Original Article

Effect of adenosine on pulmonary circulation in patients with primary pulmonary hypertension

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Background: The nucleoside adenosine is a potent vasodilator. Although its effect on the pulmonary arteries is well known, its influence on capillaries and veins has yet to be described.

Objective: To evaluate the pre- and post-administration effects of adenosine on arterial and venous resistance in the pulmonary circulation of patients with primary pulmonary hypertension.

Method: The study involved 7 patients with primary pulmonary hypertension and presenting a positive response to adenosine on the acute test. Before and after adenosine administration, arterial and venous resistances were determined by estimating pulmonary capillary pressure through analysis of pulmonary artery pressure decay curves.

Results: Following adenosine administration, there was an increase in the cardiac index (from 1.71 ± 0.23 to 2.72 ± 0.74 L/min-1/m-2) and a decrease in pulmonary vascular resistance (from 2924 ± 1060 to 1975 ± 764 dynes/s/cm-5/m-2) with no significant variations in mean pulmonary artery pressure (pre: 75.6 ± 16.8 mmHg; post: 78.1 ± 18.8 mmHg), pulmonary wedge pressure (pre: 15.3 ± 1.5 mmHg; post: 15.4 ± 1.9 mmHg) and pulmonary capillary pressure (pre: 43.8 ± 5.8 mmHg; post: 44.5 ± 4.9 mmHg). The ratio between arterial resistance and total pulmonary vascular resistance also presented a less than significant variation (pre: 50 ± 15%; post: 49 ± 17%). These findings suggest that adenosine affects the capillaries and veins as well as the arteries.

Conclusion: We can conclude that the adenosine mechanism is not restricted to the arterial aspect of the pulmonary circulation, and that analysis of pulmonary capillary pressure could prove useful in the study of various drugs that affect the pulmonary circulation.

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INTRODUCTION

Adenosine is a nucleoside that is a potent vasodilator and has an extremely short half-life[1]. In recent years, the growing interest in pulmonary hypertension has resulted in an increase in the number of studies evaluating the effects of adenosine on the pulmonary circulation and the cardiac index[2], as well as on the physiopathology of pulmonary hypertension[3].

The ability of adenosine to reduce pulmonary vascular resistance and increase the cardiac index, effectively reducing systemic circulation, has been well described, especially in patients with primary pulmonary hypertension (PPH), a disease characterized by significantly elevated pulmonary artery pressure, which leads to right ventricular hypertrophy and to *cor pulmonale*[1,4,5]. Despite the fact that adenosine-induced pulmonary artery relaxation has been demonstrated[6], there have been no studies evaluating its effect on capillaries and veins, which is of particular importance in a situation of vascular obliteration such as that seen in PPH. Considering the pulmonary circulation as a system composed of three compartments (arterial, capillary and venous), with two interposed resistances (arterial and venous), determination of the pressures in each compartment for a given cardiac index allows each resistance, and not simply total pulmonary vascular resistance, to be evaluated in isolation[7].

At the hospital bedside, arterial and venous pressure can easily be measured through the use of a pulmonary artery catheter (Swan-Ganz). However, pulmonary capillary pressure (PCP) can only be determined through analysis of the decay of the pulmonary artery pressure curve after balloon occlusion[8].

In order to determine the effects of adenosine on each of the pulmonary circulation resistances, we analyzed the hemodynamic patterns and PCPs of patients with PPH before and after adenosine administration.

METHODS

Over the course of a year, 35 PPH patients were submitted to the acute vasodilator test. Our study sample consisted of those patients who presented a positive response to vasodilator administration, defined as a drop in pulmonary vascular resistance of greater than 20%. The final sample was composed of seven patients (20% of the group tested), all female, ranging in age from 21 to 52 (mean, 29 ± 10.6). In order to verify that all patients met the criteria for a diagnosis of PPH[9], patient histories were recorded, and patients were initially evaluated through physical examination, radiology (X-ray and angiotomography of the chest), pulmonary function tests, echocardiography and ventilation/perfusion lung scintigraphy. The study was conducted prior to the initiation of any type of chronic vasodilator treatment.

