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SCIENTIFIC ARTICLE

Intravenous clonidine administration and its ability to reduce pulmonary arterial pressure in patients undergoing heart surgery

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Abstract
Objective: Evaluate the ability of clonidine to reduce pulmonary arterial pressure in patients with pulmonary hypertension undergoing heart surgery, either by reducing the pressure values from the direct measurement of pulmonary arterial pressure or by reducing or eliminating the need for intraoperative dobutamine and nitroprusside.
Method: Randomized, double-blind, placebo-controlled, comparative study conducted in 30 patients with pulmonary arterial hypertension type 2 undergoing cardiac surgery. Mean pulmonary arterial pressure and dosage of dobutamine and sodium nitroprusside were assessed four times: before intravenous administration of clonidine (2 μg/kg) or placebo (T0), 30 min after tested treatment and before cardiopulmonary bypass (T1), immediately after CPB (T2), 10 min after protamine injection (T3).
Results: There were no significant differences regarding mean pulmonary arterial pressure at any time of evaluation. There was no significant difference between groups regarding other variables, such as mean systemic arterial pressure, heart rate, total dose of dobutamine, total dose of sodium nitroprusside, and need for fentanyl.
Conclusion: Data analysis from patients included in this study allows us to conclude that intravenous clonidine (2 μg/kg) was not able to reduce the mean pulmonary arterial pressure in patients with pulmonary hypertension in group 2 (pulmonary venous hypertension), undergoing heart surgery, or reduce or eliminate the need for intraoperative administration of dobutamine and sodium nitroprusside.

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Introduction

Pulmonary hypertension (PH) is a chronic disease defined by high mean pulmonary arterial pressure above 25 mmHg at rest or 30 mmHg on exertion. Due to its varied etiology, PH is associated with three major deleterious phenomena: vascular remodeling, hypoxic vasoconstriction, and in situ thrombosis. PH is difficult to control and evolves with hypoxemia, increased resistance to ejection of blood by the right ventricle (RV), RV failure, and death.[1]

PH is classified into five groups: (I) pulmonary arterial hypertension (includes the idiopathic form); (II) pulmonary hypertension associated with left heart diseases; (III) pulmonary hypertension associated with respiratory disease and/or hypoxemia; (IV) pulmonary hypertension due to chronic thrombotic and/or embolic disease; and (V) miscellaneous group.[1]

PH is most often found in group II patients, as a result of left ventricle (LV) failure associated with other common heart disease progression, such as valvular heart disease and coronary artery disease.[2] Myocardial failure makes the LV unable to eject blood into the systemic circulation that reaches the left heart through the pulmonary veins. The high pressure of the pulmonary venous bed is transmitted backward to the arterial system. For no other reason, PH of group II is referred to as pulmonary venous hypertension (PVH).[3]

Anesthesia in these patients is an enormous challenge because it is necessary to control both the ventricular disease and pulmonary hypertension. To face it, various combinations of drugs are used, including the association of inotropic dobutamine (DBT) and the vasodilator sodium nitroprusside (NTP), which is one of the more frequently used. However, to be effective, it is often necessary to use high doses of these agents. Undesirable effects may arise, such as tachycardia with the use of dobutamine or increased intracranial pressure, coronary steal, intrapulmonary shunt, and metabolic acidosis with sodium nitroprusside.[4] Thus, the pharmacological options available are not without side effects, which justify the interest for new therapeutic options.

Clonidine, a α_2-adrenergic, imidazole agonist, was introduced into clinical practice in the early 1960s. This drug was first proposed as a nasal decongestant, but soon its systemic effects became known, such as hypotension, bradycardia, and sedation.[5]

Due to the hypotensive effect of clonidine, which decreases the exocytosis of noradrenaline in the synaptic cleft, both in the central and peripheral nervous system,[6] it is now prescribed for hypertension management. In recent decades, this agent was studied as an adjunct to anesthesia. The advantages of clonidine in this context were recognized and its use spread also in the field of anesthesia in cardiac surgery. Among other benefits, clonidine is known to reduce the need for opioids intra- and postoperatively, which allows early tracheal extubation and shortens the duration of mechanical ventilation; hemodynamic stability at lower levels of circulating catecholamines; increased diuresis due to inhibition of the release of antidiuretic hormone (ADH); and release of atrial natriuretic factor.[6]

The presence of α_2-adrenergic receptors in lung tissues[7–9] and its central hypotensive action seem to indicate that clonidine may also be useful for treating PH patients undergoing heart surgery.

