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Effect of dopamine on platelet activating factor induced-pulmonary edema in isolated and perfused rabbit lungs

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Abstract

The effect of dopamine over pulmonary edema induced by PAF was studied. Thirty preparations of rabbit lungs were used: six control preparations (CP), six PAF preparations (PP) in which we injected a dose of 1 μg/kg of rabbit weight and eighteen dopamine preparations (DAP) divided in three groups of six pretreated with a dose of 1–5 (dopaminergic range), 10–20 (Beta range) and 20–30 ug/kg/min (Alpha range) of dopamine, respectively for 30 min, followed by an injection of PAF as in the PP. DAP at Beta and Alpha-adrenergic range decreased pulmonary artery pressure (Pap) as compared to CP, with values of 11.66 (CI 95%: 10.83–12.48), 11.66 (CI 95%: 9.87–13.44) versus 17.12 (CI 95%: 16.12–18.11) cm of water, respectively. DAP in Beta and Alpha-adrenergic range prevented Pap increment as compared to PP, with values of 17.16 (CI 95%: 16.37–17.94), 17.5 (CI 95%: 14.93–20.06) versus 84 cm of water (CI 95%: 71.41–96.58), respectively. Dopamine, at its three ranges inhibited the augmentation of the fluid filtration rate observed in PP with values of 1.01 (CI 95%: 0.77–1.24), 0.03 (CI 95%: 0.01–0.04) and 0.02 g/min (CI 95%: −0.0004–0.03) versus 2.13 g/min (CI 95%: 1.56–2.69), respectively. We concluded that dopamine has a vasodilator effect on Pap and exerts an inhibiting action over PAF effects in pulmonary circulation. Such effects seem to be mainly mediated by Beta-receptors, rather than by dopaminergic receptors.

Keywords: Circulation, pulmonary; Disease, pulmonary edema; ARDS, Mammals, rabbit; Mediators, dopamine, PAF

1. Introduction

The platelet activating factor (PAF) represents a unique class of phospholipids derived from cellular membranes, with powerful biological activities which mediate a spectrum of inflammatory

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and vasoactive processes. Although the terminology PAF implies a platelet origin and target, the following cellular types are able to produce and respond to PAF: (1) Inflammatory cells such as neutrophiles, monocytes and macrophages; (2) Endothelial cells; and (3) Vascular and bronchial smooth muscle cells (Anderson et al., 1991).

This molecule has been involved in the genesis of various pathological processes such as ischemia/reperfusion injury, acute rejection of graft, septic shock, and multiple organ failure (Anderson et al., 1991).

In the lung, PAF is also released by Type II Pneumocytes and it contributes with the pathophysiology of acute pulmonary injury, causing: damage to the capillary endothelial and alveolus epithelium cells with subsequent influx of inflammatory cells to the airway and alveolus (Seale et al., 1991), pulmonary vasoconstriction (Hamasaki et al., 1984), increase of pulmonary artery pressure in isolated and perfused rabbit lungs (Comellas et al., 1999) and increase of airway pressure as well as of vascular permeability (Hamasaki et al., 1984; Uhlig et al., 1994; Comellas et al., 1999), which turns it into a powerful mediator of the pulmonary edema genesis (Hamasaki et al., 1984; Anderson et al., 1991; Comellas et al., 1999). All of these factors possibly contribute to the pathogenesis of the Acute Respiratory Distress Syndrome (ARDS) (Salzer and McCall, 1990; Anderson et al., 1991; Rabinovici et al., 1993).

On the other hand, dopamine is an endogenous catecholamine currently used in daily clinical practice for the treatment of low cardiac output with altered renal function, such as heart failure, septic and hypovolemic shock (Mentzer et al., 1976; Landsberg and Young, 1994; Hoffman and Lefkowitz, 1996).

Depending on the treatment dose, dopamine can act upon dopaminergic receptors type D1, D2, DA1 and DA2, and also Beta and Alpha adrenergic receptors. It has been described that dopamine and fenodolpam (DA1 selective agonist) produce modifications on the pulmonary vascular tone such as vasodilatation and decrease of pulmonary vascular resistance, probably due to the activation of dopaminergic and Beta adrenergic receptors in the pulmonary vascular bed (Polak et al., 1989; Loick et al., 1990; Ducas et al., 1992). Dopamine inhibits hypoxic pulmonary vasoconstriction (Loick et al., 1990; Polak et al., 1992). Fenodolpam prevents pulmonary vasoconstriction induced by prostaglandin F2 Alpha (Polak et al., 1989) and dopamine is responsible for the reabsorption of pulmonary edema in rat lungs by stimulating DA1 receptors present in type II pneumocytes (Barnard et al., 1999).

