Brief Review

Testing pulmonary vasoreactivity*

Teste de vasorreatividade pulmonar

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Abstract

Pulmonary arterial hypertension is classified as idiopathic or secondary (associated with collagenoses, heart disease, portal hypertension, pulmonary thromboembolism, and pulmonary vascular diseases). Pulmonary vasoreactivity should be tested in order to define the best treatment option. Of the many drugs that have been used to test pulmonary vasoreactivity, inhaled nitric oxide is the best choice, due to its specific pulmonary effect and very short half-life (5-10 s). The results of this test identify candidates for heart surgery among patients with congenital heart disease and candidates for the use of calcium antagonists among patients with other forms of pulmonary arterial hypertension. Performing and interpreting the results of such tests are a great responsibility, since mistakes can lead to incorrect treatment decisions, resulting in the death of patients.

Keywords: Hypertension, pulmonary/diagnosis; Nitric oxide/diagnostic use; Administration, inhalation.

Resumo

A hipertensão arterial pulmonar é classificada como idiopática ou secundária (associada a colagenoses, cardiopatias, hipertensão portal, tromboembolismo pulmonar e doenças da vasculatura pulmonar). O teste de vasorreatividade pulmonar é indicado para definir a melhor opção terapêutica. Muitas drogas têm sido utilizadas para a realização desse teste, sendo o óxido nítrico inalado a melhor opção, por apresentar ação específica pulmonar e meia vida muita curta (5-10 s). O resultado desse teste identifica candidatos à cirurgia cardíaca nas cardiopatias congênitas e candidatos ao uso de antagonista de cálcio nas outras formas de hipertensão pulmonar. A realização e interpretação do teste de vasorreatividade pulmonar exigem grande responsabilidade, e erros podem levar a decisões erradas e à ocorrência de óbitos.

Descritores: Hipertensão pulmonar/diagnóstico; Óxido nítrico/uso diagnóstico; Administração por inalação.

Introduction

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary artery pressure (MPAP) > 25 mmHg at rest and > 30 mmHg during exercise.[1] Observations suggest that vasoconstriction plays an important role in the pathogenesis of PAH. This disease is characterized by medial hypertrophy of pulmonary arterioles, decreased endothelial production of vasoconstrictors (prostacyclin and nitric oxide), and increased production of the vasoconstrictor endothelin.[2]

Pulmonary arterial hypertension (PAH) is classified as idiopathic, when the cause is unknown, or secondary, when it is associated with pulmonary parenchymal diseases, heart disease, pulmonary vasculitis, collagenoses, or pulmonary thromboembolism.

In cases of idiopathic PAH (IPAH), one-, three-, and five-year survival rates after symptom onset are 68%, 48%, and 34%, respectively.[3] Calcium antagonist drugs have a known pulmonary vasodilator effect, decreasing pulmonary pressure and increasing the survival and quality of life of patients with IPAH.[4] However, less than 20% of these patients, corresponding to those that present pulmonary vasoreactivity, should use this medication.[5] For patients not presenting pulmonary vasoreactivity, the use of calcium

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Financial support: None.
Submitted: 2 August 2007. Accepted, after review: 24 January 2008.

antagonists is inadvisable, due to the very lack of response to the medication and due to the risk of severe complications, including death.

In order to gain a better understanding of what is discussed here, normal values were listed (Chart 1).

Hemodynamic classification of pulmonary arterial pressure

The various categories of PAH are defined according to pressure and pulmonary resistance (Table 1).

Indications for testing pulmonary vasoreactivity

The following are among the various clinical indications for testing pulmonary vasoreactivity:

- cases of complicated congenital heart disease and severe PAH in which clinical and noninvasive tests are inconclusive as to the best approach
- cases of candidates for Fontan surgery, or variants, presenting pulmonary pressure above the ideal level
- cases of IPAH with level of evidence A or cases of PAH associated with systemic diseases with level of evidence E/C,[6] in order to evaluate treatment options
- cases of candidates for heart transplantation, in order to evaluate the need for concomitant lung transplantation

Chart 1 - Normal values.