Methods

After approval by the Ethics Committee of the Hospital São Paulo (Unifesp) and Hospital Beneficência Portuguesa (São Paulo-SP) and obtaining signed informed consent from all participants, 30 patients of both sexes, physical status ASA II or III, aged between 18 and 80 years, with pulmonary hypertension secondary to left heart disease were enrolled in the study between January 2009 and December 2010. Due to the expiration date of the batch of drugs, one patient was excluded from the study.

Patients underwent cardiac surgery with cardiopulmonary bypass for valvular correction or myocardial revascularization.

The diagnosis of pulmonary hypertension was previously confirmed by right heart catheterization and defined by mean pulmonary arterial pressure greater than 25 mmHg at rest.

After fasting for 8 h, the patients were taken to the operating room without receiving pre-medication. In the operating room, they were monitored with electrocardioscope on DII and V5 derivations and, pulse oximetry, and for noninvasive blood pressure. All patients underwent venipuncture and intravenous administration of 3 mg midazolam. After this step, left or right radial artery was cannulated with a catheter caliber 20G for direct blood pressure measurement and blood sample collection for laboratory testing.

Anesthesia consisted of preoxygenation for 3 min, followed by administration of fentanyl (10 μg/kg), etomidate (0.4 mg/kg), pancuronium (0.1 mg/kg), lidocaine (1 mg/kg), facemask ventilation with 100% oxygen for 5–7 min, followed by intubation and maintenance with 1% isoflurane in oxygen and air (1:1). After tracheal intubation, monitoring was complemented by analysis of anesthetic gases, capnometry, and capnography.

Intraoperatively, we try to maintain mean arterial pressure between 50 and 80 mmHg with additional doses of fentanyl (5 μg/kg) and, if necessary, sodium nitroprusside. Cases of hypotension were treated according to the etiology, either with volume management or with inotropic, chronotropic or vasopressor agents.

After sternotomy and retractor placement, an 18G teflon catheter was placed under direct vision into the pulmonary artery to allow direct measurement of pulmonary artery pressure.

During cardiopulmonary bypass, in order to keep patients under hypnosis and immobility, midazolam (0.3 mg/kg) and pancuronium (0.1 mg/kg) were administered again. At the end of this stage, all patients were treated with dobutamine (5–10 μg/kg/min), in order to ensure hemodynamic stability (compensating for impaired myocardial contractility by ischemia-reperfusion and heart manipulation during cardiopulmonary bypass).

Categorical variables, such as age, weight, gender, and diagnosis were evaluated. Mean arterial pressure (MAP), heart rate (HR), mean pulmonary artery pressure (MPAP),

and doses of sodium nitroprusside, dobutamine, and fentanyl were recorded at the following times:

After sternum opening and retractor placement, before clonidine (T0).
Thirty minutes after clonidine administration (T1).
At the end of cardiopulmonary bypass (T2).
Ten minutes after protamine (T3).

Immediately after the first measurements (T0), a coded solution (clonidine 2 μg/kg or placebo) was administered to every patient using slow intravenous injection. The tested solution decoding was made just before data analysis, as explained in the annex.

Sample size calculation was made considering the hypothesis of 15% decrease in pulmonary pressure with a standard deviation of 5.5. To obtain a test with a significance level of 5% and 80% power, 14 patients were required for the treatment group and 14 for the placebo group. Calculations were made with BioEstat 3.0.

In principle, all variables were analyzed descriptively. For quantitative variables, the analysis was performed by observing the minimum and maximum values and calculating averages, standard deviations, and medians. For qualitative variables, absolute and relative frequencies were calculated.

