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Vasopressin effects on the coronary circulation after a short ischemia in anesthetized goats Role of nitric oxide and prostanoids

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Abstract

To examine the coronary effects of arginine–vasopressin during reperfusion after a short ischemia, left circumflex coronary artery flow was electromagnetically measured, and 15 min total occlusion of this artery followed by reperfusion was induced in anesthetized goats (five nontreated, five treated with the inhibitor of nitric oxide synthesis N^{w}-nitro-L-arginine methyl ester (L-NAME) and five treated with the inhibitor of cyclooxygenase meclofenamate). The vasoactive drugs and L-NAME were intracoronarily injected, and meclofenamate by i.v. route. At 60 min of reperfusion, coronary vascular conductance was not changed significantly in nontreated and was decreased by 35% ($P<0.01$) in L-NAME-treated and by 30% ($P<0.01$) in meclofenamate-treated animals. During reperfusion, the coronary vasodilatation with acetylcholine (3–100 ng) and sodium nitroprusside (1–10 μg) was not altered in nontreated animals, and the vasodilatation with acetylcholine but not with sodium nitroprusside was partially decreased in L-NAME—but not in meclofenamate-treated animals. The vasoconstriction in response to arginine–vasopressin (0.03–0.3 μg) was increased during reperfusion in nontreated, was not changed in L-NAME-treated and was decreased in meclofenamate-treated animals. Therefore, it is suggested that during reperfusion after a short ischemia: (1) the coronary vasodilator reserve is preserved; (2) the coronary vasodilatation with acetylcholine is also preserved, but in this vasodilatation, the role of nitric oxide may be attenuated and prostanoids may be not involved; and (3) the coronary vasoconstriction with arginine–vasopressin is increased, probably due to both attenuation of the modulatory role of nitric oxide and the release of vasoconstrictor prostanoids.

Keywords: Endothelial dysfunction; Coronary vasoconstriction; Coronary vasodilatation; Vasoconstrictor prostanoid

1. Introduction

Ischemia–reperfusion is a clinical and experimental event that can produce dysfunction of coronary vessels in addition to dysfunction of the myocardium, and this dysfunction may depend on the duration and severity of coronary flow reduction. The endothelium, by releasing vasodilator and vasoconstrictor substances, may play a main role in the regulation of vascular reactivity, and some studies suggest that the coronary vasoconstriction in response to arginine–vasopressin is modulated by nitric oxide (Myers et al., 1989; García-Villalón et al., 1996), but not by prostanoids (Maturi et al., 1991). Experimental observations suggest that the endothelium is sensitive to ischemia–reperfusion and that arginine–vasopressin may be involved in the pathophysiology of this entity (Sellke and Quillen, 1992; Schafer et al., 2002). However, more studies are needed to clarify the role of this peptide and its interaction with the endothelium in the pathophysiology of ischemia–reperfusion.

Several studies report that the coronary response to acetylcholine is attenuated during reperfusion after relatively prolonged periods of ischemia (Van Benthuysen et al., 1987; Metha et al., 1989; Pearson et al., 1990; Ehring et al., 1995), but studies during reperfusion after short durations of ischemia (less than 30 min) provide contradictory results as they show that this response is attenuated (Dauber et al., 1990; Kim et al., 1992; Lockowandt et al., 2001) or is not affected (Winn and Ku, 1992; Ehring et al., 1995). Basal

