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5

Beta-Blockers and Coronary Flow Reserve

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1. Introduction

The knowledge of the impact of beta-blockers on Coronary Flow Reserve (CFR) is based on experimental and clinical studies which used invasive methods (mainly Doppler Flow Wire, DFW) and non-invasive tools including scintigraphic (mainly Positron Emission Tomography, PET), magnetic resonance and Doppler ultrasound imaging.
Beta-blockers have a large therapeutic indication in the treatment of coronary artery disease, due to their anti-ischemic and anti-arrhythmic effect. The anti-ischemic effect is based on the oxygen sparing mechanism with a reduction in rate-pressure product. Changes in coronary hemodynamics associated with the administration of beta-blockers have been extensively studied. These drugs may affect CFR by modifying either resting or maximal coronary blood flow (CBF) or even both. When assessing the impact of beta-blockers on CFR it is important to distinguish the effects exerted by first-and second generation beta-blockers from those due the mechanisms of third generation beta-blockers, which are provided of vasodilating action.

2. First and second generation beta-blockers and coronary flow reserve

Animal and human experiments have shown that first- and second generation beta-blockers (propranolol, practolol metoprolol, atenolol) induce a reduction of CBF at rest (1-7), which has been mainly attributed to coronary vasoconstriction (8,9). Both non selective (propranolol) and selective (atenolol) beta-blocking agents have shown a gradual vasoconstriction, i.e., a decrease in coronary artery diameter by approximately 20-25%, over 20 min after their acute administration, an effect which is overcome by nitrates (3). An alternative mechanisms for explaining the reduction of CBF at rest is provided by the reduction of myocardial oxygen demand since these drugs lower blood pressure and heart rate with variable degree (4,5). After acute injection, beta-blockers decrease myocardial contractility and work, leading to a reduction of resting CBF (5).
The effects of first and second generation beta-blockers on maximal CBF are more controversial. A clinical study assessing the effects of non-selective beta-blocker propranolol

(0.1 mg/kg i.v.) after cold pressure test (CPT), a stimulus completely mediated to the endothelial function ("reactive hyperemia") suggests that this drug leads to enhanced coronary vascular resistance during hyperemia, due to unopposed alpha-adrenergic vasomotor tone (6). The oral administration of the cardio-selective atenolol produces similar action in hypertensive patients without coronary artery stenosis, inducing even a reduction of CFR and raising the suspicion that it may worsen coronary microvascular function (7). On the other hand, in patients with coronary artery disease the acute intravenous administration of the selective beta-blocker metoprolol (5 mg) has shown an increase of pharmacologically induced (adenosine) CBF velocities and post-ischemic coronary flow velocity reserve (CFVR) measured by the means of DFW (5). Boettcher and coworker have reported similar results, with an increase in PET-derived CFR after 50 mg oral metoprolol, achieved by an increase in maximal CBF which is further enhanced by a decrease in resting CBF (6).

Based on these experiences, the controversial influence of first- and second-generation beta-blocking agents on CFR has to be acknowledged. It can be explained by taking into account the interaction of the pharmacological effects on CBF at rest, generally reduced under the action of these categories of beta-blockers, and after maximal hyperemia, when minimal coronary resistance can be increased (mainly by non selective beta-adrenergic antagonists and by selective atenolol) or reduced (by some selective beta-blockers such as metoprolol).

3. Third generation Beta-blockers (with vasodilating action) and Coronary Flow Reserve

The third generation beta-blockers have the common characteristic to combine a vasodilating action to the classic beta-blocking properties. The association of these two effects is particularly pronounced in carvedilol and nebivolol, which have earned important positions in the therapy of chronic heart failure, with a recognized positive influence on left ventricular (LV) function and prognosis (10-13). The influence of these two drugs on CFR has been tested in the clinical setting. The improvement of coronary microvascular function obtainable by both carvedilol (14-17) and nebivolol (7,18-21) could be at least one of the substrates underlying the improvement in LV function due to both these drugs. Except for the experience of Koepfli et al (14), where a significant drug-induced increase on PET-derived CFR was achieved only pooling 36 patients with coronary artery disease treated by either carvedilol or atenolol (12 week treatment), all the other clinical studies demonstrated a positive effect of carvedilol or nebivolol on CFR (**Table 1**) (22).

