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CORONARY PARADOX

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This work is a scientific and educational analytical review intended for practicing cardiologists. The purpose of the review is to draw physicians' attention to the role of myocardial contractility in the regulation of coronary circulation. We consider the fundamental phenomenon of arterial compression (squeezing) in the left ventricular (LV) wall, creating an obstruction to blood flow during cardiac systole. This phenomenon formally resembles functional coronary artery stenosis. Based on a review of the literature, the positive role of arterial compression in coronary hemodynamics is interpreted. Understanding the mechanical relationship between the contractile and coronary systems in the cardiac wall may be useful for practicing physicians when choosing treatment tactics for patients, optimizing LV bypass during heart surgeries, and improving the efficiency of adaptation of the transplanted heart.

Keywords: heart, left ventricle, coronary arteries, myocardial contractility, arterial compression, coronary circulation.

INTRODUCTION

The heart is a biological pump that circulates blood to all tissues of the body. Unlike the other organs, the heart participates in its own blood supply to realize the mechanical function of the myocardium. Thus, the contractile system of the heart and the myocardial life-support system, which contains an extensive network of blood vessels, are structurally concentrated in the heart wall, and are closely connected with each other.

Hemodynamics in proximal coronary arteries is fundamentally different from blood flow in other arteries of the body, where circulation is directly related to cardiac systole; more precisely, to the LV blood ejection phase, during which pressure gradient occurs in the vascular system, which determines the driving force in blood flow.

It is generally accepted that in the coronary system, systolic blood flow is limited and the main hemodynamic events occur during cardiac diastole. Such peculiarity of coronary blood flow was drawn attention to as early as 1695 [1]. The author noted that during cardiac relaxation, the coronary vessels are filled, and when they contract, they are emptied. In the first half of the last century, it was experimentally confirmed that during heart contraction, coronary arterial inflow is obstructed and venous outflow increases [2, 3].

It can be considered proven that the noted features of coronary hemodynamics are the consequence of mechanical function of the cardiac wall leading to compression of a certain part of coronary arteries and reduction of coronary blood flow [4–7]. This phenomenon seems paradoxical at first sight, since myocardial contractile function prevents coronary blood flow.

This work is intended to draw the attention of cardiologists to the above contradiction, which we have conventionally termed "coronary paradox". On the basis of literature analysis, we will attempt to give a reasonable interpretation to the presence of a nontrivial connection between mechanical phenomena in the cardiac wall and hemodynamic events in LV coronary arteries. This issue has been the subject of long-standing discussions among specialists in circulatory physiology; but it remains out of the focus of practicing physicians.

THE PHENOMENON OF CORONARY PARADOX

Fig. 1 shows a synchronous recording of pressure measurements in the aorta, right and left ventricles; volumetric blood flow velocity (VBFV) in the proximal right coronary artery and left anterior descending artery (LAD) off the left coronary artery, and VBFV in the great cardiac vein.

The figure clearly illustrates that with the beginning of the LV mechanical cycle, the VBFV in LAD sharply decreases, and during LV blood ejection (increase in aortic pressure), it increases slightly. However, with the onset of LV isovolumetric relaxation phase (the moment of aortic valve closure) there is a significant increase in coronary blood flow velocity.

Coronary blood flow limitation in LV systole can be observed in clinically healthy individuals with abnormal passage of part of the epicardial artery in myocardium. In such cases, pronounced systolic stenosis is visualized on coronarogram, disappearing with the beginning of diastole. This phenomenon is called "muscular bridges"

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and, as a rule, is not accompanied by symptoms of coronary heart disease [9].

Fig. 2 shows two angiogram frames recorded in LV systole and diastole in a patient with suspected myocardial ischemia as an example. We can clearly see that the LAD lumen of the left coronary artery sharply narrows in systole and recovers at the beginning of diastole. Muscle bridges clearly demonstrate the effect of arterial constriction during LV contraction.

