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Assessment of evaluated pulmonary vascular resistance by isoproterenol infusion in patients with atrial septal defects

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Abstract

Aim and Background

Congenital heart diseases constitute a major category of disorders associated with pulmonary hypertension in atrial septal defect there is tendency to repair essentially all large defect except some of those with severe obstructive pulmonary vascular diseases. In this study the isoproterenol is used for assessment of patients with atrial septal defect, with elevated pulmonary / systemic vascular resistance ratio.

Methods and Results

100 cases with atrial septal defect, with pulmonary hypertension received isoproterenol infusion. Haemodynamic findings found among all patients with atrial septal defect before and after isoproterenol infusion. There is a significant in pulmonary blood flow after isoproterenol infusion (from $5.34455 + 0.730$ to $6.3300 + 0.870$ liter/minute $P < 0.001$).

Conclusion

Isoproterenol is a successful and reliable pulmonary vasodilator that can be used to predict the reversible element of pulmonary hypertension in patient with left to right shunts (ASD) patients.

Keywords: Atrial septal defects, isoproterenol infusion, Pulmonary vascular resistance

INTRODUCTION

Pulmonary hypertension is defined as an increase in the pulmonary artery pressure beyond normal; that is, when the mean pulmonary artery pressure is more than 20 mmHg (normal range of mean pulmonary artery pressure: 8–19 mmHg) [1].

Congenital heart diseases constitute a major category of disorders associated with pulmonary hypertension, as in cases of intracardiac and extracardiac shunts, in which precapillary pulmonary vascular resistance is sufficiently increased to prevent elevation of pulmonary capillary pressure and excessive left-to-right shunting and to allow adequate systemic blood flow. So over a period of time, the pulmonary conductance progressively diminishes (i.e. obstruction increases).

Thus, the magnitude of left-to-right shunting gradually decreases and eventually results in a reversal of shunting and cyanosis later on [2].

In ventricular septal defect, atrial septal defect, and patent ductus arteriosus, currently, there is a tendency to repair all large defects except some of those with severe obstructive pulmonary vascular diseases essentially. In contrast, at a particular stage in the evolution of congenital heart diseases, pulmonary hypertension is produced at least in part by vasoconstriction and therefore is potentially reversible. On this basis, it is essential to know whether any of this increased resistance is because of active vasoconstriction. As vasoconstriction plays an important role, its assessment may be helpful in evaluating the condition of pulmonary hypertension for surgical correction, so the administration

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of pulmonary vasodilators during cardiac catheterization is of value [3].

Pulmonary vasodilators are classified into four groups: β -adrenergic agonists, α -adrenergic blockers, calcium channel blockers, and finally, those that act directly on vascular smooth muscle [4].

In this study, isoproterenol is used for assessment of patients with an atrial septal defect (ASD), with elevated pulmonary/systemic vascular resistance ratio.

Aim

This work aims to assess the effect of intravenously administered isoproterenol infusion during cardiac catheterization on elevated pulmonary/systemic vascular resistance ratio in patients with an ASD to help in assessing operability.

Isoproterenol and its role in the elevated pulmonary vascular resistance

Isoproterenol (isopropyl norepinephrine, isoproterenol) is the most potent of the sympathomimetic amines that act almost exclusively on β receptors [5].

Isoproterenol has a powerful action on all β receptors and almost no action on α receptors. Its primary action, therefore, is on the heart, the smooth muscles of bronchi, skeletal muscle vasculature, and the alimentary tract. Moreover, it exerts noticeable metabolic effects in adipose tissue skeletal muscle, and, in some species, the liver. [5].

Cardiovascular system

Intravenous infusion of the isoproterenol in humans lowers peripheral vascular resistance, mainly in skeletal and also in renal and mesenteric vascular beds, and decreases diastolic pressure. Cardiac output is increased because of the positive inotropic and chronotropic actions of the drug. With usual doses of isoproterenol, the increase in cardiac output is generally enough to maintain or increase the systolic pressure, although the mean pressure is reduced. In normotensive patients, renal blood flow is decreased, but it is markedly increased in patients with cardiogenic or septic shock [5]. Larger doses may cause a striking decrease in mean blood pressure [5].