To our knowledge, there is no published data about the effects of dopamine over PAF- mediated effects on the pulmonary circulation; for this reason we decided to study the effects of this catecholamine upon pulmonary edema induced by PAF in a preparation of isolated and perfused rabbit lungs developed by our laboratory group (Sánchez de León et al., 1986; Angeli et al., 1992; Pozo-Parilli et al., 1993; Martinez-Ruiz et al., 1996). Part of the results of the present study has been published in abstract form (Marcano et al., 2000).

2. Materials and methods

Thirty New Zealand rabbits ($n = 30$) weighing between 2.5 and 3.5 kg were anesthetized intraperitoneally with sodium pentobarbital (30–40 mg/kg). The method used in the preparation of the isolated and perfused lungs has been described before (Sánchez de León et al., 1986; Angeli et al., 1992; Pozo-Parilli et al., 1993; Martinez-Ruiz et al., 1996). A tracheotomy was performed and the lungs were ventilated mechanically by a piston pump (Harvard Respiratory Pump, Millis, MA) at a constant tidal volume of 10–15 ml/kg. A median sternotomy was performed and 2 ml of heparin (1000 IU/ml) was injected into the right ventricle through a cannula. Two minutes later the animal was exsanguinated through the same cannula and the volume of blood obtained (~ 100 ml) was increased to 200 ml using 0.9 NaCl solution and dextran solution at the same proportion (1:1), resulting in an oncotic pressure of ~ 22 cm of water. The blood was used to prime the perfusion circuit. The heart and lungs were rapidly removed with minimal handling. A silastic perfusion cannula was inserted into the pul-

monary artery through the right ventricle and a second one was inserted in the left atrium through the left ventricle. A ligature was used to suspend the preparation to a force transducer (Force Displacement Transducer FT03, Grass Instrument Company, Quincy, MA) at the top of the Perspex box, which was kept at an adequate temperature and humidity (see Fig. 1).

Measurements of weight changes of the preparation were used to calculate fluid filtration rate (FFR) by the isogravimetric method (Vennard and Street, 1961; Streeter and Wylie, 1975). Connections to the ventilator and perfusion circuit were led horizontally through one side of the box so the weight transmitted to the preparation remained constant, despite small vertical displacement resulting from a change in lung weight.Mean pulmonary artery pressure (Pap) and mean left atrial pressure (Pla) were measured through fine catheters which were threaded through the perfusion cannula until their tips lay at the end of the cannula. Vascular (both Pap and Pla) and airway pressure (Paw) were measured which pressure transducers (Physiological Pressure Transducer, P231, Gould, CA) and displayed on polygraph (Grass Instrument Model 79 Polygraph, Quincy, MA) together with changes in lung weight.

The zero reference for the vascular pressure was the left atrium and all the transducers were repeatedly calibrated in reference to water manometer. Since the lungs were suspended vertically, the apices were approximately at atrial level and the diaphragmatic portion 8 cm lower (Streeter and Wylie, 1975).

Perfusion was performed by and occlusive roller pump (type MHRE 200, Watson-Marlow Limited, Cornwall, UK) it began within 10 min of exsanguination and flow gradually increased over the next 10–15 min until Pap was 13–18 cm of water, resulting in an initial blood flow of ~ 70–80 ml/min. Oscillation produced by the pump was minimized by directing the flow through an air-filled damping chamber surrounded by a circulating water jacket maintained at 37°C (Fig. 1). The temperature of the perfusate was checked by a thermistor probe in the pulmonary artery line.

Ventilation was achieved with Harvard piston pump ventilator, previously used for ventilation after tracheotomy was performed, with the addition of 2 cm of the water of positive end expiratory pressure (PEEP), at a constant frequency with 5% of CO_2 in the air mixture. We stabilized all the preparations by the following criteria before introducing them in our protocol: (1) Isogravimetric state (no change in FFR); (2) blood flow between 70 and 80 ml/min with Pap of 12–18 cm of water, a Pla of $+3$ to -5 cm H_2O, a Paw of 7–12 cm H_2O; (3) blood $PO_2 = 100$ Torr, $P_{CO_2} = 35$ Torr and pH between 7.35 and 7.45.