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release of nitric oxide from rat hearts may be diminished after ischemia–reperfusion (Maulik et al., 1995), and studies into mechanisms of the latter have implicated the nitric oxide pathway. For arginine–vasopressin, studies performed in dogs show that the coronary effects of this peptide are increased in the ischemic myocardium, which can worsen hypoperfusion of collateral-dependent myocardium during exercise (Foreman et al., 1991). Another study performed also in dogs shows that the response to arginine–vasopressin in collateral arteries of ischemic myocardium is increased, and the authors suggest that it is due to increased vasopressin receptor number, affinity and/or efficiency of coupling mechanims in arterial smooth muscle (Rapps et al., 1997). In one study performed to examine the coronary effects of arginine–vasopressin after ischemia–reperfusion, it was found that the action of this peptide on isolated canine coronary arteries was augmented in small arteries, but not in large arteries, after ischemia alone or followed by reperfusion, and the authors suggest that this augmented effect might be related to alteration of nitric oxide and prostanoids, although they did not examine these mechanisms (Sellke and Quillen, 1992). Arginine–vasopressin could be of interest for understanding the pathophysiology of ischemia–reperfusion as human plasma levels of this peptide are augmented after myocardial infarction (Hart and Gokal, 1977), cardiac arrest and resuscitation (Paradis et al., 1993) and reperfusion after myocardial ischemia (Schafer et al., 2002), and it can produce coronary vasoconstriction (Heyndrickx et al., 1976) which can be severe enough to cause myocardial ischemia (Maturi et al., 1991; Krajcar and Heusch, 1993).

We have previously reported that the coronary effects of arginine–vasopressin are preserved during reperfusion after partial, moderate ischemia, but in these effects, the modulatory role of nitric oxide may be blunted and prostanoids may be not involved (Martínez et al., 2003). The present study was performed to examine the coronary response to arginine–vasopressin during reperfusion after a short, total coronary occlusion, analyzing the role of nitric oxide and prostanoids in this response. Also, the functional state of the endothelium under this reperfusion was tested by recording the coronary effects of acetylcholine. The experiments were carried out in anesthetized goats where the left circumflex coronary artery flow was electromagnetically measured, and 15 min of total occlusion followed by reperfusion of this artery was induced in nontreated and L-NAME- or meclofenamate-treated animals.

2. Methods

2.1. Experimental preparation

In this study, 15 adult, female goats (30–57 kg) were used. Anesthesia of the animals was induced with ketamine hydrochloride and 2% thiopental sodium; supplemental doses were given as necessary for maintenance. After orotracheal intubation, artificial respiration with room air was instituted by use of a Harvard respirator. A left thoracotomy in the fourth intercostal space was performed and the pericardium was opened. The proximal segment of the left circumflex coronary artery was dissected, and an electromagnetic flow probe (Biotronex) was placed on this artery to measure blood flow. A snare-type occluder was also placed around the artery, distal to the flow probe, to obtain zero-flow baselines. Systemic arterial pressure was measured through a polyethylene catheter placed in one temporal artery and connected to a Statham transducer. Coronary flow, systemic arterial pressure and heart rate were simultaneously recorded on a Grass model 7 polygraph. Blood samples from the temporal artery were taken periodically to measure pH, pCO_2 and pO_2 by standard electrometric methods (Radiometer, ABL^{TM5}, Copenhagen, Denmark). After termination of the experiments, the goats were killed with a overdose of i.v. thiopental sodium and potassium chloride.

2.2. Experimental protocol

After the experimental preparation was ended and the hemodynamic variables reached steady state, the coronary responses to acetylcholine (3–100 ng), sodium nitroprusside (1–10 μg) and arginine–vasopressin (0.03–0.3 μg) were recorded in each animal under control conditions. Then a total occlusion of the left circumflex coronary artery was achieved with another occluder, which was placed around the artery and was situated between the flow probe and the occluder used for obtaining zero-flow baselines. This occlusion was maintained for 15 min, and then this occlusion was gradually, totally released to permit its reperfusion. This occlusion release took about 3 min, and at 60 min after the start of this reperfusion, the coronary effects of acetylcholine (3–100 ng), sodium nitroprusside (1–10 μg) and arginine–vasopressin (0.03–0.3 μg) were assayed again. This study was performed in five goats nontreated, in five goats treated with N^w-nitro-L-arginine methyl esther (L-NAME), and in five goats treated with meclofenamate, and in each case, the coronary responses to the vasoactive drugs used during control conditions and reperfusion were recorded from the same animal.

