Plasma levels and vascular effects of vasopressin in patients undergoing coronary artery bypass grafting
Susana Novella, Ana Cristina Martínez, Rosa María Pagán, Medardo Hernández, Albino García-Sacristán, Angel González-Pinto, José María González-Santos and Sara Benedito

DOI: 10.1016/j.ejcts.2007.03.047

This information is current as of July 5, 2010
Plasma levels and vascular effects of vasopressin in patients undergoing coronary artery bypass grafting

Susana Novella a, Ana Cristina Martínez a, Rosa María Pagán a, Medardo Hernández a, Albino García-Sacristán a, Angel González-Pinto b, José María González-Santos b, Sara Benedito a,∗

∗Departamento de Fisiología, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

Objective: Recent studies have suggested that endogenous vasopressin (AVP) acts as a spasmogen during coronary artery bypass grafting (CABG). Given that AVP could induce vasospasm in the grafted vessel, we assessed the release of this peptide during and after CABG, and explored ways of counteracting its contractile effect on the internal mammary artery (IMA). Methods: Plasma levels of AVP were determined by radioimmunoassay in 16 patients before, during and after CABG. Using isometric force recording techniques, we also investigated the mechanisms involved in the contractile effect of AVP in ring preparations of IMA specimens taken from 95 patients. Results: Plasma AVP levels peaked after the start of cardiopulmonary bypass (CPB) and correlated well with serum osmolality (Pearson’s r = 0.9490; P < 0.0001; n = 16). An inverse correlation was observed between plasma AVP levels recorded at this stage and the maximal contraction induced in vitro by AVP in vascular rings from the same patients (Pearson’s r = −0.6968; P < 0.01; n = 16). No change in the AVP response was produced by endothelium removal, exposure to the NO precursor (3 × 10⁻⁴ M L-arginine), inhibition of nitric oxide (NO) synthase (3 × 10⁻⁵ M L-NAME) or soluble guanylate cyclase (3 × 10⁻⁶ M 1H-[1,2,4]oxadiazol [4,3,5]-quinoxalin-1-one (ODQ)), removal of the superoxide anion (100 U/ml superoxide dismutase (SOD) plus 1200 U/ml catalase) or hydroxyl radical (10⁻⁴ M deeroxamine), or specific α₁ (10⁻⁶ M prazosin) or endothelin (10⁻⁵ M bosentan) receptor antagonism. In contrast, adenylate cyclase activation (3 × 10⁻⁸ M forskolin) reduced the contractile response to AVP, while prostanol synthesis (3 × 10⁻⁶ M indomethacin) inhibition and blockade of Ca²⁺-activated potassium channels (KCa) (3 × 10⁻³ M tetraethylammonium (TEA)) enhanced AVP contraction. Age, gender and smoking also modified the AVP response. Conclusion: Our findings suggest a role for AVP as a modulator of vascular tone in human IMA. The effect of AVP is dependent on prostanoids and Ca²⁺-activated K⁺ channels, so its dysfunction in pathophysiologically cardiovascular processes could mean that AVP, among other factors, produces vasospasm in IMA grafts.

Keywords: Coronary artery bypass grafting; Vasopressin; Vasospasm; Internal mammary artery