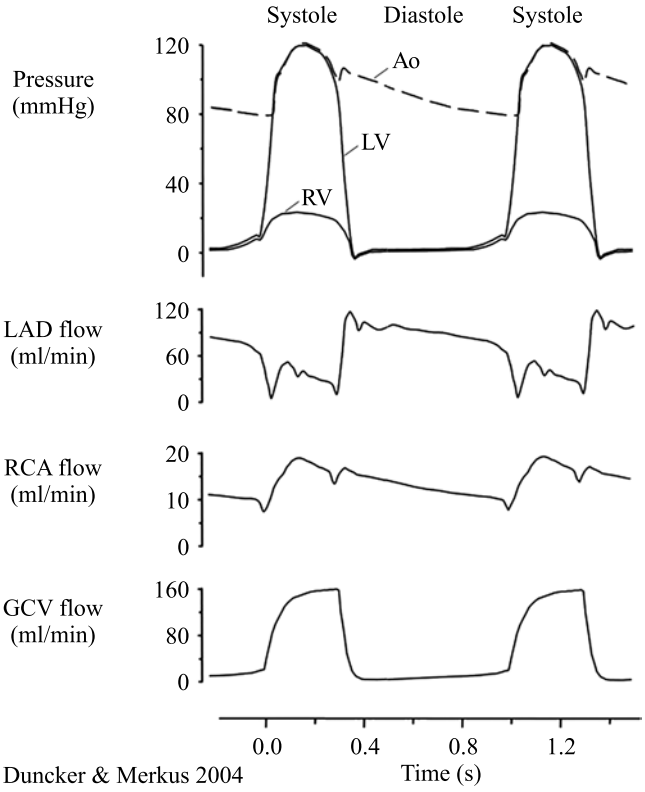

Fig. 1. Dynamics of pressure (upper panel) and Volumetric blood flow velocity in different parts of the heart. Ao, aorta; LV, left ventricle; RV, right ventricle; LAD, left anterior descending artery; RCA, right coronary artery; GCV, great cardiac vein. The diagram is borrowed from a presentation by Dirk J. Duncker (2014) in open access [8]

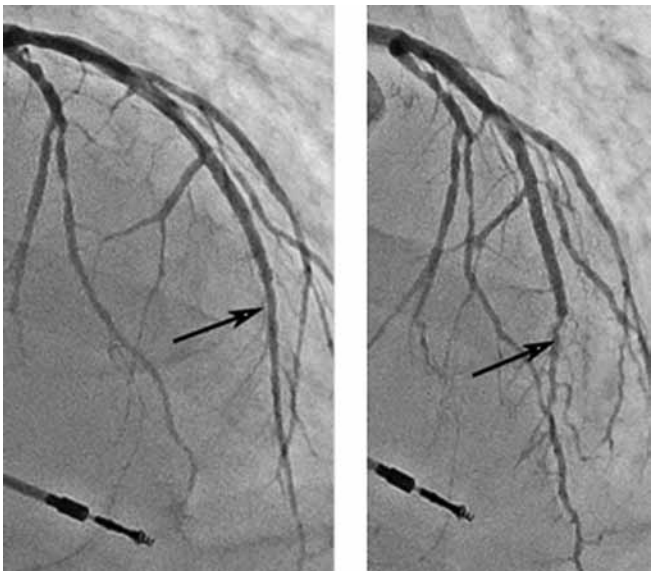

Fig. 2. An example of left coronary artery imaging with myocardial bridge (location indicated by arrow) at the end of diastole (left) and at the end of LV systole (right)

Meanwhile, in the normal heart, mechanical obstruction of blood flow in LV systole occurs at the level of blood macrocirculation system in the cardiac wall, in particular, in intramural (perforating myocardium) arteries with diameter less than 500 μm and arterioles with diameter of at least 100 μm [10]. These vessels are located in connective-tissue interlayers between bundles of muscle fibers, extend from the epicardium to the subendocardial plexus in the LV wall [6].

On the contrary, at the level of blood microcirculation in vessels with diameter <100 μm, cardiac muscle contraction has practically no effect on arterial lumen [11, 12]. Compression of arterial vessels in the microcirculatory system during LV systole is prevented by two factors. Firstly, small caliber arterioles are located parallel to cardiomyocytes and secondly, each arterial vessel is surrounded by two venules. In fact, these vessels dampen the compression of the arterioles by contracting myocytes, and the diameter of the venules changes significantly, from 48 μm in LV diastole to 31 μm in systole. Due to these two factors, a protective effect is provided, allowing to keep the lumen of arterioles of the microcirculation system almost unchanged: 38 μm in LV systole and 39 μm in diastole [13].

