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, Dopa E = Dopa L and 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 intraventricular foi colocado no ventrículo esquerdo. Foram constituídos três grupos: um grupo controle (CG); um grupo que recebeu dopamina precocemente (Dopa E) e um grupo que recebeu dopamina após 20 minutos (Dopa L). Foram feitas lendoções diretas e indiretas hemodinâmicas.

Resultados: Fluxo de coronárias: CG (7.196 ± 1.275 mL/min); Dopa E (9.477 ± 1.160 mL/min); Dopa L (14.316 ± 2.308 mL/min), com CG = Dopa E, CG ≠ Dopa L e Dopa E ≠ Dopa L. Primeira derivada positiva intraventricular da pressão (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 e CG ≠ Dopa L. Primeira derivada negativa intraventricular da pressão (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, Dopa E = Dopa L e Dopa L ≠ CG.

Conclusão: Concluímos que, no modelo experimental delineado, o uso precoce da dopamina foi deletério, como mostrado por algumas variáveis hemodinâmicas.

Descritores: Dopamina. Função ventricular; Isquemia miocárdica; Modelos, animal.
intraventricular foi localizado 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 sanguíneo 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 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. Extensão sistólica desenvolvível: 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 Dopa T=Dialdeído Malônico (MDA): GC (4,5 ± 0,52µmol/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.
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®.

Isolated heart. In this stabilization phase, using a temporary pacemaker electrode (model IMC®, with 5V stimulation and 1.5 ms 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 10 µg/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).

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 ms 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.

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Fig. 1 – Perfusion system

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.
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 $dp/$

Tabela 1. Variáveis segundo os grupos.

<table>
<thead>
<tr>
<th>Grupos</th>
<th>Fluxo coronariano ml/min</th>
<th>$Dp/dt^+$ mmHg/seg</th>
<th>$Dp/dt^-$ mmHg/seg</th>
<th>Delta V ml</th>
<th>Estresse sistólico g/cm²</th>
<th>MDA µmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controle</td>
<td>7.196±1.275</td>
<td>719±127.53</td>
<td>469.85±107.16</td>
<td>1.355±0.2432</td>
<td>27.273±10.276</td>
<td>4.5±0.53</td>
</tr>
<tr>
<td>Dopa P</td>
<td>9.477±1.160</td>
<td>947.77±116.06</td>
<td>716.07±215.66</td>
<td>0.97±0.3199</td>
<td>55.219±24.625</td>
<td>4.7±1.16</td>
</tr>
<tr>
<td>Dopa T</td>
<td>14.316±2.308*</td>
<td>1431.60±230.87*</td>
<td>931.24±181.40*</td>
<td>1.27±0.2983</td>
<td>79.152±12.166</td>
<td>4.1±0.74</td>
</tr>
</tbody>
</table>

* 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).

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


