Biomechanical Properties of Coronary Arteries Neonates – First Results

Normunds Sikora[1], *Elina Teivane*[1], *Aris Lacis*[1], *Valts Ozolins*[1], *Lauris Smits*[1], *Inta Bergmane*[1], *Vladimir Kasyanov*[2]

[1] *Children's Clinical University Hospital, Clinic for Pediatric Cardiology and Cardiac Surgery, Riga, Latvia*
[2] *Biomechanical Laboratory of Rīga Stradiņš University, Latvia*

Abstract

One of the most important issues in pediatric cardiac surgery is myocardial protection when cardioplegic solution mixed with oxygenated blood is injected in coronary arteries with the pump. In this case it is necessary to establish the right pressure of cardioplegic solution in coronary arteries taking into account their biomechanical properties. Biomechanical properties of eight specimens of coronary arteries from neonates 12.3 ± 13.7 days old and weight 4.1 ± 0.9 kg were investigated and compared with adult arteries. Specimens were pressurized from 0 to 200 mmHg with the step of 20 mmHg while maintaining the length of the sample *in situ*. We observed that the relationship between stress and strain in neonates was non-linear. There was a rapid increase of strain until the inner pressure reaches 80–100 mmHg and not as rapid regarding to the stress in the arterial wall. When the internal pressure exceeds 100 mmHg the strain of the arterial wall increases much slower but at the same time the wall stress and modulus of elasticity begin to increase rapidly. It means that the structural elements of the arterial wall have been straightened and possible damage in the wall of coronary arteries of neonates may appear. These results were compared with biomechanical properties of arterial wall of adults and differences were found.

Our first experimental results show that the pressure of the cardioplegic solution in neonatal coronary arteries should not exceed 100 mmHg to decrease the risk of structural damage of the vascular wall. Additional investigations of morphology of arterial wall of neonates and adults have to be done.

Keywords: myocardial protection, arterial wall, biomechanical properties.

Introduction

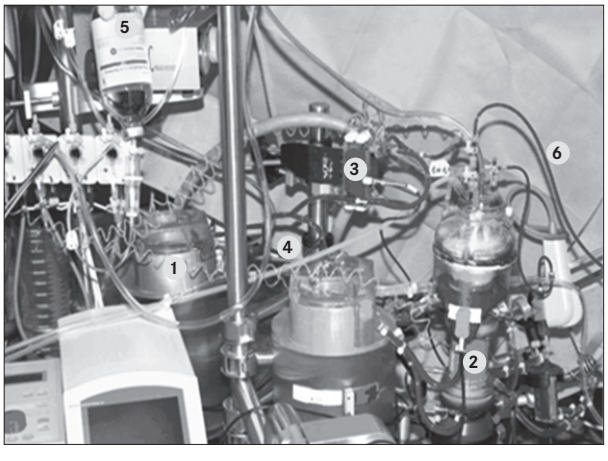
One of the most important issues in pediatric cardiac surgery is myocardial protection when cardioplegic solution mixed with oxygenated blood is injected in coronary arteries with the pump. The general principles underlying the efficacy of cold chemical cardioplegic solutions are well established. Tissue preservation is achieved by conserving energy stores through rapid arrest, decreasing the ongoing metabolic rate, and combating changes induced by ischemia with specific protective agents. Moreover, the prevention of intraoperative myocardial damage depends also on the completeness of delivery of cardioplegic solution. To maintain an adequate delivery, the right delivery pressure should be used. If it is too low or too high, it can lead to severe damage of myocardium. Therefore, it is necessary to establish the right pressure of the cardioplegic solution in coronary arteries.

It is known that myocardial ischemia and reperfusion are associated with unfavorable alterations in the physiologic mechanisms that regulate intracellular and interstitial fluid balance, leading to the development of myocardial edema. The composition of cardioplegic solutions (onconicity, hemodilution) and conditions of delivery (hypothermia, high delivery pressure) are known to exaggerate the development of edema resulting from ischemia or systemic inflammatory responses.

