METHODOLOGY

Effect of Ultrasound on the Myocardium and Cardiac Conduction (A Morphological Study)

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Focused ultrasound is used to create local foci of lesions in the myocardium. It is shown that this method can be used for the treatment of monofocal tachycardias. The effect of focused ultrasound on the myocardium, coronary artery, and atrioventricular node is studied in experiments on dogs, and the ultrasound-destroyed zones of the myocardium are investigated morphologically.

Key Words: *heart; arrhythmia; atrioventricular block; ultrasound; treatment of arrhythmias; morphological investigations*

Tachycardias are the major cause of sudden death of patients. The known surgical methods of treatment of supraventricular and, notably, ventricular tachycardias are radical but traumatic, which restricts their use, especially in patients with heart failure and in children. Noninvasive yet, at the same time, radical methods of treatment of tachycardias are still lacking. The possibility of using focused ultrasound (FUS) for creating confined foci of lesions deep inside tissues without traumatizing the surrounding tissues has been studied in experiments on the brain, liver, and kidneys, offering promise for treating a number of diseases, including oncological ones, with FUS [1,3-5]. Our first trials with FUS in experimental cardiology showed the possibility of creating confined foci of lesions in the myocardium at a distance, without causing considerable damage to surrounding structures. These results have provided a basis for the experimental development of a fundamentally new method of treating tachycardias [2].

In this study we explored the effect of FUS on the myocardium and cardiac conduction.

MATERIALS AND METHODS

The experiments were carried out on 27 mongrel dogs of both sexes weighing 8-23 kg. A right-side thoracotomy was performed along the fifth intercostal space and pericardiotomy was performed 1 cm ventral to *n. diaphragmaticus* under thiopental anesthesia (50 mg/kg) and artificial ventilation. The effect of FUS on the heart was studied using a FUS generator and emitters specially designed for this purpose (AKIN, Moscow). Good acoustic contact between the piezoceramic plate and the epicardium was maintained with a plastic cone, which was mounted on the emitter and then filled with a degassed physiological saline. The right ventricle myocardium was exposed to FUS by directly placing the focal zone (FZ) of the emitter on the epicardium by means of a cone with a height

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equal to the focal distance (70 mm). The right coronary artery was exposed to FUS in the same way (12 experiments). The atrioventricular node (AVN) was exposed to FUS via the intact wall of the right atrium (10 cases) (Fig. 1), via the right ventricle (one case), and via the intact pericardium (one case) until a complete atrioventricular (AV) block was attained. The ECG was recorded on a Mingograf-34 electrocardiograph. When a complete AV block was obtained, an EKS-222 pacemaker was hooked up to the electrode implanted in the right ventricle to maintain proper hemodynamics. In the acute experiments (8 cases) the effect was observed during 3 hours, in the chronic experiments (4 cases) for up to 2 weeks. In 3 cases FUS acted via the thoracic wall after skin dissection toward the apex of the heart. After the animals were removed from the experiment, samples of the myocardium were fixed in neutral Formalin. Histological sections were stained with hematoxylin-eosin after van Gieson, Heidenhain, and Lie. The parameters of FUS were as follows: continuous irradiation; frequency 1-2 MHz; intensity of ultrasound (US) at the FZ of the emitter 100-1000 W/cm^2 (the absorption in tissues not being taken into account). The experiments were carried out in accordance with The Rules For Humane Treatment of Laboratory Animals.

RESULTS

In the acute experiments macroscopic changes in the myocardium near the FZ of the emitter, which were caused by the action of FUS (50-300 W/cm^2; exposure time 5-15 sec) on the right ventricle, manifested themselves in a confined pale focus as large as 1 mm deep and 3-5 mm in diameter. In the case of a higher dose of US (intensity up to 700 W/cm^2; exposure time 5-15 sec and more) a clear-cut dark red focus of lesions (diameter 5-8 mm, depth 3-7 mm) was observed.

We studied the occurrence of artificial AV block in dogs depending on the exposure time at an intensity of US 1000 W/cm^2 and frequency 1 MHz. The calculated diameter and length of the US emitter were 4 and 28 mm, respectively.

When FUS acted on the AVN via the right atrium, right ventricle, and intact pericardium, complete AV block was obtained in 10 out of 12 cases, including the exposure via the intact pericardium and via the right ventricle. The time of exposure of AVN to FUS was 30 to 120 sec. Acceleration of the AV rhythm was always observed before the complete AV block was obtained.

In 3 acute experiments, when the effect was produced via the right atrial wall, the US generator was switched off after 15 sec, when the AV rhythm started to accelerate. Recovery of the sinus rhythm was observed 3-5 min later. When the exposure was continued for another 15 sec, a stable AV block was obtained.