1. Introduction

The established safety and long-term effectiveness of coronary artery bypass grafting (CABG) [1] make surgery the best treatment option for advanced coronary artery disease. The human internal mammary artery (IMA) has earned its recognition as the gold standard for use as the autogenous bypass graft in CABG on the basis of its excellent late patency and resistance to arteriosclerosis. However, in vivo and in vitro experiments have demonstrated its potent vasoconstriction response to a great variety of vasoactive agents and a 10% rate of IMA stenosis has been described in the absence of established predisposing factors. In the last 20 years, many research efforts have searched for ways to reduce the incidence of vasospasm in CABG. In effect, vasospasm may occur during harvesting, grafting or immediately following CABG, and could lead to early myocardial ischaemia and thus, increase perioperative morbidity and mortality in high-risk patients. Vasodilators such as calcium antagonists, long-acting nitrates and phosphodiesterase inhibitors are usually administered before grafting to increase IMA blood flow during surgery [2]. However, these agents seem to be more effective in reducing rather than preventing graft spasm [3]. One of the possible aetiologies of vasospasm is impaired endothelial-dependent blood flow caused by an inability of the endothelium to synthesize adequate amounts of nitric oxide (NO), evoking unopposed vasoconstriction [4]. Vasoconstriction (or spasm) may be produced by various, or a
combination of, stimuli, such as surgical trauma, nerve stimulation and the release of several vasconstrictor substances during CABG, which could include endothelin, tromboxane A2, prostaglandin F2α, extracellular nucleotides, serotonin, circulating sympathetic amines (norepinephrine and epinephrine), angiotensin II or vasopressin (AVP) [3]. In effect, it would be interesting to correlate the concentrations of these vasconstrictors that could be released in the perioperative period, with the response shown by arterial grafts to these agents [5]. AVP, a hypothalamic hormone stored and released by the neurohypophysis, has marked vasconstrictor effects and also has antiuretic effects on the renal tubular system. The release of AVP is stimulated by conditions that are common in revascularization operations such as changes in systemic blood pressure, hypotonicity or hypovolaemia, amongst others factors. In cultured vascular smooth muscle cells, all the effects of AVP are mediated through the V1a receptor, which signals through G-proteins [6]. AVP increases intracellular Ca2+ via mobilization of intracellular stores and influx of extracellular Ca2+ via voltage-activated Ca2+ channels. Increased intracellular Ca2+ also leads to increased arachidonic acid release and eicosanoid production through the action of phospholipase A2 [6].

To date, in vitro studies addressing the effects of AVP on the IMA have focused on AVP receptors [7] and the inhibitory effects of vasodilators on AVP-mediated contraction [8,9]. AVP has also recently gained attention as a possible tool against septic shock and vasodilator states associated with cardiac anaesthesia and surgery, although future prospective studies are necessary to define the role of AVP in the therapy of vasodilator shock [10].

In an effort to establish the real contribution of this neurohormone to vasospasm, the present study was designed to examine the in vitro vascular reactivity of IMA towards AVP after exposure to in vivo AVP release during CABG. The mechanisms involved in the AVP contraction were explored and we also tried to assess the effects of the main risk factors for cardiovascular disease on the AVP response.

2. Patients and methods

The study protocol was approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón, Madrid, Spain.

2.1. Anaesthesia and cardiopulmonary bypass management

Pharmacological therapy (platelet antiaggregants, ACE inhibitors and calcium channel blockers) was interrupted at least 1 week before CABG. Anaesthesia was induced in all patients according to a standardized protocol including intravenous midazolam (0.03—0.05 mg/kg), remifentanil (1.0—3.0 μg/kg) and cisatracurium (0.5 mg/kg), and maintained with 0.2—0.5% isoflurane and continuous intravenous infusion of remifentanil at 0.1—0.5 μg/kg/min.

All patients underwent a routine single surgical technique. After gaining entry through a median sternotomy, the IMA was dissected simultaneously with the saphenous vein and/or the radial artery. In all patients, the IMA was harvested as a pedicle with the surrounding muscle and fascia, avoiding any external and/or internal pharmacological manipulation. Following systemic heparinization, the IMA was clipped distally, cut and occluded proximally with a bulldog clamp. IMA samples were harvested from the distal end, just before anastomosis, to the target coronary artery.

Cardiopulmonary bypass (CPB) was established by ascending aortic and two-stage right atrial cannulation (aortic cross-clamp time 50—60 min). Heparin was given at a dose of 300 IU/kg to achieve a target-activated coagulation time over 450 s. Moderate haemodilution (haematocrit 20—25%), mild hypothermia (30—32°C) and a constant perfusion pressure (2.5 l/min/m²) were maintained during CPB (CPB time 90—100 min). The bypass circuit was primed with 750 ml of Ringer’s lactate solution, 500 ml of hydroxy ethyl starch and 200 ml of 1/6 M sodium bicarbonate. Myocardial arrest was induced through 1000 ml of antegrade and retrograde high-potassium (30 meq./l) cold (4°C) blood cardioplegia (4:1 ratio). Thereafter, and for the remainder of the procedure, 500 ml low-potassium cardioplegia (10—15 meq./l) was administered through the coronary sinus at the end of each distal anastomosis. Reperfusion was controlled with warm low-potassium retrograde cardioplegia while performing proximal anastomoses. The mean intraoperative arterial pressure of the patients was 60—70 mmHg in all the stages of surgery.

