Chronobiology of Cardiac Ventricular Fibrillation Development in Experimental Acute Coronary Failure

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Numerous experiments on simulation of acute coronary failure in initially intact rabbits showed that under the same experimental conditions irreversible ventricular fibrillation developed in some animals and did not develop anothers. We hypothesize that the probability of fibrillation development was determined by the time of the day, during which acute coronary failure developed. The study was carried out on 2 groups of rabbits in winter in Moscow. In group 1, the failure was induced by ligation of the left descending coronary artery at the interface between its middle and lower thirds at 11.00-18.00 with 30-min intervals. In group 2, the microcirculatory status of the left-ventricular myocardium was studied by light microscopy and morphometry at 12.00 and 18.00. Induction of coronary failure during the period from 15.30 to 18.00 led to irreversible ventricular fibrillation and death in 100% cases. Modeling of the condition from 11.00 to 15.00 caused no ventricular fibrillation in 89% cases, and the animals survived. The area of left-ventricular myocardial capillaries at 12.00 virtually 2-fold surpassed that at 18.00. Presumably, the electrolyte balance and metabolic characteristics of the myocardium switch over to the nocturnal mode of functioning at 15.30 due to changes in blood filling of the myocardium. The appearance of an ischemic focus in the myocardium during this period inevitably leads to the development of irreversible ventricular fibrillation.

Key Words: *acute coronary failure; myocardium; fibrillation; time-dependent; chronobiology*

The probability of the development of so hazardous condition as cardiac ventricular fibrillation (VF), responsible for 67.5-80% sudden cardiac deaths according to various sources [2,4,5], increases in the presence of some conditions predisposing to it and determined by metabolic characteristics of the myocardium. Modeling of acute focal left-ventricular myocardial ischemia under conditions of electrolyte steroid cardiopathy (ESCP) developing within 11-12 days of daily injections of cortisone, deoxycortisone acetate, and monosubstituted sodium phosphate to rabbits essentially increases heart liability to fibrillation.

Some previous morphological changes in the myocardium, such as foci of ischemic injury (3rd degree contracture changes in cardiomyocytes, zones of intracellular myocytolysis, primary lumpy degradation of myofibrils) and relaxation of the myocardium also promote the development of fibrillation [1].

On the other hand, numerous experiments on the model of acute coronary failure (ACF) in initially intact rabbits showed the development of irreversible fibrillation transforming into asystole in some animals, while other animals develop no symptoms of this kind and survive under the same conditions. Since we induced ACF in various periods of the day, we hypothesized that the development of VF in ACF is an event depending on the time of the day. In order to verify this hypothesis, we carried out this study.

MATERIALS AND METHODS

Experiments were carried out in December 2009 in Moscow on 26 adult male Chinchilla rabbits (3.5-4.0

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kg). The rabbits were kept under vivarium conditions at natural illumination and 22-23°C. In group 1 (n=16), the left descending coronary artery was ligated for inducing left-ventricular ACF. The operation was carried out from 11.00 to 18.00 with 30-min intervals under total anesthesia with artificial ventilation of the lungs. Monitoring and recording of bioelectrical activity of the heart was carried out 10 min before, during, and throughout 30 min after the operation by ECG in 6 leads (I, II, III, aVR, aVL, aVF) on a MICARD device presenting the curves reflecting the results of functional studies on the monitor in a real time mode and recording and saving the data in the PC memory.

In group 2 rabbits (n=10), blood filling of left-ventricular myocardium at the level of the microcirculatory network was studied at 12.00 and 18.00 (5 rabbits per point) by morphometry on semithin sections. The heart of intact animals was isolated under general anesthesia and perfused through the ascending aorta with 2.5% glutardialdehyde; left-ventricular papillary muscles were dissected, processed routinely, and embedded in epon and araldite mixture. Semithin sections of the myocardium were sliced on a Reichert-Jung-Ultracut ultramicrotome and stained as described previously [3]. The preparations were examined at ×1000 in a Nikon Eclipse E400 light microscope with a videosystem (Watec 221 camera) connected to a PC. Summary capillary area was estimated in 30 visual fields in volume percent (vol%) using an Avtandilov grid presented on the monitor (using special software) together with the preparation image. The data were statistically processed: the means, errors of the means, and mean square deviations were calculated.

RESULTS

A clear-cut correlation between the development of cardiac VF and time of ACF modeling was found (Fig. 1).

Ventricular fibrillation developed during minutes 9-15 postoperation in all rabbits (n=7) with modeled ACF from 15.30 to 18.00. It first manifested by short fragments alternating with the sinus rhythm (Fig. 2, *b*) and then transformed into a permanent irreversible form (Fig. 2, *c*) eventuating in asystole and animal death.

