ACADEMY OF SCIENCES OF THE USSR
SCIENTIFIC CENTER OF BIOLOGICAL RESEARCH
INSTITUTE OF BIOLOGICAL PHYSICS

INFORMATION

PERFUSION AND NONPERFUSION METHODS OF MYOCARDIUM PROTECTION WITH PERFLUOROCARBON EMULSION

PUSHCHINO • 1983

UDC 615.778.3

Information is presented on experimental reasonings of application of compounds based on perfluorocarbon emulsion for perfusion and nonperfusion methods of myocardium protection from ischemic damage in reconstructive operations on the heart.

P e r f u z o l – for perfusion of coronary vessels

Perfluorocarbon	8 vol%	NaH_2PO_4	11.4 mg%
Proxanol	2.6%	$CaCl_2$	8 mg%
NaCl	804 mg%	$NaHCO_2$	130 mg%
KCl	375 mg%	Glucose	200 mg%
$MgCl_2$	11.3 mg%	H_2O	to 100.0

F t o r e m – for cardioplegia

Perfluorocarbon	10 vol%	$NaHCO_3$	11.4 mg%
Proxanol	2.6 %	Glucose	200 mg%
NaCl	35 mg%	Mannitol	3640 mg%
KCl	37.5 mg%	Prednizolon	9 mg%
$CaCl_2$	8 mg%	Gentamycin	2 mg%
$MgCl_2$	40.6 mg%	Novocain	109.2 mg%

The clinical application of these preparations was performed by Prof. A.N.Kaydash at the Department of Acquired Valvular Diseases in A.V.Vishnevsky Institute of Surgery in December 1981.

The information reviews the essential results presented in:

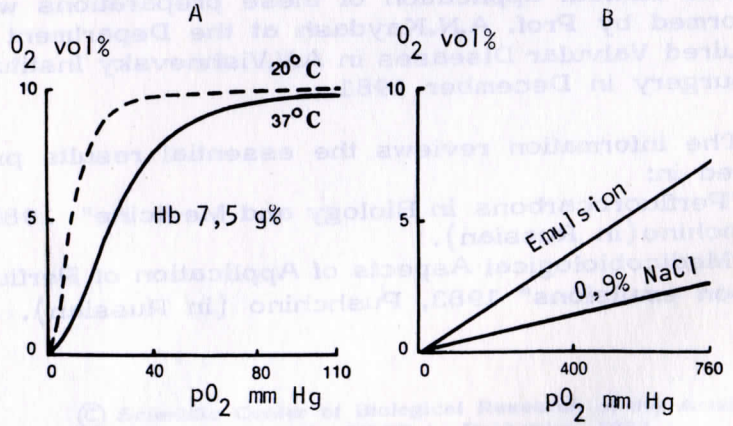
"Perfluorocarbons in Biology and Medicine" 1980, Pushchino (in Russian).

"Medicobiological Aspects of Application of Perfluorocarbon emulsions" 1983, Pushchino (in Russian).

FLUROCARBON EMULSION CHARACTERISTICS

1. Oxygen capacity	7.2 vol%
2. Average particle diameter	0.08 μm
3. Capacity for CO_2 (pCO_2=760)	60 vol%
4. Fluoride ion content	10^{-5} M
5. Osmolarity	340-360 mocm/l
6. Relative viscosity	2 cP
7. Buffer capacity (pH 7.5-7.6)	25 m-eqv/l

The temperature decrease required to protect the myocardium sharply hampers the release of the oxygen chemically bound with blood hemoglobin, increase the viscosity and hemolysis. The diffusion of the oxygen dissolved in the emulsion does not depend on temperature.



A - is the shift of the oxyhemoglobin dissociation curve upon temperature decrease.

B - is comparison of oxygen capacities for the fluorocarbon emulsion and physiological solution.

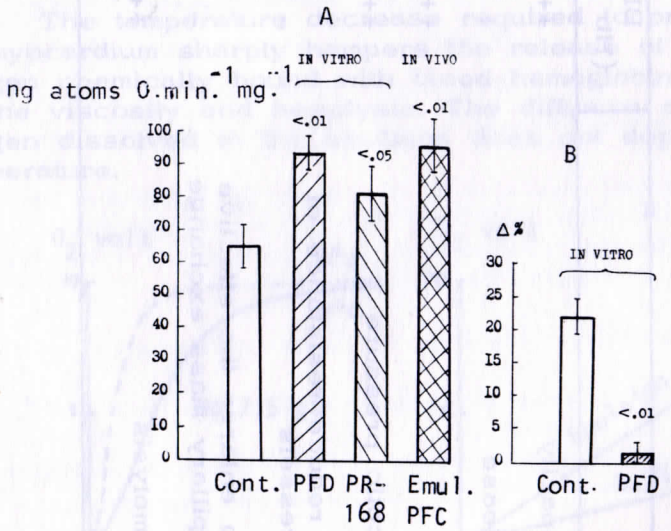
Comparative characteristics of different perfusional liquids at low temperatures (20°C)