RAP	1-8 mmHg
LAP	2-12 mmHg
PASP	18-30 mmHg
MPAP	2-16 mmHg
PRI	80-240 dynes.s^{-1}·cm^{-5}
SRI	1,600-2,400 dynes.s^{-1}·cm^{-5}
CI	2.8-4.2 L/min^{-1}/m^{-2}
AoSP	90-120 mmHg
PRI/SRI ratio	1/6-1/10
PASP/AoSP ratio	1/4-1/6

RAP: right atrial pressure; LAP: left atrial pressure; PASP: pulmonary artery systolic pressure; MPAP: mean pulmonary artery pressure; PRI: pulmonary resistance index; SRI: systemic resistance index; CI: cardiac index; and AoSP: aortic systolic pressure.

Table 1 - Hemodynamic classification of pulmonary hypertension.

Mean pulmonary pressure (mmHg)	Resistance index (dynes.s^{-1}·cm^{-5}/m^2)	Classification
< 25	< 320	Normal
25-45	320-400	Slight increase
46-65	400-640	Moderate increase
> 65	> 640	Pronounced increase

Drugs used to test pulmonary vasoreactivity

Various substances with pulmonary vasodilator properties have been used to test pulmonary vasoreactivity, as described below.

Nifedipine

Sublingually or orally administered, nifedipine involves risk of severe complications, such as systemic hypotension and death, as well as having a half-life of 2-5 h. The availability of safer drugs makes the use of nifedipine inadvisable.[7,8]

Prostacyclin

Prostacyclin has a recognized pulmonary vasodilator effect, as well as an onset of action and a half-life of a few minutes. However, prostacyclin is costly, is not available in Brazil, and has no proven superiority over other drugs that are more accessible.[9]

Sildenafil

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase type 5, abundant in the lungs. Phosphodiesterase type 5 inhibition prevents the degradation of cyclic guanosine monophosphate, which is an intracellular messenger of nitric oxide, with consequent pulmonary vasodilation. Sildenafil has been used to treat PAH of various causes,[10-13] including crisis of PAH.[14]

Although continuous venous administration of this drug could be a good option for testing pulmonary vasoreactivity, this presentation is not available on the market, and there are few published studies on the use of sildenafil in humans.[15,16]

Adenosine

Adenosine has a known pulmonary vasodilator effect, as well as an onset of action and a half-life of

a few seconds. Various studies have described its use in the treatment of PAH of various causes[17-19] and in testing pulmonary vasoreactivity,[20,21] with doses ranging from 50 to 500 μg/kg^{-1}/min^{-1}. Adenosine would have the advantage of greater availability, especially in developing countries, over inhaled nitric oxide (iNO), if the efficacy of the former were comparable to that of the latter. However, this is a question that remains unanswered.

Continuous infusion of adenosine should be given into the pulmonary artery (PA) using an additional catheter or into the opening of the right ventricle using a Swan-Ganz catheter in the absence of interventricular communication or in cases of patent ductus arteriosus. These measures prevent adenosine from reaching the systemic circulation without passing through the pulmonary circulation, which could cause systemic hypotension. The most common side effects include bronchospasm, chest pain, and bradycardia, which usually make it impossible to continue the test.

Pure oxygen

For several years, pure oxygen has been used to test pulmonary vasoreactivity, especially in cases of congenital hear disease.[22]

It has the advantage of being available in all facilities, being easily administered, and having almost no side effects. Since its effect on other forms of PAH is not well defined, pure oxygen should not be the drug of choice in these situations. When pure oxygen is used to test pulmonary vasoreactivity in cases of congenital heart disease, the dissolved oxygen should be included in the calculations of pulmonary blood flow (Qp) and systemic blood flow (Qs). Calculations performed using the simplified formula, without including the dissolved oxygen, can lead to severe interpretation errors, with false-positive results.

Example: a patient with interventricular communication and severe PAH, with no evidence of pulmonary hyperflow in the baseline state, presented the following results after using pure oxygen: arterial oxygen tension (PaO_2) and aortic peripheral oxygen saturation (SpO_2) in the aorta (Ao) = 100 (100%); PaO_2 and SpO_2 in the PA = 90 (90%); PaO_2 and SpO_2 in the vena cava (VC) = 50 (80%); and PaO_2 and SpO_2 in the pulmonary vein (PV) = 400 (100%).

- Using the simplified formula:

$$Qp/Qs = (SpO2 \text{ in the Ao} - SpO2 \text{ in the VC}) \div (SpO2 \text{ in the PV} - SpO2 \text{ in the PA}) = 2$$

an intervention should be considered.