Edema may increase microvascular resistance to the point of impending blood flow and increase diffusion distance to myofibrils, leading to inadequate oxygen delivery. It can arise with the use of cardioplegic solutions, especially in ischemic myocardium, because of high delivery pressure, particularly in severely damaged myocardium; hemodilution and hypoosmolarity from crystalloid primes of cardiovascular bypass or crystalloid cardioplegic solutions [13, 16]. Although normal myocardium tolerates relatively high infusion pressures, myocardium within and surrounding ischemic segments is vulnerable to edema induced by high delivery pressure, because ischemia not only causes a reduced autoregulation, but also renders the capillary bed more susceptible to inappropriately high pressure [11, 12].

There has been a number of researches done stating how important it is to measure the delivery pressure of cardioplegic solution when giving it into the coronary arteries. It is often given at a high flow and pressure following aortic clamping to ensure rapid diastolic arrest, and it is easy to exceed a delivery pressure of as high as 200 mmHg with standard setup in clinical practice. Irtun and Sorlie have demonstrated the importance of cardioplegic solution delivery pressure for myocardial protection in an in vitro rat heart study. They found that moderate (106.5 mmHg and 73.5 mmHg) pressures gave good myocardial protection. A considerably higher pressure (175 mmHg) gave significantly higher coronary resistance during the cardiac arrest period, and reduced coronary flow as well as left-ventricle developed pressure during the reperfusion period. High delivery pressure caused lower myocardial contents of adenosine triphosphate and creatine phosphate at the end of reperfusion period [8, 9, 12]. In another study in vitro of pig heart done by Irtun and Sorlie confirmed their results on rats and stated that the delivery pressure of cardioplegic solution as high as 175 mmHg, which is easily achieved in the aortic root with presently used cardioplegia delivery devices, is harmful to normal pig heart. They compared their model to a clinical setting, stating that there is a good reason to assume that harmful effects of high delivery pressure also pertain to human clinical situations, as in many centers it is accepted that the cardioplegia must be delivered quickly in order to induce a swift and diastolic cardiac arrest without transitorial fibrillation and with, presumably, maximum conservation of high-energy nucleotids. Instead, they showed that even though this high delivery pressure gives a fast cardiac arrest, it gives a faster breakdown of the high-energy nucleotids than a more physiological pressure. That means myocardium would have less energy to work properly after aortic occlusion and the contractility would be much worse [11].

Figure 1. Standart setup for cardiopulmonary bypass and delivery system of cardioplegic solution



The pump (1) takes oxygenated blood from the oxygenator (2) to the heat exhanger (3). There is an Y-connector (4), where the cardioplegic solution (5) has been mixed with the oxygenated blood. After the cooling of the blood in the heat exhanger (3) cold blood cardioplegia through the line (6) has been delivered into the coronary arteries.

It is known that autoregulation ensures approximately constant coronary flow, if the coronary pressure is kept between 60 and 140 mmHg [2, 11]. The precapillary sphincters regulate the vasomotion and this makes the capillary pressure nearly constant. When they are gradually relaxed and the capillaries exposed to inappropriately high pressures, this results in endothelial and myocardial damage.

Neonates

There have been very few investigations done regarding the delivery pressure of cardioplegic solution even in adults not to mention neonates. There are many structural, functional, biomechanic and metabolic differences; therefore it is crucial to give cardioplegic solution with adequate delivery pressure, which still remains undefined, especially in neonatal cardiac surgery.