The drugs used were: PAF (L-a-Phosphatidylcholine, b-Acetyl-g-O-alkyl, in a chloroform solution 0.6 ml/2 mg per ml, Sigma, St. Louis, MO)

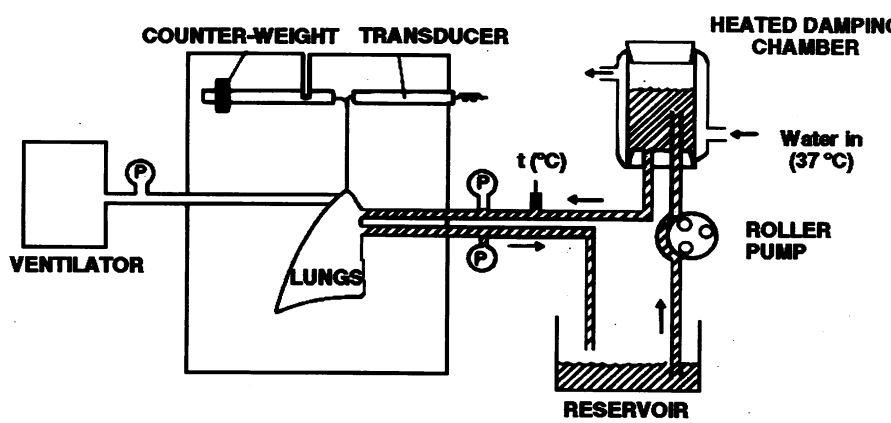

Fig. 1. Simplified diagram of the preparation.

and clorhidrate of Dopamine 40 mg/ml (Solo Pak Laboratories, USA) diluted in 0.9% NaCl solution to achieve the desired concentrations.

2.1. Protocol

The 30 rabbits utilized were divided into three groups:

1. Control group $n = 6$, in which no drugs were added after stabilization.
2. DF group $n = 6$, in which after 10 min of stabilization we injected PAF on the perfusate in a dose of 1 μg/kg of rabbit weight; the measurements of the variables were performed after 15 min (The preparation was halted if considered non-viable).
3. Dopamine group, $n = 18$, which were distributed in three groups of six rabbits each:
   - 3.1. Dopamine group in dopaminergic range (1–5 μg/kg/min), in which after 10 min of stabilization a continuous infusion of dopamine to the perfusate was initiated through an infusion pump (B. Braun Apparatebau Melsungen, made in West Germany) programmed to administer the above stated dose. Measurements were performed 30 min later. At this moment we injected the perfusate a dosage of PAF of 1 μg/kg of rabbit weight without stopping the dopamine infusion. The measurements were performed again after 15 min. (The preparation was halted if considered non-viable).
   - 3.2. Dopamine group in Beta range (10–20 μg/kg/min), in which after 10 min of stabilization a continuous infusion of dopamine to the perfusate was initiated through an infusion pump (B. Braun Apparatebau Melsungen, made in West Germany) programmed to administer the above stated dose. Measurements were performed 30 min later. At this moment we injected the perfusate a dosage of PAF of 1 μg/kg of rabbit weight without stopping the dopamine infusion. The measurements were performed again after 15 min. (The preparation was halted if considered non-viable).
   - 3.3. Dopamine group in Alpha range (20–30 μg/kg/min), in which after 10 min of stabilization, a continuous infusion of dopamine to the perfusate was initiated through an infusion pump (B. Braun Apparatebau Melsungen, made in West Germany) programmed to administer the above stated dose. Measurements were performed 30 min later. At this moment we injected the perfusate a dosage of PAF of 1 μg/kg of rabbit weight without stopping the dopamine infusion. The measurements were performed again after 15 min. (The preparation was halted if considered non-viable).

2.2. Statistical methods

Data are expressed as means with their Confidence Interval (95%). All results were analyzed using the non-parametric Kruskall Walis test. Variation was considered to be significant at a P-value ≤ 0.05.