Thus, the **coronary paradox** is a phenomenon of hemodynamically significant compression of the perforating vessels of the LV coronary blood flow macrocirculation system during cardiac systole. It is based on the mechanical relationship between myocardium and coronary arteries, which is predetermined by peculiarities of the heart structure and left ventricle in particular.

MECHANISMS OF ARTERIAL COMPRESSION IN LV SYSTOLE

A number of hypotheses are known to explain the mechanism of coronary blood flow obstruction in LV systole. In general, these hypotheses are to some extent supported by evidence, and they can be divided into two main groups. The first includes functional models explaining myocardial mediated action on coronary artery lumen due to increased intramyocardial pressure in the cardiac wall during systole. The second group of assumptions considers the direct mechanical action of the myocardium on coronary arteries.

The mediated mechanism of arterial compression is represented by two basic models: waterfall [14] and intramyocardial pump [15]. Both models are based on the assumption that myocardial contraction increases intramyocardial pressure in the cardiac wall, which acts

on the outer surface of the artery. In this case, the vessel lumen decreases and resistance to blood flow increases.

The waterfall model states that the rate of blood flow in the coronary system in LV systole will be determined by the difference between the pressure in the area of arterial compression and venous pressure, divided by peripheral vascular resistance. Additionally, the intramyocardial pump model suggests that in LV systole, arterial compression moves blood in mutually opposite directions like a pump [16]. The advantage of the intramyocardial pump model over the waterfall model is that it can explain retrograde blood flow in arteries and the increase in venous outflow in cardiac systole.

The existence of direct (mechanical) myocardial action on coronary blood flow has been convincingly demonstrated on isolated cat hearts [17] and dog hearts in situ [18]. In these experiments, conditions for isovolumetric and isobaric LV contractions were created. In the first case, ventricular pressure increased with unchanged chamber volume, i.e. there was no cardiac output. In the case of isobaric contraction, pressure in the chamber was maintained constant from the moment of myocardial excitation, while the LV volume decreased, that is, blood ejection began immediately with the beginning of the mechanical cardiac cycle. The authors found that irrespective of fundamentally different pressure dynamics in the LV, the same effect of coronary blood flow reduction in systole was observed.

To explain the mechanism of direct action of cardiac muscle on coronary blood flow, several basic models have been proposed, three of which seem to be the most realistic. They are varying elastance, muscle shortening and thickening, and vascular deformation. All models imply a direct mechanical connection between coronary vessels and myocardium in the heart wall.

The variable elastance model is based on the concept of changing myocardial elasticity in LV systole [19]. At the subcellular level, an increase in cardiomyocyte rigidity is associated with the interaction among major sarcomeric proteins (myosin with actin). After cardiac cell excitation, myocardial elasticity increases significantly, and the higher the cell contractility, the greater the active stiffness of the muscle, and the greater the elastance. Elastic force in the myocardium exerts pressure on the arterial walls, due to which the lumen and blood volume in the vessels decrease in places where they are compressed [20].

The muscle shortening and thickening model is based on the position about the constancy of cardiomyocyte volume in all phases of the cardiac cycle. Therefore, cardiac cell shortening in LV systole is accompanied by increased transverse size, which puts pressure on the vessels [21]. The proposed arterial compression mechanism can be realized in both early and late LV systole, where myocardial shortening and thickening take place to a greater or lesser degree due to a high degree of structural heterogeneity in the LV wall [5].

The vascular deformation model relates myocardial contraction to coronary blood flow not only due to changes in arterial lumen, but also due to the influence of cardiac muscle mechanics on arterial tortuosity, branching angles at their bifurcation sites [22]. It is believed that the proposed mechanism can manifest itself predominantly in the microcirculatory system of coronary blood flow.

It should be noted that all considered mechanisms of mediated and direct influence of myocardial contractile function on blood dynamics in coronary arteries are sufficiently reasonable but not universal. Probably, one or another phenomenon of blood circulation in LV systole can be explained by the combined action of mechanisms depending on specific conditions. At the same time, it is important to emphasize that, in the context of the topic of the present presentation, any of the mechanisms considered explains the limiting effect of myocardial contraction on blood flow in the heart vessels in LV systole.