It is widely accepted that the immature heart has a greater tolerance to ischemia than the adult or mature heart [13, 16]. However, most of these results have been obtained from normal hearts and it is unclear what the tolerance is when cyanosis or accidosis are present. It has to be remembered that in majority of cases in pediatric cardiac surgery myocardium has suffered from ischemia before and is more vulnerable than the normal one. What is specific for neonatal myocardium, it is more resistant to hypoxia, but less to the increased amount of water, which is an issue for those using the crystalloid cardioplegia. In addition, it stresses how important it is to clarify the right delivery pressure of cardioplegic solution into the coronary arteries of neonates, because high pressure leads to the development of myocardial edema.

The optimal cardioplegia infusion pressure is still unknown, especially in neonates. Due to the structural, functional, biomechanic and metabolic differences, it may be more prone to a pressure injury in pediatric cardiac surgery. Even though it is stated that high cardioplegic delivery pressure is deleterious, especially to ischemic tissue, it still remains undefined [2, 7]. However, an adequate delivery pressure is still needed to ensure the distribution to all areas of the myocardium [1, 2]. What is the right delivery pressure of cardioplegia and what are the consequences of elevation of this pressure, especially in the hypoxic heart, still remains an issue in neonatal cardiac surgery.

Another important issue, being investigated by Ishiyama et al. is the influence of coronary perfusion pressure on neonatal heart function. The change in cardiac function following the change of coronary perfusion pressure or coronary blood flow is called Gregg phenomenon, which is well investigated in adults, but not examined in neonates. During neonatal cardiac surgery, coronary perfusion pressure depends on cardiopulmonary bypass, empirically kept low compared to adult cases. They have concluded that due to the immaturity of coronary, autoregulation neonatal hearts did not show it in any perfusion pressure range, and both low and high perfusion pressure caused deterioration in ventricular function attributable to the immaturity of coronary autoregulatory capacity. Therefore, attention should be paid to control the infusion pressure of the cardioplegic solution [3, 10].

Cardioplegic infusion pressure must be adequate to ensure distribution to all areas of myocardium, but not as high as to cause cellular damage. The principle is very simple, but what pressure is adequate and what causes myocardial damage is still undefined. Even though most surgeons usually avoid excessively high cardioplegic infusion pressures, the pressure must be also high enough to ensure adequate myocardial distribution [1, 7]. Kronon et al. have investigated delivery pressure on animal model and concluded that it is crucial in neonatal cardiac surgery to maintain it under 100 mmHg. What is more, taking into account, that majority of neonatal patients undergoing primary repair of congenital heart disease are hypoxic, hypoxia profoundly alters the effect different cardioplegic infusion pressures have on myocardium. The authors have concluded that low cardioplegia infusion pressure not only protects heart from further damage, but allows the cardioplegia to facilitate repair of the injury caused by hypoxia and reoxygenation, resulting in complete preservation of myocardium and vascular endothelial function. They mention that this supports the safety of a cardioplegic infusion pressure of 30 to 50 mmHg and implies it to be high enough to ensure adequate myocardial distribution, without which myocardial protection is poor. Consequently, hypoxia alters the myocardium, resulting in an increased cellular injury, when the cardioplegic infusion pressures were slightly higher (80 to 100 mmHg). This injury manifested by postbypass myocardial and vascular dysfunction increased edema and decreased ATP levels [7, 16].

Biomechanics of cardiovascular system

The mechanical properties of the arterial wall are very important because they influence arterial physiology. Furthermore, stresses and strains in the arterial wall are extremely important factors in the understanding of the pathophysiology and mechanics of the cardiovascular system [5, 14, 15].

The primary function of all blood vessels is to circulate blood, but they are not merely highways or pipe, as they have a passive capacitance function that maintains blood pressure in diastole as well as an active auto-regulatory control that allows the organ to respond to local demands. Arteries are generally subdivided in two types – elastic (e.g. aorta) and muscular (e.g. coronary artery). The wall structure of both consists of intima, media and adventitia. Intima layer consists of relatively acellular fibrous tissue and ground substance covered by a monolayer of endothelial cells. Media is composed of multiple layers of smooth muscle cells separated by collagen, ground substance and elastic fibres. Adventitia has bundles of collagen and loose bands of elastic tissue. Intima, media and adventitia are separated by internal and external elastic laminae. The mechanical properties of blood vessels depend on collagen and elastic fibres as well as on smooth muscle cells and ground substances.

