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EFFECT OF NITRIC OXIDE ON EARLY MYOCARDIAL FUNCTION IN VALVULAR SURGERY

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A b s t r a c t

The aim of this study was to evaluate the effect of inhaled nitric oxide on the central (pulmonary) haemodynamics in the patients undergoing surgery for mitral valve or combined defects, with special focus on the period after weaning of the patient from the extracorporeal circulation (ECC). A total of 50 patients were randomly allocated to two groups. One had nitric oxide added to the inhalation mixture at the time of weaning (NO group) and the other was administered nitroglycerine (NTG group). The haemodynamic values were measured on four occasions: before skin incision, after sternotomy, on weaning from ECC and at the end of surgery. A comparison of pre- and intra-operative values showed that both pulmonary artery pressure and pulmonary vascular resistance were significantly reduced only in the NO group. The increase in cardiac output was higher in the NO group, though it was significant in both groups. The right ventricular systolic function, as measured by ejection fraction, increased in the NO group only. The results show that inhaled nitric oxide, a selective vasodilatator of the pulmonary vascular bed, is more effective in reducing vascular resistance than nitroglycerine and allows for a better function of the right ventricle and easier weaning from ECC after mitral valve repair.

K e y w o r d s

Nitric oxide, Pulmonary hypertension, Extracorporeal circulation, Valvular disease

INTRODUCTION

In patients with mitral valve disease, left atrial pressure may be increased, which results in a passive increase in pulmonary venous pressure and, eventually, reactive pulmonary vasoconstriction. In addition, morphological changes may develop in vascular walls, including proliferation of smooth muscle tissue and lumen reduction, which leads to a further increase in pulmonary vascular resistance. During cardiac surgery, pulmonary hypertension may further be enhanced towards the end of the surgical procedure, particularly at the time of weaning the patient from extracorporeal circulation (ECC). Peri-operative factors affecting pulmonary hypertension include the release of vasoactive substances (*1*), decreased release of nitric oxide (NO) from the endothelium (*2,3*) and, in some cases, slow adaptation of the left ventricle to haemodynamic changes due to valve replacement. The right ventricle is subjected to an acute increase in resistance in the pulmonary artery bloodstream, which occurs shortly after

weaning. The standard therapy for pulmonary hypertension includes nitrates and, when indicated, calcium antagonists or prostaglandins. In the early post-operative period, it is supplemented with pulmonary vasodilators or inotropic drugs or inotropic agents with vasodilating effects (inodilators).

The treatment of pulmonary hypertension by anti-hypertensive drugs mentioned above, however, is not optimal because it may induce systemic hypotension. Research in vascular biology has recently offered a new possibility for management of pulmonary hypertension following cardiac surgery. It considers the release of nitric oxide from intact endothelium to be a principal vasodilatation mechanism (*4*); in congestive heart failure, NO release is decreased (*5*). In congenital heart disease, pulmonary endothelial dysfunction may be an additional factor responsible for the development of pulmonary hypertension in association with weaning from ECC (*6*).

The aim of this study was to evaluate and compare the effects of nitroglycerine and inhaled nitric oxide on the pulmonary haemodynamic responses in cardiac surgery patients with a history of pulmonary hypertension.

MATERIALS AND METHODS

Patients

This retrospective study included 50 patients who underwent elective surgery for defects of one or more cardiac valves in the period from May 2001 to June 2002. The patients were in the New York Heart Association (NYHA) classes II, III and IV. The relevant data characterising the groups are presented in *Table 1*. All patients were operated on by the same team of surgeons using standard procedures. Ten patients were eventually excluded from the study because of their increased requirements for inotropic support, deviation from the standard procedure, incomplete data or complications of technical nature. The statistical evaluation included 19 patients treated with nitric oxide (NO group) and 21 patients given nitroglycerin (NTG group).