Smooth muscle

Isoproterenol relaxes almost all varieties of smooth muscle when the tone is high, but this action is most pronounced on bronchial and gastrointestinal smooth muscle. It prevents or relieves bronchoconstriction owing to drugs and bronchial asthma in human, but tolerance to this effect develops with overuse of the drug. Its effect on asthma may be owing to, in part, an additional action to inhibit antigen-induced release of histamine; selective β -receptor stimulants share this action [6].

The drug decreases the tone and motility of intestinal musculature and inhibits uterine motility [5]. Isoproterenol can cause central excitation, but this is not significant with doses used clinically [5].

Absorption fate and excretion: Isoproterenol when given parenterally or as an aerosol is readily absorbed. Its metabolism is in the liver primarily and other tissues by catechol – methyltransferase enzyme [7].

Isoproterenol is a relatively poor substrate for monoamine oxidase and is not taken up by sympathetic neurons. Therefore, the duration of action of isoproterenol may be longer than that of epinephrine, but it is still brief [5].

Preparation and routes of administration: Isoproterenol hydrochloride inhalation is available as 0.25% aerosol and as solutions (0.25–1%) for nebulization. The drug is also available as isoproterenol hydrochloride injection containing 200 mg/ml [5].

Isoproterenol sulfate is available as a powerful agent for use with an inhaler. Sublingual and oral preparations of isoproterenol are unreliable, and their use is not recommended [5].

Toxicity and adverse effects: The acute toxicity of isoproterenol is much less than that of epinephrine. Its adverse effects include palpitation, tachycardia, headache, and flushing of the skin. Anginal pain, nausea, tremor, dizziness, weakness, and sweating are less frequent.

Overdosage of isoproterenol administered by inhalation can be fatal because of the induction of ventricular arrhythmias [5].

Isoproterenol is employed clinically only as a bronchodilator in respiratory disorders and as a cardiac stimulant in heart block [6].

The role of isoproterenol in elevated pulmonary vascular resistance is that it increases pulmonary blood flow and decreases resistance in pulmonary vasculature. In normotensive pulmonary bed, each of pulmonary arterial pressure and pulmonary arterial wedge pressure remains unchanged, whereas in isoproterenol cases, there is active vasodilatation of the hypertensive vascular bed after receiving 20 mg of sublingual isoproterenol [8].

Lupi-Herrera *et al.* [3] performed the following study in 15 patients with ventricular septal defects and severe pulmonary arterial hypertension by using a short-term administration of isoproterenol. For the whole study group, the mean pulmonary artery pressure was 68 ± 2.6 mmHg, pulmonary vascular resistance index was 11.6 ± 0.9 μ/m^2 , and the pulmonary vascular gradient was 45 ± 3.5 mmHg. Infusion of isoproterenol decreased pulmonary artery pressure, pulmonary resistance index, pulmonary/systemic vascular resistance ratio, and pulmonary vascular gradient by an average of 10.2 mmHg, 2.88 μ/m^2 , 0.13, and 6.6 mmHg, respectively [3].

Of the six patients subjected to the acute intravenous administration of isoproterenol (0.5–2 $\mu g/min$), five showed decreased in their pulmonary vascular resistance. Both pulmonary artery pressure and resistance decreased in two patients, and there was no change in pressure in one

patient after the administration of isoproterenol in a dose of 0.5–1 $\mu\text{g}/\text{min}$ for 5–12 days.

All patients' values returned to the control level when isoproterenol was discontinued. Dawoud *et al.* [9] and Neutze *et al.* [10] performed a study in 87 patients with moderate to a severe elevation of pulmonary resistance owing to ventricular septal defects by using isoproterenol infusion in a dose of 0.14 $\mu\text{g}/\text{kg}/\text{min}$ for 15 min during cardiac catheterization, and the pulmonary vascular resistance was measured before and after administration of isoproterenol. Surgery was undertaken in these patients, and postoperative follow-up was done. The study showed a reliable estimate of resistance index less than 7 μ/m^2 , with vasodilator predicts an excellent postoperative response regardless of measurement at rest or other hemodynamic parameters.