The pressure-diameter relation has been very popular, because it plays an important role in the pressure-flow relationship of blood flow through the blood vessel. The compliance of the vasculature (slope of the pressure-diameter relation) is an important determinant of the non-linearity of the pressure-flow relationship. Furthermore, the pressure-diameter-length can be transformed into biaxial (circumferential and longitudinal) stress-strain relation where the mean circumferential Cauchy stress is computed from pressure, diameter and wall thickness as per Laplace's equation and strain is computed from circumference (or diameter) measurements in reference to zero-stress state [4, 6].

Blood pressure is primarily opposed by forces of elastin, collagen and smooth muscle cells that are orientated to form defined layers. Thick elastin bands form concentric lamellae while finer elastin membranes form networks between lamellae, and the collagen fibres are distributed circumferentially in the interstices. Kassab et al. have observed that the wall thickness-to-radius ratio increases in proportion to the increase in pressure such that the circumferential average wall stress is restored after some period of growth and remodeling, besides they found that strain reaches its peak sooner and normalizes faster than stress. They concluded that the vessel appears to be more sensitive to changes in strain than in stress [6].

There are experiments showing the physical nonlinearity of arterial material to be characterized by an increasing stiffness as strain increases. The origin of this behavior is found to be in the mechanical properties of the basic structural components of the artery – elastin and collagen – as well as in the architecture of the arterial wall as explained above [5].

As for neonates, it has to be taken into account that after birth coronary arteries are immature. The wall of the vessels is much thinner compared to the coronary arteries of adults, influencing the biomechanical properties of blood vessels. These arteries are much more fragile and easier to damage. In early life, elastic arteries increase in length, diameter and wall thickness in accordance with changes in body weight and length associated with growth and development. Intima becomes thicker due to the migration and proliferation of vascular smooth muscle cells followed by synthesis of scleroprotein and extracellular matrix.

The aim of the study

The aim of our study is to establish the pressure, which is not harmful for neonates, taking into account the biomechanical properties of coronary arteries of neonates.

Material and methods

There has been a research work done regarding biomechanical properties of coronary arteries [14, 15], but this study focused only on neonatal coronary arteries.

After receiving the permission of Ethical Committee, between May and December, 2009, eight samples of neonatal coronary arteries and one sample of adult coronary artery, retrieved at the autopsies, were used as experimental materials. The specimens were right coronary arteries. The mean age of neonates was 12.3 ± 13.7 days and the mean weight 4.1 ± 0.9 kg. The length of the specimens was approximately 4 cm. After resection, the specimens were stored in Custodiol Perfusion Solution no longer than 24 hours until the mechanical tests were performed. Custodiol is used for preservation of donor's organs during transport from a donor to a recipient, and for preservation of vessel grafts. It prolongs ischemia tolerance in organs requiring protection mainly by preventing the triggering of energy-consuming activation processes and by retarding the fall in pH in the tissues during organ ischemia. The specimen must be kept in hypothermia (2–4 °C) [17]. There has been no evidence regarding safe storage time for vascular specimens. Nevertheless, safe storage time for kidneys is established as 24 hours.

A special device was used to measure the internal pressure, axial force, longitudinal and circumferential deformation of the coronary artery.

