Ischemic Shifts on the Electrocardiogram and Their Correction in a Chronic Model of Angina Pectoris

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Three types of ischemic shifts are present on the ECG recorded from conscious dogs in a chronic model of angina pectoris. It is suggested that these shifts are caused, along with the ischemic factor, by excessive sustained coronary dilatation in the ischemic focus. Elimination of this focus with pituitrin may open up new prospects in the control of ischemic damage to the myocardium.

Key Words: *myocardial ischemia; ECG changes; pituitrin; angina pectoris; chronic model*

Studies performed on a dog model of chronic angina pectoris [5] revealed a substantial (but as yet insufficiently utilized) reserve for the prevention and therapy of ischemic damage to the myocardium [7-9]. Utilizing reversible and repeated circulatory disturbances in a major cardiac artery in conscious dogs, we have shown that in this model the electrocardiogram (ECG) may reflect not only the direct and stable consequences of myocardial ischemia, but also the response of the whole organism, which varies in a wide range [9]. It was also demonstrated that complex drug therapy with the use of small doses of pituitrin, which induce no changes in the ECG, may considerably reduce and in some cases abolish (for a 12-25-min period) the development of ischemic ECG shifts with subsequent blood flow cessation in the circumflex branch (behind the auricle) of the common left coronary artery [8,9]. These results inspired us to present the original data obtained in this model that laid the foundation for a new direction in the development of preventive and therapeutic measures to control myocardial ischemia.

The aim of this work was to study different kinds of ischemic ECG shifts and to test the possibility of their elimination with small doses of pituitrin.

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MATERIALS AND METHODS

For chronic experiments on conscious dogs we performed the following preliminary operation: a device allowing for clamping and restoration of the blood flow in the circumflex branch of the common left coronary artery without thoracotomy was inserted in the thorax [5]. Experiments were carried out 2-3 weeks or more after the operation. During the experiments the dogs were fixed in the standing position. Coronary blood flow was stopped for a 1.5-10-min period under ECG control (standard leads and thoracic CV^3_4 lead). In some experiments pituitrin (sterile, 0.2-1.5 U/kg body weight) was injected intravenously or intramuscularly 10-60 min prior to the restoration of the coronary blood flow. Fifty-three dogs were used in the study. In control experiments the animals were administered hexenal and difril in the conventional doses employed in pharmacological analysis [13-14].

RESULTS

It is known that in the dog disturbances of the blood flow in the left coronary artery result in

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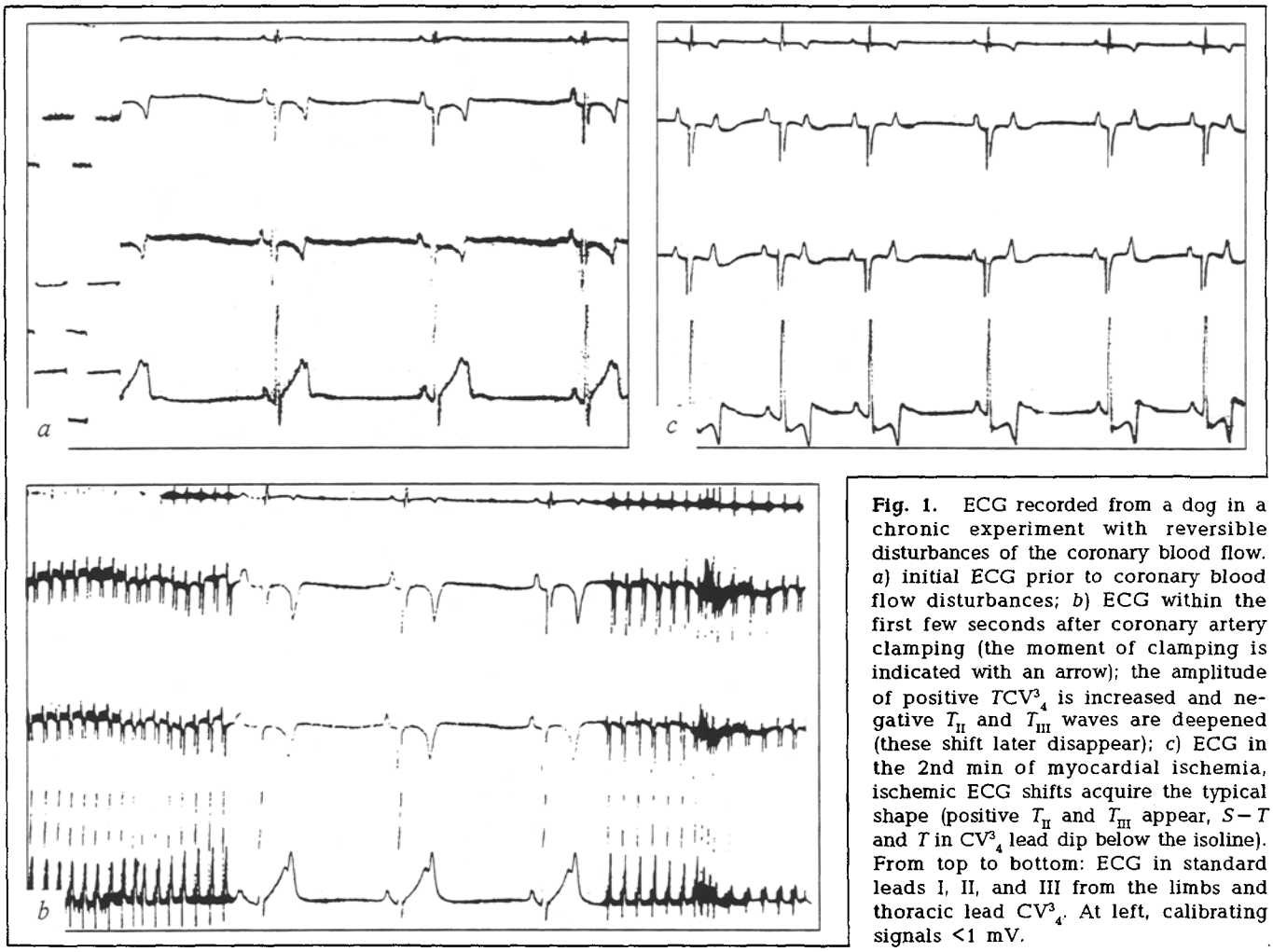

