coronary Hyperaemia; Phentolamine; Urapidil; Adenosine

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Introduction

Coronary flow reserve (CFR) and fractional flow reserve (FFR) are commonly used in the catheterization laboratory to determine the functional significance of epicardial intermediate coronary stenoses. CFR represents the number of times hyperaemic flow increases above baseline flow. FFR represents the fraction of hyperaemic myocardial flow that is preserved despite the presence of an epicardial stenosis. For both CFR and FFR, maximal hyperaemia is paramount. Less than maximal vasodilation would underestimate CFR and overestimate FFR which might lead to erroneous clinical decision making in patients with dubious stenoses.

Coronary atherosclerosis is associated with an increased \( \alpha \)-adrenergic vasoconstriction. In case of severe coronary stenosis, \( \alpha \)-adrenergic tone may contribute to myocardial ischaemia. The administration of \( \alpha \)-blocking agents in patients with coronary artery disease has been reported to reduce coronary resistance further.

Accordingly, the aim of the present study was to assess the influence of \( \alpha \)-adrenergic tone on adenosine-induced hyperaemia and, therefore, evaluate the impact of \( \alpha \)-adrenergic blockade, if any, on FFR-guided clinical decision making.

Methods

Patients

A total of 85 patients undergoing coronary angiography for a positive or a non-conclusive stress testing with the following inclusion criteria were studied: a moderate coronary stenosis (ranging between 30% and 70% by visual estimation) and normal left ventricular function (global left ventricular ejection fraction larger than 55% and no regional wall motion abnormalities). Exclusion criteria were previous myocardial infarction, conduction system disease, hypertrophic cardiomyopathy, valvular disease, chronic congestive heart failure, other severe diseases (cancer, neurological disease, etc.).

Medications potentially interfering with the central adrenergic tone were interrupted for at least 3 days before catheterization: in the phentolamine group, 3 patients were on clonidine and 1 patient was on \( \alpha \)-methyl-DOPA; in the urapidil group, 2 patients were on clonidine and 1 patient was on \( \alpha \)-methyl-DOPA. The study protocol was approved by the local Medical Ethical Committees and informed consent was obtained for all patients.

Conclusions

The administration of \( \alpha \)-adrenergic blockers in addition to adenosine unmasks a small, yet clinically irrelevant, degree of residual microvascular tone. The consequential changes in FFR values do not significantly affect clinical decision making.

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Catheterization

After the insertion of a femoral sheath, a 6F guiding catheter without sideholes was advanced into the coronary ostium. After the administration of 0.2 mg intracoronary isosorbide dinitrate, an angiogram was obtained for QCA measurements. A pressure monitoring guide wire (PressureWire 4, Radi Medical, Uppsala, Sweden) was first advanced to the tip of the guiding catheter to ensure that the pressures recorded by the guiding catheter (aortic pressure, \( P_a \)) and by the Pressure Wire were identical. The wire was then advanced in the distal part of the vessel to measure distal coronary pressure (\( P_d \)). Heart rate, aortic pressure, and distal coronary pressure were continuously recorded and digitally stored (Notocord Systems, Paris, France). FFR was calculated by dividing mean distal coronary pressure (\( P_d \)) by mean aortic pressure (\( P_a \)) during adenosine-induced hyperaemia. As previously described, the \( P_a/P_d \) ratio has been used as an index of myocardial resistance.

In fact, in the presence of an epicardial stenosis, pharmacological vasodilation of resistance vessels induces a decrease in coronary pressure distal to the stenosis and an increase in trans-stenotic pressure gradient and in trans-stenotic flow. At a constant \( P_a \), changes in \( P_d \) can mainly be due to changes in the severity of the epicardial stenosis, changes in myocardial resistance, or a combination of both. In case of a fixed stenosis, changes in \( P_d \) are related to changes in myocardial resistance.