Figure 2. The view of experimental stand

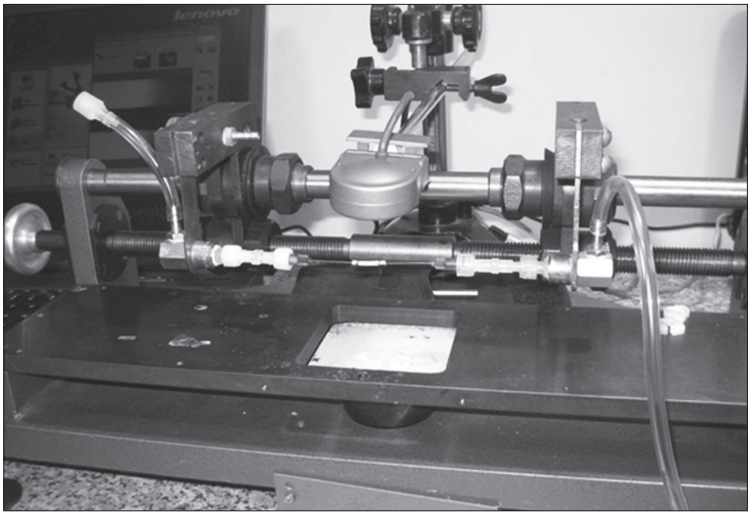
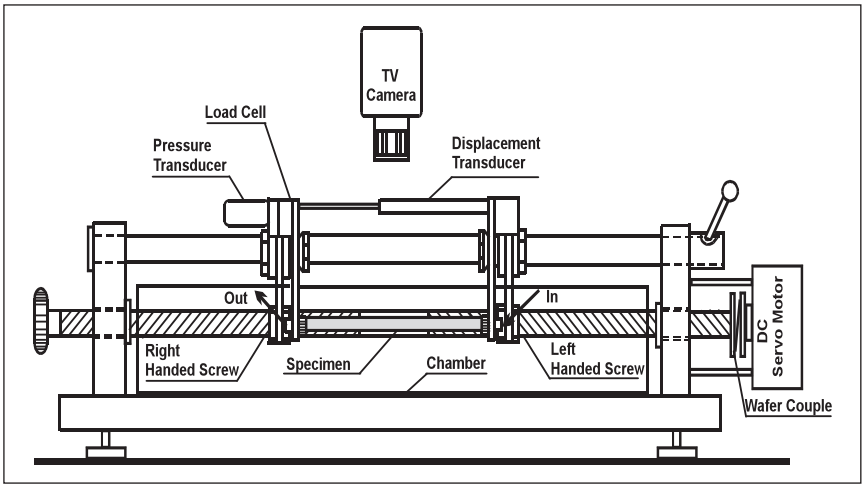


Figure 3. The scheme of experimental stand



One end of the artery was clamped to support to which a pressure transducer and specially designed inductive force transducer were connected. The other end was clamped to a support to which a pressure bottle containing fluid was connected. The force transducer recorded the force necessary to maintain the vessel at its *in situ* length. Axial stretch was introduced by a slide mechanism to which the balance arms were fixed. The axial deformation of the artery was measured with a specially designed inductive strain transducer connected to one of the arms of the balance. Diameter changes in the specimen were sensed optically with a video-dimensional analyzer coupled with a suitable lightning system for high contrast. The changes in diameter were tracked and recorded continuously.

A sample of coronary artery was gradually loaded by internal pressure from 0 to 220 mmHg while maintaining the length of the sample constant at L_0, the length *in situ*. The pressure was elevated in 20 mmHg steps. The initial external diameter at inner pressure p = 0 mmHg and at *in situ* axial length L_0 was noted as D_0. The diameter D was recorded at each pressure level.