To compare the means of both groups, the Student's *t*-test was used. When the normality assumption was rejected, the nonparametric Mann–Whitney test was used.[10]

To test homogeneity between proportions, chi-square test or Fisher's exact test was used (when expected frequencies were less than 5).[10]

To analyze the groups' behavior considering the conditions studied, analysis of variance with repeated measures was used,[11] which consists of adjusting a multivariate linear model from which the following hypotheses were tested:

H01: the average response profiles corresponding to the groups are parallel, i.e., there is no interaction between group factor and valuation condition factor (T0, T1, T2 and T3).
H02: the average response profiles are coincident; i.e., there is no group factor effect group.
H03: the average response profiles are parallel to the abscissas' axis; i.e., there is no evaluation condition factor effect.

When the assumption of data normality was rejected, nonparametric Mann–Whitney test (comparison of both groups at each time) and Friedman's test (comparison of times in each group) were applied.[10]

The significance level of 5% was used for the tests.

Results

Twenty-nine patients, aged between 27 and 75 years (mean 55.10 years, with a standard deviation of 10.54 years and a median of 56 years), were evaluated, of whom 17 were male (58.6%) and 12 (41.4%) female. The patients were divided into two groups: placebo ($n = 14$) and clonidine ($n = 15$).

Table 1 shows the comparison of groups regarding categorical variables, and it was noted that the groups did not differ significantly in age, weight, sex, and diagnosis.

Table 2 shows the comparison of groups regarding surgical variables.

Table 3 shows the comparison of groups regarding baseline pressure measurement, and it was noted that the groups did not differ significantly with respect to baseline pressure.

Table 4 shows the evolution of variables over the time periods studied. Student's *t*-test evaluation showed that the groups did not differ significantly at time T0 regarding MAP ($p = 0.779$).

In the analysis of variance with repeated measures, there was no significant difference between groups with respect to behavior ($p = 0.703$) and the average at each time point ($p = 0.051$). There was significant change in MAP at the evaluated times in both groups ($p < 0.001$). T0 differed significantly from T1 ($p = 0.001$) and did not differ from T2 ($p = 0.085$) and T3 ($p = 0.168$). T1 differed significantly from T2 ($p < 0.001$) and T3 ($p = 0.022$). T2 differed significantly from T3 ($p = 0.001$) (Fig. 1).

With the use of Student's *t*-test, we found no significant difference between groups at T0 regarding HR ($p = 0.865$) (Table 5).

Analysis of variance with repeated measures revealed no significant difference between groups regarding behavior ($p = 0.321$) and mean for each assessment time ($p = 0.979$). There was significant change in HR at the assessment times in both groups ($p = 0.036$). T0 did not differ significantly from T1 ($p = 0.059$), T2 ($p = 0.149$), and T3 ($p = 0.273$). T1 differed

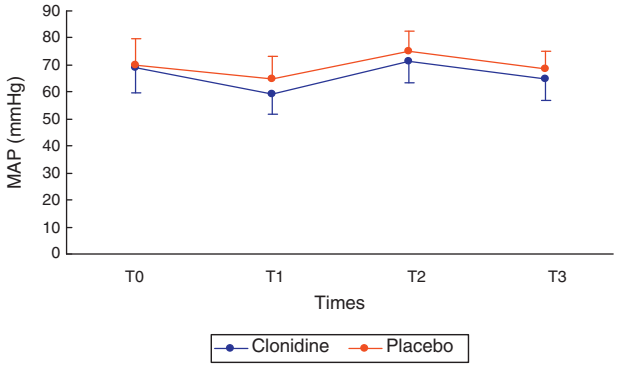

Figure 1 Evolution of MAP.

