ORIGINAL ARTICLE

Braz J Cardiovasc Surg 2004; 19(3): 309-313

Early and late use of dopamine after myocardial ischemia

Uso precoce e tardio de dopamina após isquemia miocárdica

Ademar R. SOUZA[1], Marcos A. M. SILVA[2], Rubens R. ANDRADE[2], Reinaldo A. OLIVEIRA[2], Antônio S. MARTINS[2]

RBCCV 44205-699

Abstract

Objective: **To evaluate the effect on the left ventricular function of the early and late use of dopamine in an experimental model of an isolated heart.**

Method: **Were used 60 rabbits in an isolated heart model sustained by animal support. An intraventricular balloon was placed in the left ventricle. Three groups were constituted: a control group (CG); a group that received dopamine precociously (Dopa E) and a group that received dopamine after 20 minutes (Dopa L). Direct and indirect hemodynamic readings were taken.**

Results: **Coronary artery flow: CG (7.196 ± 1.275 mL/min); Dopa E (9.477 ± 1.160 mL/min); Dopa L (14.316 ± 2.308 mL/min), with CG = Dopa E, CG ≠ Dopa L and Dopa E ≠ Dopa L. First intraventricular positive derivative of the pressure (dp/dt+): CG (719.61 ± 127.53 mmHg/s); Dopa E (719.61 ± 127.53 mmHg/s); Dopa L (1431.60 ± 230.87 mmHg/s), p<0.05, Dopa E ≠ Dopa L, CG=Dopa E and CG ≠ Dopa L. First intraventricular negative derivative of the pressure (dp/dt-): CG (469.85 ± 107.16 mmHg/s); Dopa E (716.07 ± 215.66 mmHg/s); Dopa L (931.24 ± 181.46 mmHg/s), p<0.05, Dopa E≠Dopa L≠CG. Delta V: CG (1.355 ± 0.2432 mL); Dopa E (0.97 ± 0.3199 mL); Dopa L (1.27 ± 0.2983 mL), p>0.05, Dopa E = Dopa L = CG. Developed systolic stress: CG (27.273 ± 10.276 g/cm²); Dopa E (55.219 ± 24.625 g/cm²); Dopa L (79.152 ± 12.166 g/cm²), Dopa E=Dopa L, Dopa E = CG and CG ≠ Dopa L. Malonic Dialdehyde (MDA): CG (4.5 ± 0.527 mmol/L); Dopa E (4.7 ± 1.16 mmol/L); Dopa L (4.1 ± 0.7379 mmol/L), p>0.05, Dopa E=Dopa L=CG.**

Conclusion: **We concluded that, in the delineated experimental model, the early use of the dopamine was deleterious as shown by some hemodynamic variables.**

***Descriptors*: Dopamine. Ventricular function; Myocardial ischemia; Models, animal.**

Resumo

Objetivo: **Avaliar os efeitos na função ventricular esquerda do uso precoce e tardio de dopamina, em modelo experimental de coração isolado.**

Método: **Foram utilizados 60 coelhos em modelo de coração isolado mantido por animal suporte. Um balão**

Work performed in the Experimental Laboratory of the Surgery Department - UNESP Botucatu. 1 Post Graduation course in Surgery -UNESP-Botucatu 2 Heart Surgery – Surgery and Orthopedics Department –FMB – UNESP

Correspondence address:
Ademar R. Souza. Caixa Postal 539 Campus Unesp. Botucatu – SP. CEP 18618-000. Phone (14) 9775-0505. E-mail: ademaresilviane@uol.com.br

Article received on October, 2003
Article accepted on June, 2004

intraventricular foi locado no ventrículo esquerdo. Três grupos foram constituídos: grupo controle (GC); grupo que recebeu dopamina precoce (Dopa P) e grupo que recebeu dopamina tardia (após 20 minutos) (Dopa T). Foram realizadas leituras hemodinâmicas diretas e indiretas.