Acetylcholine, sodium nitroprusside and arginine–vasopressin were dissolved in physiological saline, and each dose was administered in boluses of 0.3 ml over 5–10 s. These drugs were injected at random sequence into the left circumflex coronary artery, through a needle connected to a polyethylene catheter that pierced the artery between the two occluders. L-NAME and meclofenamate were also dissolved in physiological saline at concentrations of 10 mg/ml, and L-NAME was intracoronarily administered at a dose of 18–20 mg over 12–15 min, and meclofenamate was administered i.v. at a dose of 6–8 mg/kg body weight

over 15–20 min. L-NAME or meclofenamate were administered after ending the control tests, and about 6–8 min before induction of coronary occlusion.

The effects of acetylcholine, sodium nitroprusside and arginine–vasopressin on coronary vasculature were evaluated as changes in coronary vascular conductance at their maximal effects on coronary blood flow. Coronary vascular conductance was calculated by dividing coronary blood flow in ml/min by mean systemic arterial pressure in mm Hg.

2.3. Statistical analysis

The data are expressed as means ± S.E.M. The effects of coronary occlusion and reperfusion as well as of L-NAME and meclofenamate on the hemodynamic variables recorded and on blood gases and pH were evaluated in each case as changes in absolute values and as percentages by applying one-way, repeated measures analysis of variance (ANOVA) followed by Student's *t*-test for paired data. The effects of coronary occlusion and reperfusion on coronary hemodynamics in nontreated, L-NAME-treated and meclofenamate-treated animals were compared using data expressed as percentages by applying one-way, factorial ANOVA, followed by the Dunnett's test. All the effects of acetylcholine, sodium nitroprusside and arginine–vasopressin during reperfusion were compared with their respective controls using changes in absolute values by applying two-way, repeated measures ANOVA, followed by the Dunnett's test. Also, the effects of these drugs in each situation in the three groups of animals were compared using changes in absolute values by applying one-way, factorial ANOVA, followed by the Dunnett's test. In each case, $P<0.05$ was considered statistically significant.

The investigation conformed with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no. 85-23, revised 1996), and the experimental procedure used in the present study was approved by the local Animal Research Committee.

2.4. Drugs used

N^{w}-nitro-L-arginine methyl esther (L-NAME), acetylcholine chloride, (Arg^{8})vasopressin acetate, and sodium nitroprusside are from Sigma, and meclofenamate from Parke Davis.

3. Results

3.1. Hemodynamic changes during coronary occlusion and reperfusion

The resting hemodynamic values obtained during control, coronary occlusion and reperfusion are summarized in Table 1. In five nontreated animals, coronary occlusion abolished coronary flow, decreased mean arterial pressure by 29 ± 4% ($P<0.01$), and did not affect heart rate significantly. At 60 min after the start of reperfusion, coronary flow was decreased by 34 ± 5% ($P<0.01$) and mean arterial pressure by 25 ± 4% ($P<0.01$), without changing significantly heart rate; coronary vascular conductance was not significantly different from that under control conditions. In five animals treated with intracoronary administration of L-NAME, this drug by itself decreased basal coronary flow by 15 ± 2% ($P<0.05$) and coronary vascular conductance by 16 ± 3% ($P<0.05$), without changing significantly mean arterial pressure and heart rate; in these five animals, coronary occlusion also abolished coronary flow and decreased heart rate by 24 ± 4% ($P<0.01$) without changing significantly mean arterial pressure. At 60 min after reperfusion, coronary flow was decreased by 37 ± 5% ($P<0.01$), coronary vascular conductance by 35 ± 6% ($P<0.01$) and heart rate by 21 ± 6% ($P<0.05$), whereas mean arterial pressure was not significantly distinct from the control. In five animals treated with i.v. administration of meclofenamate, this drug by itself did not affect significantly hemodynamic variables; in these five animals, coronary occlusion abolished coronary flow, without changing significantly mean arterial pressure and heart rate. At 60 min of reperfusion, coronary flow was decreased by 23 ± 4%