	Blood (Hb 6-9 g%)	Perfusol	Colloid-salt solution
1. Oxygen capacity	++++	++	+
2. Oxygen release	+	+++(!)	+
3. Viscosity	++++	++	+
4. Colloid-oncotic pressure	++++	++	+
5. Ability to reduce resistance of coronary vessels	-	+++(!)	-(+)
6. Capacity to enlarge the effective area of capillary mass exchange	-	+++(!)	+
7. Risk of hemolysis	+++	-	-

Objects and extent of experiments on the effect of Perfusol and Ftorem on the myocardium

Object	Number of experiments
1. Isolated fibres of frog atrium	15
2. Isolated papillar muscles from rabbit heart	10
3. Perfused rabbit heart according to Langendorf	25
4. Perfused dog heart	24
5. Dog heart after heterotopic transplantation	24
In all:	98

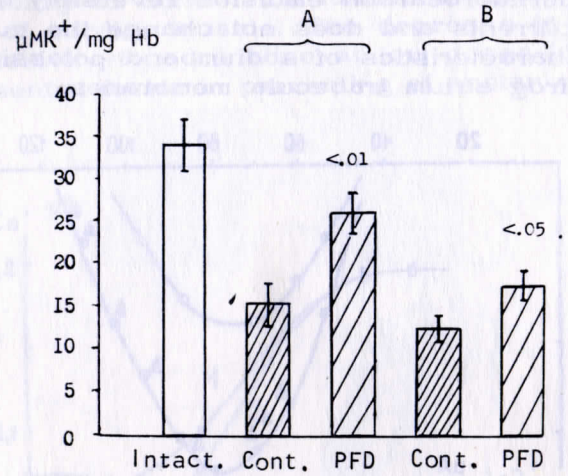
MEMBRANE EFFECTS OF PERFLUORO-CARBON EMULSION



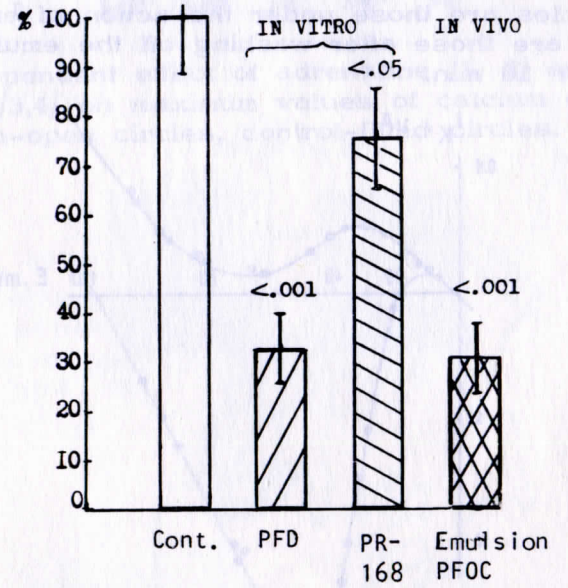
A – increase in the rate of oxidative phosphorylation of rat liver mitochondria as a result of modification of available hydrophobic membrane sites by perfluorocarbon emulsion and its components (perfluorodecaline – PFD, proxanol – PR-168).

B – contact with perfluorodecaline reduces the rate of degradation of mitochondrial membrane structures.

Protection of cell membranes against the action of damaging agents



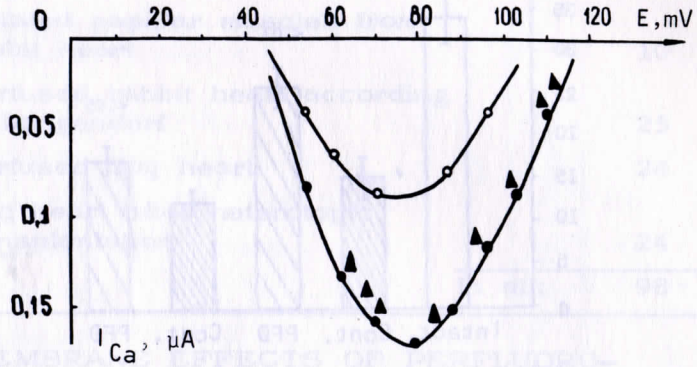
Decrease in K^+ loss of erythrocytes under the action of of perfluorodecaline. A – after mechanical trauma, B – on valinomycin action.



