Role of Variations in Pulmonary and Cardiac Hemodynamics in the Reduction of the Venous Return during Experimental Ischemia of the Left Ventricular Myocardium

V. I. Evlakhov and I. Z. Poyassov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 152, No. 10, pp. 396-399, October, 2011
Original article submitted July 7, 2010

During left-ventricular myocardial ischemia, the decrease in the venous return is determined by reduction of cardiac output, which results from heart rate deceleration and decrease in left-ventricular stroke volume. The latter is related to a decrease in myocardial contractility and blood storage in the pulmonary circuit. Blood accumulation in the lungs is not observed during stimulation of the vagus nerve or treatment with propranolol (against the background of the same values of the negative chronotropic and inotropic effects as during myocardial ischemia). The left-ventricular stroke volume increases, while the cardiac output and venous return decrease to a lesser extent under these conditions.

Key Words: *myocardial ischemia; venous return; pulmonary dynamics and cardiohemodynamics; vagus nerve; propranolol*

Our previous studies showed that myocardial ischemia is followed by a decrease in the venous return, pressure and blood flow in the pulmonary artery, and cardiac output (CO) [2,3]. Clinical trials and physiological studies demonstrated that the decrease in this parameter does not necessarily correlate with reduction of HR and myocardial contractility [7,10]. This work was designed to evaluate the cause of decreased venous return under conditions of myocardial ischemia. The type and degree of variations in venous return, pressure and blood flow in the pulmonary artery, pulmonary vascular resistance, and CO were compared during experimental ischemia of the left ventricular (LV) myocardium, electrical stimulation of the vagus nerve, and treatment with a β-adrenoceptor antagonist propranolol (obsidan).

Department for Physiology of Visceral Systems, Institute of Experimental Medicine, Northwestern Division of the Russian Academy of Medical Sciences, St. Petersburg, Russia. ***Address for correspondence:*** viespbru@mail.ru. V. I. Evlakhov

MATERIALS AND METHODS

Experiments were performed on 12 cats and 15 rabbits (body weight 4.5-5.0 kg). The animals were intramuscularly anesthetized with 35-40 mg/kg nembutal and subjected to thoracotomy under conditions of artificial pulmonary ventilation (Faza-9 device). The study was conducted according to bioethical principles of manipulations with animals. Blood pressure in the left carotid artery was measured using a PDP-400 tensiometric sensor. Blood pressure in the pulmonary artery was measured with the same sensor. A catheter (diameter 1.5 mm) was inserted into this artery through the anterior wall of the right ventricle [6]. Blood flow in the pulmonary artery, CO in the ascending aorta, and blood flow in the anterior and posterior vena cava were measured with cuff-type transducers of ultrasonic flow meters (T-106, T-206, and T-402; Transonic). Venous return was calculated as the sum of these parameters (using a computer). LV myocardial contractility was estimated from the LV pressure derivative (dP/dtmax)

0007-4888/12/1524-0416

[2]. The mean value of left atrial pressure in animals was evaluated from the end diastolic pressure in the LV [8]. It was measured with a PDP-400 tensiometric sensor. A catheter was introduced into the cavity of the LV through its apex. HR in cats was measured with a tachometer. ECG (standard lead II) was recorded to estimate the *R*-*R* interval. CO was divided by HR (using a computer) to calculate the LV stroke volume. The pulmonary vascular resistance and total peripheral vascular resistance were calculated by the Poiseuille equation [1,2,4]. These parameters were recorded to the computer hard disk using an L-Card L-783 for analogue-to-digital conversion (frequency 200 Hz). The data were then analyzed with ACT software. The test parameters were also recorded with an N-338-8P ink recorder.

Series I was conducted on 12 cats. Experimental ischemia of the LV myocardium in animals was induced by cross-clamping of the left coronary artery for 60 sec [2]. Electrical stimulation (3 Hz, 2.5 V, 60 sec) of the peripheral end of the transected right vagus nerve was performed in series II (6 rabbits). A negative chronotropic effect of this treatment was similar to that observed during myocardial ischemia. Series III was conducted on 9 rabbits. A β-adrenoceptor antagonist propranolol (2 mg/kg) was injected into the left jugular vein of animals. A negative inotropic effect of propranolol was similar to that observed during stimulation of the vagus nerve. The type and degree of changes in hemodynamic parameters were compared in series I, II, and III (under conditions of maximum variations in arterial pressure).

