The effect of the ultrashort beta-blocker esmolol on cardiac function recovery: an experimental study

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Abstract

Objective: This is an experimental work designed to determine, using the isolated perfused rat heart, the effect of the ultra-short acting beta-blocker esmolol on cardiac arrest and cardiac function recovery following esmolol withdrawal. Methods: Changes in heart rate, coronary flow, diastolic pressure and the rate pressure product were evaluated on the isolated heart (Langendorff model). Esmolol concentrations of 125, 250, and 500 mg/l were tested. In another experiment using esmolol concentration of 250 mg/l, cardiac function recovery was assessed after 20- and 45-min arrest. Results: While concentrations of 250 and 500 mg/l are necessary to produce cardiac arrest, the concentration of 500 mg/l does not result in full cardiac function recovery following esmolol withdrawal. After the highest concentration of esmolol, coronary flow, heart rate and the rate-pressure product recovered to about 80, 70 and 60% of the initial control values, respectively. When comparing 20- and 45-min arrests we found cardiac function normalization occurs later after 45-min arrest. Conclusion: The induction of cardiac arrest by esmolol is optimal at a concentration of 250 mg/l. A concentration of 125 mg/l does not result in cardiac arrest and produces bradycardia only, a concentration of 500 mg/l may be dangerous on account of persisting undesirable effects on the rat heart. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Myocardial protection is an issue constantly discussed in all journals of cardiac surgery. As novel approaches continue to be reported, it is obvious that the ideal technique of myocardial protection has, as yet, not been found.

The number of redo surgery procedures in patients in whom the internal mammary artery (IMA) was used in the primary procedure for left anterior descending (LAD) artery reconstruction is increasing. In this situation, myocardial protection is quite problematic since IMA has to be freed from adhesions so that a clamp can be placed on it; IMA may sustain injury during this procedure; antegrade perfusion is inadequate because of central LAD occlusion, and retrograde perfusion with all its attending risks has to be used. It was for this reason that we developed a technique of surgery in the arrested heart using a short-acting beta-blocker (Esmolol), which we have reported on previously [1].

In some patients with esmolol-induced cardiac arrest, we noted an effect longer than could be expected based on the drug’s pharmacokinetics. The hypocontractility of the left ventricle lasted longer, so for weaning from extracorporeal circulation, PDE III Inhibitors were needed.

None of the few authors using esmolol for cardioplegia [4–9] mentioned this observation of ours. As we were
Esmolol increased LVDP and this effect was significantly dose-related on the heart, we conducted the following study. The following experiment, described below, was performed in an effort to specify the optimal and safe esmolol concentrations needed to stop the heart.

2. Materials and methods

2.1. Heart perfusion

Adult male Wistar rats (300–350 g body weight) were killed by cervical dislocation. The heart was rapidly excised, washed in cold (5°C) saline and perfused in the Langendorff model under constant pressure of 100 cm H₂O and non-recirculating conditions [2]. A Krebs–Henseleit perfusion solution contained (mmol/l): NaCl, 118.0; KCl, 4.7; CaCl₂, 1.25; MgSO₄, 1.2; NaHCO₃, 25.0; KH₂PO₄, 1.2; glucose, 7.0; sodium pyruvate, 2.0. The solution was saturated by a mixture of 95% O₂ and 5% CO₂ (pH 7.4) and its temperature was maintained at 37°C. The contractile function of the left ventricle of the spontaneously beating heart was measured under isovolumetric conditions using an intraventricular non-elastic compliant balloon connected to a pressure transducer (HP 1260, Hewlett-Packard, Wallingford, MA). The analog pressure signal was analyzed online using our computer program. The following parameters were derived: diastolic pressure (LVDP), systolic pressure (LVSP), developed pressure (LVDevP–LVSP–LVDP) and heart rate (HR). The rate-pressure product (RPP) was calculated as the product of HR and LVDevP. Coronary flow (CF) was measured by timed collection of coronary effluent and subsequently normalized to heart weight.

