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Research Article

Rate Control in Atrial Fibrillation by Cooling: Effect of Temperature on Dromotropy in Perfused Rabbit Hearts

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Background. Cooling has emerged as a therapeutic option in critically ill patients (especially after cardiac resuscitation) and might also have a negative dromotropic effect in atrial fibrillation. We sought to determine the impact of cooling on electrophysiologic properties of Langendorff-perfused rabbit hearts. *Methods and Results*. In 20 isolated Langendorff-perfused rabbit hearts, the temperature of the tissue bath was changed between 17 and 42°C. With decreasing temperature, significant increases of the spontaneous sinus cycle length, decreases of the mean ventricular heart rate during atrial fibrillation, and relevant increases of atrial and ventricular refractory periods were observed (ANOVA $P < .01$). *Conclusions*. Cardiac hypothermia leads to a significant drop of mean ventricular heart rate during atrial fibrillation. Negative chronotropy and dromotropy induced by moderate cardiac hypothermia might be a feasible therapeutic approach in patients with hemodynamically relevant tachyarrhythmias in a CCU/ICU setting.

1. Introduction

Therapeutic hypothermia has been used in survivors of cardiopulmonary resuscitation, patients with brain trauma and with acute myocardial infarction [1–3]. Mild systemic hypothermia might theoretically be used for rate control in critically ill patients with supraventricular tachycardias instead of or on top of drug therapy.

Many drugs with negative dromotropic effects also decrease left ventricular inotropy and are thus contraindicated in patients with significant heart failure and supraventricular tachycardias. In this animal study, we sought to investigate the effect of negative chronotropy and especially dromotropy in Langendorff-perfused rabbit hearts.

2. Materials and Methods

Animal care and euthanasia were performed according to the guidelines of the American Society of Physiology with institutional approval and permission of the competent authorities (Bezirksregierung Köln). Female New Zealand white rabbits aged 3–6 months were euthanized and the beating hearts removed. After cardioplegia, Langendorff-perfusion was performed in 20 isolated hearts. The tyrode used for perfusion consisted of 130 mM NaCl, 5.6 mM KCl, 24.2 mM $NaHCO_3$, 2.2 mM $CaCl_2$, 0.6 mM $MgCl_2$, 1.2 mM NaH_2PO_4, and 12.2 mM glucose and was equilibrated with 95% O_2 and 5% CO_2.

Bipolar electrodes were positioned on the surface of right and left atrium and right ventricle. The temperature of tyrode and tissue bath was changed in 5-degree steps between 17 and 42°C (constant temperature Bath T1000, P.M. Tamson, Netherlands) (Figure 1).

The pacing threshold was determined at each temperature level. We measured the atrial and ventricular refractory period (AERP and VERP) by extrastimulus testing. The antegrade and retrograde Wenckebach periods (AWB and RWB) were determined by decremental pacing. Stimulations were performed at twice the pacing threshold. Atrial fibrillation was induced by continuous high-frequency burst stimulation with 100 ms. If atrial fibrillation could not be induced, it was simulated by continuous stimulation with

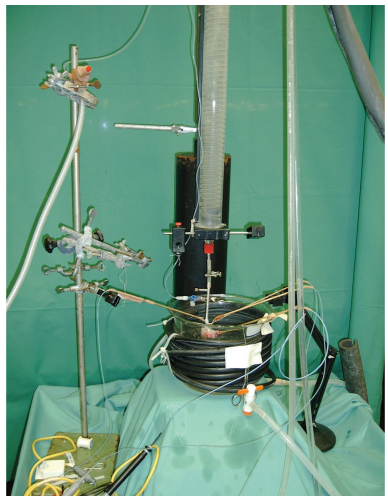

Figure 1: Langendorff-perfused rabbit heart.