Table 1
Resting hemodynamic values obtained under control conditions, at 15 min of coronary occlusion and at 60 min of reperfusion in anesthetized goats nontreated (five animals), treated with L-NAME (five animals) and treated with meclofenamate (five animals)

	CBF (ml/min)	MAP (mm Hg)	CVC (ml/min/mm Hg)	HR (beats/min)
Nontreated				
Control	31 ± 4	90 ± 4	0.34 ± 0.04	76 ± 6
Occlusion	0	64 ± 5[a]	0	73 ± 6
Reperfusion	20 ± 3[a]	67 ± 5[a]	0.30 ± 0.04	70 ± 5
L-NAME-*treated*				
Control	36 ± 3	87 ± 3	0.40 ± 0.04	82 ± 7
L-NAME	30 ± 3[b]	92 ± 4	0.33 ± 0.04[b]	71 ± 6
Occlusion	0	85 ± 5[c]	0	62 ± 6[a]
Reperfusion	22 ± 3[a]	82 ± 4[c]	0.26 ± 0.03[a]	66 ± 8[b]
Meclofenamate-treated				
Control	29 ± 3	92 ± 4	0.32 ± 0.04	71 ± 6
Meclofenamate	28 ± 3	94 ± 5	0.30 ± 0.03	70 ± 5
Occlusion	0	88 ± 5[c]	0	72 ± 5
Reperfusion	22 ± 3[a]	96 ± 5[c]	0.22 ± 0.03[a]	73 ± 8

Values are means ± S.E.M.
CBF = coronary blood flow; MAP = mean systemic arterial pressure; CVC = coronary vascular conductance; HR = heart rate.
[a] $P<0.01$ compared with its corresponding control conditions (ANOVA and Student's *t* test for paired data).
[b] $P<0.05$ compared with its corresponding control conditions (ANOVA and Student's *t* test for paired data).
[c] $P<0.01$ compared with the corresponding situation in nontreated animals (ANOVA and Dunnett's test).

($P<0.01$) and coronary vascular conductance by $30 \pm 4\%$ ($P<0.01$), whereas mean arterial pressure and heart rate were comparable to those under control conditions.

Systemic blood gases and pH did not change significantly during coronary occlusion and reperfusion as compared with control conditions in the three groups of animals (these data are not shown).

3.2. Coronary response during reperfusion

Under control conditions, acetylcholine (3–100 ng) and sodium nitroprusside (1–10 μg) induced dose-dependent increases in coronary vascular conductance (Fig. 1). In five nontreated animals, the effects of acetylcholine (3–100 ng) and sodium nitroprusside (1–10 μg) on coronary vascular conductance during reperfusion were not significantly different from those under control conditions (Fig. 1). In five animals treated with L-NAME, the coronary effects of the two higher doses (30 and 100 ng) but not those of the two lower doses of acetylcholine were significantly lower during reperfusion than under control conditions, and under this reperfusion, the effects of the two higher doses of acetylcholine were also lower than those found under reperfusion in nontreated animals (Fig. 1). In these L-NAME-treated animals, the coronary effects of sodium nitroprusside (1–10 μg) were similar under reperfusion and control conditions, and they were similar to those found under reperfusion in nontreated animals (Fig. 1). In five animals treated with meclofenamate, the increments in coronary vascular conductance produced by acetylcholine during reperfusion were similar to those under control conditions, and under this reperfusion, they were not significantly distinct to those under reperfusion in nontreated animals (Fig. 1). In meclofenamate-treated animals, the coronary effects of sodium nitroprusside (1–10 μg) were similar during reperfusion and control conditions, and under this reperfusion, they were also similar to those under reperfusion in nontreated and L-NAME-treated animals (Fig. 1).