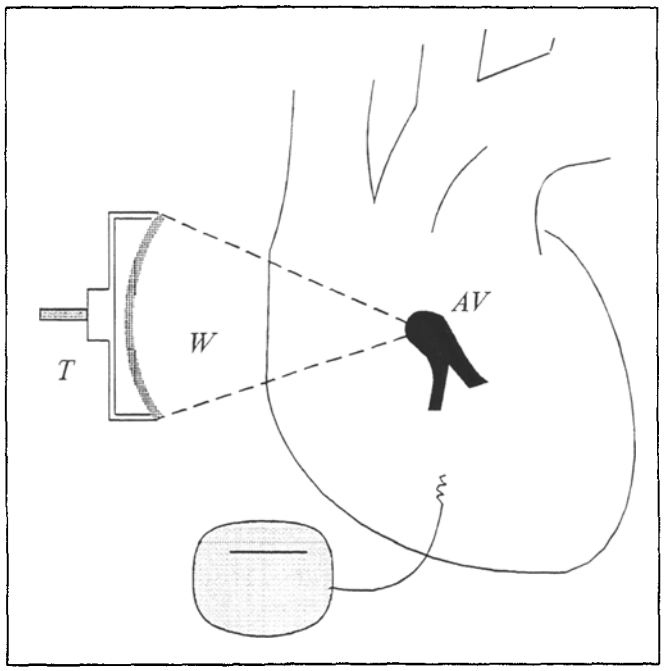

Fig. 1. Schematic of destruction of AVN using focused ultrasound emitter. *T*: emitter; *W*: water; *AV*: atrioventricular node.

In 2 acute experiments exposure to US was stopped 20 sec after the *P-Q* interval reached 0.3-0.35 sec (I degree AV block). These changes of conduction were preserved during 3 h till the end of the follow-up.

In the case where a stable AV block was obtained macroscopic changes in the zone of exposure manifested themselves in a confined dark red focus of lesions with an irregular edematous contour (1-1.5×0.6-1.0 cm, depth to 3-5 mm), which was located in the projection of AVN and sometimes reached the septal valvula of the tricuspid valve and the opening of the coronary sinus. Microscopic examination 6 days after the exposure showed a marked degradation of cells of the AVN and leukocyte infiltration of AVN tissue and of a part of the His bundle. The central fibrous body and the tricuspid valve were unchanged (Fig. 2).

Permeability of the coronary arteries was preserved even when FUS was directly trained on the arterial wall. In none of the experiments was FUS-induced fibrillation of the atria and ventricles noted. We did not observe perforations of the atrial walls or damage to the valves. The motor activity of the zone of contact between the right atrium and the emitter was preserved.

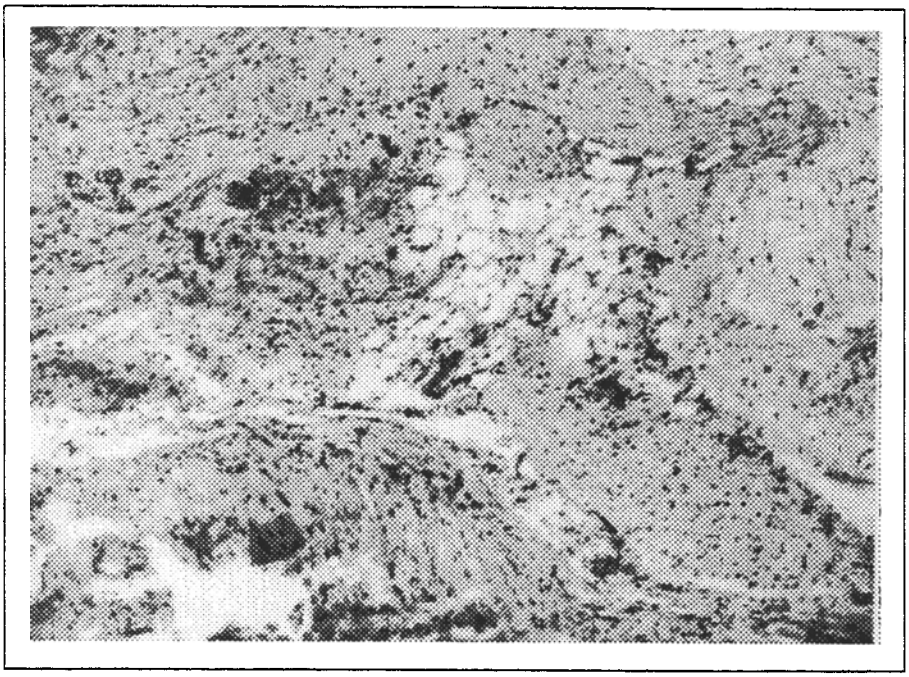

Fig. 2. Microscopic examination 6 days after exposure. Structures of central fibrous body (top) and valve (bottom left) are preserved. Hematoxylin–eosin staining, ×20.

Histological changes of tissues in the zone of exposure were also focal in nature (Fig. 3): in a strictly confined area contractures and bands of hypercontraction of muscle fibers and, for an increased US dose, coagulation necrosis with cytoplasm homogenization and myocyte cardiolysis were observed. A narrow strip of myocardium with contractures was adjacent to the boundary zone, where intracellular edema of cardiomyocytes predominated, although not reaching the degree of irreversible changes. A few scattered myocytes in the state of hypercontraction were also encountered there.