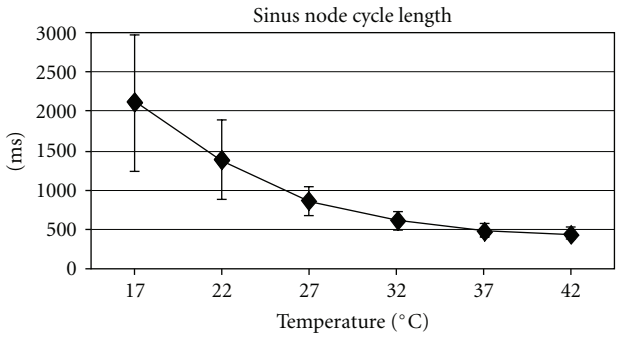

Figure 2: Spontaneous sinus cycle length depending on temperature. $P < .05$ for any temperature level.

100 ms. During atrial fibrillation, the mean ventricular heart rate was determined by averaging all cycle lengths during intervals of 30 sec.

2.1. Statistical Analysis. Results are presented as mean ±1 standard deviation. Two-sided student's t-test was used to compare spontaneous cycle length, refractory periods, AWB, RWB, and mean ventricular rate during atrial fibrillation. P values $< .05$ were considered significant.

3. Results and Discussion

3.1. Results. With decreasing temperature, significant increases of the spontaneous sinus cycle length, the mean ventricular heart rate during atrial fibrillation, and relevant increases of AERP, VERP, AWB, and RWB were observed (ANOVA $P < .01$).

At moderate hypothermia of 32°C, a 25–40% decrease of cardiac chronotropy and dromotropy could be obtained (Figures 2 and 3).

The effects of temperature on atrial and ventricular refractory periods as well as AWB and RWB are shown in Figure 4.

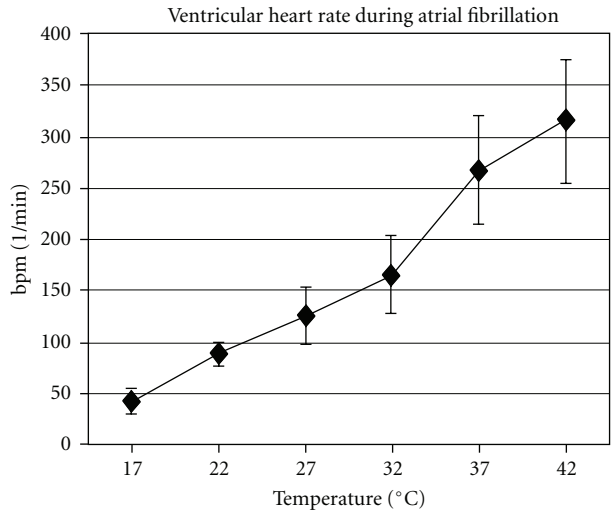

Figure 3: Average ventricular heart rate during atrial fibrillation (high-frequency atrial stimulation). A gradual cardiac hypothermia causes a gradual negative dromotropic effect. $P < .05$ for any temperature level. bpm: beats per minute.

An increased ventricular vulnerability was noted at a temperature level of 42°C; induction of ventricular fibrillation occurred in 13 hearts, whereas ventricular fibrillation was observed in 2 hearts at other temperature levels.

3.2. Discussion. The activity of biological tissue depends on its temperature. The rate of biological processes usually decreases by half to two-thirds with a decrease in temperature of 10°C [4].

Supraventricular tachycardias often complicate acute heart failure or sepsis in critically ill patients. The deleterious effect of tachycardia on cardiac output cannot be well addressed by pharmacological approaches as many drugs which exert significant negative dromotropic effects also decrease left ventricular inotropy and may decrease systemic vascular resistance.

Cardiac hypothermia has been used as a therapeutic option in patients after cardiac arrest and in patients with brain injury [1–3, 5, 6].

In our animal study, we have demonstrated a decline in ventricular heart rate of about 8% per degree C of cooling. A mild hypothermia of 32°C resulted in a significant decrease in ventricular heart rate from 267/min to 166/min (38%) during atrial fibrillation in this animal model. The spontaneous cycle length increased from 485 to 615 ms (27%) during mild hypothermia of 32°C. In addition, atrial and ventricular refractory periods increased significantly with a decrease in temperature. Appleton et al. studied cardiac electrophysiology properties in mice and used mild hypothermia (33-34°C) as well as hyperthermia [7]. The results of this in vivo mice study are congruent to our results with regard to refractory periods. Ventricular rate during atrial fibrillation, however, was not tested in the study by Appleton et al.