The study was approved by the Ethics in Research Committee of the *Faculdade de Medicina da Universidade de São Paulo* (University of Sao Paulo School of Medicine) *Hospital das Clínicas*. In the intensive care unit, all of the patients were monitored using a 7F pulmonary artery catheter (Baxter Healthcare Corporation, Irvine, CA, USA). The interfaces of each lumen were then connected to transducers (HP1290C; Hewlett-Packard, Waltham, MA, USA), which were in turn connected to pressure modules (M1006A; Hewlett-Packard) coupled to a Hewlett-Packard monitor (M1176-A; Hewlett-Packard). This monitor had been modified by adding an analog-digital out, allowing the pressure curves to be recorded on a personal computer at a frequency of 200 Hz. Acquisition and analysis of the decay of the pulmonary artery pressure curves after balloon occlusion were achieved using software developed by LabVIEW (National Instruments, Austin, TX, USA). At least three curves per patient were recorded for each of the situations studied. We analyzed the following hemodynamic parameters: mean pulmonary artery pressure; pulmonary artery occlusion pressure; pulmonary vascular resistance index; and cardiac index, the last calculated using the thermodilution technique, during which we recorded the mean of three consecutive measurements presenting a variance of no more than 10% from one to the other. After the baseline hemodynamic values had been established, we started continuous intravenous administration of adenosine, beginning at 100 ng/kg/min, and increasing the concentration by 50 ng/kg/min every two minutes[1] until achieving a 20% drop in the pulmonary vascular resistance index or until the patient presented collateral effects, such as precordialgia, cephalgia or nausea. In order to determine PCP, a bi-exponential mathematical model was applied to the post-balloon occlusion decay of the pulmonary artery pressure curves. This model presupposes that the pulmonary circulation is tri-compartmental (presenting arterial, capillary and venous components) and possesses two resistances (arterial and venous). The post-balloon occlusion decay of the pulmonary artery pressure curve provides direct pressure

values for the arterial compartment (mean pulmonary artery pressure) and the venous compartment (pulmonary artery occlusion pressure). Back extrapolation of the slow component of the bi-exponential model allows estimation of the capillary compartment pressure at the time of balloon occlusion[8,10] (Figure 1). Calculation of arterial and venous resistances was made in accordance with the formulas[11]:

$$artR = 80 \times (mPAP - PCP) / CI$$
$$venR = 80 \times (PCP - PAOP) / CI$$

where artR is arterial resistance, venR is venous resistance, mPAP is mean pulmonary artery pressure, PCP is pulmonary capillary pressure, PAOP is pulmonary artery occlusion pressure, and CI is the cardiac index. The relationship artR / (artR + venR) was used as an estimate of the percentage of the arterial component of total pulmonary vascular resistance. The paired t-test was used to make comparisons between pre-and post-adenosine administration values for each hemodynamic parameter. The level of significance adopted was 0.05.

RESULTS

Patients received adenosine in final doses varying from 150 ng/kg/min to 350 ng/kg/min (mean dose, 221 ± 64 ng/kg/min). None of the patients presented any adenosine-induced side effects.

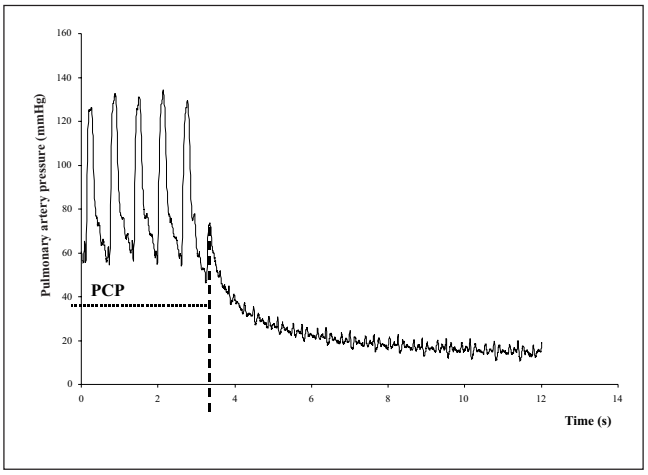

Figure 1 – Decay curve of pulmonary artery pressure
*bi-exponential model
PCP: pulmonary capillary pressure, estimated back extrapolation of the slow component of the bi-exponential model