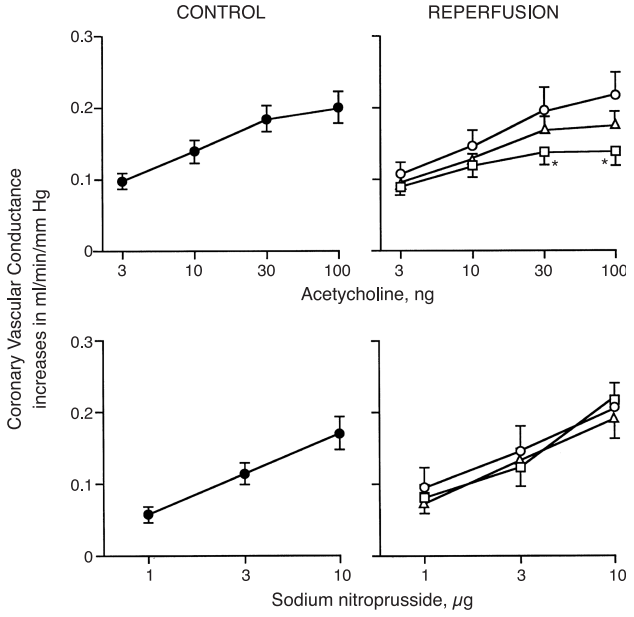

Fig. 1. Summary of the effects of acetylcholine (top) and sodium nitroprusside (bottom) on coronary vascular conductance obtained during control conditions (left, averages of the control effects in the three groups of animals) and after 60 min of reperfusion following 15 min of coronary occlusion (right) in anesthetized goats nontreated (○—○, five animals), treated with L-NAME (□—□, five animals) and treated with meclofenamate (△—△, five animals). *$P<0.05$ for difference during reperfusion between nontreated and L-NAME-treated animals (ANOVA and Dunnett's test).

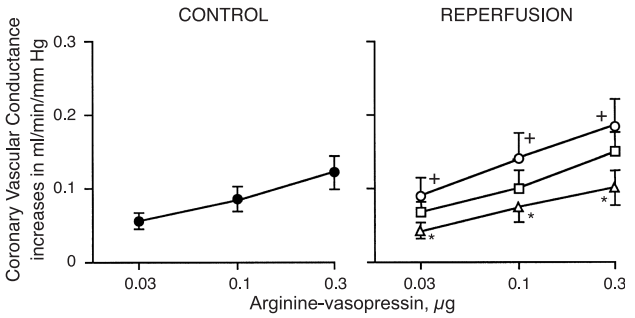

Fig. 2. Summary of the effects of arginine–vasopressin on coronary vascular conductance obtained during control conditions (left, averages of the control effects in the three groups of animals) and after 60 min of reperfusion following 15 min of coronary occlusion (right) in anesthetized goats nontreated (○—○, five animals), treated with L-NAME (□—□, five animals) and treated with meclofenamate (△—△, five animals). $^{+}P<0.05$ for difference between reperfusion in nontreated animals and control (ANOVA and Dunnett's test). *$P<0.05$ for difference during reperfusion between nontreated and meclofenamate-treated animals (ANOVA and Dunnett's test).

Acetylcholine and sodium nitroprusside did not cause systemic effects under control conditions or reperfusion in the three groups of animals.

Under control conditions, arginine–vasopressin (0.03–0.3 μg) produced dose-dependent decreases in coronary vascular conductance (Fig. 2). In five nontreated animals, the decrements in coronary vascular conductance induced by arginine–vasopressin (0.03–0.3 μg) during reperfusion were higher ($P<0.05$ for all doses) than those under the control conditions (Fig. 2). In five L-NAME-treated animals, the increments in coronary vascular conductance induced by arginine–vasopressin under reperfusion were similar to those under control conditions, and under this reperfusion, they were not significantly different to those under reperfusion in nontreated animals (Fig. 2). In five meclofenamate-treated animals, the reductions produced by arginine–vasopressin (0.03–0.3 μg) in coronary vascular conductance during reperfusion were similar to those under control conditions, but during this reperfusion, they were lower than those found under reperfusion in nontreated animals (Fig. 2).