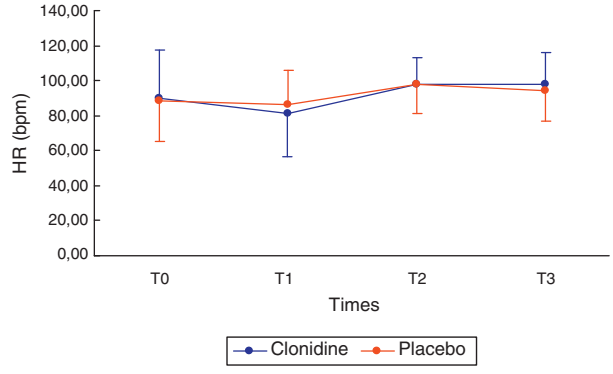

Figure 2 Evolution of HR.

Table 1 Categorical variables.

Variable	Category	Group		p
		Clonidine (n = 15)	Placebo (n = 14)	
Age		52.4 + 11.7	57.9 + 8.6	0.167[a]
Weight		67.5 + 13.8	68.2 + 12.5	0.880[a]
Sex	Female	5 (33.3%)	7 (50.0%)	0.362[b]
	Male	10 (66.7%)	7 (50.0%)	
Diagnosis	ASD/COI	0 (0.0%)	1 (7.1%)	0.675[c]
	DML	5 (33.3%)	5 (35.7%)	
	AS	1 (6.7%)	0 (0.0%)	
	SM	4 (26.7%)	3 (21.4%)	
	MI	5 (33.3%)	2 (14.3%)	
	MI/COI	0 (0.0%)	1 (7.1%)	
	AR	0 (0.0%)	1 (7.1%)	
	AR/MI	0 (0.0%)	1 (7.1%)	

ASD, atrial septal defect; COI, coronary insufficiency; DML, double mitral lesion; AS, aortic stenosis; MS, mitral stenosis; MI, mitral insufficiency; AR, aortic regurgitation.
[a] Descriptive level of probability of Student's *t*-test.
[b] Descriptive level of probability of the chi-square test.
[c] Descriptive level of probability of Fisher's exact test.

Table 2 Surgical variables according to study group.

Variable	Group	N	Mean	SD	Median	Min	Max	p
Anesthesia	Clonidine	15	258.33	35.32	255	210	345	0.173[a]
Time	Placebo	14	236.79	47.17	240	125	315	
Surgery	Clonidine	15	203.27	22.11	200	170	245	0.609[a]
time	Placebo	14	196.86	40.92	197.5	95	270	
Fluid	Clonidina	15	796.67	221.57	900	150	950	0.752[b]
balance	Placebo	14	871.43	82.54	850	800	1000	
Blood	Clonidine	15	−50.00	269.26	−200	−250	550	0.292[b]
balance	Placebo	14	70.71	295.41	0	−200	480	
Diuresis	Clonidine	15	1000.00	602.38	1000	−700	2000	0.510[b]
	Placebo	14	1122.00	293.68	1150	500	1600	

[a] Descriptive level of probability of Student's *t*-test.
[b] Descriptive level of probability of the nonparametric Mann–Whitney test.

significantly from T2 ($p = 0.015$) and T3 ($p = 0.035$). T2 did not differ significantly from T3 ($p = 0.188$) (Fig. 2).

Student's *t*-test revealed that the groups did not differ significantly at T0 in relation to MPAP ($p = 0.068$) (Table 6).

Analysis of variance with repeated measures revealed no significant difference between groups regarding behavior ($p = 0.334$) and mean for each assessment time ($p = 0.223$). There was significant change in MPAP times evaluated in both groups ($p < 0.001$). T0 differed significantly from T1 ($p < 0.001$), T2 ($p < 0.001$), and T3 ($p < 0.001$). T1 did not differ significantly from T2 ($p = 0.807$) and T3 ($p = 0.106$). T2 differed significantly from T3 ($p < 0.001$) (Fig. 3).

In the following analyses, the study of drugs used is presented.

Table 7 shows the comparison of groups regarding the evolution of sodium nitroprusside.

The nonparametric Friedman's test revealed that there was significant change in nitroprusside dosage in the

Table 3 Baseline pressure according to study group.