After adenosine administration, there was a significant increase in the cardiac index, as well as a significant reduction in the pulmonary vascular resistance index. Mean pulmonary artery pressure, pulmonary artery occlusion pressure and PCP were not significantly altered. The artR / (artR + venR) relationship followed the same pattern.

Pre- and post-adenosine administration hemodynamic data obtained from the patients are presented in Tables 1 and 2.

DISCUSSION

Our results suggest that the observed drop in pulmonary vascular resistance after adenosine administration was caused not only by arterial dilation but also increased the capacitance of all pulmonary circulation compartments. The vasodilator effect of adenosine is likely mediated by the increase in intracellular adenosine 3',5'-cyclic monophosphate (cAMP), despite the fact that non-cAMP-dependent mechanisms have been described. Similarly, it has been demonstrated that adenosine is purified in its passage through the pulmonary circulation, which, together with the ability of erythrocytes to metabolize adenosine, explains the limited systemic repercussions of adenosine administration[5,12]. In cases of pulmonary hypertension, total plasma concentration of adenosine is reduced. This finding, in conjunction with the vasodilation response seen in pulmonary hypertension patients receiving adenosine, suggests that adenosine regulates pulmonary vascular tone, although the true mechanism has yet to be fully clarified[3].

In the present study, the influence of the baseline level of serum adenosine on the secondary hemodynamic effect of intravenous adenosine administration was not evaluated. It is possible that the dose required in order to generate a hemodynamic response or a side effect is dependent on the baseline level, which would explain the individual variations in the maximum dose used in our study. The lack of any significant variation in mean pulmonary artery pressure, pulmonary artery occlusion pressure or PCP, with the concomitant increase in the cardiac index, suggests that the vasodilation effect of adenosine is not restricted to pulmonary artery aspects. Venous involvement in the physiopathology of PPH has been well documented, although, with the exception of pulmonary veno-occlusive disease, it is believed to be of little clinical relevance[13]. Our findings suggest that the venous compartment is also dilated as an

TABLE 1

Pre- and post-adenosine administration hemodynamic data

Patient	CI (L.min^{-1}.m^{2})		mPAP (mmHg)		PAOP (mmHg)		PVRi (dyne s cm^{-5} m^{-2})	
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
1	1.62	2.16	97.65	84.65	16.33	17.76	4015.80	2479.98
2	1.88	2.40	70.92	57.65	15.02	14.28	2378.72	1446.38
3	1.95	3.97	51.38	59.35	15.27	14.14	1481.44	911.20
4	1.88	2.94	56.40	65.03	13.62	16.85	1820.43	1312.20
5	1.77	2.58	81.82	87.29	15.05	12.15	3017.85	2334.36
6	1.61	3.28	86.79	110.25	14.05	16.79	3614.41	2282.83
7	1.28	1.73	84.49	82.69	18.25	16.40	4140.00	3061.63
Mean	1.71	2.72 *	75.64	78.13	15.37	15.48	2924.09	1975.51*
SD	0.23	0.74	16.86	18.81	1.54	1.99	1060.84	764.86

CI: cardiac index; mPAP: mean pulmonary artery pressure; PAOP: pulmonary artery occlusion pressure; PVRi: pulmonary vascular resistance index; SD: standard deviation. *p< 0.005

TABLE 2

Pre- and post-adenosine administration pulmonary capillary pressure and partition of pulmonary vascular resistance

