Volatile cardioplegia: fast normothermic cardiac arrest induction and recovery with halothane in isolated rat hearts

O.M. Gomes, H.J. Neves, W.S. Lima, E.S. Gomes and M. Pitchon

Abstract

To study the effect of halothane as a cardioplegic agent, ten Wistar rats were anesthetized by ether inhalation and their hearts were perfused in a Langendorff system with Krebs-Henseleit solution (36°C; 90 cm H2O pressure). After a 15-min period for stabilization the control values for heart rate, force (T), dT/dt and coronary flow were recorded and a halothane-enriched solution (same temperature and pressure) was perfused until cardiac arrest was obtained. The same Krebs-Henseleit solution was reperfused again and the parameters studied were recorded after 1, 3, 5, 10, 20 and 30 min. Cardiac arrest occurred in all hearts during the first two min of perfusion with halothane-bubbled solution. One minute after reperfusion without halothane, the following parameters reported in terms of control values were obtained: 90.5% of control heart rate (266.9 ± 43.4 to 231.5 ± 71.0 bpm), 20.2% of the force (1.83 ± 0.28 to 0.37 ± 0.25 g), 19.8% of dT/dt (46.0 ± 7.0 to 9.3 ± 6.0 g/s) and 90.8% of coronary flow (9.9 ± 1.5 to 9.4 ± 1.5 ml/min). After 3 min of perfusion they changed to 99.0% heart rate (261.0 ± 48.2), 98.9% force (1.81 ± 0.33), 98.6 dT/dt (45.0 ± 8.2) and 94.8% coronary flow (9.3 ± 1.4). At 5 min 100.8% (267.0 ± 40.6) heart rate, 105.0% (1.92 ± 0.29) force and 104.4% (48.2 ± 7.2) dT/dt were recorded and maintained without significant differences (P>0.01) until the end of the experiment. These data demonstrate that volatile cardioplegia with halothane is an effective technique for fast induction of and prompt recovery from normothermic cardiac arrest of the rat heart.

Introduction

Since the first attempt by Melrose et al. (1) to induce heart arrest with a high potassium concentration solution through the aortic root, many types of cardioplegic solutions have been employed (2-5). However, based on the studies by Gay Jr. and Ebert (6) potassium arrest continues to be the fundamental substrate used to abolish cardiac contractions in most of the cardioplegic techniques used today.

The novel concepts introduced by Buckberg (7), Salerno et al. (8) and Lichenstein et al. (9) led to worldwide acceptance of warm heart cardioplegia with continuous potassium-enriched, antegrade and/or retrograde coronary vessel blood perfusion. The
only problem with this technique is the high systemic blood potassium concentration occurring after cardioplegic perfusion which lasts more than one hour.

The objective of the present investigation was to induce a cardiac arrest with a rapidly removable pharmacologic agent such as a volatile anesthetic. We report here the effect of halothane used as a cardioplegic agent on the isolated rat heart.

Material and Methods

Ten adult Wistar rats weighing 250 to 300 g were studied. All animals received humane care in compliance with the “Ethical Principles of Animal Experimentation” formulated by the Brazilian College for Animal Experimentation (COBEA) (10), and the “Guide for Care and Use of Laboratory Animals” published by the National Institutes of Health (11).

After anesthesia by ether inhalation, the hearts were removed through a wide thoracotomy, the ascending aorta was cannulated and the left chambers were decompressed. Coronary artery perfusion was continuously maintained with Krebs-Henseleit (12) solution under constant pressure (90 cm of water) and temperature (36.0-36.5°C) in a Langendorff system. This solution was continuously bubbled with 96% O₂ and 4% CO₂. Gasometric control was performed with a Radiometer model ABL-5 (Copenhagen, Denmark). pO₂ was maintained at 352.0 ± 16.0 mmHg, pCO₂ at 34.6 ± 4.5 mmHg and pH at 7.37 ± 0.03 throughout the experiment.

Two isolated solution reservoirs, microaggregate retention filters (Cardioprot, Flvmen Prod. Med. Ltda., RJ, Brazil) and two separate disposable heat exchangers (Flvmen Prod. Med. Ltda.) were used, allowing alternate coronary perfusion with plain or halothane-enriched (15%) Krebs-Henseleit solution. A Grass Force Transducer (model FT 03, Grass Instrument Co., Quincy, MA) coupled to a polygraph (model DH 073, Bese Co., MG, Brazil) was used to analyze heart rate (bpm) and contractile performance, evaluated by force (T) and dT/dt (g/s) variation.