Although observation on the postoperative progress of patients with a resistance index more than 7 μ/m^2 with a vasodilator is limited, an excellent postoperative cause is unlikely unless resistance can be lowered to a level close to 7 μ/m^2 [10].

PATIENTS AND METHODS

Patients

The study was conducted in the National Heart Institute on 100 cases with an ASD with pulmonary hypertension.

History for establishing the diagnosis, clinical examination, resting ECG, chest radiography, echo-Doppler study, and cardiac catheterization in only patients with pulmonary/systemic vascular resistance ratio above 0.7 due to the defects were studied.

Patients with ASD were divided into subgroups: subgroup A had patients younger than 20 years and subgroup B had patients older than 20 years.

- (1) History:
 - (a) Parents were asking about the infants' ease of breathing on feeding, repeated chest infection, grunting breathing, and history of cyanosis.
 - (b) In older patients, particular emphasis was placed on cyanosis, easy fatigability on effort syncopal attack, and chest pain.
- (2) Clinical evaluation: It including general and local examination for all patients.
 - (a) General examination:

Weight and length of the patients have also been recorded. Veins were examined to detect congestion and presence of prominent 'a' wave because of pulmonary hypertension with increased right atrial and ventricular pressures [2].
 - (b) Local examination:

The physical findings included those attributable to pulmonary hypertension, related to hypertensive persistence, right ventricular failure, right ventricular hypertrophy, accentuated pulmonary component of a commonly split second heart sound, and palpable

systolic pulsation in the second left intercostals space. Detection of the dilated main pulmonary artery and valve annulus often results in systolic ejection click and decrescendo diastolic murmur along the left sternal border for pulmonary valve regurgitation.

Moreover, we searched for right ventricular hypertrophy that produces a palpable left parasternal heave. Hypertrophy may also associate with fourth heart sound as evidence of systemic venous congestion.

Dilated right ventricle and tricuspid valve annulus cause functional tricuspid regurgitation (holosystolic murmur that may be accentuated by inspiration).

- (3) ECG:

A conventional 12-lead resting ECG was done for each patient with emphasis on the presence of the following:

 - (a) Deviation of the mean QRS axis to the right.
 - (b) Left ventricular hypertrophy.
 - (c) Biventricular hypertrophy.
 - (d) Right ventricular hypertrophy.
 - (e) Right atrial enlargement.
 - (f) Arrhythmias.
- (4) Chest radiography:

Chest radiography was done for each patient in posteroanterior view to show the following:

 - (a) Cardiothoracic ratio.
 - (b) Pulmonary artery size.
 - (c) Vasculature of the lungs.
- (5) Echo-Doppler study:
 - (a) Each patient underwent complete M-mode, two-dimensional pulsed, continuous, and color flow Doppler before cardiac catheterization. The patients were examined in supine and left lateral positions, and the following views were taken: parasternal, long axis, the short axis at multiple levels, apical four chambers, subcostal four chambers, and suprasternal views. The following dimensions were taken by using M-mode echocardiography: left ventricular dimensions in the peak systolic and end diastolic phase, posterior and septal wall thickness, right ventricular dimension, aortic root, and left atrial dimensions.
 - (b) The anatomic diagnosis was searched for by two-dimensional echocardiography.
 - (c) Continuous wave Doppler study was performed using an imaging transducer to estimate the maximal velocity and the pressure gradient across the shunt. Estimation of the systolic pulmonary artery pressure was done through estimation of pressure across the tricuspid valve regurgitation plus 10 mmHg.
 - (d) The accurate anatomic diagnosis was made by using color Doppler flow mapping to image the high-velocity jet across the defect.

