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INFLUENCE OF XENON PERFUSION ON ADRENALIN DEPENDENT ATRIAL CONTRACTILITY

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Background: Many anesthetic agents show a cardiodepressant effect. In cardiac surgery this may limit their application. We tested the hypothesis that xenon does not affect the positive inotropic effect of adrenalin in human right atrial muscle bundles.

Methods: 18 right atrial appendages from 17 patients were harvested. Thin myocardial muscle strips were prepared under stereomicroscopic control, connected to isometric force transducers and placed in an organ bath. Force of contraction was analysed from 10 µmol to 1 mmol adrenalin. Differences in force development were compared after perfusion of the Krebs-Henseleit solution with 100 % xenon for 30 minutes at 60 bpm and 37 °C in the open contraction chamber.

Results: Xenon perfusion did not alter myocardial force of contraction. The positive inotropic impact of adrenalin did not differ between the muscles exposed to xenon and the control group.

Conclusion: The present findings indicate that the inotropic effect of adrenalin is not affected by xenon perfusion of human right atrial muscle strips.

1. Introduction

Xenon is an anestetic gas with a potent hypnotic effect.[1] As an inert noble gas it forms no toxic metabolites in the body and is well tolerated.[2]

But most volatile anesthetics exhibit a myocardial depressant effect.[3] This side effect often limits their application in patients with impaired cardiac function.[4] The negative inotropic effect is especially detrimental in cardiac surgery after cold ischemic cardioplegic arrest.[5] Then positive inotropic support is necessary to improve force of contraction.[6]

The authors therefore studied the effects of xenon perfusion on human right atrial muscle strips during stimulation with adrenalin.

2. Material and Methods

2.1 Patients

The present study was reviewed and approved by the ethical committee of the University of Ulm. Isometric force of contraction was determined in myocardium from 17 patients. Atrial myocardium was obtained before venous canulation from all patients undergoing elective cardiac surgery for coronary revascularisation and/or aortic respective mitral valve replacement. The clinical characteristics of the patients are given in Table 1. (Patient 1 - 17). Anesthesia was the same for each patient. Cardiopulmonary bypass was established with a priming solution (1000 ml Ringer, 400 ml human albumin, 200 ml Trasylol, 5000 IU Heparin) at a flow rate of 2,4 l/min/m² body surface area. All patients were cooled to 32 °C (esophageal). In addition, there was aortic crossclamping, with a myocardial arrest induced by antegrade infusion of cold Brettschneider cardioplegic solution at a myocardial temperature of approximately 4°C.

Table 1

Characteristics of the patients

Group	Patients
number pat./strips	17/18
age y	68,9 ± 8,6
sex m/f	12/5
rhythm SR/AF	15/2

pat. patients; strips muscle strips; y years; m male; f female; SR sinus rhythm; AF atrial fibrillation

2.2 Muscle strip preparations

Immediately after surgical excision, right atrial appendages were submerged in Tyrode's solution (pH 7.4, gassed with 5% CO_2, 95% O_2) with protective BDM additive. Thin atrial muscle strips were prepared in parallel under stereomicroscopic control and placed in oxygenated Krebs-Ringer solution to wash out the protective solution. The solution contained (mmol/L) Na^+ 152, K^+ 3.6, Cl^- 135, $HCO3^-$ 25, Mg^{2+} 0.6, $H2PO^{4-}$ 1.3, $SO4^{2-}$ 0.6, Ca^{2+} 1.25, glucose 11.2 and insulin 10 IU/L The length of the bundles ranged from 4 to 6 mm. They were connected to isometric force transducers and placed in an organ bath filled with prewarmed (37°C) bathing solution. After an equilibration period of 30 minutes, resting tension was increased in 0.2-mN steps until the muscle length providing maximal active force generation was reached. External field stimulation was performed with rectangular pulses (5ms, 5% to 10% above threshold) at a frequency of 1 Hz. At the end of each experiment, muscle length at L_{max} was measured, and blotted weight of this segment was obtained. Cross sectional area for normalisation of force values was calculated as the ratio of blotted weight to muscle length (L_{max}). Average cross-sectional area of the muscle strips investigated was 0.54 ± 0.03 mm².

2.3 Xenon application

Xenon, provided by Linde Germany, was continuously perfused in a sealed glas cylinder and in the open contraction chamber filled with Krebs-Ringer solution (37°C) at a flow rate of 30 ml/min. All connections were made of silicon tubes and sealed with silicon rubber to prevent exchange of Xenon. The Krebs-Henseleit solution was perfused 30 minutes prior to the contraction experiments.