Changes of the circulatory bed with constricted or dilated capillaries and stasis, frequently attended by stromal edema, were revealed in the perifocal zone. Outside the zone of exposure the myocardium was virtually unchanged, a few scattered contractures of cardiomyocytes being observed.

Macroscopic changes for the action of FUS on the heart via the intact thoracic wall were less pronounced. Although in this case the changed myocardial focus (up to 20 mm in diameter) was larger, lesions in the myocardium were local, and a rather well-defined contour was preserved. Outside the zone of exposure the myocardium was unchanged.

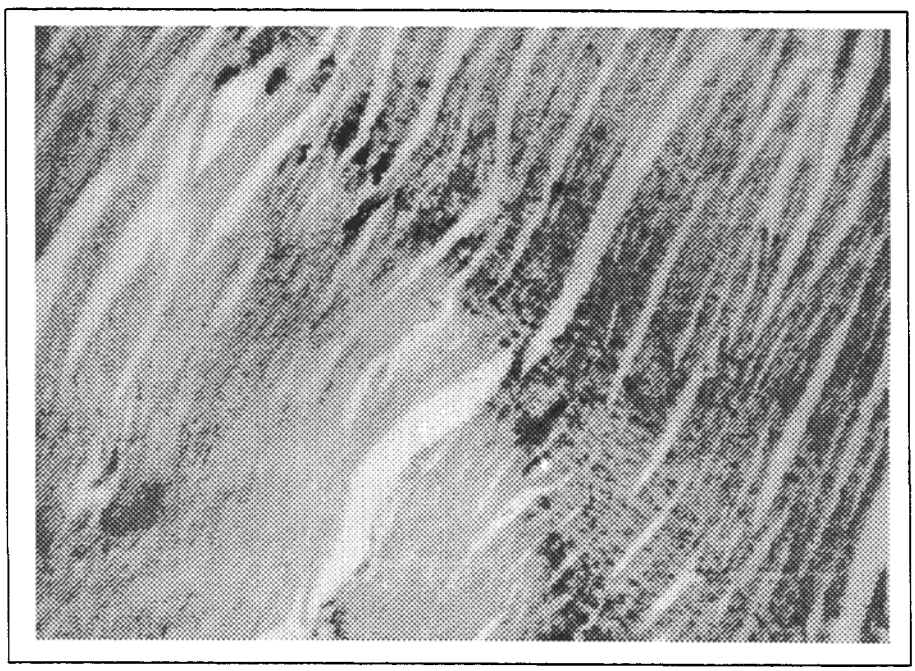

Fig. 3. Histological changes of tissues in zone of exposure. Longitudinal section of muscle fibers; relatively light region of coagulation necrosis where dilated capillaries with sludged erythrocytes are identified; sharply–defined boundary is formed by zone of cells with contracture bands. Heidenhain staining, ×20.

Damage to the tissues of the thoracic wall after passage of the US beam was not destructive in nature. Ten days after the exposure we observed local cellullitis and confined myositis with signs of regeneration occurring at a normal rate.

The radical treatment of monofocal tachycardias consists in destruction of the arrhythmogenic zones of the myocardium. Supraventricular tachycardias can be successfully treated using transvenous catheterization with high-frequency destruction. The few reports on the use of catheterization for the destruction of arrythmogenic zones in ventricular tachycardias provide evidence that this method is complicated and has a low efficacy. Endocardial resection or cryodestruction under conditions of artificial circulation are now the most widespread methods of radical treatment of monofocal ventricular tachycardias.

We made an attempt to use remote FUS for noninvasive intervention in the myocardium in order to create local foci of lesions. Local damage is achieved by focusing the US beam at the FZ of the emitter, where the maximum energy is concentrated. The possibility of having a focused US beam penetrate biological tissues without markedly damaging them is the basis for the development of a noninvasive method of action upon the arrhythmogenic foci in the myocardium. The fact that the damage to tissues was local was corroborated both electrophysiologically (discontinuation of conduction at the AVN) and morphologically.

It should be mentioned that FUS exhibits such positive properties as the absence of thrombosis of the coronary artery even when the FZ of the emitter is directly placed on the artery. The absence of perforation in the walls of the heart and aorta and the absence of serious damage to the cardiac valves even in the case of targeted action of FUS (1000 W/cm^2, exposure time 15 sec) on these structures attest to the relative safety of this method. Along with this, a stable discontinuation of conduction at the AVN points to the fundamental possibility of suppressing any arrhythmogenic focus with US by remote action.

Hence, remote bombardment of a segment of the myocardium with FUS without traumatizing surrounding tissues and without thoracotomy may become an effective method of treating arrhythmias, provided that the FZ of the emitter is precisely trained at the arrhythmogenic zone. Ultrasonic scanning in combination with electrophysiological investigations seems the most feasible method of visualizing intracardiac structures and guiding the FZ of the emitter. In this case the AVN can be localized by following-up the US image of adjacent structures (tricuspid valve, aorta origin, and interatrial septum). Noninvasive determination of the arrhythmogenic focus in the ventricles is a more complicated problem which awaits solution.

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