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Effects of Clonidine and Isoflurane on the Myocardial Contractility Behavior of Isolated Rat Hearts

João Bosco Dupin, Alfredo Inácio Fiorelli, João Henrique Dupin, Ana Elisa Dupin, Isabela Maria Dupin, Otoni M. Gomes

São Francisco de Assis Truth is Jesus Cardiovascular Foundation, Belo Horizonte, Brazil

ABSTRACT

Isoflurane is chosen as an anesthesia drug for cardiac surgeries, and its effectiveness and safety have been proved in countless clinical studies. Clonidine, a central α-agonist, has recently been added to isoflurane to attenuate sympathetic hyperactivity by acting directly on its site of origin in the central nervous system. The ability of α_2-adrenoceptor agonists to inhibit central sympathetic outflow may benefit patients at risk of myocardial damage by improving myocardial oxygen demand and the supply ratio and contributing to hemodynamic stability. We investigated the effects of clonidine and isoflurane, alone and in combination, on the myocardial contractility of isolated rat hearts and found that use of clonidine plus isoflurane decreased the systolic pressure somewhat, but use of the drugs separately did not exhibit this effect. Clonidine plus isoflurane did not affect $+(dP/dt)_{max}$, but it did decrease $-(dP/dt)_{max}$ significantly compared with the use of isoflurane alone. These results indicate that clonidine and isoflurane have the capacity to interact with each other. The capacity of clonidine to decrease isoflurane's inotropic effect could theoretically contribute to improving the myocardial oxygen demand and the supply ratio, decreasing surgical stress, and benefiting patients at risk of myocardial damage.

INTRODUCTION

Isoflurane is chosen as an anesthesia drug for cardiac surgeries, and its effectiveness and safety have been proved in countless clinical studies, many of which have described cardioprotecting effects [Crystal 2000; Rivenes 2001; Agnew 2002]. Recently, clonidine, a central α-agonist, has been added to isoflurane to attenuate sympathetic hyperactivity by acting directly on its site of origin in the central nervous system [Dupin 2008]. The ability of α_2-adrenoceptor agonists to inhibit central sympathetic outflow may benefit patients at risk of myocardial damage by improving myocardial oxygen demand and the supply ratio [Stühmeier 1996; Yin 2002] and contributing to hemodynamic stability [Kobinger 1978; Mauer 1983; Reid 1984]. In the present study, we investigated the effects of clonidine, isoflurane, and the combination of clonidine and isoflurane on the myocardial contractility of isolated rat hearts.

METHODS

We used 24 hearts from sulfuric ether–anesthetized male Wistar rats. The modified Langendorff model [Gomes 1997] was used, and the hearts were perfused with Krebs-Henseleit solution, gasified with 95% oxygen and 5% carbonic acid (pH 7.35°C ± 0.05°C) and under constant pressure of 90 cm water. The rats weighed between 260 and 290 g (mean, 273 g), and the heart weights were between 0.95 g and 1.19 g (mean, 1.10 g). The investigation conformed to the Guide for the Care and Use of Laboratory Animals [ILAR 1996] and had approval of the ethics commission of the Fundação Cardiovascular São Francisco de Assis. The hearts were divided into 4 groups: group I, control; group II, clonidine; group III, isoflurane; group IV, clonidine and isoflurane. The hearts were perfused with Krebs-Henseleit solution alone for 20 minutes to reestablish physiological conditions before the start of testing. Systolic pressure (SP) measurements were taken with the aid of a flexible stem catheter.

A balloon [Dupin 2001] was placed inside the left ventricle by passing it through the left atrium and the mitral valve. Data were recorded at 0, 1, 2, 3, 5, 10, and 15 minutes (t_0, t_1, t_2, t_3, t_5, t_{10}, and t_{15}, respectively). Myocardial contractility was evaluated by measuring $+(dP/dt)_{max}$ (maximum speed of increase in the left ventricular pressure) and $-(dP/dt)_{max}$ (maximum speed of decrease in the left ventricular pressure). The data were analyzed by analysis of variance, and the Tukey method was used to identify the significance of differences between groups when differences were found. Results were considered statistically significant at P values <.05.

RESULTS

The use of clonidine, isoflurane, and the combination of clonidine and isoflurane did not alter the SP at any of the studied times, compared with the control. Combined used of clonidine and isoflurane decreased the SP at t_1 compared with the control, and at t_2, t_3, t_5, and t_{10} compared with isoflurane alone. The combination of the 2 drugs maintained the SP at less than the SP values for isoflurane alone at all measurement

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Correspondence: Prof. Dr. João Bosco Dupin, Rua Paineiras, 107, Horto – 35160-310, Ipatinga, MG, Brazil (e-mail: dupinjb@terra.com.br).