The results were analyzed by Student's *t* test (testing of the hypothesis about differences of variations in hemodynamic parameters from zero). The data were processed with the original and standard software (Axum 5.0, Math Soft Inc.) on an IBM PC Pentium IV.

RESULTS

Experimental ischemia of the LV myocardium (region of the left common coronary artery) was followed by a decrease in arterial pressure (by 36±8%, $p<0.001$), HR (by 22±6%, $p<0.01$), and myocardial contractility (by 18±6%, $p<0.01$). The changes were accompanied by a 43±7% decrease in the venous return ($p<0.001$). CO was reduced by 42±5% ($p<0.001$ compared to the baseline; Table 1). Variations in the venous return under these conditions were shown to correspond to the decrease in CO. Therefore, the decrease in the venous return during LV myocardial ischemia can be considered as the cause of reduced CO.

CO is the product of HR and LV stroke volume [1]. Hence, it was important to evaluate the cause of changes in the latter parameter. During myocardial ischemia, the stroke volume decreased by 26±5% ($p<0.001$ compared to the baseline). The decrease in this parameter is probably related to the reduction of LV myocardial contractility. This conclusion was derived from an increase in LV pressure (by 38±10%, $p<0.01$) and decrease in blood inflow to the left heart. We analyzed the degree of variations in blood flow in the pulmonary artery.

Blood flow in the pulmonary artery during myocardial ischemia decreased by 24±3% ($p<0.001$), which corresponds to a decrease in the stroke volume (Table 1). Our results indicate that the decrease in the LV stroke volume during myocardial ischemia is related not only to the deceleration of HR and reduction of myocardial contractility, but also to the impairment of blood flow in the pulmonary artery. However, this conclusion contradicted the results of experiments with electrical stimulation of the vagus nerve and administration of a β-adrenoceptor antagonist propranolol (Table 1). Vagus nerve stimulation and intravenous injection of propranolol were followed by a decrease in HR by 31±6 and 32±7%, respectively ($p<0.001$). Myocardial contractility was reduced by 14±4 and 17±3%, respectively ($p<0.01$ compared to the baseline). Therefore, the negative chronotropic and inotropic effects of these treatments were similar to those observed during myocardial ischemia (22±6% [$p<0.001$] and 18±6% [$p<0.01$], respectively). However, CO was reduced by only 14-20% after electrical stimulation of the vagus nerve and intravenous injection of propranolol (*vs*. 42±5% during myocardial ischemia, $p<0.001$). At the same time, vagus nerve stimulation and administration of propranolol were followed by an increase in the LV stroke volume (by 24±5% [$p<0.001$] and 7±2% [$p<0.01$], respectively). By contrast, this parameter was reduced by 26±5% during myocardial ischemia ($p<0.001$; Table 1).

After vagus nerve stimulation and administration of propranolol, blood flow in the pulmonary artery decreased by 19-25%. These changes were similar to those observed during myocardial ischemia (decrease by 24%; Table 1). These data suggest that blood storage in pulmonary vessels is the cause of a decrease in the LV stroke volume, which accompanies the reduction of HR and LV myocardial contractility [4]. This conclusion was derived from the decrease in the estimated parameter of pulmonary vascular resistance (by 37±12%, $p<0.01$) during myocardial ischemia and reduction of pulmonary circulation. Pulmonary vascular resistance was reduced by 12±6% during electrical stimulation of the vagus nerve, but increased by 24±7% after treatment with propranolol ($p<0.01$). However, pulmonary artery pressure was shown to decrease similarly under these influences on the circulatory system (Table 1). Although the

estimated parameter of pulmonary vascular resistance increases by 11±5% during myocardial ischemia, these variations are not significant for the decrease in CO. It was confirmed by experiments with electrical stimulation of the vagus nerve and administration of propranolol. CO decreased, while the total peripheral vascular resistance remained unchanged under these conditions (Table 1). These data indicate that the decrease in the LV stroke volume and CO during LV myocardial ischemia is associated not only with reduction of HR and myocardial contractility, but also with blood storage in the lungs. This conclusion is supported by a discrepancy (imbalance) between the decrease in CO and pulmonary circulation during myocardial ischemia (by 42±5 and 24±3%, respectively, $p<0.001$). It should be emphasized that these parameters decreased similarly upon stimulation of the vagus nerve and administration of propranolol (Table 1). The animals with myocardial ischemia were also characterized by various changes in the venous return and pulmonary circulation (43±6 and -24±3%, respectively, $p<0.001$). The imbalance between variations in CO and pulmonary circulation during myocardial ischemia can be related not only to blood storage in the lungs, but also to different changes in myocardial contractility of the right and left ventricles [10]. However, the cause of the imbalance between CO and pulmonary circulation during myocardial ischemia requires further investigations.