2.2. Plasma AVP and serum osmolality, sodium and potassium

Blood samples were collected at the following stages into vacuum tubes from the arterial line of 16 patients subjected to routine CABG involving cardiopulmonary bypass:

1. Before induction of anaesthesia
2. After induction of anaesthesia and/or 10 min before CPB
3. Shortly after starting CPB
4. In the intensive care unit

Once collected, the blood samples were kept in ice slush, and plasma and serum separated by centrifugation (10 min, 4°C) at 1620 × g. All samples were then frozen at −70°C and stored until analysis.

Plasma AVP and serum osmolality, sodium and potassium were determined by the following methods:

- AVP was determined using the radioimmunoassay kit Vasopressin Direct RIA (Buhlmann Laboratories AG, Switzerland), whose sensitivity is 1.2 pg/ml.
- Blood osmolality was determined by the freezing-point osmometric method using an osmometer mod. 3D II (Advanced Instruments, USA). This procedure has a resolution of 50 mOsm/kg.
- Serum sodium and potassium concentrations were measured by flame photometry using a photometer mod. 943 (Instrumentation Laboratory, USA). Sensitivities for sodium and potassium were 3 mmol/l and 0.1 mmol/l, respectively.

In the 16 patients in whom plasma AVP levels were determined, the postoperative course was uncomplicated, so there was no need for vasoactive drugs, with the exception of...
nitroglycerine, which was occasionally required to control arterial pressure.

2.3. Arterial rings

Artery segments were obtained from the portions of the IMA harvested for use as grafts during CABG surgery. The segments were placed in chilled, cold physiological saline solution (PSS) of composition (mM): NaCl, 119; KCl, 4.7; CaCl2, 1.5; MgSO4, 1.2; NaHCO3, 25; glucose, 10; KH2PO4, 1.2 and ethylene diaminetetraacetic acid (EDTA), 0.026, and transported to the laboratory. Once in the laboratory, adjacent tissue was carefully dissected away under a stereomicroscope (Nikon SMZ 2B, Japan) and each IMA segment was cut into rings, 2—3 mm in length, for isometric force recordings. The rings (external diameter = 1.35 ± 0.02 mm and internal diameter = 0.75 ± 0.01 mm; n = 201) were suspended on two parallel L-shaped stainless steel wires (diameter 150 μm) in 5 ml organ baths containing PSS at 37 °C and gassed with carbogen (95% O2 and 5% CO2) to maintain the pH at 7.4. One wire was fixed to a displacement unit allowing fine adjustment of tension while the other was attached to a force transducer (Grass FT03C, USA). The isometric tension of the artery wall was displayed and recorded using a PowerLab data acquisition system (PowerLab/8, model MLS013/W, AD Instruments Pty. Ltd., Australia). In some experiments, the endothelium was mechanically removed by careful rubbing of the inner surface of the segment with a stainless steel wire before mounting the segment.

2.4. Mechanical responses

After an equilibration period of 30 min in PSS, each ring was stretched in a stepwise fashion to the optimal point of its length—tension ratio (≈25 mN) determined in previous experiments. The arterial rings were allowed a 2-h normalization period before testing. In all the experiments, arterial specimens were exposed to a depolarizing potassium solution (124 mM, K-PSS) to evaluate the viability of the specimens were exposed to a depolarizing potassium channels (KCa) blockade) (all from Sigma Chemical Co., USA) and bosentan (non-specific endothelin receptor antagonist; a gift from Hoffmann-La Roche, Inc., USA).

All drugs were dissolved in distilled water with the following exceptions: indomethacin and papaverine were prepared in 96% ethanol, and ODQ and forskolin were dissolved in dimethyl sulphoxide and further diluted in water. Previous experiments showed that the solvents used had no effect on the preparations.

2.6. Data and statistical analysis

Plasma AVP and serum osmolality, sodium and potassium were compared with the Student’s t-test for paired observations, using the values obtained in stage 1 (before anaesthesia) as controls. The level of significance was set at a P-value less than 5% (P < 0.05). Plasma AVP was compared to serum osmolality and serum sodium and potassium levels for each sampling period by the Pearson’s correlation method. Maximal plasma AVP concentrations were also correlated with the maximal AVP contractions recorded in vitro for the same patient.