- (6) Cardiac catheterization:
Cardiac catheterization was done for each patient in the following steps:
- (a) Premedication:
In childhood: mild sedation with a cocktail, which composed of chlorpromazine 6.25 mg, promethazine 6.25 mg, and pethidine 25 mg in 1 ml solution, given in a dose of 0.1 ml/kg with a maximum dose of 2 ml.
In adult: using xylocaine in a dose of 200 mg as infiltration anesthesia.
 - (b) Right-sided catheterization was done by venous Seldinger technique using National Institute of Health angiocatheter no. 5 or 6 Fr.
 - (c) Left-sided catheterization was done by arterial Seldinger technique using pigtail catheter no. 5 or 6 Fr.
 - (d) Angiography:
- (i) Aortography was done in the left anterior oblique view of about 55° to exclude the presence of aortic regurgitation, patent ductus arteriosus, and abnormalities of the coronary arteries.
 - (ii) Four chamber view was done in the left anterior oblique view of 60°, with cranial angulation of 20° in the left atrium, to show the site and size of the ASD. After complete left and right cardiac catheterization and absorption of the dye, blood oxymetry was performed from superior venacava; inferior venacava; high, mid, and low right atrium; pulmonary artery, that is, right ventricle, left ventricle, and aorta; and also pressures were measured from right atrium right ventricle, pulmonary artery, pulmonary wedge, left ventricle, and aorta. Then isoproterenol infusion was given in the peripheral venous line in a dose of 0.14 µg/kg/min for 15 min. After isoproterenol infusion was terminated, all blood samples and pressures were taken similarly as before isoproterenol infusion.

RESULTS

Hemodynamic findings obtained from all patients with an ASD (100 cases) before and after isoproterenol infusion are as follows:

- (1) Pulmonary blood flow showed a significant increase after isoproterenol infusion (from 5.3445 ± 0.730 to 6.3300 ± 0.870 l/min, $P < 0.001$).
- (2) There was no significant change in systemic blood flow after isoproterenol infusion (from 3.8382 ± 0.486 to 3.7809 ± 0.417 l/min, $P > 0.1$).
- (3) There is a significant increase in pulmonary/systemic blood flow ratio after isoproterenol infusion (from 1.3864 ± 0.055 to 1.6700 ± 0.129 , $P < 0.001$) [Figure 1].
- (4) There is a significant decrease in pulmonary vascular resistance after isoproterenol infusion (from 14.1900 ± 1.387 to 11.3373 ± 2.142 U, $P < 0.001$).

- (5) There is no significant difference in systemic vascular resistance after isoproterenol infusion (from 18.1000 ± 1.132 to 18.1755 ± 1.153 U, $P > 0.1$).
- (6) There is a significant decrease in pulmonary/systemic vascular resistance ratio after isoproterenol infusion (from 0.7782 ± 0.037 to 0.6155 ± 0.087 , $P < 0.001$) [Figure 2].

Hemodynamic findings found among patients with ASD who are younger than 20 years (50 cases) before and after isoproterenol infusion are as follows:

- (1) Pulmonary blood flow showed a significant increase after isoproterenol infusion (from 5.0880 ± 0.812 to 6.1300 ± 0.883 l/min, $P < 0.001$).
- (2) There is no significant change in systemic blood flow after isoproterenol infusion. (from 3.5960 ± 0.475 to 3.5760 ± 0.451 l/min, $P > 0.1$).
- (3) There is a significant increase in pulmonary/systemic blood flow ratio after isoproterenol infusion (from 1.4040 ± 0.041 to 1.7080 ± 0.047 , $P < 0.001$).
- (4) There is a significant change in systemic vascular resistance after isoproterenol infusion (from 17.4400 ± 0.911 to 17.4980 ± 0.881 U, $P > 0.1$).
- (5) There is a significant decrease in pulmonary/systemic vascular resistance ratio after isoproterenol infusion (from 0.7460 ± 0.011 to 0.5420 ± 0.033 , $P < 0.001$).