We conclude that the decrease in venous return during experimental ischemia of the LV myocardium is related to reduction of CO, which accompanies the negative chronotropic and inotropic effects and decrease in the LV stroke volume. The latter is associated with not only the decrease in myocardial contractility (one of the factors that affect the venous return "*vis a tergo*"), but also blood storage in pulmonary vessels. This conclusion is derived from a significant decrease in pulmonary vascular resistance, which accompanies the reduction of pulmonary circulation. Vagus nerve stimulation and administration of β-adrenoceptor antagonist propranolol are accompanied by negative chronotropic and inotropic effects (similar to those observed during myocardial ischemia). However, these treatments do not induce blood storage in the lungs. The LV stroke volume increases, while CO and venous return decrease to a lesser extent under these conditions.

This work was supported by the Russian Foundation for Basic Research (grant No. 09-04-00914).

REFERENCES

1. D. Morman and L. Heller, *Physiology of the Cardiovascular System* [in Russian], St. Petersburg (2000).
2. B. I. Tkachenko, V. I. Evlakhov, and I. Z. Poyassov, *Byull. Eksp. Biol. Med.*, **147**, No. 1, 32-35 (2009).
3. B. I. Tkachenko, V. I. Evlakhov, I. Z. Poyassov, and V. I. Ovsyannikov, *Ros. Fiziol. Zh.*, **96**, No. 5, 521-527 (2010).

TABLE 1. Changes in Systemic and Pulmonary Hemodynamics during Experimental Myocardial Ischemia in the Region of the Left Common Carotid Artery (Cats) and after Electrical Stimulation of the Right Vagus Nerve or Intravenous Injection of Propranolol (Rabbits, % of Baseline; *M±m*)

Parameter	Baseline (cats)	Myocardial ischemia	Baseline (rabbits)	Vagus nerve stimulation	Intravenous injection of propranolol
Blood pressure, mm Hg	96±5	-36±8***	66±3	-17±5*	-19±6*
Pulmonary artery pressure, mm Hg	24±3	-14±2***	13±1	-14±3*	-9±2**
Left atrial pressure, mm Hg	6.8±0.4	38±10**	4.4±0.1	24±3***	-12±3**
Venous return to the heart, ml/min	243±22	-43±7***	174±16	-20±5**	-23±6**
Pulmonary artery circulation, ml/min	255±16	-24±3***	172±12	-19±4**	-25±4***
CO, ml/min	238±27	-42±5***	175±18	-14±3**	-21±5**
LV stroke volume, ml	1.35±0.3	-26±5***	0.77±0.2	24±5***	7±2**
LV myocardial contractility, mm Hg/sec	2425±92	-18±6**	1500±86	-14±4**	-17±5**
HR, bpm	176±7	-22±6***	222±6	-31±6***	-32±7***
Total peripheral vascular resistance, dyn×sec×cm^{-5}	537±46	11±5	506±35	-5±4	4±3
Pulmonary vascular resistance, dyn×sec×cm^{-5}	94±10	-37±12**	77±12	-12±5	24±7**

Note. *$p<0.05$, **$p<0.01$, and ***$p<0.001$ compared to the baseline.

4. *Physiology and Pathophysiology of Pulmonary Vessels* [in Russian], Eds. E. K. Wari and G. T. Revs, Moscow (1995).
5. E. D. Aymong, K. Ramanathan, and C. E. Buller, *Med. Clin. North. Am*., **91**, No. 4, 701-712 (2007).
6. A. Deten, H. Millar, and H. G. Zimmer, *Am. J. Physiol. Heart Circ. Physiol*., **285**, No. 3, H2212-H2217 (2003).
7. H. Gosselin, X. Qi, and J. L. Rouleau, *Can. J. Physiol. Pharmacol*., **76**, No. 1, 53-62 (1998).
8. Y. Hadano, K. Murata, J. Liu, *et al*., *Circ. J*., **69**, No. 4, 432-438 (2005).
9. J. S. Hochman, *Circulation*, **107**, No. 24, 2998-3002 (2003).
10. A. Luchner, F. Muders, O. Dietl, *et al*., *Cardiovasc. Res*., **51**, No. 5, 601-607 (2001).