The tension of the vessel wall was measured in mN. Contractions obtained both on basal tone and in precontracted vessels were expressed as the percentage of contractions induced by K-PSS. Relaxations were expressed as the percentage of the vascular contraction induced by NA.

Sensitivity to AVP was expressed in terms of pEC50 values, where pEC50 = −log EC50, EC50 being the agonist concentration needed to produce a half-maximal response. pEC50 was estimated by computerized non-linear regression analysis (GraphPad Prism, USA).

Biochemical determinations and mechanical vascular responses were expressed as mean values ± standard error of the mean (SEM). Statistical analysis using the Student’s t-test for paired and unpaired observations was performed when appropriate. For testing the effects of cardiovascular risk factors on the in vitro AVP response, the data were analysed by analysis of variance (ANOVA) and Duncan’s post hoc comparison. In this analysis, a P-value less than 5% (P < 0.05) was also considered to denote significance.
3. Results

3.1. Patient characteristics

Segments of the IMA were obtained from 95 patients (mean age 64.2 ± 0.9 years): 80 men and 15 women. Their characteristics and risk factors for cardiovascular disease are shown in Fig. 1.

3.2. Plasma AVP concentrations and variables measured

Circulating AVP levels recorded at stage 1 (before anaesthesia) were taken as baseline values for the statistical tests. These values were within physiological limits (≤7.6 pg/ml). At stage 2 (after anaesthesia induction but before CPB) AVP levels were 10-fold compared to baseline levels and continued to rise, peaking after the start of CPB (stage 3) and declining in the intensive-care unit after surgery (stage 4) (Table 1).

Among the remaining variables measured, only serum osmolality showed a significant increase, with similar sodium and potassium levels detected before, during and after CPB (Table 1). The elevated AVP plasma levels recorded in stage 3 correlated well with serum osmolality determined at the same sampling time for the same patient (Pearson’s r = 0.9490; P < 0.0001; n = 16).

3.3. Vascular function

3.3.1. AVP response

Segments of human IMA contracted in a concentration-dependent manner in response to AVP (10^{-12} to 3 × 10^{-7} M).

AVP (≤7.6 pg/ml)

Circulating AVP plasma levels recorded in stage 3 correlated well with serum osmolality determined at the same sampling time for the same patient (Pearson’s r = 0.9490; P < 0.0001; n = 16).

3.2. Plasma AVP concentrations and variables measured

Circulating AVP levels recorded at stage 1 (before anaesthesia) were taken as baseline values for the statistical tests. These values were within physiological limits (≤7.6 pg/ml). At stage 2 (after anaesthesia induction but before CPB) AVP levels were 10-fold compared to baseline levels and continued to rise, peaking after the start of CPB (stage 3) and declining in the intensive-care unit after surgery (stage 4) (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Physiological limits</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVP (≤7.6 pg/ml)</td>
<td>1.5 ± 1.3</td>
<td>21.9 ± 9.7</td>
<td>305.3 ± 57.9</td>
<td>67.9 ± 11.3***</td>
</tr>
<tr>
<td>Osmolality (275–300 mOsmol/kg)</td>
<td>306.8 ± 3.8</td>
<td>305.8 ± 2.2</td>
<td>316.2 ± 2.9</td>
<td>319.8 ± 3.3***</td>
</tr>
<tr>
<td>Sodium (135.0–155.0 mmol/l)</td>
<td>140.3 ± 0.7</td>
<td>140.2 ± 1.0</td>
<td>140.4 ± 3.2</td>
<td>141.8 ± 0.7</td>
</tr>
<tr>
<td>Potassium (3.60–5.50 mmol/l)</td>
<td>5.0 ± 0.4</td>
<td>5.0 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>4.7 ± 0.5</td>
</tr>
</tbody>
</table>

Blood samples were collected from the arterial line at the following stages: stage 1, before anaesthesia induction; stage 2, after the induction of anaesthesia and/or 10 min before cardiopulmonary bypass (CPB); stage 3, shortly after starting CPB and finally stage 4, in the intensive care unit after bypass surgery. Results are expressed as mean ± SEM.

* P < 0.05.