- Using the complete formula, including the dissolved oxygen:

$$Qp/Qs = [(13.6 \times \text{hemoglobin} \times SpO_2 \text{ in the Ao}) + (0.031 \times PaO_2 \text{ in the Ao})] - [(13.6 \times \text{hemoglobin} \times SpO_2 \text{ in the VC}) + (0.031 \times PaO_2 \text{ in the VC})] \div [(13.6 \times \text{hemoglobin} \times SpO_2 \text{ in the PV}) + (0.031 \times PaO2 \text{ in the VC})] - [(13.6 \times \text{hemoglobin} \times SpO2 \text{ in the PA}) + (0.031 \times PaO2 \text{ in the PA})] = 1.2$$

surgical correction of heart disease would be contraindicated.

Inhaled nitric oxide

Due to its selective pulmonary vasodilator effect and rapid onset of action (< 10 s), iNO is currently considered the drug of choice for testing pulmonary vasoreactivity. Doses range from 5 to 80 ppm, and there are rarely any side effects, since it is used for a short time during the procedure.[23-25]

In order to test pulmonary vasoreactivity, iNO is administered via an endotracheal tube, a laryngeal tube, or a face mask, the last being the most common method of administration in adults. The iNO is introduced into the airway using a "T" or "Y" connector, at approximately 35 cm from the entrance of the airway connections (Figure 1). The

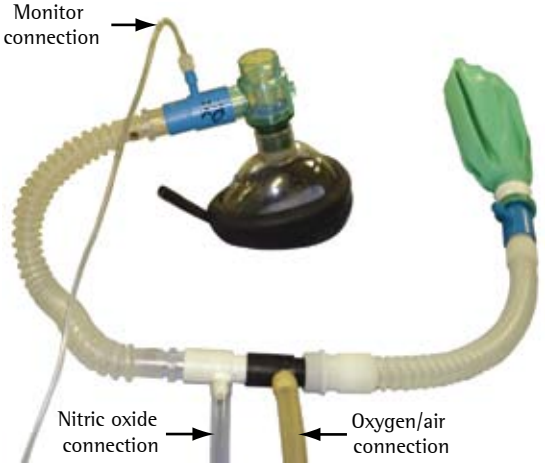

Figure 1 - Model for the use of nitric oxide via a mask.

closest port is reserved for the monitor connection. Of the two distal ports, one (the most distal) is used for the oxygen/air connection, and the other is used for the nitric oxide connection.

The face mask should be comfortably adjusted, and the expiratory valve should be working properly, in order to prevent carbon dioxide retention. Since it preferably acts on well-ventilated airways, decreasing pulmonary shunt, iNO has advantages over other vasodilators. It is stored in 300-, 800-, and 2,000-ppm cylinders. The concentration to be used is determined by increasing the iNO flow until the desired value is identified on the monitor. In the absence of a monitor, the estimation of the iNO flow needed to reach the desired concentration can be calculated using the following formula:

iNO flow offered = (oxygen/air flow used × desired iNO dose × 1,000) ÷ concentration of the cylinder used

Examples:

- In the case of a 300-ppm cylinder, an oxygen/air flow of 10 L/min, and a desired iNO dose of 10 ppm, the iNO flow needed will be 333 mL/min—(10 × 10 × 1,000) ÷ 300.
- Using an 800-ppm cylinder, the iNO flow will be 125 mL/min—(10 × 10 × 1,000) ÷ 800.

The cost of using iNO to test pulmonary vasoreactivity is low (less than R$100.00, or US$50.00), since it is used for a short time during the procedure. However, a cylinder and a monitor need to be available, and this makes the procedure more costly in facilities where it is rarely used. Unfortunately, there are few facilities in Brazil where iNO is available for testing pulmonary vasoreactivity.

Technique

The ratio between pulmonary circulation and systemic circulation should be determined based on readings obtained simultaneously in order to avoid momentary pressure changes that can cause interpretation errors.

In the absence of intracardiac shunt, cardiac and pulmonary outputs can be calculated by the thermodilution technique or using the Fick method. In the presence of shunt, the thermodilution technique should not be used, since it yields false results.

The pressures should be carefully monitored after confirming that the equipment is correctly calibrated, with the baseline (zero) calibrated for the midaxillary line.