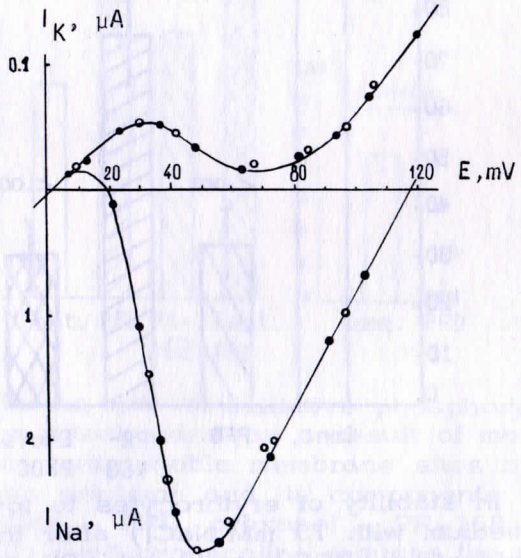
Increase in stability of erythrocytes to low osmotic pressure (medium with 75 mM NaCl) after the action of perfluorodecaline (PFD), proxanol (PR-168) or the emulsion (the quantity of hemolyzed cells in the control is taken 100%).

Effect of the emulsion on ionic currents in isolated frog heart preparations

The perfluorocarbon emulsion reversibly supresses calcium currents and does not change the current-voltage characteristics of sodium and potassium currents in frog atrium trabecula membranes.

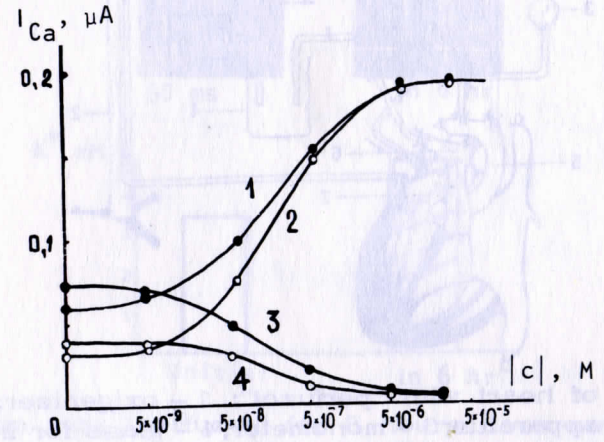


Filled circles are values of Ca^{2+}-currents in Ringer, open circles are those under the action of emulsion, triangles are those after washing off the emulsion with Ringer for 10 min.



Filled circles are values of currents in Ringer, open circles are those under the action of perfluorocarbon emulsion.

Due to persistance of the reaction of calcium cannels of adrenaline and acetylcholine ($5x10^{-7}$ M) in the presence of perflurocarbon emulsion, there persists the possibility to control the functional state and contractility of cardiac muscle. The decrease in myocardium sensitivity to adrenaline at low doses ($5x10^{-9}$ M) is an essential factor in preventing of postanoxic damages.



Dose-dependent effect of adrenaline /1, 2/ and acetylcholine /3,4/ on maximum values of calcium current. Emulsion-open circles, control-filled circles.

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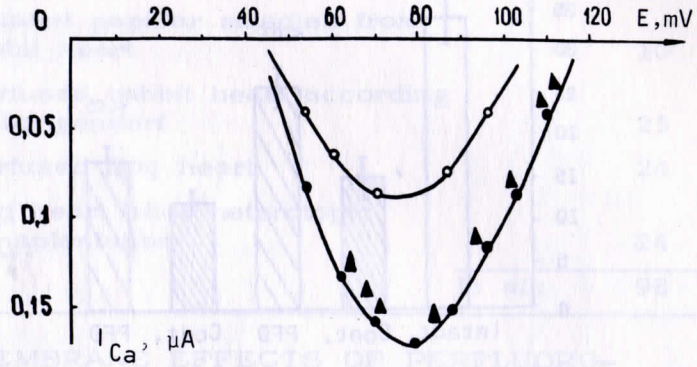

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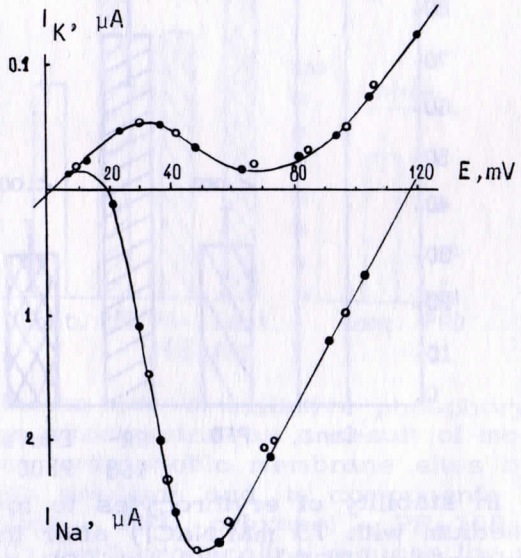