Variable	Group	N	Mean	SD	Median	Min	Max	p*
MPAP	Clonidine	15	48.80	17.94	44	28	100	0.200
(catheterization)	Placebo	14	40.50	15.93	35.5	26	77	
MAP	Clonidine	15	80.07	16.29	79	59	125	0.315
(baseline)	Placebo	14	74.00	15.58	72	52	100	

MPAP, mean pulmonary artery pressure; MAP, mean arterial pressure.
* Descriptive level of probability of Student's *t*-test.

Table 4 Evolution of MAP according to study group.

Group	Time	*n*	Mean	SD	Min	Max
	T0	15	68.93	9.32	52	80
Clonidine	T1	15	59.00	7.22	50	79
	T2	15	71.47	7.92	58	80
	T3	15	64.73	7.62	51	80
	T0	14	69.93	9.61	56	81
Placebo	T1	14	64.93	8.18	53	77
	T2	14	74.93	7.80	59	92
	T3	14	68.71	6.14	60	79

Table 5 Evolution of heart rate according to study group.

Group	Time	*n*	Mean	SD	Min	Max
	T0	15	90.07	27.65	61	145
Clonidine	T1	15	81.60	25.13	55	143
	T2	15	97.93	15.29	68	122
	T3	15	97.73	18.45	63	128
	T0	14	88.43	23.41	49	130
Placebo	T1	14	86.50	19.22	60	125
	T2	14	97.79	16.56	61	121
	T3	14	94.07	16.87	60	123

clonidine ($p < 0.001$) and placebo ($p < 0.001$) groups. In clonidine and placebo groups, T2 differed significantly from T0 ($p < 0.05$) and T1 ($p < 0.05$), with significantly higher value; other comparisons showed no significant difference.

Nonparametric Mann–Whitney test showed that the groups did not differ regarding nitroprusside at T0 (=0.901), T2 (=0.138), and T3 (=0.147). The groups differed at T1 (=0.022), when the clonidine group showed a significantly lower value compared to placebo.

Table 8 shows the comparison of groups regarding dobutamine evolution.

Nonparametric Friedman test revealed that there was significant change in dobutamine dosage in clonidine ($p < 0.001$) and placebo groups ($p < 0.001$). In clonidine and

Table 6 Evolution of MAP according to study group.

Group	Time	*n*	Mean	SD	Min	Max
	T0	15	38.40	13.02	36.00	26.00
Clonidine	T1	15	30.93	19.16	24.00	18.00
	T2	15	28.80	11.03	27.00	11.00
	T3	15	25.47	7.98	25.00	11.00
	T0	14	31.36	5.09	31.00	25.00
Placebo	T1	14	24.50	7.55	25.00	12.00
	T2	14	27.64	8.16	27.50	19.00
	T3	14	22.86	5.60	22.00	10.00

Table 7 Evolution of sodium nitroprusside according to study group.

Group	Time	*n*	Mean	SD	Min	Max	Group
	T0	15	0.16	0.23	0.00	0.00	0.64
Clonidine	T1	15	0.01	0.05	0.00	0.00	0.21
	T2	15	0.90	0.55	0.75	0.00	2.10
	T3	15	0.48	0.62	0.24	0.00	2.10
	T0	14	0.19	0.32	0.00	0.00	1.00
Placebo	T1	14	0.25	0.39	0.00	0.00	1.29
	T2	14	1.27	0.84	1.05	0.00	3.40
	T3	14	0.79	0.66	0.63	0.00	2.10

Table 8 Evolution of dobutamine according to study group.

Group	Time	*n*	Mean	SD	Min	Max	Group
	T0	15	0.33	1.29	0	0	5
Clonidine	T1	15	2.00	2.54	0	0	5
	T2	15	5.00	1.89	5	0	10
	T3	15	5.67	1.76	5	5	10
	T0	14	0.00	0.00	0	0	0
Placebo	T1	14	0.36	1.34	0	0	5
	T2	14	5.00	0.00	5	5	5

Table 9 Total dose of fentanyl according to study group.