Fig. 1. ECG recorded from a dog in a chronic experiment with reversible disturbances of the coronary blood flow. *a*) initial ECG prior to coronary blood flow disturbances; *b*) ECG within the first few seconds after coronary artery clamping (the moment of clamping is indicated with an arrow); the amplitude of positive TCV^3_4 is increased and negative T_{II} and T_{III} waves are deepened (these shift later disappear); *c*) ECG in the 2nd min of myocardial ischemia, ischemic ECG shifts acquire the typical shape (positive T_{II} and T_{III} appear, $S-T$ and T in CV^3_4 lead dip below the isoline). From top to bottom: ECG in standard leads I, II, and III from the limbs and thoracic lead CV^3_4. At left, calibrating signals <1 mV.

ischemia of the posterior lateral wall of the ventricle, an increase in the T wave amplitude, and an increase of the S-T interval in ECG leads (II, III standard leads, etc.) directed toward the ischemic focus [5]. Restoration of the blood flow abolishes ischemic shifts, and the ECG acquires its original shape (often after transitory electronegativity of the T_{II} and T_{III} peaks). Two types of ECG changes were observed after ischemia was induced several times at 0.1-15-min intervals. In some animals ischemic shifts were the same after the first and subsequent clampings of the coronary artery. In others (about 50%), the ECG shifts after the first clamping were much greater than after subsequent clampings, and the amplitude of the shifts after the second clamping remained the same during the subsequent clampings. The decrease in the amplitude of ischemic peak T_{II} after the second clamping was not less than 0.33 ± 0.08 mV compared with the first clamping ($p<0.01$, $n=11$). The value for the S-T_{II} interval was 0.17 ± 0.02 mV ($p<0.001$). In control experiments (0.1 g/kg hexenal, intramuscularly), there were differences in the ECG after the first and second clamping. The second type of shift after repeated disturbances of the coronary blood flow is not totally related to ischemia, since a decrease in the amplitude of ischemic shifts occurs even after a short-term (less than 10 sec) reperfusion, and subsequent, even long-term, ischemization does not result in restoration of the original amplitude of the S-T_{III} interval and T_{II} peak. It was suggested that in this model the first disturbance of the coronary blood flow is accompanied by an additional perifocal coronary spasm, which does not occur after subsequent disturbances [10]. However, direct measurements of the blood flow in the zones adjacent to the ischemic focus have revealed pronounced coronary dilatation, which confirmed the assumption about coronary spasm [11]. On the other hand, direct measurements of contractile activity (left ventricular dP/dt_{max}) showed an increase in this parameter: 288 ± 56 mm Hg/sec, $p<0.01$) within the first few seconds after the first disturbances in the coronary blood flow, which was absent after subsequent clampings in 7 out of