3. Results

With regard to Pap values, dopamine groups at Beta and Alpha range significantly decreased Pap values with respect to the control groups and the dopamine group at dopaminergic range: 11.66 cm of water (CI 95%: 10.83–12.48) and 11.66 cm of water (CI 95%: 9.87–13.44), respectively, versus 17.12 cm of water (CI 95%: 16.12–18.11) and 16.28 cm of water (CI 95%: 14.53–18.02), respectively ($P < 0.05$) (Fig. 2).

No significant differences were shown in Pap values between the dopamine Beta and Alpha groups. We observed no differences in the Pap values between the control groups and the dopaminergic range group.

Upon injecting PAF to the PAF groups we observed a significant increase of Pap as in contrast to the control groups: 84 cm of water (CI 95%: 71.41–96.58) versus 17.12 cm of water (CI 95%: 16.12–18.11) ($P < 0.05$) (Fig. 2). This effect was significantly inhibited in the pretreated groups with dopamine at Beta and Alpha range

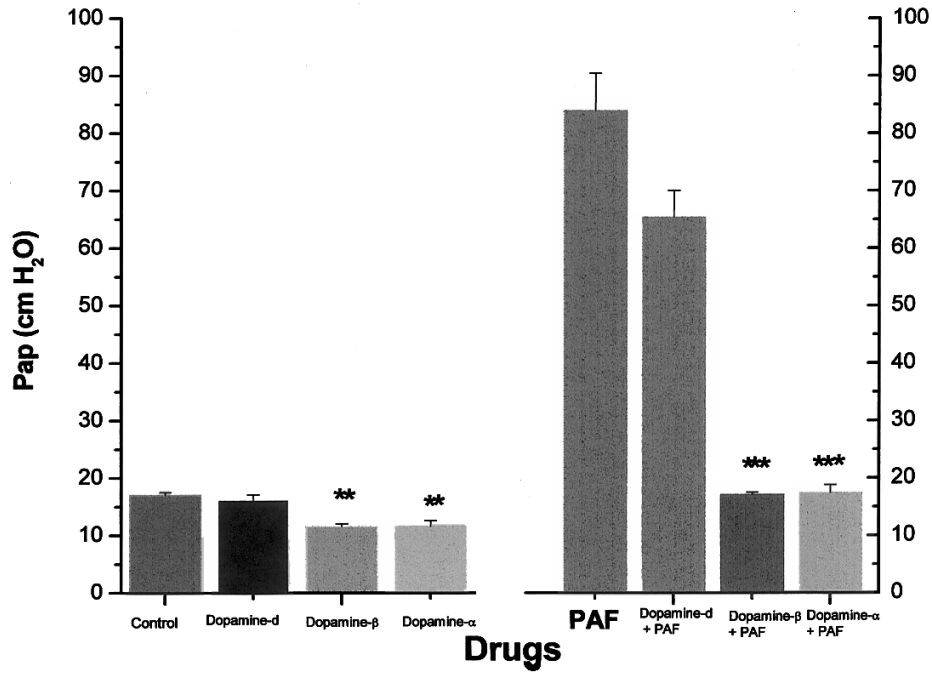

Fig. 2. Drugs versus Pap. **Statistically different with respect to control. ***Statistically different with respect to PAF.

when PAF was administered: 17.16 cm of water (CI 95%: 16.37–17.94) and 17.5 cm of water (CI 95%: 14.93–20.06), respectively ($P < 0.05$) (Fig. 2). The pretreated group with dopamine at dopaminergic range did not inhibit the increase over Pap produced by PAF (Fig. 2).

With regard to FFR, no significant statistical differences were observed between the control group and the dopamine groups at any doses.

The PAF dose in the PAF group produced a significant increase of FFR as in contrast to the control group: 2.13 g/min (CI 95%: 1.56–2.69) versus 0.09 g/min (CI 95%: 0.07–0.10), respectively ($P < 0.05$) (Fig. 3).

This increase in the FFR was significantly inhibited in the pretreated groups with all dopamine doses: 1.01 g/min (CI 95%: 0.77–1.24), 0.03 g/min (CI 95%: 0.01–0.04) and 0.02 g/min (CI 95%: −0.0004–0.03), respectively ($P < 0.05$) (Fig. 3).

No significant differences were observed in the Pla and Paw values among any of the groups.