Group	*n*	Mean	SD	Min	Max	Mean	*p**
Clonidine	15	19.33	4.17	20	10	25	0.208
Placebo	14	21.43	4.57	20	15	30	

* Descriptive level of probability of Student's *t*-test.

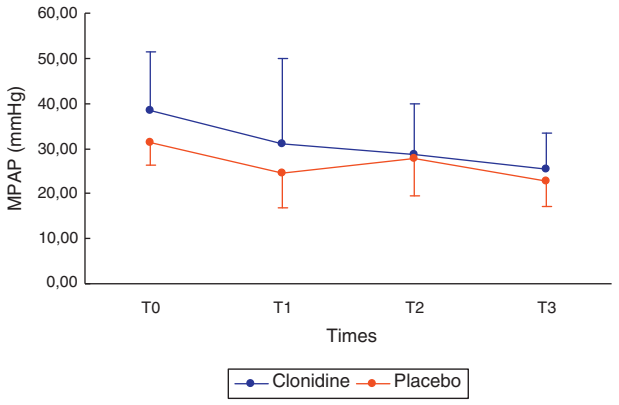

Figure 3 Evolution of PMAP.

placebo groups, T0 and T1 differed significantly from T2 ($p < 0.05$) and T3 ($p < 0.05$) and had significantly lower values. Other comparisons showed no significant difference.

Nonparametric Mann–Whitney test showed no difference between groups in relation to dobutamine at T0 ($p = 0.370$), T2 ($p = 1.000$), and T3 ($p = 0.180$). There was difference between groups at T1 ($p = 0.045$), with a significantly higher value for clonidine compared to placebo.

Table 9 shows the comparison of groups regarding total fentanyl, and it was observed that there was no significant difference between groups regarding total dose of fentanyl.

Discussion

Pulmonary hypertension associated with left heart diseases has the same pathophysiological processes of other forms of the disease. Early in the development of PH, hypoxic vasoconstriction that, a priori, is a reversible physiological mechanism becomes constant and difficult to reverse.[12]

Unlike what happens in physiological conditions, endogenous vasodilators, such as nitric oxide and prostacyclin, are unable to balance the effects of mediators responsible for vasoconstriction, such as thromboxane A2, endothelin, and serotonin. Vascular remodeling involves the three coats of the pulmonary bed arteries and consists of intimal hyperplasia, medial hypertrophy, and proliferation of adventitious.[13]

In situ thrombosis results from change in flow pattern, which becomes slower; changes in the endothelium;[14] and increased platelet activity by increased activity of thromboxane A2.[13]

Patients with group II pulmonary venous hypertension exhibit ventricular dysfunction (on the left) secondary to valvular heart disease and ischemic cardiomyopathy (on the right) by pressure overload.[2] Hypotension is part of this complex picture. Pulmonary resistance precludes the passage of blood and limits the left ventricle filling. Therefore, stroke volume, cardiac output, and blood pressure are reduced.

PH causes hypoxemia and hypercapnia, which in a vicious circle aggravate pulmonary vasoconstriction. Metabolic acidosis and nociceptive stimulation, common events during anesthesia, may also accentuate the PH.

For the reasons cited above, pharmacological intervention is mandatory in these patients perioperatively.

Clonidine, due to its action on locus coeruleus, promotes sedation and spinal cord analgesia, hence, the anesthesiologists' interest in using it in the perioperative period. The cardiovascular action of clonidine is well known. Its vasodilator activity is due to peripheral and central mechanisms. Peripherally, the activation of α_2-adrenergic receptors on presynaptic nerve terminals inhibits noradrenaline exocytosis, which partially explains the hypotensive effect. At central level, it acts on the vasomotor center α_2-receptors in the nucleus of the solitary tract, decreases sympathetic outflow, with potentiation of parasympathetic nervous activity, and leads to reduced blood pressure.[6,15,16]

Despite the presence of α_2-adrenergic receptors on nerve endings and other pulmonary structures[7–9] and the recognized central vasodilator effect of clonidine, there are no reports in the literature of the use of this drug to attenuate pulmonary hypertension in PH adult patients undergoing cardiac surgery.