The beneficial action of carvedilol on CFVR was observed in three reports, including exclusively patients with idiopathic dilated cardiomyopathy, with a therapy time duration ranging between 1 month and 6 months (16-18). In these experiences, the increase of CFVR was mainly due to the increase of maximal CBF velocity, attributable to diminution of extravascular compressive forces and of LV filling pressure (5,6), to blunted heart rate response beneficially affecting the diastolic myocardial perfusion during hyperemia (6), to alpha-adrenergic blocking action and to improved endothelial function (23,24) possibly producing a better hyperemic microvascular vasodilation..

The studies performed by using nebivolol involved several clinical settings, such as patients with arterial hypertension (7,18,21), idiopathic dilated cardiomyopathy (19) and coronary artery disease (20). In particular, Togni et al (20) evaluated the acute effect of intracoronary administration of nebivolol, while the other studies evaluated the therapeutic effect of oral

Drug	Authors	Method for measuring CFR	Setting / therapy duration	Effect on CFR
Carvedilol, 20 mg/day	Sugioka K et al, JACC 2005	TTE, Aden 0.14 mg/Kg/min	12 IDCM pts, 3-6 months	2.6±0.9 (baseline) 3.5±0.7 (3 months) 3.7±0.6 (6 months)
Carvedilol 25-50 mg/day	Neglia D et al, Heart 2007	PET Dip 0.56 mg/Kg	16 IDCM pts, 6 months	1.67±0.63 (baseline) 2.58±1.04 (6 months)
Carvedilol 20 mg/day	Sugioka K et al, Am Heart J 2007	TTE, Aden 0.14 mg/Kg/min	18 IDCM pts, 1 month	CFR change = 1.3±0.6*
Nebivolol, 5 mg/day	Galderisi M et al, J Hypertens 2004	TTE, Dip 0.56 mg/kg	14 HTN pts, 4 weeks	1.89±0.31 (baseline) 2.12±0.33 (4 weeks)
Nebivolol, 5mg/day	Gullu H et al, Heart 2006	TTE, Dip 0.84 mg/Kg	30 HTN pts, 8 weeks	2.45±0.48 (baseline) 2.56±0.52 (8 weeks)
Nebivolol, 5 mg/day	Erdogan D et al, Heart 2007	TTE, Dip 0.56 mg/Kg	21 IDCM pts, 1 month	2.02±0.35 (baseline) 2.61±0.43 (1 month)
Nebivolol, 0.1 mg, 0.25 mg, 0.50 mg (intracoronary)	Togni M et al, Cardiovasc Drug Ther 2007	DFW, Aden 12-18 μg (intracoronary)	8 CAD pts, Acute effect	2.10±0.4 (baseline) 2.30±0.7 (0.1 mg) 2.60±0.9 (0.25 mg) 2.60±0.5 (0.50 mg)
Nebivolol 5 mg/day	Galderisi M et al, J Hypertens 2009	TTE, Dip 0.84 mg/Kg	20 HTN pts, 3 months	2.07±0.2 (baseline) 2.20±0.2 (3 months)

* CFR change in patients with improvement of LV ejection fraction ≥ 10%.
Aden = Adenosine, CAD = Coronary artery disease, DFW = Doppler flow wire, Dip = Dipyridamole, HTN = Hypertension IDCM = Idiopathic dilated cardiomyopathy, PET = Positron emission tomography, pts = Patients, TTE = Trans-thoracic echocardiography

Table 1. Main studies showing favourable effect of beta-blockers with vasodilator action on CFR in humans (Modified by Galderisi M et al, Ref # 21).