2.4 Statistical analysis

Data are expressed as mean ± SEM. Statistical significance was determined with the Student t test. A value of $P < 0,05$ was considered to be statistically significant.

3. Results

The surgical outcome was uneventful in all patients, and there was no complication from right atrial dissection. Twitch tension was measured from the recordings. Experiments were performed in 18 muscle strip preparations from 17 human hearts. Resting tension at L_{max} was 3,2 ± 2 mN/mm². Contractility was studied in muscles perfused with 100% Xenon for 30 minutes. To exclude hypoxia and metabolic derangements we monitored pH and pO2.

Contraction at baseline conditions (37°C, 1 Hz, 1 mmol/l free Ca^{2+}) of all muscles (n=18) are shown in figure 1. In

trabeculae from patients without xenon perfusion the strength of contraction with 10 µmol/l adrenalin was 18,4 mN/mm². Muscle bundles perfused with xenon developed a force of contraction of 17,2 mN/mm² with 10 µmol/l adrenalin. At low catecholamine (50 µmol/l) stimulation, the force of contraction was still lower (17,7 mN/mm² versus 18,4 mN/mm²) in the xenon group. Up to a suprarenin stimulation of 100 µmol/l, the force of contraction was lower (25,6 mN/mm² versus 26,7 mN/mm²) in the muscles perfused with xenon. Maximal force of contraction was reached at 500 µmol/l suprarenin, where fibres in the xenon group reached more force (31,1 mN/mm² versus 28,8 mN/mm²) At maximal adrenalin concentration force development without xenon was lower and showed a small increase whereas force with xenon perfusion did not change. (29,6 mN/mm² versus 31,0 mN/mm²)

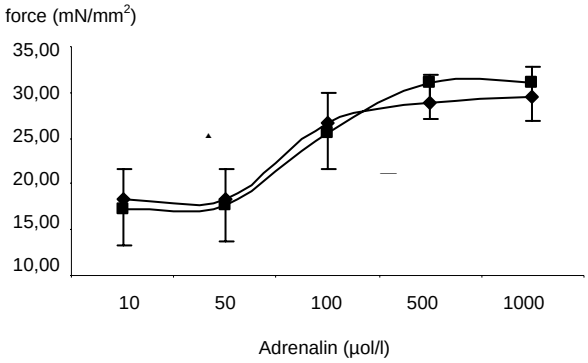

Fig. 1
Influence of xenon on adrenalin dependent force of contraction (18 fibres, 60 bpm, 37°C, filled romboids without xenon, filled squares xenon perfusion)

The ß-adrenoreceptor agonist adrenalin exerted a pronounced positive inotropic effect, with an s-shaped curve in both groups. However, in the xenon group, the concentration-response curve was shifted to the right, with increased amplitude. In the xenon group, the half-maximal positive inotropic effect was reached at 100 µmol/l (EC50), whereas in the group without xenon 75 µmol/l (EC50) was needed to elicit a half maximal response. Thus the positive inotropic response of adrenalin was not markedly different in both groups. (P<0,01)

4. Comment

Xenon is one of the noble gases whose outer shell is filled with electrons.[7] Although it is virtually inert and does not form covalent bonds with other elements, the very large electron shell of xenon can be polarized and distorted by nearby molecules. The distorsion of the electron orbitals permits xenon to interact with and bind to proteins as well as bilayer lipids.[8]

An important mechanism controlling myocardial force in atrial myocardium is the ß-adrenergic signal transduction pathway. The present study demonstrates that xenon does not markedly interfere with the ß-adrenergic pathway. Our data demonstrate that in the xenon group, the positive inotropic effect is shifted to higher adrenalin concentrations. At low catecholamine stimulation there is a small but consistent decrease in force development, whereas at higher adrenalin concentrations there is an increase in contractile force in the xenon group.

The data confirm previous experimental observations in animals, in which the systolic shortening was not significantly reduced. In cardiomyopatic dogs, xenon did not alter myocardial contractility.[9] Additionally, isolated guinea pig ventricular muscle bundles, did not change myocardial contractility.[10] Moreover, xenon did not cause functional depressant effects in an isolated rat heart model.[11]

Although the present study has demonstrated, that in atrial muscle bundles perfused with xenon, contractility is not significantly reduced, xenon may exert an influence on the vascular system. Additionally right atrial myocardium is not representative for the left ventricle. A further limitation concerns our experimental set up. Xenon rapidly evacuates in the atmosphere in our open system and we don't know how much xenon was accumulated in the muscle strip.

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