Arterial pressure can be measured through cannulation of the femoral or radial artery, as well as through noninvasive methods.

Right atrial pressure (RAP) is easily measured using a catheter or through the proximal opening of the Swan-Ganz catheter, and pulmonary capillary pressure (PCP) can be measured using a wedged Swan-Ganz catheter. In patients with right-to-left shunt, even if only through a patent foramen ovale, the catheter balloon should be insufflated with carbon dioxide, due to the risk of rupture and paradoxical embolism when it is insufflated with air.

When it is difficult to obtain a reliable PCP curve, as sometimes occurs in the presence of greatly dilated pulmonary vessels, left atrial pressure (LAP), measured through the foramen ovale, when it is patent, or retrogradely, when it is closed, can be used. Another alternative is to use left ventricular end-diastolic pressure (LVEDP), which is usually equal to LAP in the absence of mitral stenosis. When LVEDP is used, its curve should leave no room for doubt as to the pressure thresholds.

When the Swan-Ganz catheter is used, there can be difficulties in positioning it in the PA, due to dilated right heart chambers and tricuspid or pulmonary insufficiency. In this situation, the use of a guide wire is generally recommended. It is not always possible to position the catheter without creating a large loop in the right ventricle, which can cause arrhythmias. In such cases, by insufflating the balloon in a distal branch and pulling the catheter gently, it is usually possible to undo the loop

Table 2 - Patient with idiopathic pulmonary arterial hypertension presenting pulmonary vasoreactivity.

Criterion	Baseline	After 20 ppm of iNO for 5 min
Right atrial pressure	10	10
Pulmonary capillary pressure	10	10
Cardiac index	3.2	3.6
Pulmonary output/systemic output	1	1
Mean pulmonary artery pressure	40	28
Mean aortic pressure	95	95
Pulmonary resistance index	750	400
Pulmonary resistance/ systemic resistance	0.48	0.29

iNO: inhaled nitric oxide.

without moving the catheter out of the desired position.

Factors that can have a transient effect on the results

Transient alterations in pulmonary pressure and systemic pressure can cause errors in the interpretation of the results.[26] Simultaneous measurements and the comparison between them are more important than the analysis of the result in isolation. In order to avoid errors, arterial carbon dioxide tension, body temperature, catheter permeability and position, as well as the level of anxiety and sedation, should be controlled, and the first measurements should not be taken until at least 5 min after parameter stabilization.

Summary

Regardless of the medication selected to test pulmonary vasoreactivity, factors that can have a transient effect on pressure values should be eliminated. Such factors include acidosis, systemic arterial hypotension or hypertension, changes in temperature, arrhythmias, pulmonary ventilation asymmetry (when blood is collected from the PVs), and variations in the level of sedation during the measurements. After these factors have been eliminated, the following steps should be taken:

- monitor RAP, LAP (or PCP or LVEDP), PA pressure, and systemic pressure
- collect blood samples for oximetry at the shortest intervals possible
- if, during the measurements, there are alterations in the clinical profile (level of consciousness, changes in temperature, pulmonary abnormalities, or delayed sample collection from different sites), allow 10 min for stabilization and repeat the process
- collect blood from PVs through the interatrial communication, when present, or retrogradely through the left ventricle when pure oxygen is used in the presence of intracardiac shunt
- wait for the results of the tests before removing the catheters, and, in cases of inconclusive results, repeat the steps
- take the baseline measurements with the patient breathing room air, and repeat them after pure oxygen inhalation for 15 min and after nitric oxide inhalation via a mask or an endotracheal tube at graded doses (increased every 5 min in the absence of response) of 10, 20, 30, 40, 50, 60, and 80 ppm
- in the absence of response, combine pure oxygen and iNO
- measure the pressures, the Qp/Qs ratio, pulmonary resistance (PR), and systemic resistance (SR), as well as the ratio between them
- calibrate the manometer, maintaining the value of zero at the level of the midaxillary line

Interpreting the results of tests used to determine pulmonary vasoreactivity

The interpretation of the results of tests used to determine pulmonary vasoreactivity in cases of IPAH or in cases of PAH associated with systemic diseases should focus on changes in pulmonary and systemic pressures. However, in cases of congenital heart disease, the focus should be on alterations in resistances and in pulmonary and systemic outputs. In cases of heart disease, there can be significant output changes, with resistance alterations, but without significant pressure changes.