Figure 4. Neonatal coronary artery pressurized with the pressure of 0 mmHg

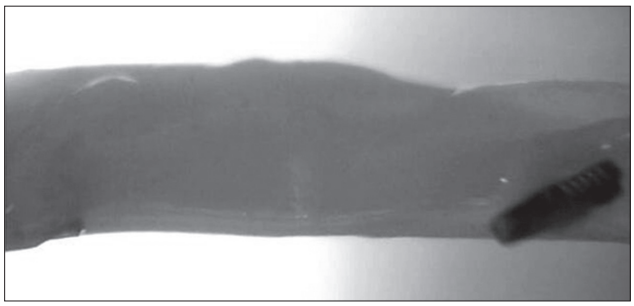
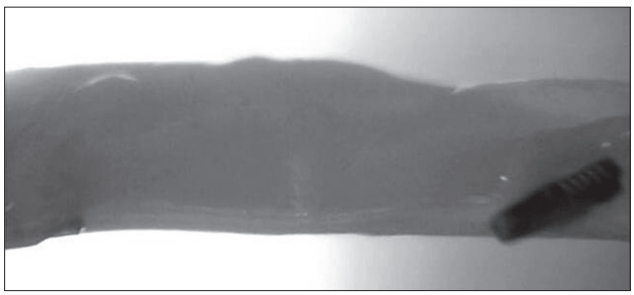


Figure 5. Neonatal coronary artery pressurized with the pressure of 220 mmHg



The value of wall thickness h was calculated as follows:

$$h = h_2 \times \lambda_3 \quad (1)$$

where

$$\lambda_3 = 1 / \lambda_1 \times \lambda_3 \quad (2)$$

$$\lambda_2 = (D / D_0) \quad (3)$$

and

$$\lambda_1 = (L / L_0) = 1.0 \quad (4)$$

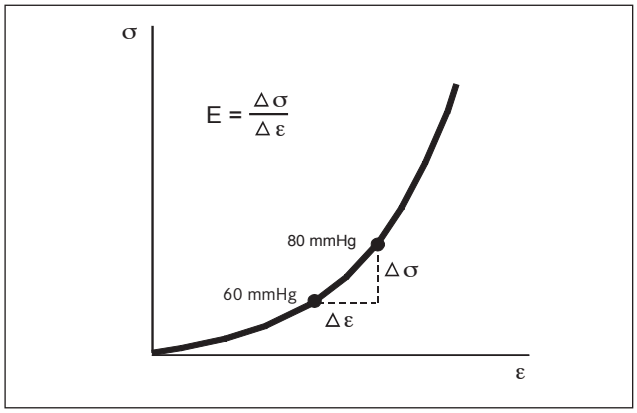
In these equations h_0 is the initial thickness of the specimen and λ_1, λ_2 and λ_3 are, respectively, the stretch ratios in the axial, circumferential, and radial directions. Because the length of the artery was maintained constant at L_0, the value of λ_1 was 1.

The initial wall thickness h_0 was measured with a cathetometer to ± 0.0001 mm accuracy.

The flexibility and stiffness of arteries has been frequently characterized by the values of compliance, pressure-strain elastic modulus and stiffness parameters. Compliance is the fractional change in external diameter with change in pressure.

Because the pressure-diameter relation of an arterial wall is generally nonlinear, compliance and pressure-strain elastic modulus are not usually material constants but change with the internal pressure.