Rabbits subjected to coronary artery ligation from 11.00 to 15.00 survived in 89% cases (8 of 9 animals). No signs of even reversible short-term fibrillation were detected in this group. Only one rabbit of those operated during these hours died from VF.

In group 2, the area of left-ventricular myocardial capillaries at 12.00 was 2-fold larger than at 18.00 (Fig. 3). The differences between the means were statistically significant.

The results of our experiment and published data on the impact of ESCP for the probability of fibril-

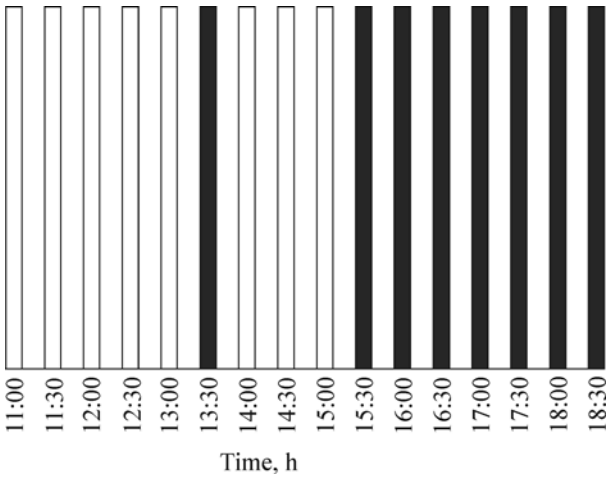

Fig. 1. Outcome of ACF depending on the time of its modeling. Light bars: no VF, survival; dark bars: irreversible VF eventuating in asystole and animal death.

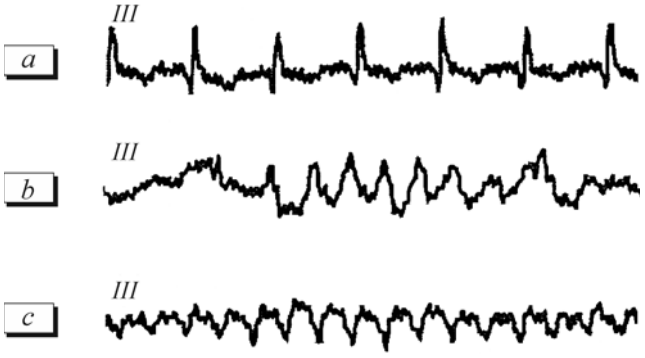

Fig. 2. Fragments of ECG in standard lead III for one animal. *a*) intact rabbit sinus rhythm; *b*) short fragment of reversible VF developing during minute 11 after coronary artery ligation; *c*) permanent irreversible VF which developed during minute 15 after ligation of the coronary artery and eventuated in asystole.

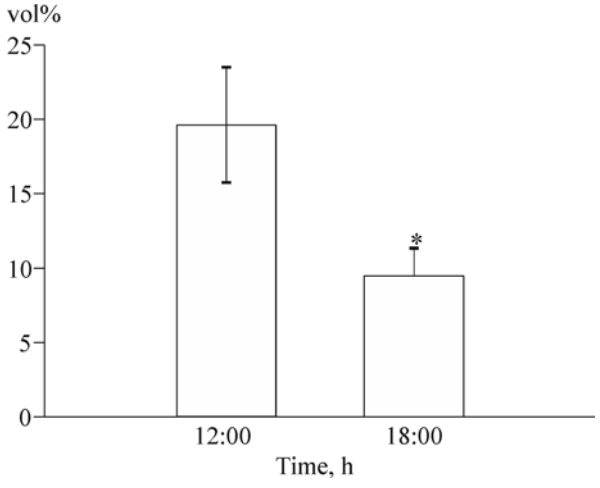

Fig. 3. Relationship between summary area of capillaries in the left ventricular myocardium and time of the day. *$p \leq 0.05$ compared to the value at 12.00.

lation development suggest that at 15.30 changes in the myocardial blood filling leads to transition of the electrolyte balance and metabolic parameters of the cardiac muscle to the nocturnal functioning mode. The appearance of an ischemic focus in the myocardium during this period inevitably leads to fulminant formation of an arrhythmogenic zone and results in the development of irreversible VF.

These data are important from both theoretical and practical viewpoints. To begin with, scientists using the ACF model in experiments on rabbits are recommended to carry out coronary artery ligation no later than 15.00, in order to minimize animal mortality. The present research should be continued also in a clinical setting, in order to develop the measures aimed at drug chronoprevention of VF in patients with heart diseases of different origin.

Importantly that the results of our study can be extrapolated only to the winter for the Moscow time zone. The time border (15.30) defined in our experiments can be due to the fact that sunset in December in Moscow is rather close to this time (from 15.56 to 16.05). Presumably, in summer the transition of the electrolyte and metabolic parameters of the myocardial to the nocturnal mode takes place later, but this hypothesis is to be verified.

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