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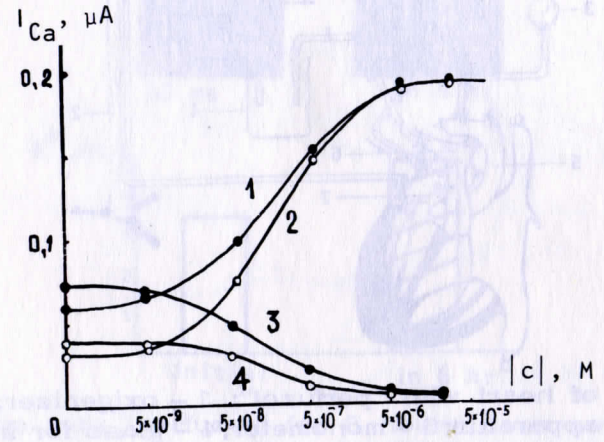
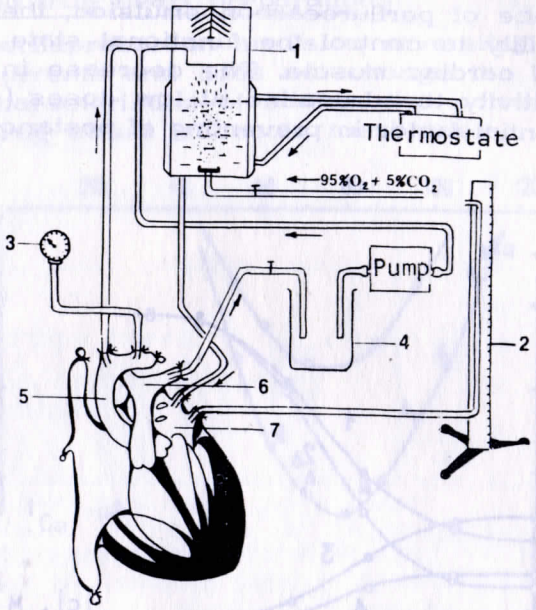
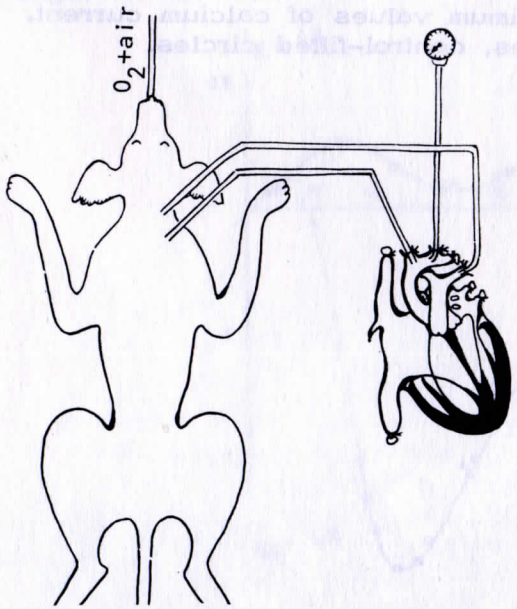


Dose-dependent effect of adrenaline /1, 2/ and acetylcholine /3,4/ on maximum values of calcium current. Emulsion-open circles, control-filled circles.

PERFUSION OF CORONARY ARTERIES WITH PERFLUOROCARBON EMULSION ("PERFUZOL")

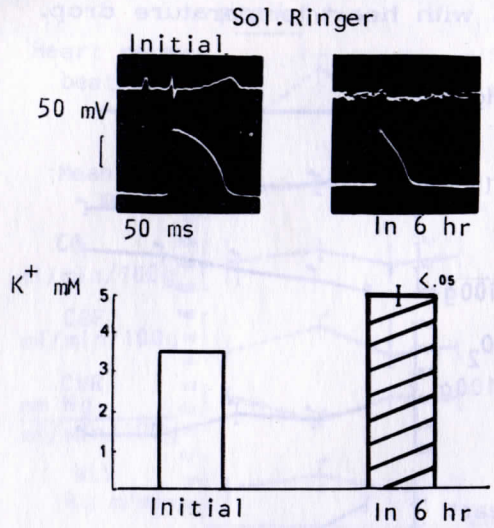


Perfusion of heart with "perfuzol": 1 – oxigenizer; 2 – Waldmann apparatus; 3 – monometer; 4 – glass for intake of coronary blood; 5 – aorta; 6 – pulmonary artery; 7 – left atrium.

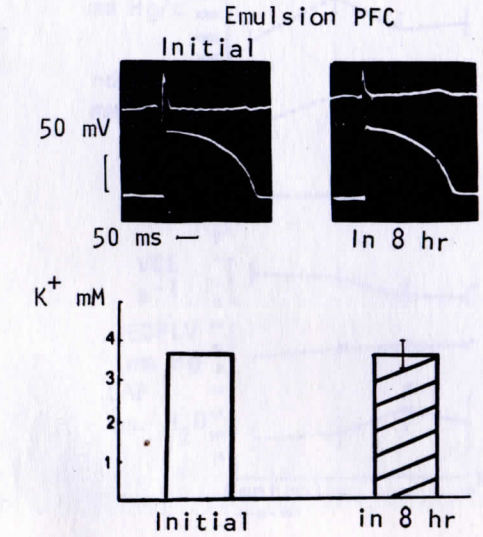


Heterotopic transplantation of heart after preservation with "Perfuzol".