Resultados: **Fluxo sangüíneo coronariano: GC(7,196 ± 1,275ml/min); Dopa P (9,477 ± 1,160ml/min); Dopa T (14,316 ± 2,308ml/min), com GC=Dopa P, GC ≠Dopa T e Dopa P≠Dopa T. Primeira derivada temporal da pressão intraventricular (dp/dt+): GC (719,61 ± 127,53ml/min); Dopa P (719,61 ± 127,53ml/min); Dopa T (1431,60 ± 230,87ml/min), p<0,05, Dopa P≠Dopa T, GC=Dopa P e GC ≠ Dopa T. Primeira derivada temporal da pressão intraventricular negativa (dp/dt-): GC (469,85 ± 107,16mmHg/s); Dopa P (716,07 ± 215,66mmHg/s); Dopa T (931,24 ± 181,46mmHg/s), p<0,05, Dopa P≠Dopa T≠GC. Delta V: GC (1,355 ± 0,2432ml); Dopa P (0,97 ± 0,3199ml); Dopa T (1,27 ± 0,2983ml), p>0,05, Dopa P=Dopa T=GC. Estresse sistólico desenvolvido: GC (27,273 ± 10,276g/cm²); Dopa P (55,219 ± 24,625g/cm²); Dopa T (79,152 ± 12,166g/cm²), Dopa P=Dopa T, Dopa P=GC e GC ≠ Dopa T.Dialdeído Malônico (MDA): GC (4,5 ± 0,527μmol/L); Dopa P (4,7 ± 1,16μmol/L); Dopa T (4,1 ± 0,7379μmol/L), p>0,05, Dopa P=Dopa T=GC.**

Conclusões: **Concluiu-se que, no modelo experimental delineado, o uso precoce da dopamina foi deletério, segundo algumas variáveis hemodinâmicas.**

Descritores: **Dopamina. Função ventricular. Isquemia miocárdica. Modelos animais.**

INTRODUCTION

Since the beginning of the modern era of heart surgery, myocardial protection has been the object of numerous studies, evolving from the "clamp and go" method published by Cooley to the sophisticated methods of Hearse, Buckberg and Braile [1,2].

Over the last decade, the type of patient being submitted to heart surgery has changed considerably and today older patients with worse ventricular functions and more associated diseases are being considered [3-5]. These patients require, at the end of the surgery, the support of vasoactive drugs [6-11] or even prolonged circulatory assistance and intra-aortic balloons. KOMAI et al. [11] and LASAR et al. [12] reported the deleterious effects of inotropic agent use in this kind of patient, in particular, with the early use of these drugs [13], that is, soon after interruption of aortic clamping. Since then, very few investigations have considered this concept either clinically or experimentally. Several inotropic drugs with varying results have been reported in the literature, however, dopamine continues to be the most common agent used in the postoperative period of heart surgery, generally because of its well known effects and low cost.

The objective of the present study is to evaluate the repercussions of early and late use of dopamine on the left ventricular function in an experimental model.

METHOD

A total of 60 Norfolk-2000 Botucatu-variant rabbits of both genders, with weights varying from 2000 to 3000 grams were used. These animals were provided by the animal house on the campus of the São Paulo State University in Botucatu, Brazil.

In each experiment two rabbits were utilized, one of them was denominated the support animal and the other the donor (the rabbit which donated the isolated heart). The animals were randomly allocated to the different groups. The support animal was anesthetized using pentobarbital (30 mg/kg EV), which was slowly introduced through the auricular vein. If necessary before the sternotomy, another 7.5 mg/kg of the drug was applied in bolus. Anesthesia was maintained by additional doses (15 mg/kg) at 60-minute intervals.

After trichotomy of the cervical region a 3.5-cm incision in the skin and subcutaneous tissue of the neck was performed. The right jugular vein was dissected and cannulated using a polyvinyl catheter. Systemic heparinization (5,000 IU of heparin in bolus with additional EV doses of 2,500 IU at 45-minute intervals) was performed and subsequently the right carotid artery was dissection and cannulated. Ventilatory support was established by the dissection and cannulation of the trachea and the use of a polyvinyl tube. The system of ventilatory support utilized was the one described by MARTINS [14], with oxygen enhancement.

The donor animal was anesthetized in a similar way to the support animal. Systemic heparinization (5,000 UI of heparin in bolus) was performed together with the anesthesia. Trichotomy of the lower thoracic region was made and the animal was placed on a Claude Bernard drip. A medium-sternal thoracotomy was performed with a 10-cm incision of the skin and subcutaneous tissue using a Nº 11 scalpel blade starting in the cervical region and finishing 2 cm below the xiphoid. Sectioning along the length of the sternum was performed using Mayo scissors. An orthostatic retractor was positioned, the pleura were punctured and the thymus removed. The aorta was clamped using Halsted forceps and the heart was removed from the mediastinum.