Protocols

Measurements of FFR were performed in 33 patients during adenosine administration before and after intracoronary bolus of the non-selective \( \alpha \)-adrenergic blocker, phentolamine (12 \( \mu \)g/kg). Among them, adenosine was given in 13 patients as an intracoronary bolus (40 \( \mu \)g) twice before and twice after phentolamine administration; twenty other patients received a continuous intravenous infusion of 140 \( \mu \)g/kg/min of adenosine and, after 4 min, an intracoronary bolus of phentolamine. Adenosine infusion was maintained for 5 additional minutes.

In 32 other patients, FFR was measured during adenosine administration before and after an intracoronary bolus of the selective \( \alpha_1 \)-adrenergic blocker, urapidil (10 mg). Among them, adenosine was given in 19 patients as an intracoronary bolus (40 \( \mu \)g) twice before and twice after urapidil administration; thirteen other patients received a continuous intravenous infusion of 140 \( \mu \)g/kg/min of adenosine and, after 4 min, the intracoronary bolus of urapidil. Adenosine was maintained for 5 additional minutes.

In 20 patients, FFR was measured during intracoronary adenosine (40 \( \mu \)g bolus), twice before and twice after an intracoronary bolus of saline (10 ml).

When adenosine was administered intracoronarily, the average value among the two injections was taken into account.
Quantitative coronary angiography

Quantitative coronary angiography (QCA) was obtained with contrast injections immediately before the administration of the β-adrenergic blockers (or saline) and at the end of the protocol in the group of patients receiving intracoronary adenosine (5 min after the β-blocker administration). In the group of patients receiving intravenous adenosine, QCA was obtained in addition to hyperaemia, and 5 min after β-blocker administration (before stopping adenosine). Minimal lumen diameter (MLD), percentage diameter stenosis (DS%), and reference diameter (RD) of the stenotic coronary were then measured using the tip of the catheter as a scaling device.14

Statistical analysis

Data are expressed as means ± SEM. The sample size was calculated according to Altman.26 Statistical comparisons between the values of $P_d$, $P_a$, FFR, and changes in vessel dimensions before and after β-adrenergic blockade were analysed by the two-sided Student paired t-test. Heart rate and systemic blood pressure changes along the study period, as well as between groups comparisons for FFR changes, were analysed by one-way ANOVA, followed by the Newman–Keuls test.

Results

Patients’ characteristics

Patients’ characteristics are reported in Table 1.

Vessel dimensions

Vessel dimensions before and after β-adrenergic blockade remained similar, suggesting that the epicardial vessels were fully dilated after intracoronary nitrates (Table 3 and Fig. 1, upper panels). Consequently, it can be assumed that changes in FFR are directly proportional to changes in microvascular resistance.15

Haemodynamic data

Haemodynamic data are shown in Table 3 and Fig. 1, lower panels. Heart rate was not influenced by intracoronary adenosine nor by intracoronary β-adrenergic blockade. Intravenous infusion of adenosine significantly increased heart rate (phentolamine group: from 72 ± 3 to 76 ± 2 bpm, $p < 0.05$; urapidil group: from 62 ± 3 to 71 ± 4 bpm, $p < 0.05$). Urapidil (but not phentolamine), on top of intravenous adenosine, further increased heart rate. Intracoronary saline did not influence heart rate.

Intracoronary adenosine did not affect mean aortic blood pressure ($P_a$). Yet, phentolamine and urapidil administration induced a transient decrease in mean aortic blood pressure, which was reversed after 3 min.

Mean distal coronary pressure ($P_d$) decreased after adenosine (intracoronary and intravenous) in all three groups, reflecting the increase of blood flow.