Perfusion of rabbit heart with balanced Ringer for 6 hours leads to a substantial shortening of the action potential of myocardial cells and decreases the ECG amplitude almost to zero. The increased K^+ concentration in perfusate points to damages in cell membranes.

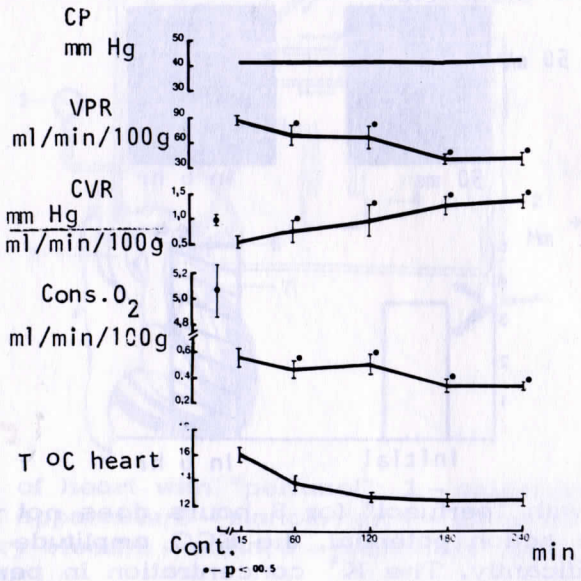


Perfusion with "perfuzol" for 8 hours does not virtually change the action potential, the ECG amplitude reduces insignificantly. The K^+ concentration in perfusate does not change.

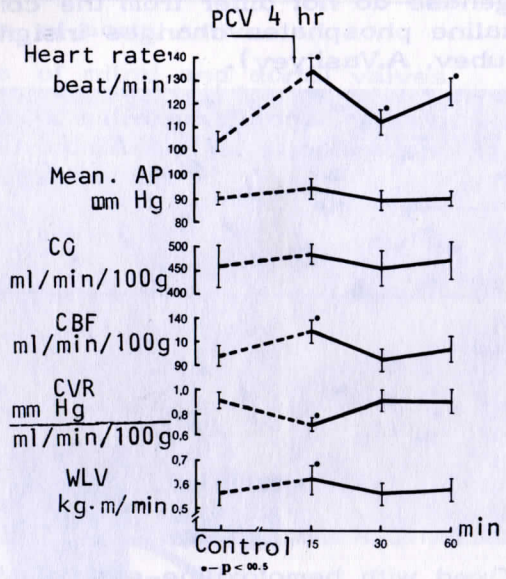


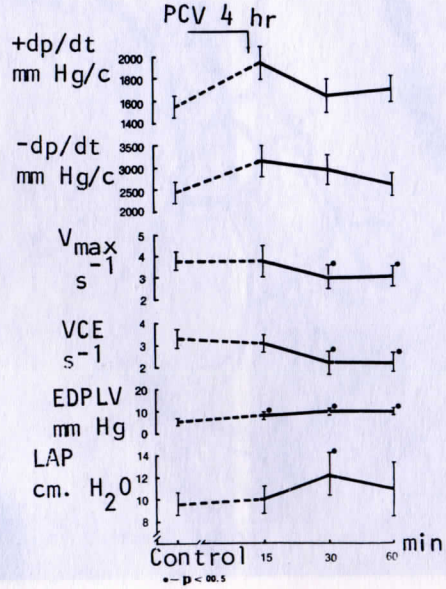
The coronary perfusion of dog heart with "Perfuzol" at a constant coronary pressure (CD) provides that: the volume perfusion rate (VPR) and coronary vessel resistance (CVR) remains within the norm.

Oxygen consumption by myocardium (consumption O_2) decreases with heart temperature drop.

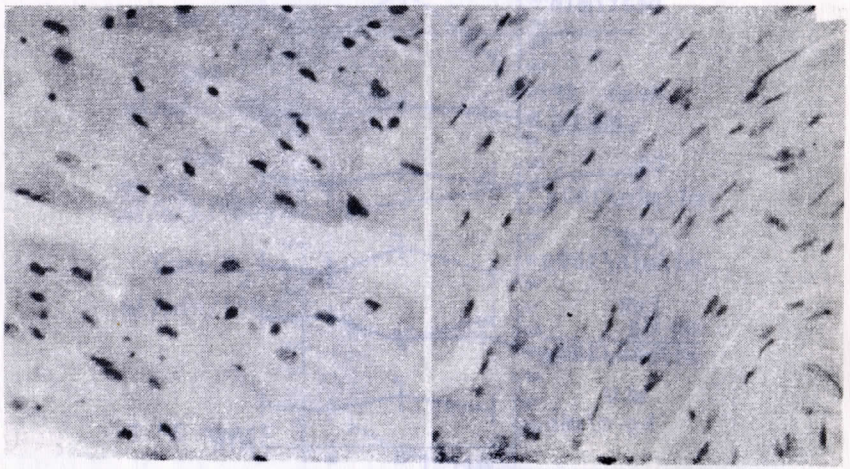


After 4 hour perfusion of coronary vessels with "Perfuzol" the contractile status parameters for dog myocardium persist within physiological norms and the hemodynamic parameters return to the control in 30 minutes.