Arginine–vasopressin, at the highest dose used, increased mean arterial pressure by 11 ± 4 mm Hg under control conditions, and this effect was comparable under reperfusion in the three groups of animals. This effect of

arginine–vasopressin was present after its maximal effect on coronary flow.

4. Discussion

The present study was performed to examine the coronary reactivity to arginine–vasopressin during reperfusion after a short, total coronary occlusion, analyzing the role of nitric oxide and prostanoids in this reactivity. Also, the functional state of the coronary endothelium under reperfusion was evaluated by recording the coronary action of acetylcholine. The coronary effects of the vasoactive drugs used were analyzed by using the changes in coronary vascular conductance because these probably reflect better the in vivo vascular effects, especially when blood flow is the variable mainly affected (Lautt, 1989).

Total coronary occlusion abolished coronary flow in the three groups of animals as expected, and this condition was accompanied by moderate systemic hypotension only in nontreated animals. After 60 min of reperfusion, coronary flow but not coronary vascular conductance was decreased in nontreated animals, and both coronary flow and coronary vascular conductance were decreased in L-NAME- and meclofenamate-treated animals; it was accompanied by moderate systemic hypotension only in nontreated animals. This confirms previous studies from our laboratory, and similar hemodynamic changes were also present during reperfusion after 60 min partial coronary occlusion, where this issue is commented (Fernández et al., 2002, 2003; Martínez et al., 2003). Under control conditions, we found that L-NAME by itself reduced resting coronary flow without changing systemic arterial pressure and heart rate, and meclofenamate by itself did not affect coronary hemodynamics, suggesting, respectively, that nitric oxide may produce a basal vasodilator tone in the coronary circulation and that prostanoids are not involved in the regulation of vascular tone under normal conditions as we previously reported (García et al., 1992, 1996; Fernández et al., 1998, 2002, 2003; Martínez et al., 2003).

The present results with acetylcholine and sodium nitroprusside during reperfusion in nontreated and treated animals reproduce those obtained in a previous study from our laboratory, where this issue is commented (Fernández et al., 2003). These particular data suggest that vasodilator reserve is preserved during reperfusion after a short ischemia. On the other hand, the data with acetylcholine during reperfusion treated with L-NAME or meclofenamate suggest, respectively, that the mediator role of nitric oxide in the cholinergic coronary response is attenuated and that prostanoids may be not involved in this vasodilatation during reperfusion after a brief ischemia. Studies performed after 30 min of reperfusion following 60 min of partial, moderate coronary ischemia in anesthetized goats also suggest that the role of nitric oxide in the cholinergic coronary vasodilatation is attenuated and that prostanoids may be not involved in this vasodilatation (Fernández et al., 2002; Martínez et al., 2003). Thus, it seems to be that the function of endothelial nitric oxide in the regulation of coronary vascular reactivity is very sensitive to ischemia–reperfusion, a feature that has been previously reported by others (Headrick et al., 1990; Kim et al., 1992; Lockowandt et al., 2001).