Example: a patient with interventricular communication and pulmonary and systemic pressures of 100 mmHg who, after being tested for pulmonary vasoreactivity, presents no pressure changes, but in whom the Qp/Qs ratio increases from 1.2 to 2.4, indicating a significant decrease in PR, that is, the presence of pulmonary vasoreactivity.

Criteria indicating the presence of pulmonary vasoreactivity

Heart disease with shunt

An increase in the Qp/Qs ratio greater than 1.8 and accompanied by a decrease in the PR index/SR index ratio greater than 30% should be interpreted together with other information, such as auscultation findings during the test, alterations in systemic oxygen saturation during exercise, and clinical examination findings, as well as the results of electrocardiography, chest X-ray, echocardiography, and angiography (pulmonary flow).

A patient with interventricular communication who presents decreased systemic oxygen saturation during exercise, even if the Qp/Qs ratio remains

between 1.5 and 1.8 at rest, is hardly likely to benefit from surgical treatment.[8,27]

Idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension associated with noncardiac causes

A recent criterion defines the presence of pulmonary vasoreactivity as a decrease in MPAP of at least 10 mmHg, its final value being ≤40 mmHg, without changes or with improvement in cardiac output. Table 2 shows data on the presence of pulmonary vasoreactivity.

Common errors in interpreting the results of tests used to determine pulmonary vasoreactivity

As previously mentioned, the results of tests used to determine pulmonary vasoreactivity can be influenced by various transient factors, which should be recognized and eliminated. In addition, there can also be errors in the interpretation of the results of tests used to determine pulmonary vasoreactivity.[8] The following are the most common such errors:

- Designating as unresponsive a patient with heart disease and shunt who, after being tested for pulmonary vasoreactivity, does not present decreased pulmonary pressure, without taking resistance values and the Qp/Qs ratio into account.
- Using the simplified method of calculating the Qp/Qs ratio in a patient on pure oxygen, in which the elimination of the dissolved oxygen can falsely increase pulmonary flow, with a consequent decrease in PR, even in inoperable cases.
- Analyzing the results without considering the alterations in the systemic circulation, absence of response being indicated by a significant decrease in PR in congenital heart disease—with an equal or greater decrease in SR and without a significant change in the PR/SR ratio—or a significant decrease in the PA pressure/arterial pressure ratio in other causes of PAH.
- Collecting blood samples for oximetry at different times can cause severe errors in interpreting the results of tests used to determine pulmonary vasoreactivity.
- Interpreting the results of tests used to determine pulmonary vasoreactivity without correlating them with other clinical parameters can lead to errors in the final treatment strategy adopted.
- Accepting an inconclusive PCP value in cases of an intact interatrial septum preventing the measurement of the left atrium by this route; in cases in which a good PCP measurement cannot be obtained and there is no communication between the atria, LAP should be measured retrogradely, or a good LVEDP curve should be obtained, after excluding mitral valve stenosis.
- Not waiting for the results of blood gas analysis before finishing a test used to determine pulmonary vasoreactivity, which makes it difficult to repeat the test when the results are inconclusive.

Final considerations

Testing pulmonary vasoreactivity in severe patients is an invasive procedure whose result can indicate the best treatment option to be adopted. Recently, the European Society of Cardiology established a criterion to define the presence of pulmonary vasoreactivity in cases of IPAH: a decrease in MPAP of at least 10 mmHg accompanied by a decrease in absolute PAP values to less than 40 mmHg.[14] This same criterion has been used for other forms of PAH, except for congenital heart disease with pulmonary hyperflow. However, it is important to emphasize that the precise definition of pulmonary vasoreactivity is still controversial.

Various substances with pulmonary vasodilator properties can be used to test pulmonary vasoreactivity. However, since many of these substances can have severe side effects and a long half-life, these risks should be considered when they are used. Due to its specific pulmonary vasodilator effect, minimal systemic effect, and short half-life (only a few seconds), iNO has been the drug of choice. Due to the fact that it is available at all facilities and is inexpensive, pure oxygen is a good option in the absence of iNO or can be combined with iNO in the absence of response to one or the other. Interest in using adenosine for this purpose has increased, although its role in this process has yet to be well defined.

The results of tests used to determine pulmonary vasoreactivity can be influenced by various transient changes, which should be recognized and corrected.

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