After a stabilizing period (25 min), the volume of the intraventricular balloon was gradually increased to reach LVDP of 8–10 mmHg. The hearts which exhibited LVSP values lower than 80 mmHg and/or HR values lower than 200 beats/min were excluded from the study. Then the perfusion was switched to the same solution containing 125, 250, or 500 mg/l esmolol hydrochloride (Brevibloc, Du Pont Pharm., UK). There were six rats in each group. After 20 min, the perfusion was returned to the solution without esmolol, and recovery of functional parameters was followed for an additional 40 min. In one group of hearts, the period of perfusion with 250 mg/l esmolol was extended to 45 min. The recovery of functional parameters was expressed as the percentage of initial pre-drug values. The increase in LVDP during perfusion with esmolol and its subsequent recovery is expressed in mmHg. Samples of coronary effluent were collected during the experiment for analysis of esmolol concentration.

The investigation conforms to the ‘Guide for the Care and Use of Laboratory Animals’ published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1985).

2.2. Determination of esmolol concentration

Esmolol samples were analyzed on a Spectra-Physics HPLC liquid chromatograph (Spectra-Physics, San Jose, CA). Samples collected during the experiment were directly injected (50 ml) on a reverse-phase column (Nova-Pak C18, 4 µl, 3.9 × 150 mm). Flow rate of the mobile phase was 1.5 ml/min and absorbance was measured at 229 nm. Column temperature was ambient and the temperature of the sample tray was 15°C.

2.3. Statistics

All results are expressed as the mean ± SEM. Data were evaluated using ANOVA and subsequent Bonferroni test for multiple comparisons. Values of P < 0.05 were considered statistically significant.

3. Results

The initial control values of functional parameters of the isolated perfused hearts (n = 24) were as follows: CF, 15.8 ± 0.7 ml/g/min; HR, 284 ± 27 beats/min; LVDP, 8.6 ± 0.2 mmHg; LVSP 107.1 ± 5.1 mmHg; LVDevP, 98.6 ± 4.9 mmHg; RPP, 28puncso124 ± 1822 mmHg beats/min. No differences were detected among the groups in any parameter.

Esmolol at a concentration of 125 mg/l decreased CF during 20-min heart perfusion to 60% of the initial control value. This effect was significantly more pronounced with higher concentrations of 250 and 500 mg/l and reached about 40%. CF gradually returned to normal during the subsequent recovery period, except for the group with the highest concentration of esmolol, whereby, recovery was about 80%. On the other hand, perfusion with the lowest concentration was followed by hyperemia reaching 120–130% of the initial control value (Fig. 1A).

Whereas, esmolol concentrations of 250 and 500 mg/l rapidly arrested the heart, the concentration of 125 mg/l only decreased HR markedly, but the heart continued beating for the whole 20-min period. HR recovery was concentration-dependent, particularly during the first 10 min of subsequent perfusion without esmolol. The lowest concentration resulted in the most rapid recovery. HR eventually returned to initial control values, except for the highest concentration which caused a persistent reduction in HR to about 70% (Fig. 1B).

The RPP was zero during heart perfusion with 250 and 500 mg/l esmolol, and close to zero with 125 mg/l esmolol. Again, the time course of recovery was the most rapid following the lowest concentration of esmolol. The two lower concentrations resulted in complete recovery of RPP, whereas, it remained decreased to about 60% of the control value after 500 mg/l (Fig. 1C).

Esmolol increased LVDP and this effect was significantly
more pronounced with the highest concentration. During the recovery phase, LVDP gradually returned to normal, except for the group subjected to the highest concentration, where a

Fig. 1. Functional parameters of the isolated rat heart during 20-min perfusion with a solution containing esmolol in concentrations of 125 mg/l (circles), 250 mg/l (triangles), or 500 mg/l (squares) and during the subsequent 45-min recovery period. (A) Coronary flow (CF); (B) heart rate (HR); (C) rate-pressure product (RPP); (D) diastolic pressure (LVDP). Data are expressed as a percentage of the initial control values, except for LVDP which is shown as the increment above the control value in mmHg (Δ). Each point represents the mean ± SEM of six hearts in each group. *P < 0.05 versus the group with 125 mg/l esmolol.