** P < 0.01.

*** P < 0.001 vs stage 1 (n = 16).
The possible role of contractile \( \alpha_1 \)-adrenergic receptors was ruled out, since no effect on AVP action was shown by the specific \( \alpha_1 \)-receptor antagonist (\( pEC_{50} = 9.30 \pm 0.11 \) and MC = 41.9 ± 17.7\% for controls; \( pEC_{50} = 8.92 ± 0.20 \) and MC = 36.3 ± 7.2\% for \( 10^{-6} \)M prazosin; \( n = 7 \)). Papaverine (\( 10^{-4} \)M) caused full relaxation of the AVP-elicitd contraction within approximately 25 min (\( n = 11 \)).

An inverse correlation was observed between plasma AVP levels recorded at stage 3 (patient under anaesthesia shortly after starting CPB) and the maximal contraction induced by AVP *in vitro* in vascular rings from the same patients (Pearson’s \( r = -0.6968; P < 0.01; n = 16 \)) (Fig. 2B).

### 3.3.2. Effects of endothelial denudation, NO synthase and guanylate cyclase inhibition, prostanoid synthesis and \( K_{Ca} \) blockade on basal tone and AVP-induced contraction

Mechanical removal of the endothelium failed to modify both basal tension and the contraction response to AVP, which was similar in arterial rings with an intact endothelium (\( pEC_{50} = 9.33 ± 0.32 \) and MC = 57.1 ± 12.9\%) and denuded rings (\( pEC_{50} = 9.28 ± 0.24 \) and MC = 54.1 ± 12.2\%; \( n = 13 \)). The NO precursor, L-arginine (\( 3 \times 10^{-4} \)M), failed to decrease the AVP contraction response after incubation periods of both 30 min (\( pEC_{50} = 8.98 ± 0.14 \) and MC = 51.9 ± 6.7\% for controls; \( pEC_{50} = 9.18 ± 0.18 \) and MC = 63.6 ± 7.8\% for L-NAME; \( n = 13 \)) (Fig. 2A).

The following experiments were, nevertheless, performed to determine whether the AVP response could be modulated by the release of endothelium-derived relaxant and contractile factors in a delicate balance. Inhibition of NO synthase with L-NAME (\( 3 \times 10^{-5} \)M) produced a discrete 4.7 ± 0.9\% rise in basal tension with no significant displacement of the AVP concentration—response curve (\( pEC_{50} = 8.98 ± 0.14 \) and MC = 51.9 ± 6.7\% for controls; \( pEC_{50} = 9.18 ± 0.18 \) and MC = 63.6 ± 7.8\% for L-NAME; \( n = 13 \)). The NO precursor, L-arginine (\( 3 \times 10^{-4} \)M), failed to decrease the AVP contraction response after incubation periods of both 30 min (\( pEC_{50} = 8.94 ± 0.13 \) and MC = 63.7 ± 11.8\% for controls; \( pEC_{50} = 9.26 ± 0.16 \) and MC = 57.4 ± 7.9\% for \( 3 \times 10^{-4} \)M L-arginine; \( n = 11 \)) and 8 h (\( pEC_{50} = 8.92 ± 0.10 \) and MC = 42.0 ± 1.7\% for controls; \( pEC_{50} = 9.00 ± 0.08 \) and MC = 39.2 ± 4.5\% for L-arginine; \( n = 8 \)).

In intact and denuded arterial rings, blockade of cyclooxygenase with indomethacin (\( 3 \times 10^{-6} \)M) evoked a moderate increase in basal tone (17.0 ± 2.2\%; \( n = 7 \) and 19.2 ± 2.8\%; \( n = 6 \), respectively). However, the simultaneous addition of L-NAME (\( 3 \times 10^{-5} \)M) and indomethacin (\( 3 \times 10^{-6} \)M) to a markedly enhanced basal tone both in intact (70.8 ± 14.3\%; \( n = 9 \); \( P < 0.01 \)) and denuded arterial rings (60.0 ± 19.5\%; \( n = 8 \); \( P < 0.05 \))

Indomethacin (\( 3 \times 10^{-6} \)M) produced a moderate yet significant increase in the sensitivity of the AVP concentration—response curve (Fig. 3A). The adenylate cyclase activator, forskolin (\( 3 \times 10^{-8} \)M), inhibited the contractile response to AVP (Fig. 3A). Simultaneous pre-treatment with L-NAME (\( 3 \times 10^{-5} \)M) and indomethacin (\( 3 \times 10^{-6} \)M) significantly enhanced the sensitivity and maximal contractile response to AVP (Fig. 3B). Indomethacin (\( 3 \times 10^{-6} \)M) plus ODQ (\( 3 \times 10^{-6} \)M), however, did not modify the contractions to AVP (Fig. 3B).