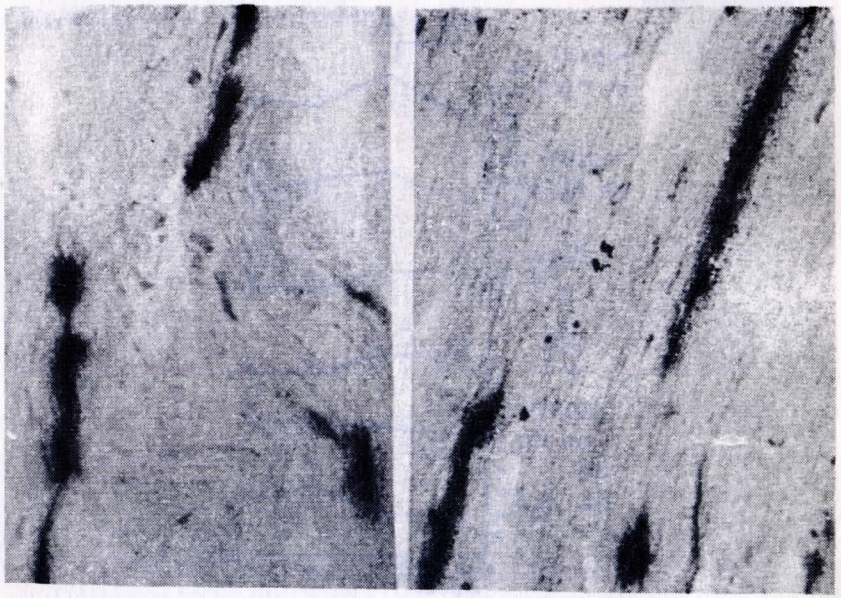




4-Hour coronary perfusion of dog heart with "perfuzol" does not produce any sharp damage in morpho-functional state of myocardium /1/. The activity of oxidoreductases: NAD-H_2, NADP-H_2 diaphorases, succinate dehydrogenase do not differ from the control. The activity of alkaline phosphates changes insignificantly /11/ (A.M.Golubev, A.Vasilyey).



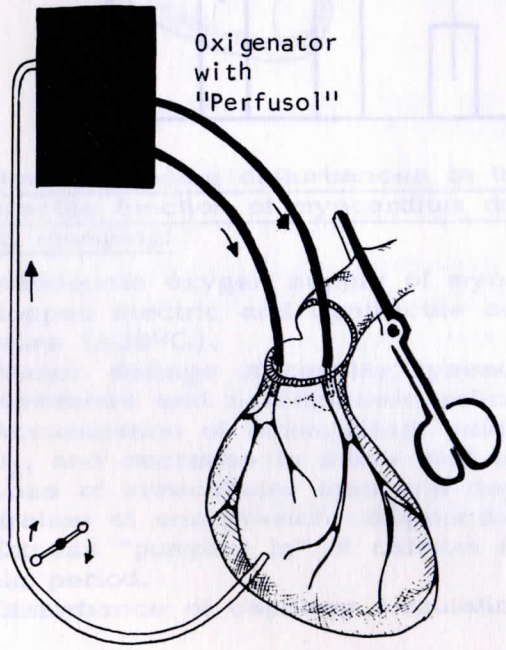
Myocardium. Dyed with hemotoxiline-eosine. Magn.x500



Activity of alkaline phosphatase. Pirs method. Magn.x500.

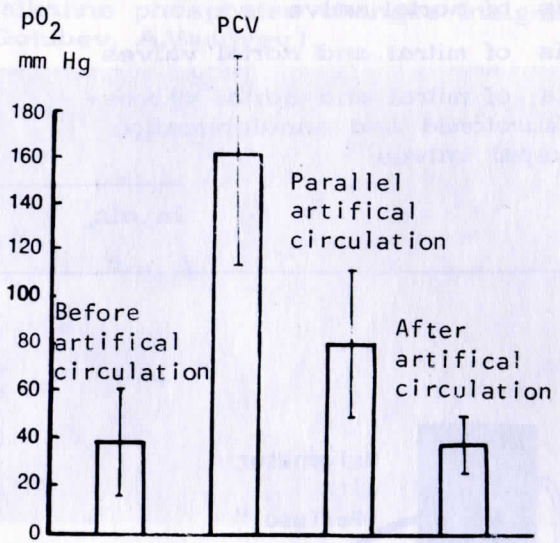
Operations made under constant perfusion of coronary arteries with "Perfuzol" (time of aorta clamping 35 to 125 min)