Halothane was administered with a universal vaporizer (HB Anest. Equip. Inc., São Paulo, Brazil).

After a 15-min stabilization perfusion period control values were recorded. The hearts were then perfused with the halothane-enriched solution until complete arrest, when normal Krebs-Henseleit perfusion was started again, with heart activity being recorded after 1, 3, 5, 10, 20 and 30 min.

Statistical analysis was performed by ANOVA and the Wilcoxon rank sum test (matched) using an EPI-INFO (version 5.01B) program (13). The level of significance was set at 0.05.

Results and Discussion

Cardiac arrest was obtained in all hearts studied during the first two min after the beginning of perfusion with the halothane-enriched solution. Figure 1 shows a record of one experiment (rat No. 2).

The results of the heart rate variation are presented in Table 1. One minute after reperfusion without halothane, 86.6% recovery of the control value for heart rate was observed, increasing to 97.5% at the third min (P>0.05).
Volatile cardioplegia with halothane and remaining without statistically significant differences from control values thereafter (Figure 2A).

The mean value for the force was 0.37 ± 0.25 g during the first min of cardiac reperfusion without halothane, rising to 1.81 ± 0.33 g during the third min, corresponding to 98.9% of the mean control value (1.83 ± 0.28 g) and without significant differences from control (P>0.05) (Table 1). Mean values of 105.0%, 104.0%, 104.0% and 104.0% were recorded at 5, 10, 20 and 30 min (P>0.05), respectively (Table 1).

The mean value for dT/dt was 9.3 g/s (SD ± 6.0 g/s) during the first min of cardiac reperfusion without halothane, rising to 45.0 ± 8.2 g/s during the third min, corresponding to 97.8% of the mean control value (46.0 ± 7.0 g/s) and without significant differences from control thereafter (Table 1). Although without statistical significance, the dT/dt values remained 2.9 to 4.7% higher than the control value until the end of the experiment (30 min) (Figure 2B).

Data about coronary flow variation are presented in Table 1 and Figure 2C showing that even during the heart arrest period a mean value of 9.4 ± 1.8 ml/min (94.7% of the control) was observed, without statistically significant variation (P>0.05).

The normothermic continuous antegrade and/or retrograde coronary perfusion proposed by Buckberg (7) and Salerno et al. (8), together with the concept of warm heart surgery introduced by Lichenstein et al. (9), represent the most striking contribution to modern methods of myocardial protection. Although shown to be clinically safe and efficient, these techniques are a source of concern due to the continuous elevation of the systemic blood potassium concentration with time of the coronary perfusion, reaching values above 6.0 mEq/l after one hour in our patients. To obviate this inconvenience, the substitution of potassium or reduction of its concentration by use of other cardiac arresting drugs would be quite desirable, and is currently being investigated worldwide (14-16).

We suggest that a volatile agent could be

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Table 1 - Halothane-induced arrest and recovery of isolated rat hearts.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Halothane</th>
<th>Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart rate (bpm)</td>
<td>266.9 ± 43.4</td>
<td>231.5 ± 71.0</td>
</tr>
<tr>
<td>Force (g)</td>
<td>1.83 ± 0.28</td>
<td>0.0 ± 0.0</td>
<td>0.37 ± 0.25</td>
</tr>
<tr>
<td>dT/dt (g/s)</td>
<td>46.0 ± 7.0</td>
<td>0.0 ± 0.0</td>
<td>9.3 ± 6.0</td>
</tr>
<tr>
<td>Coronary flow (ml/min)</td>
<td>9.9 ± 1.5</td>
<td>9.4 ± 1.8</td>
<td>9.4 ± 1.5</td>
</tr>
</tbody>
</table>

Figure 2 - Halothane-induced arrest and recovery in the isolated rat heart. A, Heart rate; B, dT/dt; C, coronary flow. Data are reported as means ± SEM for 10 rats. Abscissa: C = control; H = halothane; 1-30 min recovery period. *P<0.05 compared to control (Wilcoxon rank sum test).
used because the oxygenator, a common part of the extracorporeal circulation apparatus, could remove the agent. We chose halothane because of its well-known myocardial depressant effect via calcium and potassium channels (17-20) and its antiarrhythmic and myocardial protective effect during hypoperfusion (21-24) and hypoxic (25) states.

The results of the present investigation demonstrate that volatile cardioplegia with halothane is a viable method for normothermic cardiac arrest in rat heart, with the advantage of its fast removal and prompt cardiac recovery. Further investigations are currently underway at our institution to establish the safest conditions for the clinical use of halothane.

References