The wide range of values of FFR illustrates the wide range of the physiologic stenosis severity studied. Overall, phentolamine and urapidil induced a slight but significant decrease in FFR (phentolamine: 0.79 ± 0.02 vs. 0.77 ± 0.02, $p < 0.05$; urapidil: 0.78 ± 0.02 vs. 0.75 ± 0.02, $p < 0.05$), while saline did not induce any significant change (Table 2). A decrease in FFR value larger than the largest change observed with saline, occurred in 9 of 33 patients (27%) who received phentolamine and in 11 of 32 patients (34%) who received urapidil. In all patients receiving intracoronary adenosine, FFR values associated with the first and the second injections were identical both before (0.79 ± 0.02 vs. 0.79 ± 0.02, ns) and after (0.77 ± 0.02 vs. 0.77 ± 0.02, ns) β-adrenergic blockade, suggesting that the effect observed after administration of β-adrenergic blocker was indeed due to the latter medication.

In only 6 of the 65 patients (9%) receiving β-adrenergic blockers, the value of FFR dropped from above 0.75 to below this threshold value. In addition, in no patients did the value drop from above 0.80 to below 0.75.

A subgroup analysis was performed by pooling together all non-smoking patients vs. all smoking patients, regardless the β-blockers administrated. In smokers, there was a 5% decrease in FFR (from 0.77 ± 0.03 to 0.73 ± 0.03, $p < 0.01$) that was significantly higher when compared to the 2% decrease in FFR (from 0.79 ± 0.01 to 0.78 ± 0.01, $p < 0.01$) observed in non-smokers ($p = 0.01$ vs. smokers). Within this group, 3 patients had an FFR above 0.75 that dropped below 0.75. No single patient had an FFR above 0.80 that dropped below 0.75.

Discussion

The present study investigates the effects of β-adrenergic blocking agents on adenosine-induced hyperaemia

<table>
<thead>
<tr>
<th>Table 1 Patients’ characteristics</th>
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<tr>
<td>Age (years)</td>
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<td>Male gender</td>
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<td>Smoking habit</td>
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<td>Hypertension</td>
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<td>Hypercholesterolaemia</td>
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<td>Diabetes</td>
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Data are in absolute number (percentage data).
**Alpha-adrenergic receptor blockade and hyperaemic response in patients with angiographically intermediate coronary stenosis.** The administration of phentolamine, a non-selective $\alpha$-adrenergic blocker, and urapidil, an $\alpha_1$-selective blocking agent, exerted a significant, albeit modest enhancement of coronary hyperaemia. Yet this further recruitment of resistance reserve had only trivial consequences for FFR-based clinical decision making, as none of the 65 patients shifted from above the upper threshold to below the lower threshold of the narrow grey zone.

### Alpha-adrenergic receptors in the normal coronary circulation

In animal models, $\alpha_1$-adrenergic receptors mediate epicardial vasoconstriction, while $\alpha_2$-adrenergic receptors mostly mediate microvascular constriction.\(^{16–18}\)

In humans, under resting conditions, a non-selective or selective $\alpha_1$-adrenergic blockade resulted in no or only a slight decrease in coronary resistance.\(^{13,19,20}\) The latter also remained unaffected by sympathetic activation during the cold pressor test.\(^{13,21}\) On the other hand, an oral treatment with an $\alpha_1$-antagonist increased dipyridamole-recruited coronary reserve,\(^{20}\) suggesting a more prominent role for $\alpha_1$-adrenergic receptors during hyperaemia. Nevertheless, $\alpha_1$-adrenergic stimulation with methoxamine did not induce any effect on epicardial coronary cross-sectional area, nor on coronary blood flow.\(^6\)

Of note, intracoronary infusion of yohimbine, a selective $\alpha_1$-antagonist, did not change coronary diameter or coronary blood flow velocity,\(^{22}\) while the stimulation with BHT-933, a selective $\alpha_2$-adrenergic receptor agonist, mediates microvascular constriction.\(^6\)