Paciente	PCP(mmHg)		artR (dyne s cm^{-5} m^{-2})		venR (dina s cm^{-5} m^{-2})		artR/totalR (%)	
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
1	53.62	44.06	1461.58	1011.71	1237.84	655.33	54.14	60.69
2	44.92	47.97	617.28	180.09	709.72	626.79	46.52	22.32
3	36.05	39.35	494.68	316.21	670.16	398.58	42.47	44.24
4	46.52	48.82	300.59	314.76	1000.70	620.78	23.10	33.64
5	45.41	49.23	1082.78	778.72	902.94	758.67	54.53	50.65
6	42.04	46.17	1591.11	1121.77	995.20	514.29	61.52	68.57
7	38.11	36.40	1892.90	1397.40	810.78	603.80	70.01	69.83
Média	43.81	44.57	1062.99	731.52 *	903.91	596.89 *	50.33	49.99
DP	5.82	4.96	609.61	470.22	195.88	113.46	15.07	17.88

PCP: pulmonary capillary pressure; artR: arterial component of pulmonary vascular resistance; venR: venous component of pulmonary vascular resistance; artR/totalR: percentage of the arterial component involvement in the total pulmonary vascular resistance; SD: standard deviation. *p < 0.005

effect of adenosine administration since the PCP stability observed could only be explained by increased capillary/venous capacitance. The stability of pulmonary artery occlusion pressure levels also supports this hypothesis. In order to clarify this effect, we compared the relationship between the arterial component of pulmonary vascular resistance and the total pulmonary vascular resistance value. This relationship, which reflects the percentage of total pulmonary resistance for which the arterial component is responsible, also presented no significant alteration, indicating that the effect of adenosine is not limited to arterial aspects. If this were the case, a marked reduction in this relationship would be expected. Despite the small size of our study sample, the observed adenosine effect on the venous aspects in our patients allows us to speculate regarding its use in other clinical situations arising in patients with pulmonary hypertension, in which the venodilation concomitant to systemic arterial dilation can have a beneficial effect, as it does in acute respiratory distress syndrome. As for the methodology used, elevated PCP in PPH patients has previously been described[14-16]. The characteristic absence of edema in these patients is probably attributable to adaptive mechanisms that can become activated in the presence of chronic processes of PCP increase, and such mechanisms are capable of preventing increased fluid exchange by the lung interstitium[17]. However, we must point out a potential limitation to our study represented by the fact that we determined PCP through back extrapolation of the slow component of the bi-exponential model. In the case of vascular obliteration, which is characteristic of PPH,

the time required to clear the arterial compartment is probably greater than in normal situations. Therefore, the back extrapolation used in our study, validated in situations of normal clearance, might partially reflect aspects of pre-capillary pressure. Nevertheless, the lack of acuity in the measurement of PCP does not alter the fact that the determined pressure was unchanged by adenosine administration, which can be explained by the concomitant vasodilation of the pulmonary venous system. Analysis of the decay of the pulmonary artery pressure curve after balloon occlusion and the consequent determination of PCP can result in a more accurate assessment of the phenomena related to the various drugs used in the treatment of patients with PPH. It has previously been reported that PPH patients may develop a mechanism of tolerance to increased dosages of intravenous prostacyclin, a vasodilator commonly used in the chronic treatment of PPH patients. Some related symptoms have been interpreted as being secondary to a high-deficit state generated by the increased dosage[18]. We speculate that some aspects of the symptomatology could be secondary to an increase in PCP related to arterial dilation being proportionally greater that venodilation as a result of the veins having reached maximum compliance, for example. This secondary PCP increase can lead to greater fluid exchange by the lung interstitium, bringing about the dyspnea symptomatology seen in this patient population. The determination of PCP in these patients can be used to prove this hypothesis.

In conclusion, the study of PCP allowed us to identify some targets of the adenosine effect in patients with PPH. Adenosine, while selective for the pulmonary circulation, is not selective for the arterial compartment and thus provokes concomitant venodilation. Analysis of arterial and venous resistance through determination of PCP may further the understanding of the mechanisms involved in the effects of, as well as the tolerance to, other drugs that act on the pulmonary circulation.

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