ROLE OF CORONARY ARTERY COMPRESSION IN MYOCARDIAL CIRCULATION

The systolic role of LV in coronary blood flow is about 20–25% of the total per mechanical cardiac cycle [6, 23]. This circumstance was the basis for talking about the limiting effect of myocardial contractile function on coronary blood flow. There is an opinion that systolic compression (squeezing) of cardiac arteries is a "forced situation" negatively influencing coronary circulation. Below, we will try to formulate possible mechanisms to support the hypothesis about the positive contribution of coronary paradox to blood circulation in heart vessels.

So, cardiac systole occurs immediately after electrical excitation of the myocardium and begins with LV isovolumetric contraction phase, which proceeds with closed valves, and takes a short time interval (50–70 ms). During this period, cardiomyocytes generate force, active cell stiffness rapidly increases, which leads to increased mechanical tension in the LV wall, intraventricular and intramyocardial pressures.

Ultimately, a combination of the above events leads to compression of the perforating arteries, resulting in a rapid decrease in VBFV in the proximal parts of the coronary bed to almost zero (see Fig. 1). In some cases, during this period of the cardiac cycle, one can observe retrograde blood flow, i.e. in the direction towards the aorta [3, 24]. It means that in the places of compression of perforating arteries, there is not only blood flow limitation but also the driving force (pressure on vessels) that ensures blood flow. The mechanism of such myocardial action on the arteries is well described within the concepts of intramyocardial pump [15] and/or variable elastance [19, 20] (see above). The contribution of LV isovolumetric contraction phase to myocardial blood

supply is usually not taken into account due to the lack of the possibility of quantifying it.

The isovolumetric phase of LV systole passes into the phase of blood ejection into the aorta. Cardiomyocytes during this period are significantly shortened, active cell stiffness continues to increase to the maximum value. The pressure in the aorta increases up to the value of the LV end-systolic pressure. In relation to systemic hemodynamics, where blood flow is determined by arteriovenous pressure difference, coronary circulation is critically different due to prior compression of perforating arteries during isovolumetric LV contraction phase. Similar to hemodynamic changes in arterial stenosis, increased resistance to blood flow in early systole leads to a decrease in its volumetric characteristics, systolic and pulse pressure values, and the emergence of a pressure gradient in the arteries at their narrowing level.

In LV coronary macrocirculation system, blood flow during the ejection phase is determined by pressure difference in the aorta and perforating arteries. Compression of perforating arteries during this cardiac cycle phase continues to increase and, therefore, makes additional pumping contributions to antegrade blood flow below the level of arterial compression. The systolic contribution of arterial compression to coronary blood flow can be explained within any or all of the known concepts discussed above.

Noteworthy are the few studies that have investigated functional differences in myocardial and circulation mechanics in the layers of the cardiac wall. In particular, significant axial differences in both regional myocardial function and perfusion density by wall thickness have been shown. The relationship between these characteristics has also been demonstrated [25, 26].

Evidence suggests that in LV systole, there is not just compression of perforating coronary arteries, but sequential compression of vessel sections along its axis, coordinated in space and time. In terms of the intramyocardial pump and/or variable elastance concepts, this circumstance increases blood pumping capacity in the corresponding direction. It is similar to the principle of peristaltic pump operation, where volumetric liquid flow velocity directly depends on the number of rollers squeezing the tube.

It should be added that in the system of precapillary arterioles of coronary microcirculation, there is also a myocardial compression role, but on the venules surrounding arterioles [13]. This fact gives grounds to speak about the presence of the pumping role of cardiac muscle in venous outflow in LV systole.

Thus, mechanical (contractile) function of the myocardium in LV systole determines coronary blood flow due to two factors: 1) compression of the perforating arteries, which begins even before an increase in arterial pressure and, 2) increase in aortic pressure. In the context of the coronary paradox, LV can be formally considered as a dual-purpose mechanical pump – providing global hemodynamics for the body as a whole on one hand, and a pump for coronary blood circulation, in particular, on the other hand.

Cardiac diastole begins with the LV isovolumetric relaxation phase, when actin-myosin interaction in cardiomyocyte sarcomeres rapidly subsides. At the same time, myocardial stiffness, intramyocardial pressure and LV pressure rapidly decrease at a constant chamber volume. Fig. 1 clearly shows that during a short period of time (~50 ms), VBFV in the LAD, off the left coronary artery, increases sharply and reaches its maximum value by the beginning of the LV diastolic filling phase.

