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International Journal of Cardiology 101 (2005) 465–472

International Journal of Cardiology

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Effect of estrogen on coronary vasoconstriction in patients undergoing coronary angioplasty

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Received 26 January 2004; accepted 27 May 2004
Available online 1 September 2004

Abstract

Background: Estrogen has an antioxidant potential which may contribute to its cardioprotective effect. We sought to determine whether estrogen administration can affect coronary vasomotor tone in patients after angioplasty by reducing 8-*iso*-prostaglandin (PG) $F_{2\alpha}$ concentrations, a bioactive product of lipid peroxidation.

Methods: The study was designed to prospectively investigate 30 consecutive patients scheduled for elective coronary angioplasty. Patients were randomized into two groups according to whether they did not (group 1, n=15) or did have (group 2, n=15) intracoronary (i.c.) treatment with estrogen prior to coronary angioplasty.

Results: There were no significant differences of collateral circulation assessed by intracoronary Doppler flow velocity during balloon inflations between the study groups. The diameters of the coronary artery at the dilated and distal segments were significantly reduced 15 min after dilation compared with those immediately after dilation in group 1 (both P<0.0001). The vasoconstriction was significantly blunted in group 2. The 8-*iso*-$PGF_{2\alpha}$ levels in plasma from the coronary sinus rose significantly from 194±45 to 390±97 pg/ml (P<0.0001, 95% confidence intervals=142–249 pg/ml) 15 min after angioplasty in group 1, which was attenuated after administering estrogen. Significant correlation was found between the changes of coronary vasomotion of the dilated segment and 8-*iso*-$PGF_{2\alpha}$ levels in group 1 (r=0.73, P=0.002).

Conclusions: 8-*iso*-$PGF_{2\alpha}$ is released into the coronary circulation during angioplasty, and this vasoactive substance may contribute to the occurrence of vasoconstriction. Estrogen administration attenuated vasoconstriction by reducing the 8-*iso*-$PGF_{2\alpha}$ levels. This finding may provide a new strategy to treat coronary vasoconstriction after angioplasty.

Keywords: 8-*iso*-$PGF_{2\alpha}$; Estrogen; Coronary angioplasty; Vasoconstriction

1. Introduction

Although percutaneous transluminal coronary angioplasty provides effective recannulization of coronary atherosclerosis, routine vasoconstriction occurs after angioplasty [1]. Coronary vasoconstriction is associated with a greater residual stenosis after angioplasty, which is associated with an increased incidence of restenosis [2,3]. Thus, a better understanding of possible mechanisms involved and potential strategies to limit its extent should be sought. Free radicals are thought to contribute to coronary spasm after angioplasty in dogs [4]. Pretreatment with a superoxide scavenger (superoxide dismutase) had a protective effect on coronary vasomotion [4], suggesting that oxygen radicals were the cause of coronary vasoconstriction. Although animal studies have demonstrated that myocardial ischemia/reperfusion causes free radicals, there were controversies whether brief coronary occlusions in angioplasty might be

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doi:10.1016/j.ijcard.2004.05.044

an ischemia/reperfusion model for oxidative stress in humans. Clinical studies in which coronary sinus blood has been sampled after balloon inflation have shown negative and positive results of free radical generation [5–11]. The conflicting evidence can largely be attributed to the fact that most methods previously available to assess oxidative stress have been inaccurate and unreliable [12].

Recently, a novel family of prostanoids, isoprostanes, has been described that is produced in vivo by a nonenzymatic free radical peroxidation of arachidonic acid [13]. F_2-isoprostane can be produced in conditions of oxidant stress and, as they are stable within the circulation, have been quantified as a reliable marker of oxidant injury in vivo [14]. Among these products, 8-*iso*-prostaglandin (PG) $F_{2\alpha}$ has been shown to be an extremely potent coronary vasoconstriction [15]. F_2-isoprostanes have been shown to increase in diverse conditions in which generation of free radicals is strongly implicated, such as chronic cigarette smoking [16], advanced age [17], and diabetes mellitus [18]. A variety of inhibitors of free radicals production or scavengers of free radicals are able to reduce formation of F_2-isoprostane in a dose-dependent manner [19], reflecting this marker a quantitative measurement for lipid peroxidation.