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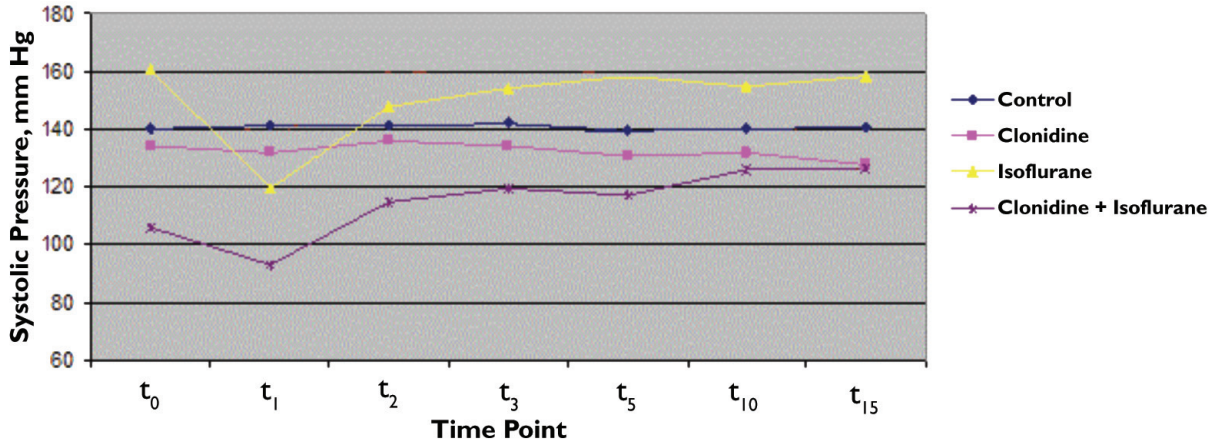

Figure 1. Behavior of systolic pressure in the study groups. Data were recorded at 0, 1, 2, 3, 5, 10, and 15 minutes (t_0, t_1, t_2, t_3, t_5, t_{10}, and t_{15}, respectively).

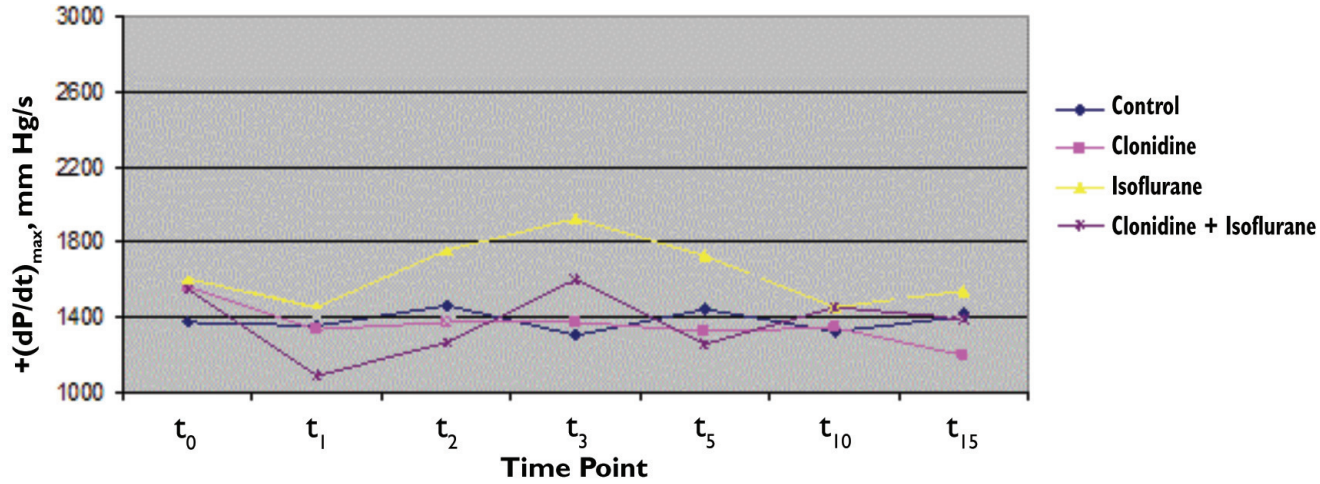

Figure 2. Behavior of the maximum speed of increase of the left ventricular pressure, $+(dP/dt)_{max}$, in the study groups. Data were recorded at 0, 1, 2, 3, 5, 10, and 15 minutes (t_0, t_1, t_2, t_3, t_5, t_{10}, and t_{15}, respectively).