Prosthesis of aortal valve	15
Prosthesis of mitral and aortal valves	8
Prosthesis of mitral and aortal valves+ +comissurotomia and annuloplication of tricuspid valves	5
In all:	28 operations



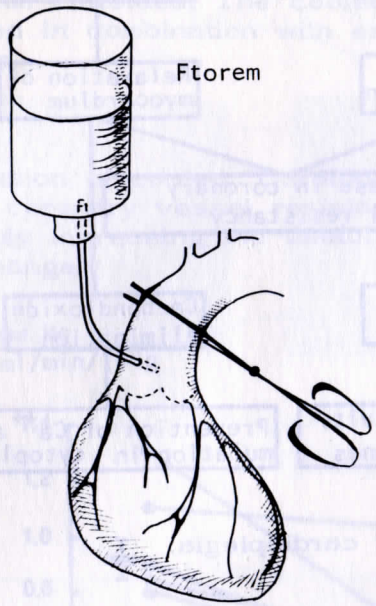
Coronary perfusion during heart operations.

Perfusion of coronary vessels (PCV) with Perfuzol provides a high oxygen content in myocardial tissue at the intracardial operation stage (pO_2 monitoring according to the device was kindely submitted by Dr. Landau I.; patients with acquired valvular deseases).



CARDIOPLEGIA WITH "FTOREM"

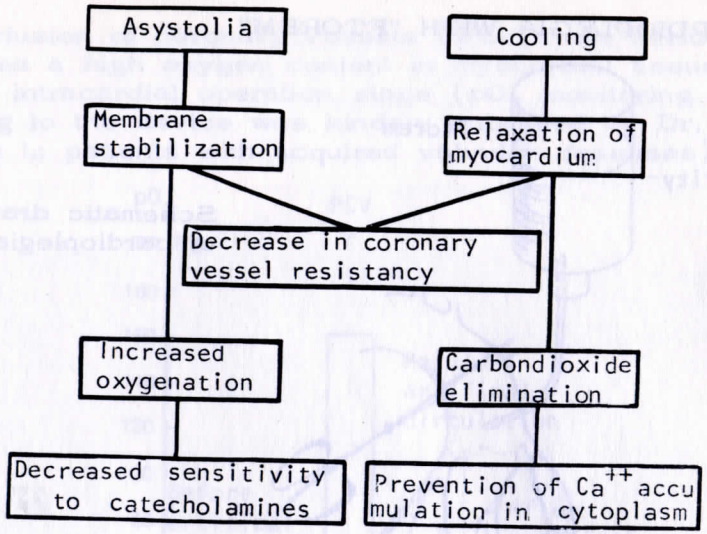
t=3°C
pH-7,6
osmolarity-
340



Schematic drawing of cardioplegia

Factors producing disturbances in the contractile function of myocardium during aorta clamping:

1. Inadequate oxygen supply of myocardium in spite of stopped electric and contractile activity and low temperature (+20°C).
2. Anoxic damage of cellular, lysosomal, mitochondrial membranes and sarcoplasmic reticulum.
3. Accumulation of incompletely oxidized metabolites, CO_2, and decrease in intra- and extracellular pH.
4. Loss of intracellular ions and decrease in the concentration of energy-rich compounds.
5. Excess "pumping in" of calcium ions in the postischemic period.
6. Disturbance of capillary circulation in myocardium.
7. Liberation of endogenous catecholamines.
8. Edematozation of myocardium.



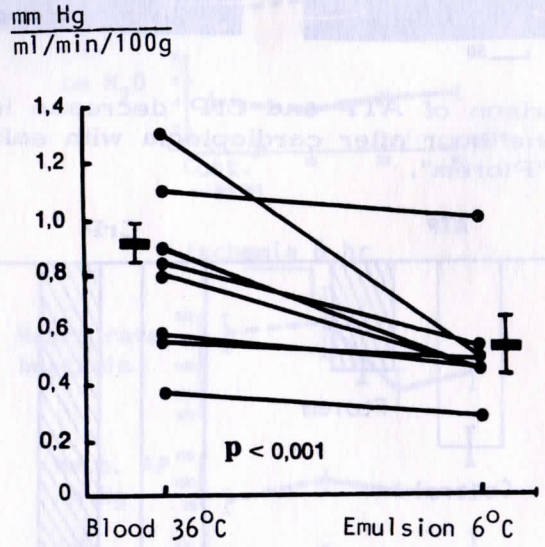
Basic components of cardioplegia.