The coronary action of arginine–vasopressin was increased during reperfusion in nontreated animals, and this increase was not affected by L-NAME treatment but was decreased by meclofenamate treatment. One study performed in dogs show that the response to arginine–vasopressin in collateral arteries of ischemic myocardium is increased, and the authors suggest that this increase is due to augmented vasopressin receptor number, affinity, and/or efficiency of receptor coupling mechanims in arterial smooth muscle (Rapps et al., 1997). Sellke and Quillen (1992) report that the response to arginine–vasopressin in canine isolated small coronary arteries, but not in large arteries, was increased similarly after 1 h of partial ischemia alone and followed by 1 h of reperfusion. In this study, it is suggested that the augmented coronary response after ischemia and reperfusion may be related to upregulation of vasopressin receptors on the vascular smooth muscle and alteration in the release of nitric oxide and prostanoids, although the authors did not examine these mechanisms (Sellke and Quillen, 1992). Our data suggest that meclofenamate inhibits the response to arginine–vasopressin during reperfusion, a feature not seen under normal conditions in anesthetized goats (Fernández et al., 1998) and anesthetized dogs (Maturi et al., 1991). Thus, it is suggested that vasoconstrictor prostanoids may be involved in the observed increased coronary action of arginine–vasopressin during reperfusion after 15-min coronary occlusion in nontreated animals. On the other hand, our data indicate that L-NAME did not affect the coronary action of arginine–vasopressin during reperfusion as compared with reperfusion in nontreated animals, and this feature also contrasts to that found under normal conditions, where L-NAME potentiated the coronary vasoconstriction in response to this peptide (Fernández et al., 1998). The absence of the potentiating effects of L-NAME on the vasoconstriction with arginine–vasopressin during reperfusion may be due to the fact that ischemia–reperfusion attenuates the modulatory role of nitric oxide in the coronary effects of this peptide present under normal conditions (Myers et al., 1989; García-Villalón et al., 1996; Fernández et al., 1998). Also, as inhibition of nitric oxide synthesis with N^G-nitro-L-arginine may result in increased production of prostacyclin in perfused rabbit hearts (Aitchison and Coker, 1999), it is possible that this feature has occurred also in our experiments after treatment with L-NAME; thus, prostacyclin might have counteracted and masked the possible potentiating action of L-NAME on the coronary response to arginine–vasopressin. We have previously described that during partial, moderate ischemia, the coronary reactivity to arginine–vasopressin is attenuated

with preservation of the modulatory role of nitric oxide and probable involvement of vasoconstrictor prostanoids. Also, during reperfusion after this partial ischemia, the coronary response to this peptide was as in control conditions with attenuation of the modulatory role of nitric oxide and without involvement of prostanoids (Martínez et al., 2003). The different results with regard to the role of prostanoids in the coronary response to arginine–vasopressin found during reperfusion after 15 min total occlusion (present study) and after 60 min partial, moderate occlusion (Martínez et al., 2003) may be related to differences in severity of ischemia and durations of ischemia and reperfusion between these two studies. The present results with arginine–vasopressin differ, in part, from those obtained with endothelin-1 during reperfusion after 15 min total coronary occlusion (Fernández et al., 2003). In this study (Fernández et al., 2003), we found that the coronary response to endothelin-1 is also increased, and it may be related to inhibition of nitric oxide release, but without involvement of prostanoids. Therefore, the role played by prostanoids may be distinct in the coronary response to arginine–vasopressin (present results) and endothelin-1 (Fernández et al., 2003) during reperfusion after a short ischemia, and this difference may be related to the vasoactive stimulus applied. In that same study (Fernández et al., 2003), we report that the increased coronary action of endothelin-1 is more pronounced during reperfusion after a longer ischemia (60 min), and in this case, prostanoids may be neither involved.

As vasoactive drugs were given as bolus injection into the coronary circulation during control and reperfusion, and coronary blood flow was decreased by about 30% during reperfusion, it may be argued that the probable increased levels of arginine–vasopressin reached in the coronary circulation during reperfusion might explain the increased coronary effects induced by this peptide during this situation. This, however, may be not the reason as we have previously observed that the vasopressin coronary action is decreased during partial coronary ischemia and is not changed during reperfusion after this particular ischemia, situations where coronary flow was also decreased by about 30%. Therefore, the observed increased coronary response to arginine–vasopressin is rather related to changes induced by ischemia–reperfusion on coronary vasculature. This same explanation might be also applied to our previous study with endothelin-1 (Fernández et al., 2003).

In conclusion, the present study suggests that during reperfusion after a short, total coronary occlusion: (1) the coronary vasodilator reserve is preserved; (2) the coronary vasodilatation with acetylcholine is also preserved, but in this vasodilatation, the mediator role of nitric oxide may be attenuated and prostanoids may be not involved; and (3) the coronary vasoconstriction with arginine–vasopressin is increased, which is probably due to both attenuation of the modulatory role of nitric oxide and the release of vasoconstrictor prostanoids.

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