Figure 6. Determination of elastic modulus

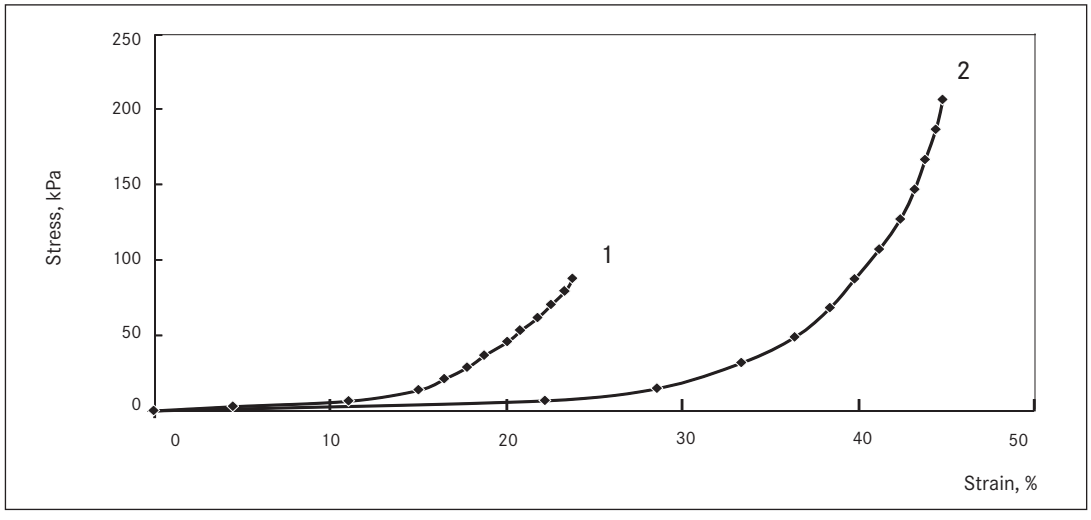


The ultimate stress and ultimate strain were expressed as mean values plus one standard deviation. A *p* value of less than 0.05 was considered statistically significant. When two groups were compared, data were analyzed using student *t* test with a *p* value of less than 0.05 indicating statistical significance.

Results

We observed that relationships between pressure and strain and stress and strain in neonates were non-linear. There was a big difference between neonates and adults in terms of elastic modulus (Fig. 7).

Figure 7. Relationship between stress and strain in coronary arteries; 1 – adults, 2 – neonates



There was a rapid increase of strain until the inner pressure reaches 80–100 mmHg and not as rapid regarding to the stress in the arterial wall. When the internal pressure exceeds 100 mmHg, the strain of the arterial wall increases much slower, but at the same time the wall stress and modulus of elasticity begin to increase rapidly.

The strain in the wall of neonatal coronary artery, when the inner pressure is 80 mmHg, reaches 36.50 ± 3.75%, which is more than twice higher compared to the adult coronary artery – 17.6%. As for stress, it reaches 68.61 ± 10.17 kPa with the same inner pressure in neonatal coronary artery and increases rapidly, when increasing the pressure (Table 1). When it achieves 120 mmHg, the strain is 108.52 ± 15.19 kPa, which is more than twice higher, compared to the strain with inner pressure of 80 mmHg. The strain in the wall of adult coronary artery was 45.84 kPa ($p < 0.05$).

Table 1. Stress and strain in neonatal and adult coronary arteries, when applying different inner pressure

Age group	σ, kPa				ε, %			
	60 mmHg	80 mmHg	120 mmHg	220 mmHg	60 mmHg	80 mmHg	120 mmHg	220 mmHg
Neonates	49.02 ± 7.34	68.61 ± 10.17	108.52 ± 15.19	215.25 ± 36.67	33.35 ± 3.35	36.5 ± 3.75	40.35 ± 4.68	46.49 ± 9.88
Adults	21.15	28.81	45.84	87.84	16.41	17.6	20.01	23.78

The stiffness in the wall of neonatal coronary artery increases rapidly compared to adults', when the inner pressure exceeds 80 mmHg (Table 2).

Modulus of elasticity of the wall of neonatal coronary artery is 735.70 ± 319.54 kPa, when the inner pressure is 80 mmHg (Table 1), but when it reaches 100-120 mmHg – 1462 ± 717.74 kPa ($p < 0.05$). In adults modulus of elasticity in the same pressure is 756.67 kPa, which is twice lower compared to neonates. When the inner pressure increases from 60 mmHg to 120 mmHg, it increases from 638.33 to 756.67 kPa (Table. .2). In neonatal coronary artery it increases from 735.70 ± 319.54 to 1462 ± 756.67 kPa. It can indicate the possible damage in the wall of neonatal coronary artery, when the inner pressure exceeds 100–120 mmHg.