Effect of perfluorocarbon emulsion on myocardium

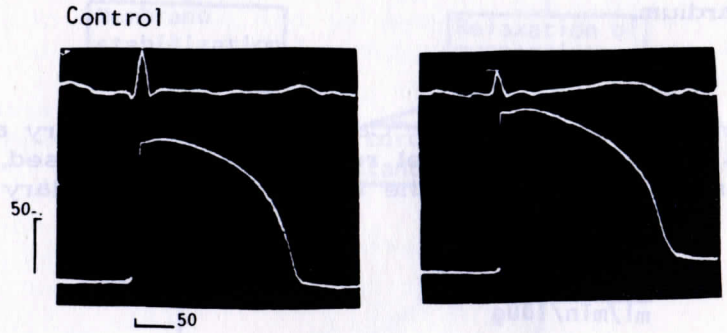
1. Decrease in the loss of intracellular K^+.
2. Retardation of Ca^{2+} inflow into the cell.
3. Decrease in sensitivity of myocardium to low doses of catecholamines and acetylcholine.
4. Decrease in arrhythmia in the recovery period.
5. Retarded acidoses development in stopped myocardium.
6. Increased relaxation of myofibrils.
7. Decreased oedema of tissues.

Rapid asystole is provided with addition of procaine or potassium chlorides. The cooled cardioplegia solution is used in combination with external cooling of myocardium.

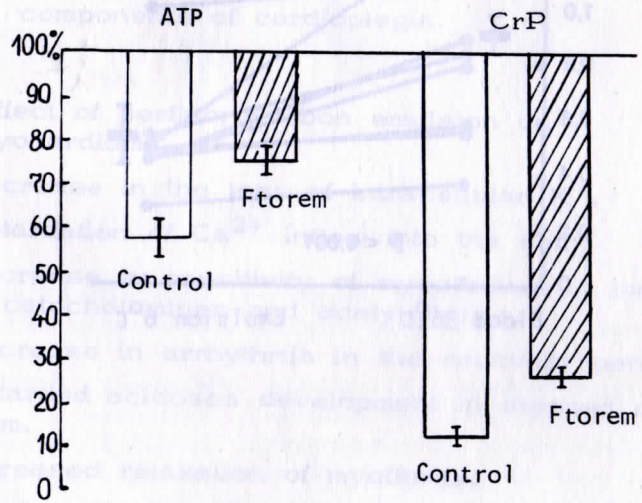
On infusion of cooled "Cardiopleg" to coronary arteries the coronary vessel resistance is decreased, thus sharply increasing the useful area of capillary mass exchange.

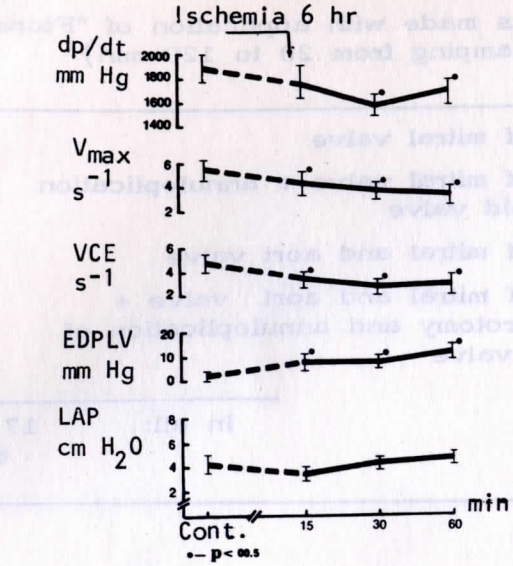


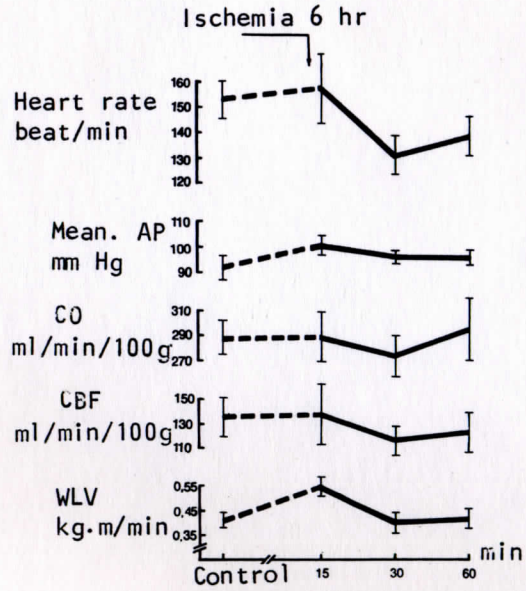
Action potential of rabbit myocardium cells 6 hours after cardioplegia with "Fluorem".



Comparison of ATP and CrP decrease in rat myocardium one hour after cardioplegia with salt solution and with "Ftorem".







6 hours after cardioplegia with Ftorem the parameters of the contractile status of dog myocardium remain within physiological norm, the hemodynamic parameters do not differ from the control.

Operations made with application of "Ftorem"
(Aorta clamping from 20 to 120 min)

Prosthesis of mitral valve	11
Prosthesis of mitral valve + annuloplication of tricuspid valve	3
Prosthesis of mitral and aort valve	2
Prosthesis of mitral and aort valve + commissurotomy and annuloplication of tricuspid valve	1
In all:	17 operations

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