The pericardium was incised using scissors and the aorta was sectioned using a Nº 11 scalpel blade. The aorta was cannulated (Braile cannula ® for retrograde cardioplegia) and repaired with a cotton 2-0 thread. A left atriotomy was performed and an intraventricular balloon was inserted. The

heart was placed in Ringer lactate solution at 35-37º.

The modified Langendorff system was filled with the blood from the donor rabbit heart and Ringer lactate solution.

The hearts were connected to the perfusion line of the modified Langendorff perfusion system. The chambers of the circuit were topped up with the rest of the donor animal's blood.

The system (Figure 1) constituted of an arterial circuit that, by means of a peristaltic pump (model 1250 A, Harvard Apparatus®), removed the blood from the support animal and infused it in the donor heart. The fluid, which had been infused in the donor heart was collected in a reservoir and suctioned by the peristaltic pump (at the same speed as the infusor) and returned to the jugular vein of the support animal. The blood was continuously re-circulated, with the aim of maintaining a constant perfusion pressure of 70 mmHg. To warm the blood, warmed water was utilized in a cardioplegia heat exchange unit produced by Macchi®.

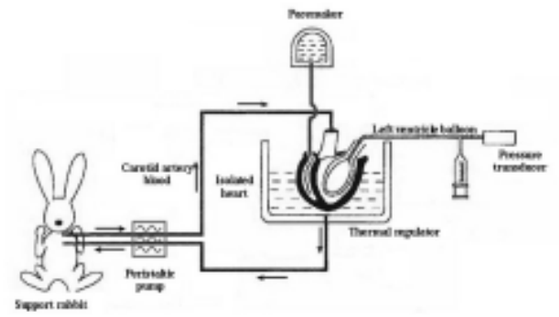

Fig. 1 – Perfusion system

The flow of the pumps was checked during the experiment, using a measuring cylinder graduated in millimeters (Vidrolabor ®) over a period of one minute. The rate of the coronary artery blood flow was directly measured by timed collections.

As is standard in our laboratory, the guide wire of a balloon was passed through the top of the left ventricle and using light traction the balloon was placed in the left ventricle. A purse string suture was adjusted to avoid prolapse of the balloon to the left atrium. The balloon was connected to a pressure transducer to measure volume and pressure of the left ventricle. Adjustment of the volume of the intraventricular balloon was achieved though the infusion of saline solution into the balloon (using a 1-mL syringe – for greater accuracy), thereby determining the greatest volume that did not increase the diastolic pressure to more than zero. This value was denominated V0.

The electrode of the thermometer was placed in the arterial line and in the right ventricle, in order to check that the temperature was about 37 ºC.

After the initiation of perfusion within the system, a period of 20 minutes was allowed for stabilization of the isolated heart. In this stabilization phase, using a temporary pacemaker electrode (model IMC®, with 5V stimulation and 1.5 mseg pulse width), the heart received artificial electrical stimulation to the right ventricle at 120 stimuli per minute. Increases of 0.1 mL in the intraventricular balloon volume were performed sequentially until a diastolic pressure of 25 mmHg was obtained (final diastolic volume approximated that of a normal rabbit heart during external work). Utilizing the Biopac 100® polygraph with its transducers, the hemodynamic attributes were verified throughout the experiment. After acquiring the initial data, the fluid in the balloon was adjusted to obtain a final diastolic pressure of 0 mmHg.

Three groups were established:

- Group 1: Control Group, without dopamine
- Group 2: Group with early dopamine infusion (Dopa E).
- Group 3: Group with delayed dopamine (Dopa L).

All groups went through the following stages (Figure 2): period of stabilization (20 minutes) ⇨ period of ischemia (30 minutes) ⇨ period of reperfusion (20 minutes).

Dopamine was utilized at a dose of 10µg/kg/min. In the Dopa E Group, its administration started soon after the period of ischemia of the isolated heart and in the Dopa L Group, after the reperfusion process (Figure 2).