14 observations. In addition, it was demonstrated previously that, all other things being equal, the pressor response of arterial pressure is more frequent after the first clamping than after the subsequent ones [6]. Taken together, these findings brought us to the conclusion that the second type of ischemic ECG shifts is related to different (greater after the first and smaller after the subsequent coronary flow disturbances) manifestations of a positive inotropic response of the heart, which occurs at the initial stage of myocardial ischemia. However, this conclusion was confirmed only after a third type of ECG shift had been revealed in our model, when the CV^3_4 thoracic lead ECG was recorded in conscious dogs with initially negative T_{II}-T_{III} waves. In these cases (Fig. 1), an increase (0.1±0.04 mV) in the T wave amplitude was observed in 81.8% of dogs (n=11) during the first 15 sec of ischemia. At the same time, the difference in the amplitude of the first (low) and the second (high) peaks of the T wave became greater (in this lead the T wave has a split peak). Parallel to these shifts, there was a certain deepening of the T_{II}-T_{III} interval. The first phase in ECG changes gives way to the second one: S-TCV^3_4 and TCV^3_4 are displaced under the isoelectric line, while the S-T_{II-III} interval and T_{II-III} waves rise over it. The second phase in ECG changes which is related to ischemia is reproduced without changes after repeated clamping of the coronary artery, and the shifts characteristic of the first phase become less pronounced and disappear in control experiments (0.05-0.1 g hexenal intramuscularly). These facts corroborate the notion that in our model the positive inotropic response of the heart may correlate in time with the development of the first phase of changes recorded in CV^3_4 lead and, consequently, lasts not less than 10-15 sec. Afterthis, the contraction force cannot but decrease. However, it may be assumed that this response has certain consequences: the initial increase in contraction force (during the first few seconds of ischemia) induces an adequate coronary dilatation, and then, after this reaction has played itself out, the myocardial ischemia developing in the damaged focus supports the coronary dilatation. It can be assumed that this pathophysiological mechanism is the factor that maintains the relatively high amplitude of ischemic ECG shifts in a conscious animal after the first disturbance of the coronary blood flow in cases when a short-term reperfusion destroying the mechanisms maintaining excessive coronary dilatation determines a decrease in ischemic ECG shifts for repeated coronary blood flow disturbances not accompanied by an initial positive inotropic reaction which is not as pronounced as after the first clamping of the artery.

Thus, comparison and analysis of the three types of ECG changes occurring in a model of chronic angina pectoris provide a reasonable explanation for the electrophysiological shifts observed in our model. At the same time, this analysis revealed a factor that can affect the development of various negative consequences of coronary flow disturbances developing in conscious dogs (this is also characteristic of ischemic heart disease patients). This factor is the excessive and self-maintaining coronary dilatation that emerges (in an ischemic focus) in the myocardial zone with reduced contractile activity. Obviously, the presence of this second factor and elucidation of its actual role can be more effectively studied in an angina pectoris model by preventing excessive coronary dilatation with pituitrin. Such experiments were performed, and it was found that even small doses of this hormone considerably inhibit the development of ischemic ECG shifts after local disturbances of the coronary blood flow. The latency in ECG changes increases from 4.0±1.0 to 65.8±5.1 sec (p<0.001). The S-T_{II} interval rise decreases by 0.22±0.08 mV (p<0.05) and the amplitude of the positive T_{II} wave decreases by 0.44±0.13 mV (p<0.05). At the same time, the maximum rate of increase of the ischemic T_{II} wave decreases from 0.16±0.01 to 0.03±0.003 mV/sec (p<0.01). In control experiments (intravenous administration of the coronary dilatator difril (10 mg/kg) all these parameters showed a tendency toward opposite changes (for example, the maximum rate of increase of T_{II} rose by 0.013±0.002 mV/sec, p<0.05). It was demonstrated that the prevention of excessive self-maintaining coronary dilatation with pituitrin may lay the basis for the development of effective anti-ischemic therapy. Our further studies [7-9] confirmed this possibility, indicating that complex drug therapy, based on the inhibition of excessive coronary dilatation and reduction of myocardial contractility in the ischemic focus for its simultaneous increase in the compensation zones with sufficient blood supply, is feasible; in fact, the beneficial effect of this therapy has been demonstrated. In addition to the practical interest associated with broadening the arsenal of preventive and therapeutic measures in the management of ischemic heart disease, elucidation of the "second" factor is of theoretical interest. The influence of this factor, which is shaped not by ischemia itself, but rather by the secondary reaction to ischemia, which may vary widely, explains why a severe limitation of

blood flow in all the major cardiac arteries (due to the presence of atherosclerotic damage) is not necessarily accompanied by myocardial infarction or angina pectoris [2]. The presence of such a "second" factor also accounts for the frequently lethal cardiac rhythm and function disorders, which occur during treatment of acute myocardial infarction with a number of effective coronary dilatatory agents [3,12]. And finally, it becomes clear why an increase in the influence of this factor on the heart - as a result of postischemic or postnecrotic coronary dilatation - increases the risk of further myocardial necroses [1]. In all cases excessive coronary dilatation provides the need for undesirable transcoronary [4] stimulation of the ischemic myocardium predominantly in the marginal zone of the ischemic focus. This creates foci of ectopic rhythm and stimulates the formation of necroses [2]. From these findings it can be concluded that in a certain initial period of ischemic damage the "second" factor (excessive self-maintaining coronary dilatation) plays not a smaller but even a larger negative role (compared with the primary triggering factor) in the development of local myocardial ischemia.

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