Hemodynamic findings found among patients with ASD older than 20 years (50 cases) before and after isoproterenol infusion are as follows.

- (1) Pulmonary blood flow showed a significant increase after isoproterenol infusion (from 5.5583 ± 0.646 to 6.4967 ± 0.904 l/min, $P < 0.001$).
- (2) There is no significant change in systemic blood flow after isoproterenol infusion (from 4.0400 ± 0.429 to 3.9517 ± 0.329 l/min, $P > 0.1$).
- (3) There is a significant increase in pulmonary/systemic blood flow ratio after isoproterenol infusion (from 1.3717 ± 0.064 to 1.6383 ± 0.171 , $P < 0.01$).
- (4) There is a significant decrease in pulmonary vascular resistance after isoproterenol infusion (from 15.1083 ± 1.091 to 12.8133 ± 1.747 U, $P < 0.01$).
- (5) There is no significant change in systemic vascular resistance after isoproterenol infusion (from 18.6500 ± 1.048 to 18.7400 ± 1.094 U, $P > 0.1$).
- (6) There is a significant decrease in pulmonary/systemic vascular resistance ratio after isoproterenol infusion (from 0.8050 ± 0.027 to 0.6767 ± 0.067 , $P < 0.01$).
- (7) There is a significant decrease in pulmonary vascular resistance after isoproterenol infusion (from 13.0880 ± 0.733 to 9.5660 ± 0.686 U, $P < 0.001$).

DISCUSSION

Pulmonary hypertension is defined as an increase in the pulmonary artery pressure beyond normal; that is, when the mean pulmonary artery pressure is more than

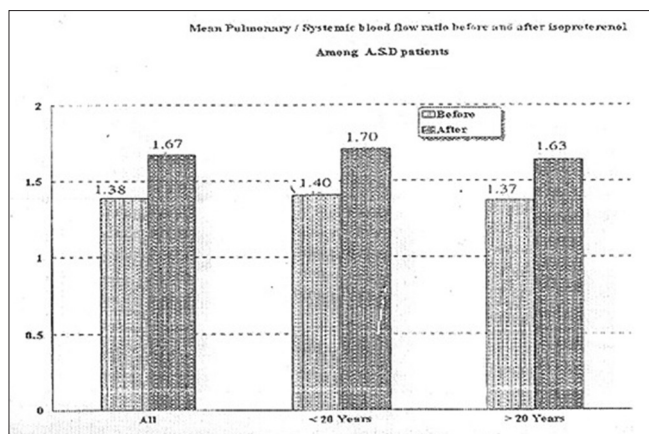


Figure 1: Mean pulmonary/systemic blood flow ratio before and after isoproterenol among ASD patients.

20 mmHg (normal range of mean pulmonary artery pressure: 8–19 mmHg) [1].

Congenital heart diseases constitute a major category of disorders associated with pulmonary hypertension, as in cases of intracardiac and extracardiac shunts, in which precapillary pulmonary vascular resistance is sufficiently increased to prevent elevation of pulmonary capillary pressure and excessive left-to-right shunting and to allow adequate systemic blood flow. So, over a period of time, the pulmonary conductance progressively diminishes (i.e. obstruction increases).

Thus, the magnitude of left-to-right shunting gradually decreases and eventually results in a reversal of shunting and cyanosis later on [2].

α -Adrenergic blocking agent (tolazoline) has been reported to produce a transient fall in pulmonary vascular resistance in patients with pulmonary hypertension, having a major reversible component, including primary pulmonary hypertension and congenital heart diseases [11].

Angiotensin-converting enzyme inhibitor (enalapril) was used to treat patients with a ventricular septal defect, ASD, and patent ductus arteriosus associated with pulmonary hypertension.

It was concluded that enalapril might be a useful drug in the treatment of pulmonary arterial hypertension secondary to congenital cardiopathy [12].

Abenzothiadiazine zinc derivative (diazoxide) may be used to improve pulmonary vascular obstructive disease if there is a favorable response to intravenous diazoxide in cases of ventricular septal defect [13].