Surgical proceure

Before surgery, all patients received pre-medication with diazepam (10 mg) and, immediately before the operation, morphine (10 mg) and atropine (0.5 mg). Anaesthesia was induced with a bolus dose of sufentanil (2.5 mg/kg) and pancuronium (0.1 mg/kg) and continued with sufetanile (50 mg/h), mizadole (3 mg/h) and pancuronium (2 mg/h). Till the end of surgery it was maintained with sufentanile (50 mg/h), midazolam (3 mg/h) and pancuronium (2 mg/h). In order to administer nitric oxide, a connector was inserted in the inspiratory branch of the ventilation circuit at the site before the tracheal cannula. Blood samples for haemodynamic assessment were collected from catheters inserted in the pulmonary vein and pulmonary artery. The values were calculated by means of Vigilance and Explorer (Edwards) haemodynamic monitors. Extracorporeal circulation was used at normothermia, employing a capillary oxygenator filled with crystalloids and manitol (1300 ml); haematocrit was maintained between 20% and 27%. Equal filling ventricular pressures were provided by the administration of crystalloids (700 – 1200 ml) before ECC introduction, the rest of oxygenator priming after weaning from ECC and 10% starch solution with erythrocyte mass thereafter. The vasodilator (40 ppm nitric oxide or 1 to 3 mg nitroglycerine per kg per min) was administered shortly before weaning from ECC.

Table 1

Patient demographic and clinical data

	NO group (n = 19)	NTG group (n = 21)
Age	67 ± 7	62 ± 11
Men	7	8
Women	12	13
NYHA class II / III / IV	6 / 9/ 14	6 / 11/ 3
ECC (duration in min)	67 ± 15	61 ± 16
Aortic clamping (min)	46 ± 11	39 ± 8
Diagnosis		
Mitral valve defect	7	10
Mitral and tricuspid valve defect	5	4
Mitral and tricuspid valve defect and aortic defect	4	5
Mitral valve defect and revascularisation	3	2

NO, nitric oxide; NTG, nitroglycerin; NYHA, New York Heart Association classification.

Table 2

Haemodynamic values during the surgical procedure in NO and NTG groups

Haemodynamic value	Before incision	After sternotomy	At 15 min after ECC	End of surgery	Statistical significance
NO group					
MPAP (mm Hg)	35±5	35±5	29±4	28±4	$P < 0.05$
PCWP (mm Hg)	19±5	19±6	16±5	15±4	$P < 0.03$
PVRI (dyne.sec.cm^{-5}.m^{-2})	310±80	250±80	250±80	220±60	$P < 0.05$
CI (1.min^{-1}.m^{-2})	2.3±0.4	2.6±0.5	2.9±0.7	2.9±0.4	$P < 0.001$
RVEF (%)	32±10	30±9	37±8	37±8	$P < 0.05$
NTG group					
MPAP (mm Hg)	36±6	31±6	29±3	29±3	NS
PCWP (mm Hg)	17±4	17±5	15±4	15±5	NS
PVRI (dyne.sec.cm^{-5}.m^{-2})	330±90	320±100	280±90	290±80	NS
CI (1.min^{-1}.m^{-2})	2.6±0.7	2.6±0.5	3.2±0.6	3.0±0.6	$P < 0.05$
RVEF (%)	35±11	35±11	37±10	35±9	NS

NO, nitric oxide; NTG, nitroglycerin; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; CI, cardiac index; RVEF, right ventricular ejection fraction; NS, no significant difference between pre- and post-operative values within the group.

HAEMODYNAMIC ASSESSMENT

The haemodynamic parameters studied included the mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance index (PVRI), cardiac index (CI) and right ventricular ejection fraction (RVEF). The first measurements were taken after the introduction of anaesthesia just before making a skin incision and the second were made after sternotomy and haemodynamic stabilisation of the patient. After weaning from ECC, 10 min. after circulation stabilisation, the third measurements were made. The last measurements were carried out after sternum closure.

STATISTICAL METHODS

The results of pre- and intra-operative haemodynamic measurements in each group were compared and evaluated by the paired *t*-test and the differences between the NO and NTG groups were analysed by Student's *t*-test. *P* values of less than 0.05 were considered statistically significant. The data were expressed as mean ± standard deviation values.

RESULTS

There were no differences in demographic data, NYHA classes, ECC duration or aortic declamping between the NO and NTG groups. The initial haemodynamic values were also very similar (*Tables 1* and *2*).