### Alpha-adrenergic receptors in the atherosclerotic coronary circulation

In atherosclerotic coronary arteries, the $\alpha$-adrenergic tone increases, probably due to the dysfunctional endothelium unable to offset vasoconstrictive forces. In fact,
removal of endothelium in canine iliac arteries augments $\alpha_1$-adrenergic vasoconstriction in response to noradrenaline. Vasoconstriction following cold pressor test, exercise, or smoking was abolished by non-selective $\alpha$- or selective $\alpha_1$-adrenergic blockers in patients with coronary artery disease. Baumgart et al. demonstrated that in human atherosclerotic coronaries, both $\alpha_1$- and $\alpha_2$-adrenergic activation elicit vasoconstriction in both conduit and resistance vessels. The present data obtained in atherosclerotic vessels pre-treated with nitrates suggest that the influence of $\alpha$-adrenergic blockers on the microvascular component, albeit present, is clinically very modest. Consistently with previous data, in the subgroup of smokers a slightly higher 5% decrease in FFR was observed after $\alpha$-blockade. As expected in the control group, IC saline did not significantly affect the microvascular resistance.

The $\alpha$-adrenergic tone is also increased immediately after PCI. Gregorini et al. demonstrated that the epicardial coronary vasoconstriction and coronary blood flow reduction observed early after PCI, were abolished or prevented by phentolamine, urapidil and yohimbine. Moreover, phentolamine and urapidil reversed the observed decreases in systolic wall thickening in the previously ischaemic and non-ischaemic myocardium.

**Limitations of the study**

The present study aimed at assessing the presence and clinical importance of residual microvascular tone during adenosine-induced hyperaemia. Therefore, only patients with intermediate stenosis were analysed, i.e. those in whom FFR measurements are most desirable. In addition, intracoronary nitrates were given as state-of-the-art when manipulating a guide wire in the coronary tree. These two factors might contribute to explain the modest effect of the $\alpha$-adrenergic blockade on adenosine-induced hyperaemia. The moderate degree of stenosis might indeed be accompanied by a partial preservation of endothelial function and pre-treatment with nitrates might partially offset the potential effect of $\alpha$-adrenergic receptor blockers.

Interestingly, urapidil appeared to have a slightly higher efficacy; this was not expected as the major effect of this $\alpha_1$-adrenergic blocker was supposed to occur in the macro-circulatory compartment. In human atherosclerotic coronary arteries, Indolfi et al. found that the $\alpha_2$-adrenergic receptor antagonist yohimbine induced a vasoconstriction. This was interpreted as the result of the inhibition of presynaptic noradrenaline re-uptake and subsequent $\alpha_1$-adrenergic vasoconstriction. In our setting, we may speculate that a higher concentration of noradrenaline, subsequent to pre-synaptic $\alpha_2$-adrenergic receptor blockade, could offset the vascular post-synaptic blockade of both $\alpha_1$/$\alpha_2$-adrenergic receptors, leading to a weakened response to phentolamine.

The relatively small sample size of the present study advocates for a larger randomized double-blinded study in order to definitively evaluate the role of $\alpha$-adrenergic
microvascular tone in physiological diagnostic assessment of intermediate coronary stenoses.

Clinical implications

Even though α-adrenergic blockade induced a mild but statistically significant decrease in FFR, the clinical consequences of this finding are minimal. It has indeed been shown that an FFR value >0.80 could be considered a surrogate of a normal non-invasive stress test, while a value <0.75 was almost uniformly associated with inducible signs of myocardial ischaemia.24 In the present study, adenosine-induced hyperaemia could be further increased by α-adrenergic blockade in 9% of patients. All of them had a FFR value located in the “grey zone” (i.e. between 0.75 and 0.80) suggesting that it might be helpful to administer 10 mg IC urapidil. However, in all these patients, FFR did not decrease from values above 0.80 prior to α-adrenergic blockade to ‘ischaemic’ values below 0.75 after α-adrenergic blockade. This indicates that the administration of α-adrenergic blockers on top of classical vasodilators would not change clinical decision making in the vast majority of patients.

References