administration (5 mg daily) after 8 weeks (7) and 4 weeks (18,19) and 3 months (21). With the exception of the observation of Gullu (7), where the improvement of CFVR was exclusively due to the decrease of CBF velocities at rest, in the other 4 studies nebivolol increased significantly hyperemic CBF velocities (18-21). Coronary vasodilation due to either adenosine or dipyridamole is primarily endothelium independent but the increment in CBF may trigger further flow-induced vasodilation, which is endothelium dependent (25,26). Nebivolol has vasodilating properties with increasing endothelial NO release due to effects on the L-arginine/NO pathway that reduce peripheral vascular resistance (27). It is able not only to increase NO release but also to inhibit the synthesis of endothelin-1 (28), a mediator contributing to vascular resistance (29). Although these effects cannot be automatically applied to the coronary circulation of the studies which demonstrated the beneficial effects of nebivolol on CFVR – since they did not use any NO antagonist to target the mechanism of action - in our experience (18) dipyridamole-induced increase in rate-pressure product during pharmacological stress was similar before and during nebivolol therapy and could not explain alone the changes induces on CBF velocities. This highlights indirectly the possible beneficial effect of the drug on the endothelial function. A similar effect of nebivolol has been demonstrated in humans on brachial artery flow mediated dilation (30), a completely endothelium-dependent stimulus (31).

The increase of CFR induced by beta-blocking agents with vasodilating properties has potential clinical implications. This increase appears clearly beneficial in patients with coronary artery disease, where a better hyperemic CBF (increase of O_2 supply), combined with a reduction of rate-pressure product (decrease of O_2 demand), may be the cause underlying the anti-ischemic effect of these drugs. The increase of CFR might also indicate an improvement of coronary microvascular dysfunction, responsible of microvascular angina pectoris or silent ischemia in patients without epicardial artery stenosis (32). The improvement of coronary microvessel function could be even one of the mechanisms sustaining the improvement of LV function demonstrated by both carvedilol and nebivolol (33-40). Sugioka and coworkers (17) observed that CFVR improvement after carvedilol was greater in patients with LV ejection fraction increase ≥ 10% (1.3 ± 0.6) than in those with election fraction increase < 10% (0.4 ± 0.5) ($p<0.01$). Data from our laboratory have shown a relation between the positive influence exerted by 3-month oral administration of nebivolol on CFVR and the reduction of non invasively determined LV filling pressure in uncomplicated arterial hypertension (21). Accordingly, the absence of a significant restoration of CFVR after short-term third-generation beta-blockers may imply a poor chance of improvement in LV function, while a great CFVR increase may indicate a higher chance of it. Therefore, one possible clinical implication is that changes of CFVR after short-term beta-blocking therapy is helpful to predict the response or the further improvement of LV function to treatment.

4. Conclusions

The impact of beta-blocking medications on coronary flow reserve is related to the specific characteristics of the drug. First- and second-generation beta-blockers significantly reduce coronary flow at rest (because of reduction of myocardial oxygen demand and vasoconstriction effects) while their action on the hyperemic coronary flow is variable. Third-generation beta-blockers induce a true amelioration of the maximal hyperemia of coronary blood flow which appears be possibly due to alpha-adrenergic blockade and to

nitric oxide-mediated vasodilator action. These effects might have potential beneficial prognostic impact in the setting of patients where CFR reduction has a recognized independent, negative predictive value on outcome and mortality (41-43).

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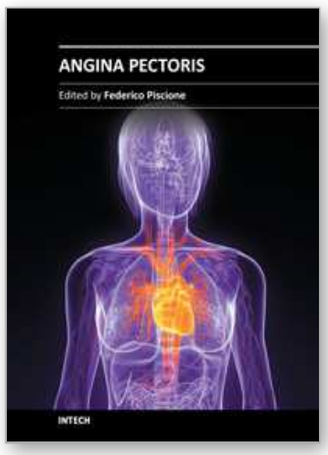

Angina Pectoris

Edited by Prof. Federico Piscione

ISBN 978-953-307-359-0
Hard cover, 184 pages
Publisher InTech
Published online 10, October, 2011
Published in print edition October, 2011

Angina is the most common disorder affecting patients with ischemic heart disease. This book provides a thorough review of fundamental principles of diagnosis, pathophysiology and treatment of angina pectoris, representing an invaluable resource not only for cardiologists, but also for general practitioners and medical students.

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