With the administration of anti-hypertensive therapy, there was an improvement in haemodynamic values in both group, with the NO group showing better results. When the pre- and post-operative values were compared, decreases in the mean pulmonary arterial pressure and pulmonary vascular resistance were significant only in the NO group ($P<0.05$). Cardiac output increased in both groups but, in the NO group patients, its increase was more significant ($P< 0.05$ against $P < 0.001$). The right ventricular systolic function improved only in the NO group while, in the NTG group, it remained unchanged. A decrease in pulmonary capillary wedge pressure was significant in the NO group only ($P<0.05$), which also might indicate a significant improvement in left ventricular function (*Table 2*).

DISCUSSION

A patient weaned from the ECC system is at risk of acute failure of the right ventricle. This exists in all patients undergoing cardiac surgery but is highest in heart transplant recipients. The causes of right ventricle failure are either a temporary reduction of right ventricle function after ischaemic cardioplegic arrest and an increased resistance of the pulmonary artery bed resulting from the pulmonary reaction to ECC (systemic inflammatory response syndrome), or a passive increase in pressure due to transient maladaptation of the left ventricle to valve defect correction. The current therapy is based on nitrates that effectively reduce resistance in the pulmonary vascular bed but often induce systemic hypotension. Consequently, noradrenaline must be administered or blood volume

must be increased to prevent a decrease in coronary perfusion pressure and subsequent deterioration of myocardial function (5).

Nitric oxide, a ubiquitous substance in biology, is involved in many functions in the organism and, among other things, induces relaxation of vascular smooth muscle. Although its dilation effect has been used in clinical medicine, for instance, in controlling hypoxic pulmonary insufficiency in newborn infants, its application is still thought to be at the clinical research level because of the need to elucidate its role in pathophysiological mechanisms of several diseases in which it was detected (6).

Nitric oxide is used in the treatment of post-operative hypoxemia arising from ventilation-perfusion mismatch after cardiac surgery (*7,8*). The beneficial effects of nitric oxide on pulmonary hypertension in patients undergoing surgery for congenital defects (*9*) or ischaemic heart disease (*10*) have been demonstrated.

In our patients surgically treated for valvular disease, inhaled nitric oxide had a significantly higher effect on the reduction of resistance in the pulmonary vascular bed than routinely used nitroglycerin. It resulted in an improved systolic function of the right ventricle that was not found in the patients receiving nitroglycerin. Although both agents increased cardiac output, nitric oxide was more effective, which implies that the decrease in dynamic resistance in the pulmonary vascular bed also had a positive effect on left ventricular function.

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EFEKT OXIDU DUSNATÉHO NA ČASNOU FUNKCI MYOKARDU PO OPERACI CHLOPENNÍCH VAD

S o u h r n

Cílem studie bylo prozkoumat účinek inhalovaného oxidu dusnatého na centrální (plicní) hemodynamiku pacientů, operovaných pro mitrální či kombinované vady,se zaměřením na období po zastavení mimotělního oběhu (MTO).Pacienti s mitrální vadou či kombinací této vady s další chlopenní vadou nebo ICHS byli rozděleni náhodně do dvou skupin (25+25), přičemž jedna skupina měla při odpojování od mimotělního oběhu přidán do inhalační směsi oxid dusnatý a druhá skupina byla léčena nitroglycerínem. Hemodynamický profil byl měřen čtyřikrát: před incizí kůže, po sternotomii, po zastavení MTO a na konci operace. Pokles tlaku v a.pulmonalis oproti předoperační hodnotě byl statisticky významný jen ve skupině s NO a stejně tak tomu bylo s plicní cévní rezistenci. Srdeční výdej se zvýšil sice v obou skupinách, ale statisticky významnější vzestup byl pozorován ve skupině s NO. Rovněž systolická funkce pravé komory, měřená ejekční frakcí se zvýšila jen ve skupině s NO. Oxid dusnatý, selektivní vazodilatátor plicnicového řečiště, více snížil plicní cévní rezistenci než nitroglycerín.

Při operaci mitrální chlopně se tento efekt projevil v lepší funkci pravého srdce a ve snadnějším odpojení pacienta od mimotělního přístroje.

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