Estrogens, especially estriol and 17 β-estradiol, which include a phenolic hydroxyl group, have an effective antioxidant action and inhibit lipid peroxidation [20]. Kim et al. [21] showed that chronic administration of estrogen as an antioxidant prevents dysfunction of myocardium damage after ischemia and reperfusion in canine models. In vitro studies have shown that estrogens effectively scavenge radicals [22,23]. It remains unknown whether the antioxidant effect of estrogen contributes attenuation of coronary vasoconstriction after angioplasty. The aims of the study were (1) to test whether free radicals as measured by 8-*iso*-$PGF_{2\alpha}$ act as a mediator of the vasoconstriction effect after coronary angioplasty, and (2) to evaluate whether estrogen administration improves vasomotor response by reducing the oxidative stress.

2. Methods

2.1. Patient selection

The study was conducted prospectively. All patients fulfilled the entry criteria of: (1) history of chronic stable angina pectoris ≥3 months and a positive standard stress test for myocardial ischemia; (2) neither pathologic Q waves nor bundle branch block on the electrocardiogram (ECG) that could have interfered with the interpretation of ST-segment changes; and (3) successful balloon angioplasty resulting in residual stenosis <30% immediately after the procedure. To avoid the effect of the severity of the culprit lesion on coronary vasomotion [24], patients were highly selected with similar diameter stenosis between 70% and 90%. To make collateral circulation of these study patients homogenous, patients with angiographically visible collateral blood at baseline were excluded. Women included in this study were confirmed to be menopausal for at least 5 years by measuring serum follicle-stimulating hormone and estrogen levels. No patients received hormone replacement therapy, vitamins, dietary supplements, or drugs with known antioxidant activity for at least 6 months before the study began. Medications, including calcium channel and β-adrenergic blockers and caffeine-containing beverages, except aspirin (100 mg/day) were withheld for 24 h before the procedure. Any patients who had taken nitroglycerin within 4 h of catheterization were excluded from this study. A total of consecutive 30 patients were included. Patients were randomized into two groups on the basis of the use of intracoronary (i.c.) estrogen: group 1 (n=15), without pretreatment with estrogen; group 2 (n=15), with dosing estrogen. The clinical characteristics of patients are given in Table 1. All subjects provided informed written consent before participation.

2.2. Study protocol

2.2.1. Catheterization procedures

After completion of the diagnostic catheterization, a 6F Judkins guiding catheter was advanced to the ostium of the left or right coronary artery. To assess collateral flow during coronary occlusion, a 0.014-in. Doppler wire (FloWire, Cardiometrics, Mountain View, CA) was first introduced

Table 1
Clinical and angiographic characteristics in the two groups

	Group 1 (n=15)	Group 2 (n=15)	P value
Sex (M/F)	12/3	13/2	NS
Age	55±7	52±6	NS
Risk factor			
Hypertension (%)	9 (60)	10 (67)	NS
Diabetes mellitus (%)	3 (20)	4 (27)	NS
Smoking (%)	7 (47)	9 (60)	NS
Total cholesterol (mg/dl)	229±36	226±35	NS
HDL cholesterol (mg/dl)	38±6	34±5	NS
LDL cholesterol (mg/dl)	145±33	139±43	NS
Triglycerides (mg/dl)	235±44	265±84	NS
Coronary lesions			
LAD (%)	10 (67)	11 (73)	NS
LCX (%)	3 (20)	3 (20)	NS
RCA (%)	2 (13)	1 (7)	NS
Degrees of stenosis (%)			
Before angioplasty	80±6	82±5	NS
After angioplasty	11±4	9±5	NS

Values are mean±S.D. or number (%). Group 1: patients without estrogen pretreatment; Group 2: patients with estrogen pretreatment; HDL: high-density lipoprotein; LAD: Left anterior descending artery; LCX: left circumflex artery; LDL: low-density lipoprotein; RCA: right coronary artery.