4. Discussion

PAF is an inflammatory mediator with powerful edematogenic effects on pulmonary circulation. Previous studies from this laboratory have shown that a dose of 1 μg/kg of rabbit weight in isolated lungs produces a Pap and FFR increase without affecting Pla (Pesce et al., 1998; Comellas et al., 1999; Friedman et al., 2000).

We have demonstrated that these phenomena could be prevented through pretreatment with Beta-2 agonists such as Fenoterol, which probably inhibits the vasoconstrictor effect of PAF by stimulating Beta-2 receptors found in the vascular pulmonary bed that mediates vasodilatation. Our laboratory group has also determined that the same effects are obtained through the previous use of steroids such as hydrocortisone, which blocks phospholipase A2 inhibiting the synthesis of eicosanoids such as TXA2, LTD4 and LTC4, which are mediators through which PAF produces pulmonary edema and vasoconstriction of

pulmonary artery (Uhlig et al., 1994; Bochnowicz and Underwood, 1995; Friedman et al., 2000).

On the other hand, the presence of dopamine post-synaptic vascular receptors (DA1) that mediate vasodilatation have been suggested in the pulmonary circulation and in the alveolar epithelium in animals as in human beings.(Polak et al., 1989; Loick et al., 1990; Kobayashi et al., 1995; Barnard et al., 1999). However, the physiological significance of these receptors in the pulmonary vasculature has not been completely defined, although it is possible that said receptors participate in the maintenance of the low pulmonary vascular tone and to counterbalance vasocontrictor effects of factors such as norepinephrine, serotonin, angiotensin II, vasoactive prostanoids and hypoxia (Polak et al., 1989, 1992).

Dopamine, depending on its concentration, can act on dopaminergic, Beta and Alpha-adrenergic receptors (Landsberg and Young, 1994; Hoffman and Lefkowitz, 1996). In the dopaminergic range (1–5 μg/kg/min), it stimulates DA1 receptors present in smooth vascular muscle cells of the mesenteric, renal, coronary and pulmonary vascular beds stimulating adenyl cyclase, with a subsequent increment of the intracellular concentration of the cyclic-AMP which translates into vasodilatation (Kobayashi et al., 1995; Carcoana and Hines, 1996; Hoffman and Lefkowitz, 1996).

Likewise, it has been reported that dopamine, at concentrations of 10^{-4} M can stimulate DA1 receptors located in type II pneumocytes of rat lungs which induces the recruiting of Na, K ATPase pumps towards the cellular membrane of the type II pneumocytes, contributing to the removal of edema encountered in the alveolar space (Barnard et al., 1999).

At a dose of 5–10 μg/kg/min, dopamine continues to stimulate dopaminergic receptors but also starts the stimulation of Beta adrenergic receptors. At a concentration of 10–20 μg/kg/min, it behaves as a Beta-adrenergic agonist, due to the fact that it acts upon the B1 myocardial receptors by exerting a positive inotropic effect and producing relaxation of smooth muscle of the pulmonary vasculature by stimulation of Beta 2 receptors present in the pulmonary circulation (Kam and Stull, 1985; Hoffman and Lefkowitz, 1996).