When \( K_{Ca} \) channels were blocked with TEA (\( 10^{-5} \)M) a significant increase in the maximal response to AVP was produced with no effects on resting tension (Fig. 4).
dent and involves smooth muscle prostanoids and $K_{Ca}$ channels; (b) maximal AVP-induced vasoconstriction of IMA in vitro is inversely related to the plasma AVP concentration and (c) age, gender and smoking seem to affect the IMA response to AVP.

The AVP hormone is essential for osmotic and cardiovascular homeostasis. Given that AVP could provoke graft spasm [8], we examined the release of AVP before, during and after CABG surgery, and assessed ways to prevent its contractile effect.

An increase in plasma levels of AVP was observed during CABG that was most pronounced at the onset of CPB, in agreement with the previous findings [11]. AVP release is thought to be mainly influenced by the activity of osmoreceptors, volume receptors, baroreceptors, and pain and visceral sensory input [11]. The high level of osmolality observed here just after the start of CPB and after surgery and its correlation with AVP plasma concentrations suggest that osmoreceptor activation could be one of the key triggers for elevating plasma AVP levels. A mechanism involving volume receptors would also likely be induced by the lowered left atrial pressure during extracorporeal circulation, although AVP is more sensitive to small osmolality changes than equivalent variations in plasma volume [11]. Given that the mean perfusion pressure did not change during CPB, the activation of baroreceptors by hypotension is unlikely. Neither does the involvement of a mechanism related to pain and visceral sensory input, which is known to release AVP, seems plausible, since the AVP increase started after inducing anaesthesia, when there would be no sensory input. The surge of AVP detected during and after CPB could therefore promote the undesirable effect of reducing organ perfusion [11]. Our findings indicate that, through the mechanisms cited, CPB seems to be associated with the AVP surge recorded here in patients undergoing CABG. Comparable levels of plasma AVP at the end of surgery have been reported by Velissaris et al. [12]. These authors, however, examined hormone release related to perioperative stress in patients undergoing CABG with and without CPB, and did not assess AVP changes during the CPB process.

AVP is regarded as being among the most potent vasoconstrictors in the organism in terms of both the maximal contractile effect induced and the duration of this effect. Our results reveal that AVP provokes a slow-onset, long-lasting in vitro contraction persisting for up to 2 h.
Today, V₁ₐ is established as the subtype of AVP receptor involved in vascular contraction [10] and it is this receptor that displays rapid tachyphylaxis [13]. Hence, the desensitization of IMA towards AVP noted in the present study indirectly indicates that V₁ₐ is the receptor involved in the AVP response.

Moreover, the rapid desensitization of IMA to AVP could explain the inverse correlation we observed between plasma AVP and the maximal contraction induced by AVP in vitro. Desensitization is a complex process that plays an important role in turning off receptor-mediated signal transduction pathways. Signal transduction pathways that turn on also need to be turned off. This ensures that signalling occurs in a spatiotemporal manner so that cell function can be finely regulated [14]. Some authors suggest that V₁ₐ receptors are downregulated when blood concentrations of AVP are high, which would explain the decreased sensitivity to the vascular effects of AVP observed in induced sepsis [15] and in transgenic rats overexpressing AVP [16]. These findings suggest there may be a protective mechanism against AVP elevation to maintain normal cardiovascular regulation. However, the precise mechanism responsible for this remains unclear.

Vascular smooth muscle relaxation is related to the biological activity of second messengers such as cyclic adenosine monophosphate and cyclic guanosine monophosphate, which are hydrolysed by phosphodiesterases. Papaverine is a phosphodiesterase inhibitor widely used in patients undergoing CABG since it seems to be effective in reversing the AVP-induced contraction in every vessel ring preventing graft spasm. In our experiments, papaverine was used in vitro. AVP-induced supra-maximal contraction in the IMA. Moreover, interaction between the two signal transduction pathways could occur at the NO synthesis enzyme level because treatment with indomethacin plus ODQ caused no further enhancement of the AVP response beyond that observed when indomethacin was added separately.

