# PHARMACOLOGIC PREVENTION OF FIBRILLATION IN ACUTE CARDIAC ISCHEMIA AND ELECTROLYTE DYNAMICS

(UDC 616.127-005.4-06:616.12-008.313.2-085.7-039.71]-07:616.152.32/.33-07+616.12-008.313.2-02:616.127-005.4]-085.7-039.71-616.152.32/33-07)

N. K. Popova and É. I. Ivashkevich

Pharmacology Laboratory, Department of Experimental Biology of the Institute of Cytology and Genetics, Siberian Division USSR Academy of Sciences, and Clinical Laboratory of the Institute for Experimental Biology and Medicine, Ministry of Public Health of the RSFSR, Novosibirsk

(Presented by Academician V. V. Zakusov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 59, No. 5, pp. 64-67, May, 1965
Original article submitted January 18, 1964

Recently, there have been gathered a large number of facts concerning the relation between fibrillation arising during acute myocardial infarction and changes in electrolyte exchange. It may be considered well established that during acute cardiac ischemia the consequence of disturbances in cellular membrane permeability in ischemic myocardial cells is a decrease in potassium content, which exits in the blood flowing out from the injured area which is partially diverted at the borders of the infarcted zone; at the same time the sodium and chloride levels in the ischemic region are increased [4, 5, 7, 8, 16].

A definite relation has been noted between disruption of potassium exchange arising during acute myocardial ischemic injury and the occurrence of ventricular fibrillation [5-8, 12, 13]. With use of the anti-arrhythmic drug quinidine, a decrease was noted in the potassium loss from cells of isolated auricle [14].

However, the problem of the pathological significance of changes in electrolyte exchange in the origin of ventricular fibrillation cannot be considered as definitely solved. Some authors have not observed changes in potassium level in blood plasma coming from the heart after coronary artery ligation [20] and in experimental epinephrine arrhythmia against a pentobarbital background [10, 17]. It appeared to us that additional data could be obtained by studying the dynamics of electrolytes during the action of substances which prevent development of ventricular fibrillation—substances belonging to various groups in terms of chemical structure and pharmacologic properties. The latter permitted the exclusion of a possible nonspecific effect of the different preparations on electrolyte exchange.

The effect of a number of pharmacologic studies on the potassium and sodium contents of the blood flowing from the heart during experimental acute coronary insufficiency: monoamine oxidase (MAO) inhibitors, the isopropyl hydrazide of isonicotinic acid (iprazid), the antifibrillatory property of which has been established by several authors [1, 18, 19]; the hydrazide of isonicotinic acid (isoniazid)—a substance similar to iprazide in chemical structure and antifibrillatory properties [2] but distinguished by its very weak MAO inhibition [21]; reserpine, which also possesses anti-arrhythmic properties [3], and the classic anti-arrhythmic compound, novocainamide (procaine amide).

## METHODS

In 83 dogs a lateral incision was made in the thorax under morphinethiopental anesthesia, the descending branch of the left coronary artery was isolated and ligated at the site of origin of the circumflex artery. Blood for potassium and sodium study was taken from the coronary sinus and from the chambers of the right and left ventricles before coronary artery ligation and at 3 min after this manipulation (if fibrillation had not developed). The plasma potassium and sodium concentrations were determined by Zeiss flame photometer.

Reserpine (0.3 mg/kg) was injected intraperitoneally in a 10% solution of ascorbic acid one day prior to coronary artery ligation; all other drugs were injected intraperitoneally at 30 min prior to the procedure—novocainamide, in a dose of 40 mg/kg, iprazid and isoniazid, 4 mg/kg.

Effect of Preparations Used on the Development of Fibrillation in Dogs after High Ligation of the Coronary Artery

| Preparation | Number of dogs | Result of high coronary artery ligation | | |
|---|---|---|---|---|
| | | no fibrillation* | fibrillation arose | level of significance |
| Control | 30 | 2 | 28 | $<0.05$ |
| Iprazid | 15 | 6 | 9 | $<0.05$ |
| Isoniazid | 15 | 6 | 9 | $<0.05$ |
| Reserpine | 10 | 6 | 4 | $<0.05$ |
| Novocainamide | 13 | 5 | 8 | $<0.05$ |

* One dog in the control group, 2 dogs given reserpine and 3 given novocainamide died from cardiac arrest.

## RESULTS

In the control group of dogs (30 animals), in 1-1½ min after coronary artery ligation, the EKG recorded extensive myocardial ischemia (ST-segment elevation, "gigantic" R wave, monophasic wave formation) and following this, in 94% of animals, ventricular fibrillation (see table). Fibrillation usually developed during the first 3-5 min, never remitted spontaneously, and the dogs died.

In the group of animals receiving iprazid, isoniazid, reserpine and novocainamide, a picture of acute myocardial ischemia also developed in the first minutes after coronary artery ligation; however, all the drugs used exhibited a protective effect, preventing the development of fibrillation in a certain percent of experiments and enabling resuscitation of some of the animals (see table).

The antifibrillatory action of iprazid, isoniazid and reserpine was more clearly expressed in our experiments than was that of novocainamide, which appeared to have a weak effect in the model used (see table).