Arachidonic acid metabolite (prostacyclin) is a pulmonary vasodilator in congenital heart diseases (ventricular septal defect, ASD, and patent ductus arteriosus) with pulmonary hypertension, but its cause in systemic hypotension necessitates caution in its use [14].

Calcium channel blockers (verapamil, diltiazem, and nifedipine) can be used as pulmonary vasodilators in patients

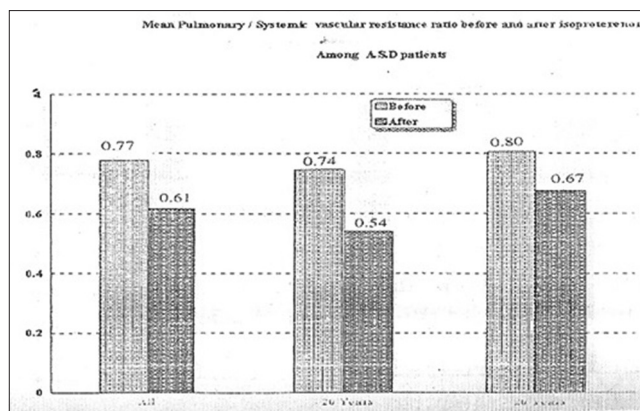


Figure 2: Mean pulmonary/systemic vascular resistance ratio before and after isoproterenol among ASD patients.

with pulmonary hypertension secondary to congenital heart diseases or primary pulmonary hypertension. High doses were required to produce marked hemodynamic responses, but many patients cannot tolerate these doses [15].

In the present study, we administered isoproterenol as a pulmonary vasodilator to 100 patients with severe pulmonary hypertension (pulmonary/systemic vascular resistance ratio above 0.7) secondary to ASD. Isoproterenol is cheap and available drug with minimal adverse effects.

The drug was given by intravenous route in a dose 0.14 $\mu\text{g}/\text{kg}/\text{min}$ for 15 min, as recommended by Neutze *et al.* [10], but not as done by Lupi-Herrera *et al.* [3] who injected isoproterenol in the pulmonary artery, and unlike Lee *et al.* [8], who administered isoproterenol tablets sublingual, and a significant increase in the pulmonary blood flow and pulmonary/systemic blood flow ratio after isoproterenol infusion was found.

This study was performed on 100 patients with ASD with pulmonary hypertension. There were 60 males and 40 females, and their ages ranged from 13 to 47 years. The patients had moderate to severe pulmonary hypertension of diverse etiology. Pulmonary vascular resistance before isoproterenol ranged between 8 and 23 U and after isoproterenol infusion ranged between 4.4 and 23 U ($P < 0.01$).

The pulmonary/systemic vascular resistance ratio before isoproterenol infusion ranged between 0.34 and 0.84 and after isoproterenol ranged between 0.2 and 0.84, values less than 0.01. In this study, isoproterenol failed to give any appreciable hemodynamic effect in six patients: two younger than 20 years and four older than 20 years

From the clinical, ECG, and radiographic data of different groups, it showed that isoproterenol was more effective in patients younger than 20 years in each group, with no cyanosis, accentuated pulmonary second sound, no syncopal attack, right ventricular hypertrophy, sinus rhythm prominence pulmonary trunk, or increased heart size. Moreover, it was less significantly effective in patients older than 20 years in each group, with cyanosis, single second sound, syncopal attack,

mild right axis deviation, rhythm, mild increase pulmonary trunk, and average heart size.

Conclusion and recommendation

From the aforementioned data, it can be concluded that isoproterenol is a potent and reliable pulmonary vasodilator that can be used to predict the reversible element of pulmonary hypertension in patients with left-to-right shunts (ASD).

The effect of isoproterenol is more significant in patients younger than 20 years and less in those older than 20 years. Moreover, postoperative follow-up studies are needed to evaluate the surgical results with left-to-right shunts.

In conclusion, isoproterenol can be used routinely for assessment of elevated pulmonary vascular resistance due to ASD.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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