In addition to these mechanisms, KCₐ channels seem to attenuate AVP contraction since blockade with TEA increased the contractions to AVP. K⁺ channels induce the relaxation or reduce the contraction of blood vessels through hyperpolarization of vascular smooth muscle cells and reducing the concentration of cytoplasmic Ca²⁺. AVP increases intracellular Ca²⁺ by mobilizing intracellular stores and allowing the influx of extracellular Ca²⁺. Hence, KCₐ channels may, through negative feedback, limit active vasoconstriction induced by AVP. This potentiation effect of KCₐ channel blockade on AVP contraction has also been observed in the renal arteries of male rats [19].

KCₐ channels may compensate for the loss of other vasodilatory mechanisms in disease states in which contractile factor levels are elevated. In effect, increased levels of superoxide radicals have been observed in cardiovascular disorders. Although these radicals may activate Ca²⁺-activated K⁺ channels [20], this is probably not the activation mechanism of these channels in the IMA, since the superoxide scavengers, SOD plus catalase, did not modify the AVP contraction. Further, we were able to rule out the participation of another endothelium-derived contractile factor since deferoxamine and bosentan did neither reduce the basal tone nor compromise the AVP contractile response.

Among all the risk factors examined, the maximal contraction induced by AVP in the rings of IMA was significantly modified by age, gender and cigarette smoking. Several studies have revealed an increased effect of vascular constrictors with age in agreement with the greater response recorded in arterial specimens corresponding to the eldest patients included in our study. This finding could be attributable to the reduced release of NO or EDHF as vasodilators, or the increased release of vasoconstrictor prostaglandins. Although the mechanism of AVP-induced vascular hyperreactivity remains to be elucidated, due to its endothelial-independent nature, Ca²⁺ and/or K⁺ channels located in smooth muscle could be involved.

Nicotine stimulation induced by cigarette smoking has previously been identified as a potent stimulus for AVP release in humans [21]. Our results indicate a reduced contractile response to AVP in smokers. The higher circulating plasma AVP levels in this patient group may contribute to the in vivo AVP receptor desensitization mechanisms mentioned above, possibly translating to a reduced vascular response to AVP in vitro. Another possible explanation could be that since many people seem to give up smoking as they become older, the group of smokers was of a younger mean age.

It is well established that the risk of developing coronary artery disease and hypertension is much higher (3–4 times) in men than in premenopausal women, whereas in women, after the menopause, this gender difference is reversed. The women in our study were postmenopausal and AVP showed a more pronounced response in women than in men. An inhibitory role of oestrogens in AVP’s actions has been reported in various studies.
suggested [22], which would be consistent with the present results. Notwithstanding, numerous clinical and epidemiologic studies describe a controversial relationship between gender and cardiovascular disease, as well as between gender and vascular reactivity [23]. Li and Stallone [24] recently established that oestrogen potentiates AVP-induced contraction in the aorta of the female rat by enhancing cyclooxygenase-2 and tromboxane function. Sex hormones may be involved in this gender difference, although we cannot rule out the possible effects of age on women vasopressinergic vasocostriction [25].

In conclusion, our findings suggest a role for AVP as a modulator of vascular tone in human IMA. The effect of AVP is dependent on prostanoids and Ca2+-activated K+ channels, so its dysfunction in pathophysiological cardiovascular processes could mean that AVP is responsible, among other factors, for the vasospasm observed in IMA grafts.

Acknowledgement

The authors would like to thank the surgeons and nurses of the heart surgery unit of the Hospital General Universitario Gregorio Marañón (Madrid, Spain) for their help in the operating room.

References

Plasma levels and vascular effects of vasopressin in patients undergoing coronary artery bypass grafting

Susana Novella, Ana Cristina Martínez, Rosa María Pagán, Medardo Hernández, Albino García-Sacristán, Angel González-Pinto, José María González-Santos and Sara Benedito

DOI: 10.1016/j.ejcts.2007.03.047

This information is current as of July 5, 2010