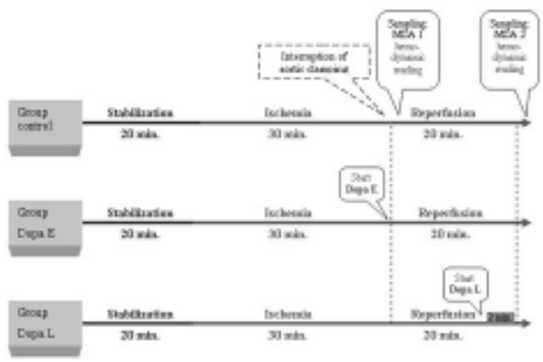

Fig. 2 – Sequence of events

At the beginning of reperfusion (interruption of aortic clamping) and 20 minutes after its initiation, the coronary artery flow, myocardial injury (MDA- Malonic Dialdehyde) and left ventricular complacency (intraventricular balloon) were measured and myocardial performance was calculated (using dp/dt).

Statistic analysis was achieved using variance analysis (factorial ANOVA) and the Tukey statistical test. Differences were considered significant when the p-value was less than 0.05.

Tabela 1. Variáveis segundo os grupos.

Grupos	Fluxo coronariano ml/min	Dp/dt+ mmHg/seg	Dp/dt- mmHg/seg	Delta V ml	Estresse sistólico g/cm2	MDA µmol/L
Controle	7.196±1.275	719±127.53	469.85±107.16	1.355±0.2432	27.273±10.276	4.5±0.53
Dopa P	9.477±1.160	947.77±116.06	716.07±215.66	0.97±0.3199	55.219±24.625	4.7±1.16
DopaT	14.316±2.308*	1431.60±230.87*	931.24±181.46*	1.27±0.2983	79.152±12.166	4.1±0.74

* p-value < 0.05

RESULTS

The coronary artery flow variables, dp/dt + and dp/dt- were significantly greater in the Dopa L Group. There were no differences in the other variables (Table 1).

COMMENTS

Experimental models constitute the basis of research by fulfilling the ethical principles however, transferring these results to clinical practice must be performed with great care. The model of the isolated heart is sacred in research, being utilized in studies about myocardial protection. The support animal model allows perfusion of an isolated heart with blood, which leads to better physiological results [14-16]. The use of rabbits as the experimental animals enables easier surgical manipulation and more reliable results, as the rabbit presents a similarity to humans in respect to calcium kinetics, composition of the myosins and the response to ischemic injury.

Despite the numerous publications about vasoactive drugs that exist, dopamine continues to the most widely utilized mainly due to its easy manipulation, the greater understanding of the drug by anesthesiologists and intensivists and to its low cost. [17]. When a patient needs to use this drug because of low cardiac output, the standard dose is 10µg/kg/minute hence we adopted this dose in the experiment.

We evaluated the systolic function using the variable: dp/dt+ and resulting systolic stress. The first derivative of the intraventricular pressure in its positive deflection was significantly greater in the Dopa L Group when compared to the Dopa E and the Control Groups. However, there were no statistically expressive differences in the resulting systolic stress. This latter index is based on the relationship between stress and deformation, assessing the heart muscle itself. The dp/dt+ is based on the relationship between pressure and volume, assessing the left ventricular performance as a chamber [18]. Thus, the results reported here are not conflicting, but complementary, the early use of dopamine affected the left ventricular performance as a chamber, which was corroborated by the diastolic function index. The dp/dt- evaluates the active phase of the diastole, nevertheless this is closely related to the calcium kinetics. The worst performance was evidenced in the Dopa E Group, that is, the early use of dopamine affected the active phase of relaxation, which may explain the worse systolic performance when the perspective of chamber was evaluated [18].

The other diastolic evaluation index, Delta V, evaluates the volumetric capacity of the left ventricle, which is an indirect gauge of the diastolic function. This index reflects myocardial edema, common in this experimental model and in the reperfusion processes. This index was similar in all the three groups, indicating similar edema and confirming that the deleterious action of the early dopamine use happens in the active phase of the relaxation.

Malonic Dialdehyde (MDA) is a product of peroxidation and is indicative of ischemic and reperfusion injury mediated by free radicals [19,20]. We did not identify differences among the three groups, indicating that the deleterious action of the early use of the dopamine does not happen by this mechanism and therefore continues unclear.