Clonidine could be a viable option for pH control, because in addition to the benefits already mentioned,

clonidine is known to be safe. Its effects, which may sometimes interfere with cardiac output, such as bradycardia or hypotension, are easily reversed with atropine or vasopressor such as ephedrine. The cost of its use should also be taken into account because it has a low price and is available in most hospitals worldwide.

The possibility of reducing pulmonary arterial pressure with the use of clonidine may still allow a reduction or even elimination of drugs that are routinely used in pH and—even though effective for disease control—are not without relevant undesired side effects.

This is the case of dobutamine, which is used in this research to improve cardiac performance and reduce pulmonary vascular resistance in PH patients. Dobutamine is a synthetic catecholamine, isoproterenol derivative, adopted in our service and widely used worldwide for treating PH patients undergoing heart surgery.[9] It can be administered alone or in combination with other drugs. Dobutamine is a β-adrenergic agent with predominant action on β1-receptors, which increases the concentration of cyclic adenosine monophosphate and leads to increased cardiac inotropy and chronotropy, reducing systemic vascular and pulmonary resistance. Dobutamine at a dosage of 5–10 μg/kg/min improves cardiac contractility.

Due to its activity in β2-adrenergic receptors and increased release of endogenous adenosine, it has coronary vasodilator effect (with normofunctioning vascular endothelium).[17] However, doses higher than 10 μg/kg/min, as it is often necessary to achieve the vasodilator effect in pulmonary artery and increase RV contractility in PH patients, increase cardiac work and myocardial oxygen consumption. Thus, there is an imbalance between supply and consumption of O_2, followed by myocardial ischemia. Its vasodilator effect may exacerbate systemic hypotension found in PH patients.[3]

Another drug routinely used in cardiovascular surgery and also in this study is sodium nitroprusside.[5,18] This drug reduces right ventricle afterload by decreasing pulmonary vascular resistance. Recognized as a potent vasodilator, NTP may, even in recommended therapeutic doses, cause very undesirable side effects. Undesirable effects such as coronary steal, increased intracranial pressure, volume compensatory need, toxicity by its metabolites, metabolic acidosis, and intrapulmonary shunt are particularly found in cardiac patients undergoing heart surgery.

The potential effect of clonidine by lowering pulmonary vasculature pressure could result beneficial for dose reduction or even elimination of these drugs.

Patients in this study underwent heart surgery to treat their underlying diseases causing pulmonary hypertension, such as valvular heart disease and heart failure, with cardiopulmonary bypass under general balanced anesthesia. Regarding diagnostic method to select them, we opted for the right heart catheterization, because it is regarded as the gold standard examination for PH diagnosis.[12]

All patients were ventilated with a mixture of oxygen and air (1:1) to avoid low fraction of inspired oxygen, which could worsen pulmonary hypertension, as we know. Ventilation was set to maintain capnometry between 30 and 35 mmHg in order to prevent hypercarbia, an aggravating factor for pulmonary hypertension. The gradient of about 5 mmHg or less was considered,[19] which is recorded by the capnometry device as a result of gas that does not participate in gas exchange (alveolar dead space).

We try to keep the same regime of fluid and blood replacement in both groups during surgery, even during CPB (same volume in milliliters per kilogram of body weight in the perfusate and control of hemoconcentration in the presence of perfusion). Therewith, we had no significant difference regarding water and blood balance or urine output between the two groups in the perioperative period. Differences in blood volume could result in significant changes in systemic and pulmonary arterial pressures and hinder the reliability of the research.

Still on the method used, after the registration of the first variables (T0) and the slow administration of clonidine or placebo, it was decided to wait 30 min to measure the variables of the subsequent time (T1), because this is the approximate time of this drug latency. We opted to perform the last measurements (T3) 10 min after protamine. Because this drug is alkaline, it may release histamine when injected rapidly[20,21] and, combined with its ability to activate the complement system when circulating through the pulmonary vasculature (in a complex formed with heparin),[22] it could worsen PH and thus alter the measurements of pulmonary arterial pressure.