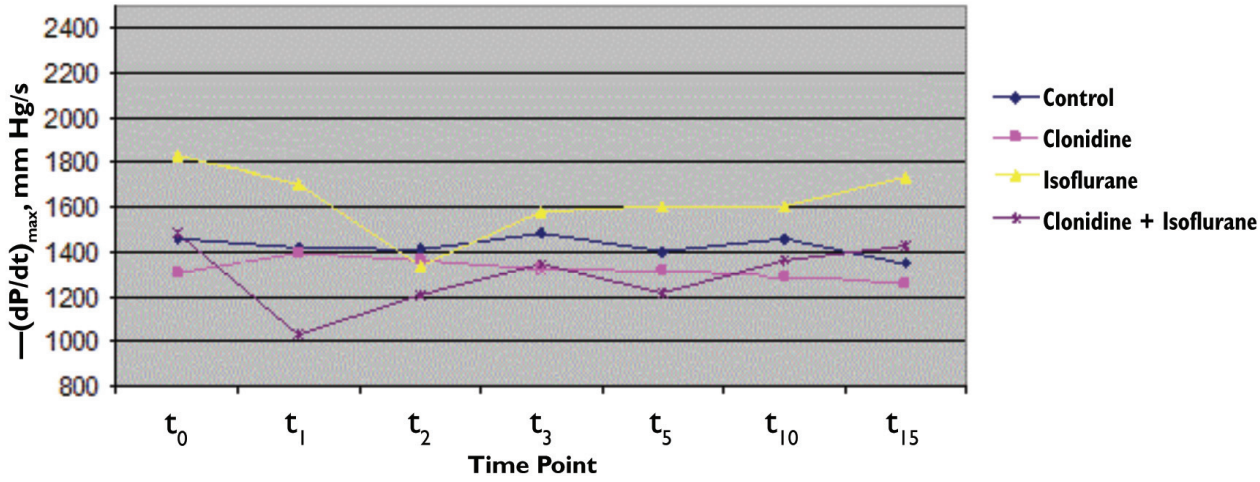

Figure 3. Behavior of the maximum speed of decrease in the left ventricular pressure, $-(dP/dt)_{max}$, in the study groups. Data were recorded at 0, 1, 2, 3, 5, 10, and 15 minutes (t_0, t_1, t_2, t_3, t_5, t_{10}, and t_{15}, respectively).

times; however, the difference was statistically significant only at times t_2, t_3, t_5, and t_{10} (Figure 1).

Clonidine alone, isoflurane alone, and the clonidine/isoflurane combination did not alter either $+(dP/dt)_{max}$ or $-(dP/dt)_{max}$ at any time point compared with the control (Figures 2 and 3). Nevertheless, combined use of clonidine and isoflurane decreased the $-(dP/dt)_{max}$ at t_1 and t_5, compared with isoflurane alone (Figure 3).

DISCUSSION

The combined use of clonidine and isoflurane decreased the SP somewhat, although these drugs did not exhibit this effect when they were used separately. These data suggest an interaction between clonidine and isoflurane. Otherwise, the shape of the isoflurane/clonidine curve for SP in Figure 1 is similar to that of the curve for isoflurane alone but is shifted to lower SP values, suggesting that clonidine only attenuates the isoflurane effect on SP, just reducing the isoflurane inotropic effect and thereby protecting the heart. The combination of clonidine and isoflurane does not affect $+(dP/dt)_{max}$, but it does decrease $-(dP/dt)_{max}$ compared with isoflurane alone, and, again, this effect occurred only with combined use of the 2 drugs. This result shows the capacity of the 2 drugs to interact with each other. These data are in agreement with the results of Rivenes et al [2001], who stated that isoflurane is capable of preserving myocardial contractility at basal levels; with the results of Coetzee et al [1993], who found an isoflurane cardioprotective effect in a study with isolated hearts subjected to cardioplegy and reperfusion; and with Agnew et al [2002], who also reported isoflurane to act as a myocardial protective drug capable of reducing or limiting ischemic areas. The capacity of clonidine to decrease isoflurane's inotropic effect could theoretically contribute to improving the myocardial oxygen demand and the supply ratio, decreasing surgical stress, and benefiting patients at risk of myocardial damage.

CONCLUSION

The results of this study show that the combined use of clonidine and isoflurane can decrease myocardial contractility. We also conclude that clonidine and isoflurane in combination act directly on rat hearts, besides its central effect, considering that the results were obtained with an isolated heart preparation with autonomic nerves devoid of any central nervous system input.

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