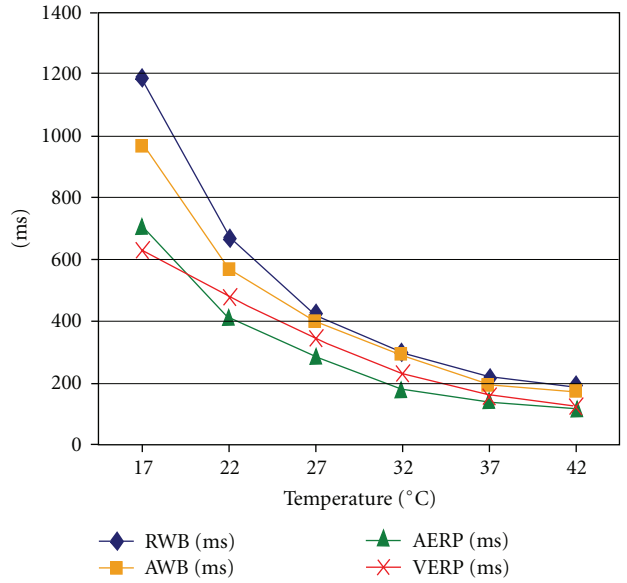

FIGURE 4: Antegrade and retrograde Wenckebach point (AWB/RWB) and atrial/ventricular refractory periods (AERP/VERP) with regard to temperature. Hypothermia causes negative dromotropy and an increase in effective refractory periods. $P < .05$ for any temperature level.

A high percentage of patients treated by mild hypothermia after resuscitation due to cardiac arrest suffer from acute myocardial infarction. Those patients are prone to develop arrhythmias including atrial fibrillation. The incidence of atrial fibrillation after cardiac arrest is around 15%, and atrial fibrillation is associated with a higher mortality rate [8, 9]. Hypothermia might reduce the ventricular rate during atrial fibrillation. Although we can only speculate on the effect of cooling in patients, extrapolation of our animal data would suggest a reduction in ventricular heart rate of about 30% during mild hypothermia, for instance, from 150/min to 105/min. In the majority of patients, a ventricular heart rate <110/min during atrial fibrillation has been shown to be sufficient for rate control [10]. In addition, cooling might be a therapeutic approach of last resort in critically ill patients with sustained supraventricular tachycardias which cannot be controlled by cardioversion and pharmacotherapy. There is initial experience with a right atrial cooling system used for cardiothoracic surgery [11]. Hypothetically, selective AV nodal cooling could slow down the ventricular rate in critically ill patients with refractory atrial fibrillation without the need for systemic hypothermia. However, this would require technical solutions in order to deliver cooling to a distinct cardiac area.

4. Limitations

The results we obtained were from an isolated heart model, and no in vivo data are available. Data on repolarization, left ventricular refractory periods or inotropy were not gathered.

Differences between human and rabbit electrophysiology may limit the applicability of the results of the study. Although the rabbit cardiac action potential is of shorter duration than the human action potential, its shape is very similar. In addition, the kinetic properties of human and rabbit cardiac slow delayed rectifier potassium current (IKS) are comparable [12]. Even though the numerically reconstructed human If is considerably smaller than the typical rabbit If, Verkerk and Wilders describe a striking similarity between human and rabbit If with regard to the net membrane current [13].

5. Conclusions

Cardiac hypothermia induces a relevant decrease in ventricular heart rate during atrial fibrillation. Thus, moderate cardiac hypothermia might be used as a new therapeutic tool in critically ill patients nonresponding to electrical cardioversion or pharmacotherapy.

Conflict of Interest

The authors declared that there is no conflict of interests.

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