In the present study, except at T1, the administration of clonidine was not associated with reduced pulmonary artery pressure or decreased need for infusion of drugs used for this purpose. At T1, clonidine group received significantly lower doses of sodium nitroprusside and significantly higher doses of dobutamine. These differences were not repeated at other times and perhaps may be explained by the less intense surgical stimulation in this phase of the intervention. At that time, the surgical team waited for the latency time of clonidine, without manipulating patients, before starting CPB.

Reducing pulmonary arterial pressure in patients with pulmonary hypertension of any disease classification group is a difficult task. For this purpose, endothelin antagonists (bosentan), prostacyclin analogs (iloprost) or sildenafil has been clinically used. Intraoperatively, phosphodiesterase inhibitors such as milrinone and inhaled nitric oxide are used. These options are not always able to reverse the right ventricle deterioration by exacerbation of PH or improve gas exchange.[23]

Therefore, the fact that there is no statistically significant difference between the clonidine and placebo groups regarding pulmonary arterial pressure measurements is not surprising, although the ability of this drug to decrease vascular tone is known. However, it is surprising that there was no difference between the two groups regarding systemic blood pressure, heart rate, and fentanyl consumption. After all, among other effects, the ability of this drug to reduce blood pressure and heart rate is well established.

Similarly, the potential of clonidine to reduce the need for anesthesia in cardiac surgery is known.[24] Perhaps the positive chronotropic activity of dobutamine has suppressed the bradycardic effect of clonidine and not allowed difference between both groups with respect to heart rate. Furthermore, catecholamine levels are high during CPB and remained so even after aortic declamping[25–27] and may overcome the effects of clonidine on heart rate and blood pressure.

Thus, it was necessary to maintain the opioids dosage. Clonidine has a long half-life (approximately 12 h). Thus, although there has been no reduction in intraoperative PH, one cannot rule out that the pulmonary vasodilatory action of clonidine is expressed in the late postoperative period, when the endogenous adrenergic activity is reduced.

The dose of clonidine used in this research may also be questioned. Intravenous dosage prescribed by several authors[28–30] and in our everyday practice is 2 μg/kg. However, when Kulka et al. examined the clonidine dose–response in cardiac surgery, with 2, 4 or 6 μg/kg IV[28] on sympathetic-adrenal response, they only found effectiveness in blocking catecholamine and hemodynamic responses with 4 or 6 μg/kg.

In fact, higher doses may be associated with more significant vasodilator effect on pulmonary artery and reduce the need for dobutamine and sodium nitroprusside. However, high doses could also cause (in a counterproductive way) hypertension and worsen PH by acting on postsynaptic α_2-adrenergic receptors in walls of the pulmonary arteries.[31]

Due to the desirable effects reported by several authors,[32–34] such as diuretic, reduced tremors with decreased myocardial oxygen consumption, and perioperative hemodynamic stability, among others, which were not goals of our research, clonidine will continue to be considered a useful adjuvant for heart surgery.

Conclusions

The analysis of data obtained in this study allows us to conclude that in patients of group 2, with pulmonary hypertension undergoing cardiac surgery, clonidine (2 μg/kg) administered intravenously after sternotomy was not able to reduce the pulmonary arterial pressure or reduce or eliminate the need for intraoperative dobutamine or sodium nitroprusside.

Conflicts of interest

The author declare no conflicts of interest.

Appendix.

A box of 30 ampoules with equal external labels, 15 with 150 μg clonidine in 1 mL solution and 15 with 1 mL distilled water, without the active ingredient (placebo), was sent by the Cristália laboratory.

Ampoules and patients were randomized by the laboratory. A list to be followed in numerical order was sent with the box. A sealed envelope containing the clonidine and placebo ampoules could only be opened at the end of the investigation.

During the study, both patients and the investigator were blind to the treatment used; therefore, it was a controlled, comparative, randomized and double-blind study.

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