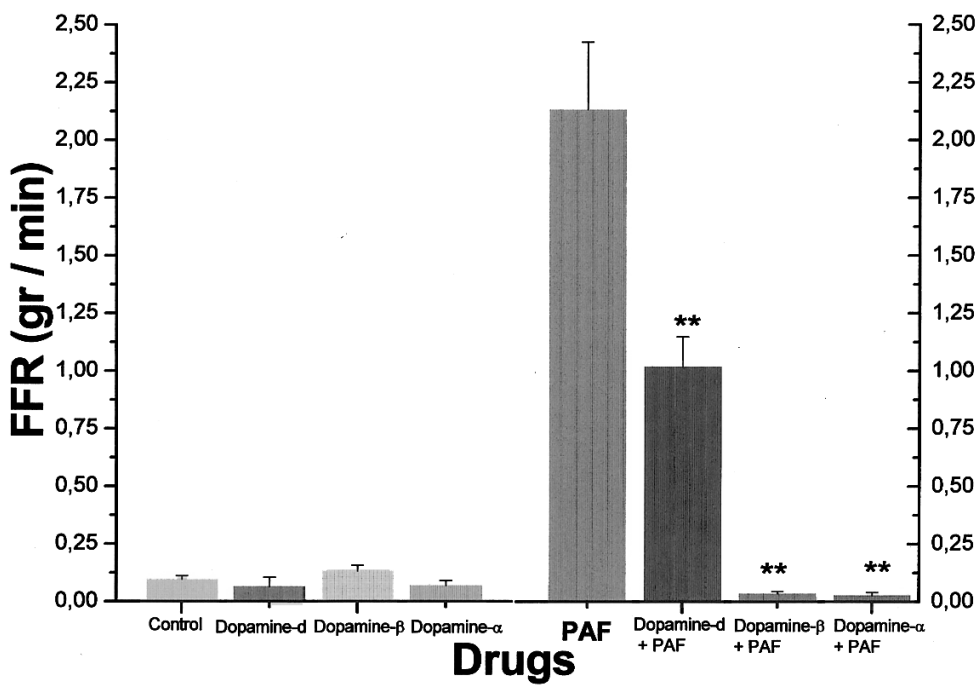

Fig. 3. Drugs versus FFR. **Statistically different with respect to PAF.

At this concentration we speculate that dopamine can be attributed some of the same non-bronchodilator effects of Beta-adrenergic agonists. These include: inhibition in the release of the leukotrienes and tromboxanes, which, as pointed out in medical literature, are mediators through which PAF produces vasoconstriction and pulmonary edema (Uhlig et al., 1994; Bochnowicz and Underwood, 1995), increase of the reabsorption of pulmonary edema by stimulating Na transportation in the alveolar epithelium of many species, including human lungs, probably by an increment in the intracellular concentration in cyclic-AMP (Pittet et al., 1994; Sakuma et al., 1994), inhibition of the pulmonary activation and infiltration of inflammatory cells (Loick et al., 1992; Sakamoto et al., 1993; Johnson, 1995), which are indispensable elements in the production of PAF effects in pulmonary circulation, as it was shown by our laboratory group (Comellas et al., 1999) since it is known that inflammatory cells are the ones that, when stimulated by PAF, release chemical mediators involved in the pathophysiology of acute pulmonary damage such as leukotrienes, tromboxanes and toxic oxygen metabolites (Anderson et al., 1991; Minamiya et al., 1998).

An Alpha-adrenergic range (20–50 μg/kg/min), dopamine stimulates vascular Alpha 1 receptors producing vasoconstriction.

To our knowledge, this is the first study describing the effects of dopamine on pulmonary edema induced by PAF, although there are few studies which have evaluated the response of dopamine and fenodolpam to the vasoconstrictor and edematogenic effects of euconasoids and hypoxia.

The utilization of fenodolpam diminished the increase of the pulmonary artery pressure induced by prostaglandin F2 Alpha in rat lungs (Polak et al., 1989), while dopamine, at a dose of 9 μg/kg/min, prevented the hypoxic pulmonary vasoconstriction (HPV) induced by nitrogen and CO_2 in sheep lungs (Loick et al., 1990), thereby suggesting the vasodilator dopaminergic influence in pulmonary hypertensive conditions. Dr Heinz Loick, 2 years after the above mentioned investigation, described that dopamine, at a dose of 9 μg/kg/min, significantly reduced the HPV induced by smoke inhalation in ovine models and prevented an increase on the pulmonary tissue damage in this group of animals, hypothesizing that these events were most likely due to a combined vasodilator effect of dopamine on dopa and Beta 2 adrenergic receptors accompanied by a high removal of inflammatory mediators and by the inhibition in the activation of the inflammatory cells mediated by Beta-receptors (Loick et al., 1992). Finally, Dr Mark Polak et al. studied the response of the dopaminergic receptors located in the pulmonary vasculature of rat lungs before HPV induced by nitrogen and CO_2, describing that fenodolpam significantly reduced the vasoconstriction, establishing the presence of DA1 receptors that mediate vasodilatation in the pulmonary vascular bed (Polak et al., 1992).

In our study, dopamine was used to prevent pulmonary edema induced by PAF in isolated and perfused rabbit lungs. We observed that the increase of Pap seen after a PAF injection was significantly inhibited when the preparations were previously treated with dopamine at Beta and Alpha range. This seems to suggest that the vasoconstrictor effect produced by PAF was prevented by the combined effect of dopamine when interacting over dopaminergic and Beta 2 adrenergic receptors, both of which mediate a vasodilatator effect over the pulmonary circulation, as was suggested by Loick et al. (1992) and Polak et al. (1992).