CONCLUSIONS

The present study showed that, using the described experimental conditions, with the variables evaluated here, early use of dopamine was deleterious to the left ventricular function.

BIBLIOGRAPHIC REFERENCES

1. Buckberg GD. Myocardial protection during cardiac operations. In: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Glenn´s thoracic and cardiovascular surgery. 5a ed.Norwalk:Appleton&Lange;1991.p.1417-42.

2. Buckberg GD. Update on current techniques of myocardial protection. Ann Thorac Surg 1995;60:805-14.

3. Green JA, Botti RE. Cardiovascular clinical pharmacology. In: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Glenn´s thoracic and cardiovascular surgery. 5a ed.Norwalk:Appleton&Lange;1991.p.1367-78.

4. Butterworth IV JF, Legault C, Royster RL, Hammon Jr. JW. Factors that predict the use of positive inotropic drug support after cardiac valve surgery. Anesth Analg 1998;86:461-7.

5. Tempe DK, Virmani S. Pharmacologic support of circulation in patients undergoing cardiac surgery. J Indian Med Assoc 1999;97:411-8.

6. Bailey JM, Levy JH, Hug Jr. CC. Cardiac surgical pharmacology In: Edmunds LH. Cardiac surgery in the adult. São Paulo:McGraw-Hill;1997. p. 225-54.

7. Rumsey WL, Abbott B, Bertelsen D, Mallamaci M, Hagan K, Nelson D et al. Adaptation to hypoxia alters energy metabolism in rat heart. Am J Physiol 1999;276(1pt2):H71-80.

8. Kurokawa T, Takagi H. Mechanism and prevention of ischemia-reperfusion injury. Transplant Proc 1999;31:1775-6.

9. Fiolet JW. Reperfusion injury and ischemic preconditioning: two sides of a coin? Cardiovasc Res 2000;48:185-7.

10. Maseda E, Suarez L, Peinado R, Moreno I, del Campo JM, Criado A. Predictive factors of inotropic support in myocardial revascularization surgery. Rev Esp Anestesiol Reanim 1996;43:123-5.

11. Komai H, Yamamoto F, Tanaka K, Ichikawa H, Shibata T, Koide A et al. Harmful effects of inotropic agents on myocardial protection. Ann Thorac Surg 1991;52:927-33.

12. Lazar HL, Buckberg GD, Foglia RP, Manganaro AJ, Maloney Jr JV. Detrimental effects of premature use of inotropic drugs to discontinue cardiopulmonary bypass. J Thorac Cardiovasc Surg, v. 82, n. 1, p. 18-25, Jul. 1981.

13. Hasenfuss G. Animal models of human cardiovascular disease, heart failure and hypertrophy. Cardiovasc Res 1998;39:60-76.

14. Martins AS. Modelo experimental de coração suportado em coelhos. Padronização e análise de variáveis hemodinâmicas, laboratoriais e anátomo-patológicas. [Dissertação de mestrado]. Botucatu:Universidade Estadual Paulista, Faculdade de Medicina de Botucatu,1996. 239p.

15. Weber KT, Janicki JS. Interdependence of cardiac function, coronary flow, and oxygen extraction. Am J Physiol 1978;235:H784-93.

16. Ganz P, Braunwald E. Fluxo sangüíneo coronário e isquemia miocárdica. In:Braunwald E. Tratado de medicina cardiovascular. 5ª ed. vol. 2. São Paulo:Roca;1999. p.1240-64.

17. Little WC, Braunwald E. Avaliação da função cardíaca. In:Braunwald E. Tratado de medicina cardiovascular. 5ª ed. vol. 1. São Paulo:Roca;1999. p.447-71.

18. Opie LH. Mecanismos de contração e relaxamento cardíacos. In:Braunwald E. Tratado de medicina cardiovascular. 5ª ed. vol. 1. São Paulo:Roca;1999. p.381-417.

19. Kukreja RC, Hess ML. Radicais livres, disfunção cardiovascular e estratégias de proteção. Rio de Janeiro:Interlivros;1996. p.140.

20. Yoshida WB. Radicais livres na síndrome da isquemia e reperfusão. Cir Vasc Angiol 1996;12:82-95.