Fig. 2. Recovery of functional parameters of the isolated rat heart during a 40-min period following 20-min (full triangles, redrawn from Fig. 1) or 45-min (open triangles) perfusion with a solution containing esmolol in concentrations of 250 mg/l. (A) coronary flow (CF); (B) heart rate (HR); (C) rate-pressure product (RPP); (D) diastolic pressure (LVDP). Data are expressed as a percentage of the initial control values, except for LVDP which is shown as an increase above the control value in mmHg (Δ). Each point represents the mean ± SEM of six hearts in each group. *P < 0.05 versus the group perfused with esmolol for 20 min.
significant degree of contracture persisted even after 40 min (Fig. 1D).

Recovery of all parameters was significantly slower following 45 min of heart perfusion with 250 mg/l esmolol as compared with the group perfused with the same concentration for 20 min only. At the end of the recovery period, however, no differences were observed between the two groups in any parameters (Fig. 2A–D).

Mean effluent esmolol concentration is shown in Fig. 3. Although the decrease in effluent concentration was exponential after the termination of esmolol, wash-out lasted significantly longer when higher concentrations of esmolol were administered. Left ventricular function appeared at mean effluent esmolol concentrations of 54–106 mg/l. Mean time of left ventricular function recovery is shown in Fig. 3 (indicated by arrows). Left ventricular function recovery was, statistically, significantly delayed at the higher perfusate esmolol concentrations.

4. Discussion

A technique of optimal protection of the myocardium during surgery is still being searched for. One option is to use the ultrashort acting beta-blocker esmolol. In some patients with cardiac arrest induced by esmolol, we noted an effect longer than could be expected based on the drug’s pharmacokinetics. Since we were unable to find this observation in the literature, we designed an experimental study to establish the concentrations of esmolol necessary to produce cardiac arrest without any adverse effect on the heart. The Langendorff model continues to be the ‘gold standard’ when testing the effects of various drugs on the heart. We are aware that, with the heart, the situation is substantially different from that in clinical practice, as esmolol degradation occurs primarily in erythrocyte esterases which, of course, are not present in the perfusate of the experimental model used. Moreover, a role in esmolol metabolism is played by temperature [3]. As a result, we are well aware that caution has to be exercised when interpreting the results of our experiment for clinical practice.

The results suggest that perfusate esmolol concentrations of 125 mg/l do not lead to cardiac arrest but only to a decrease in HR. Esmolol concentrations of 250 and 500 mg/l do result in cardiac arrest. However, a major difference was found between the two concentrations in the resumption of cardiac function. While the monitored parameters tend to normalize at 250 mg/l, the side effects including decreased CF, HR, RPP and LVDP associated with esmolol concentrations of 500 mg/l persist throughout the experiment. We can only speculate as to the cause. Pharmacokinetic data suggest that the degradation potential has been exhausted at the higher concentrations and drug elimination is not of the first order, but prolongs progressively.

Several papers have been published in 1997 reporting the use of an ultrashort-acting beta-blocker for myocardial pro-
tection. All the authors use the technique to slow, but not to stop, cardiac function. Some authors [4–6] employ a technique similar to ours, i.e. without aortic clamping, while others use a beta-blocker actually as part of blood cardioplegia [7–9] in a bid to reduce esmolol dose. This strategy can be challenged. As we found when determining esmolol concentrations in the effluent from the coronary sinus during surgery for congenital defect of interatrial septum, only a minor part of esmolol uptake is in the myocardium. It follows its blood concentrations would not rise, only provided blood from the coronary sinus would be aspirated outside ECC.

As a result, the blood used for cardioplegia already contains some esmolol, a fact making esmolol addition possibly useless.

Another reason making us believe that aortic cross clamping is unnecessary is that, when administering esmolol into the aortic root even without cross clamping, under conditions of extracorporeal circulation on the beating non-working heart, the coronary arteries are the only conduit blood can flow into.

The persistence of a prolonged esmolol effect in clinical practice can be explained by the fact that, in some patients, the initial concentrations were in excess of 500 mg/l (1200 mg/l in one patient).

It can be reasonably concluded that myocardial protection by an ultrashort-acting beta-blocker is a prospective method which, however, needs to be refined before it can be translated into everyday clinical practice.

Caution must be exercised not to have too high a concentration of esmolol in the blood as this could have a long-lasting adverse effect on the myocardium.

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References