This hemodynamic phenomenon is commonly referred to as "suctioning" or decompression effect in coronary arteries [27, 28]. It is based on rapid reduction of elasticity in the cardiac wall during myocardial relaxation, which leads to restoration of perforating arterial lumen within a short period of time. A sharp decrease in arterial hydrodynamic resistance is accompanied by increased gradient between the pressure in the proximal and distal parts of the coronary system, leading to rapid filling of the arteries with blood below the vessel compression places in LV systole. Further, blood flow in LV diastole is determined by arteriovenous pressure difference and peripheral resistance in the coronary system.

Thus, arterial compression realizes its effect on coronary hemodynamics in all phases of the cardiac cycle, from the moment of myocardial excitation. Coronary artery compression provides not only systolic contribution to coronary circulation, e.g., by the intramyocardial pump principle, but also sets the conditions for blood flow through the heart vessels in LV diastole. The ratio of the systolic and diastolic contributions of the "coronary paradox" to cardiac hemodynamics depends on the inotropic state of the myocardium. This plays an important role in the adaptation of the heart to increasing load, regardless of whether the load is physical or related to the development of pathological processes in the heart [5, 7, 29].

THE ROLE OF CORONARY ARTERY COMPRESSION IN THE HEART

The history of coronary blood flow studies dates back more than three centuries. Centuries-old scientific ideas about blood flow regulation in heart vessels were based on the study of hemodynamics in large coronary arteries. Development of modern medical diagnostic technologies in the last few decades has allowed a new perspective on many aspects of coronary blood flow regulation due to the possibility of assessing blood flow in the microcirculatory system. In particular, it became clear that normal blood flow in branched capillary networks is nonpulsating and has ~0.5 mm/s velocity at 25–35 mmHg pressure [30]. It can be considered that such hemody-

namic parameters are optimal for blood-cardiomyocyte metabolic processes. However, how this optimality is achieved is still not completely clear.

At rest, myocardial contractile activity provides a systolic pressure of about 110–120 mmHg in the aorta, with a pulse pressure of about 40 mmHg. The coronary system, being in close proximity to the heart, experiences approximately the same hemodynamic loads in the large subepicardial arteries. Taking into account the small length of the coronary system compared to the large circulatory circle, it can be assumed that pressure boundary conditions at the inlet of the coronary system are excessive to provide the necessary parameters in the blood microcirculation system in the heart.

Compression of perforating arteries in LV systole increases resistance to blood flow, reduces arteriovenous pressure difference in the system and, therefore, prevents hydrodynamic stroke in the distal parts of the coronary bed. In its essence, the "coronary paradox" is a kind of "systolic barrier" to blood flow at the inlet of the coronary hemodynamic system.

Let us pay attention to the fact that the systolic barrier principle is also realized in the cerebral circulation system, where straightening siphons (S-shaped bends) of main arteries play the damping role of blood flow in LV systole [31]. Curiously, the organs more distant from the aortic orifice do not have such protection.

A priori, obstruction of blood flow in the large coronary arteries is likely to reduce LV efficiency. However, as noted above, nature has been able to "turn" what seems to be disadvantages in heart design into advantages of its functioning. Indeed, the presence of arterial vessel compression is able to optimize coronary hemodynamics in all phases of the cardiac cycle, thus providing blood flow conditions necessary for metabolic processes in cardiomyocytes. Hence, the "coronary paradox" can be considered as an integral determinant in coronary circulation regulation.

In conclusion, it should be said that the issues raised are the subject of ongoing discussions [6, 7]. This is due to the extraordinary complexity of studying the coronary system, in which all regulatory links are closely interconnected with each other. It concerns not only mutual humoral influences between the myocardium and smooth muscle of coronary vessels, but also mechanical interactions caused by structural heterogeneity of the heart and left ventricle in particular [32].

In this work, we have tried to convince the interested reader that systolic arterial compression is not a "forced" but a strictly "grounded" natural phenomenon. A phenomenon aimed at solving the problem of optimization of the joint activity of contractile and coronary systems in biological pump design. We hope that interpretation of the facts proposed in the paper gives grounds to suggest that LV systolic contribution to coronary blood flow is clearly underestimated. Understanding the role of the "coronary paradox" in the heart can be useful for practicing physicians when choosing treatment tactics for patients, optimizing left ventricular bypass during heart surgeries, as well as improving the efficiency of adaptation of the transplanted heart.

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