With measurement of the plasma potassium from blood from the coronary sinus, left and right ventricles, it was established that already at 3 min after coronary artery ligation there occurred a clearcut increase in the potassium of left ($3.6\pm0.06$ to $4.13\pm0.18$ mEq/liter, $<0.01$) and right ($3.69\pm0.09$ to $4.35\pm0.18$ mEq/liter, $P<0.01$) ventricular blood. The increase in potassium content was greatest in coronary sinus blood ($3.82\pm0.08$ to $4.63\pm0.21$ mEq/liter, $P<0.002$).

Against a background of the effect of all antifibrillatory compounds used, the original potassium level was somewhat lower. After coronary artery ligation in all those series there were no substantial changes in the potassium level; a slight increase in potassium level, more marked in coronary sinus plasma, was statistically invalid except for experiments with novocainamide. In the latter case the potassium content of left ventricular blood was increased after coronary artery ligation from $3.32\pm0.08$ to $3.7\pm0.1$ mEq/liter ($P<0.02$), in right ventricular blood from $3.36\pm0.09$ to $3.87\pm0.15$ mEq/liter ($P<0.02$) and in coronary sinus blood from $3.40\pm0.08$ to 3.97 mEq/liter ($P<0.02$).

The plasma sodium concentration of blood from the various chambers after coronary artery ligation fell slightly in control experiments, this fall being of greater degree, as with changes in potassium, in coronary sinus plasma. Thus, the sodium content of left ventricular blood fell from $159.5\pm2$ to $151\pm2.6$ mEq/liter ($P<0.05$), of right ventricular blood—from $162.7\pm2$ to $153\pm2.7$ mEq/liter ($P<0.05$), and of coronary sinus blood—from $162.7\pm1$ to $153\pm2.7$ mEq/liter ($P<0.05$). With iprazid, isoniazid and novocainamide substantial changes in the sodium level after coronary artery ligation were not observed (with iprazid and isoniazid there was even a tendency to some increase in the sodium level) and only against a background of reserpine was there a small (smaller than in the control) but statistically valid fall in the sodium level of coronary sinus blood from $150\pm2$ to $144\pm2$ mEq/liter.

Hence, these antifibrillatory substances of widely different chemical structure and pharmacological properties acted in a similar manner on electrolyte metabolism. Whereas in the control experiments a considerable rise in the potassium level and a slight fall in the sodium level took place very soon after ligation of the coronary artery, and were most marked in the blood plasma from the coronary sinus (thus confirming the "cardiac" origin of these changes in the electrolyte dynamics), during the action of the tested antifibrillatory drugs the changes observed were much less severe in degree and, as a rule, they were not statistically significant.

The regular decrease in potassium level of blood leaving the heart, as compared with controls, and the absence of a decrease in sodium level during the action of various antifibrillatory substances permits the suggestion that the active exodus of potassium from the ischemic part of the myocardium and the change in potassium/sodium ratio plays a definite role in the origin of ventricular fibrillation. The antifibrillatory action of various pharmacologic agents is to prevent or slacken these changes.

## LITERATURE CITED


1. N. K. Popova, Thesis symposium on surgical treatment of coronary disease [in Russian], Moscow (1962), p. 65.
2. N. K. Popova, P. Yu. Il'yuchenok, and V. S. Sergievskii, Izv. Sibirsk. otdeleniya AN SSSR, No. 8 (1963); Seriya biol.-med. nauk, No. 2, p. 121.
3. N. K. Popova et al., Farmakol. i toksikol, No. 4 (1964), p. 454.
4. V. S. Sal'manovich, In book: Atherosclerosis and myocardial infarction [in Russian], Moscow (1959), p. 266.
5. V. S. Sergievskii and É. I. Ivashkevich, Pat. fiziol., No. 3 (1963), p. 37.
6. A. H. Briggs and W. C. Holland, Am. J. Physiol, 200 (1961), p. 122.
7. A. Cherbakoff and S. Toyama, Fed. Proc., 15, No. 1, Pt. 1 (1956), p. 35.
8. A. Cherbakoff, S. Toyama, and W. F. Hamilton, Circulat. Res., 5 (1957), p. 517.
9. J. R. Cummings, Ibid, 8 (1960, p. 865.
10. P. E. Dressel and M. J. Nickerson, Pharmacol. exp. Ther., 125 (1959), p. 142.
11. A. S. Harris, A. Bisteni, and R. A. Russele et al., Science, 119 (1954), p. 200.
12. W. C. Holland, Am. J. Physiol, 190 (1957), p. 63.
13. W. C. Holland and J. H. Burn, Brit. med. J., 1 (1957), p. 1031.
14. W. C. Holland and R. L. Klein, Circulat. Res., 6 (1958), p. 516.
15. L. Iseri, L. C. Alexander, and R. S. McCaughey et al., Am. Heart J., 43 (1952), p. 215.
16. H. Kreuziger, H. Asteroth, and K. Zipf, Z. Kreisl. Forsch., Bd. 43, S. 385 (1954).
17. G. S. O'Brien, Q. R. Murphy, Jr., and W. J. Meek, J. Pharmacol. exp. Ther., 109 (1953), p. 453.
18. J. Pisanty, A. Pineyro, and R. Moreira et al., Cardiologia (Basel), 37, 2 (1960), p. 74.
19. W. Regelson, F. S. Hoffmeister, and H. Wilkens, Ann. N. Y. Acad. Sci., 80, 3 (1959), p. 981.
20. J. Wexler and H. H. Patt, Am. Heart. J., 60 (1960), p. 618.
21. E. A. Zeller, J. Barsky, and J. R. Fouts et al., Experientia (Basel), 8 (1952), p. 349.


---



---