With regard to FFR, we observed that the pretreatment with dopamine at Beta and Alpha range prevented the increase of FFR induced by PAF. It is possible that such inhibition could be also explained by the vasodilator effect of this catecholamine due to the fact that a previous work by our laboratory group (Pesce et al., 1998) demonstrated that the increase of FFR induced by PAF with the subsequent formation of pulmonary edema depended on high hydrostatic capillary pressure, which in our preparations was translated as high Pap. Therefore, when Pap increase was inhibited by the vasodilator effect of dopamine, it is possible that FFR growth produced by PAF was prevented. Only a partial inhibition over FFR increase induced by PAF was

observed in preparations pretreated with dopamine at dopaminergic range.

On the other hand, part of the goals of this work was to describe on an experimental model the effects of dopamine on pulmonary circulation, because the medical literature is confusing with regard to the effects that this drug exerts on the pulmonary vasculature. Harrison et al., 1969, reported that, in anaesthetized dogs, dopamine, at a dose of 25–30 μg/kg/min produced a significant increase over Pap, Pla, cardiac output and stroke volume, without affecting the pulmonary vascular resistance (PVR). In another study, Mentzer et al. (1976), using a preparation of isolated and perfused dog lungs, described that the dopamine infusion at the dose of 20 μg/kg/min, increased lobar vascular resistance by 50%. Klausen et al. (1982) reported the development of pulmonary hypertension in a patient with severe acute pulmonary failure, after the treatment with dopamine at a dose of 3–5 μg/kg/min. In contrast to the afore mentioned findings, Beregovitch et al., 1974, reported that in nine patients, the dopamine infusion at a dose of 1–10 μg/kg/min did not alter the PVR. Hemmer and Suter (1979), used dopamine infusions to restore the cardiac output and urine production in patients with Acute Respiratory Distress Syndrome and did not encounter detrimental effects over PVR. Ducas et al. (1992), described in dogs with acute pulmonary hypertension induced by autologous blood clot, that dopamine did not affect the pulmonary vascular tone.

It is possible that the discrepancies observed among these results could be explained by the variations on the experimental model used, the method used to evaluate vascular tone, dopamine dose or the type of underlying disease, as was suggested by Ducas et al. (1992).

Our results show that the dopamine infusion at dopaminergic range produced no significant change over Pap, FFR, Pla or Paw. However, dopamine, in Beta and Alpha adrenergic range produced a significant reduction upon Pap with regard to the control group and the infusion group in dopaminergic range without affecting FFR, Pla or Paw.

These results can be explained by the fact that we employed an in-vitro preparation of isolated and perfused rabbit lungs, in which the cardiac output (flow) depended on a roller pump (Type MHRE 200, Watson-Marlow Limited, Cornwall, UK) and not on the positive inotropic effect that could have been exerted by dopamine over the Beta 1 and Beta 2 myocardic receptors of a rabbit heart; we believe that the increase observed by other authors about Pap depended on an increment in cardiac output. In our in-vitro preparation, the flow (cardiac output), depended on the roller pump; therefore, the effect of dopamine was basically observed over the pulmonary vascular bed, and the increase of Pap described by earlier authors was not detected by our laboratory group. Likewise, we describe that, even in Alpha adrenergic range, Pap diminished significantly, thereby suggesting the absence of Alpha adrenergic receptors in pulmonary circulation and also, a vasodilator effect of dopamine, probably mediated by the combined action over DA1 and Beta 2 adrenergic receptors located in the pulmonary vascular bed.

We have concluded that dopamine exerted a vasodilator effect on Pap, principally mediated by Beta 2 receptors. Dopamine has an inhibiting effect upon PAF actions over pulmonary circulation, which also seems as though it is mediated by the activation of Beta 2 receptors.

Whether inhibition of PAF effects on pulmonary circulation that dopamine prevents is a result of: (a) a direct vasodilator effect; (b) activation of intracellular mechanisms which reabsorb edema; and (c) removal and inhibition of mediators and inflammatory cells, or a combination of any or all of these, is a question that shall be dilucidated in posterior studies.

Acknowledgements

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