Table 2. Modulus of elasticity in neonatal and adult coronary arteries, when applying inner pressure from 60 until 120 mmHg

Age group	ε, %		
	60–80 mmHg	80–100 mmHg	100–120 mmHg
Neonates	36.5 ± 3.75	40.35 ± 4.68	46.49 ± 9.88
Adults	17.6	20.01	23.78

Discussion

One of the most important goals in pediatric cardiac surgery is to maintain an adequate myocardial protection. It can be achieved by the cardioplegic solution mixed with oxygenated blood injected in coronary arteries with the pump. The general principles underlying the efficacy of cold chemical cardio-plegic solutions are well established. Tissue preservation is achieved by conserving energy stores through rapid arrest, decreasing the ongoing metabolic rate, and combating changes induced by ischemia with specific protective agents. The prevention of intraoperative myocardial damage depends also on the completeness of the delivery of cardioplegic solution. If it is too low or too high, it can lead to severe damage of myocardium. Therefore, it is necessary to establish the right pressure of the cardioplegic solution in coronary arteries, because too low would lead to inadequate delivery, but too high would damage the coronary arteries and myocardium. In any case this injury manifested by postbypass myocardial and vascular dysfunction, increased edema and decreased ATP levels [7]. The composition of cardioplegic solutions (onconicity, hemodilution) and conditions of delivery (hypothermia, high delivery pressure) are known to exaggerate the development of edema resulting from ischemia or systemic inflammatory responses [16].

It can arise with the use of cardioplegic solutions, especially in ischemic myocardium, because of high delivery pressure, particularly in severely damaged myocardium. Although normal myocardium

tolerates relatively high infusion pressures, myocardium within and surrounding ischemic segments is vulnerable to edema induced by high delivery pressure, because ischemia not only causes a reduced autoregulation but also renders the capillary bed more susceptible to inappropriately high pressure [8, 9, 11, 12].

There are a number of researches done [1, 2, 7, 8, 9, 10, 11, 12] stating how important it is to measure the delivery pressure of cardioplegic solution when giving it into the coronary arteries. But these investigations have been done based on different animal models. There have been very few researches done regarding the delivery pressure of cardioplegic solution even in adults not to mention neonates. Antegrade cardioplegia is often delivered without directly monitoring delivery pressure. The surgeon or perfusionist can only measure the actual perfusion pressure, which can result in cardioplegia being delivered at higher or lower pressure than desired. Besides the optimal cardioplegia infusion pressure is still unknown, especially in neonates. Due to structural, functional, biomechanic and metabolic differences, it may be more prone to a pressure injury in pediatric cardiac surgery. Even though it is stated that high cardioplegic delivery pressure is deleterious, especially to ischemic tissue, it still remains undefined [2, 7]. However, an adequate delivery pressure is still needed to ensure the distribution to all areas of myocardium [1, 2]. What is the right delivery pressure of cardioplegia and what are the consequences of elevation of this pressure, especially in the hypoxic heart, still remains an issue in neonatal cardiac surgery.

There is almost no evidence how important it is to maintain the right delivery pressure of cardioplegic solution, taking into account the biomechanical properties of neonatal coronary arteries. Therefore, we decided to establish the right pressure after having investigated the samples of neonatal coronary arteries. Our results show that in the wall of these arteries there was a rapid increase of strain until the inner pressure reaches 80–100 mmHg and not as rapid regarding to the stress in the arterial wall. When the internal pressure exceeds 100 mmHg, the strain of the arterial wall increases much slower, but at the same time the wall stress and modulus of elasticity begin to increase rapidly. It means that the structural elements of the arterial wall have been straightened and possible damage in the wall of coronary arteries of neonates may appear.

Our results show that modulus of elasticity of the wall of neonatal coronary artery appear to be two times higher compared to adults', when the inner pressure reaches 100–120 mmHg. It can indicate the possible damage in the wall of neonatal coronary artery, when the inner pressure exceeds 100–120 mmHg.

Conclusions

Our first experimental results show that, taking into account the biomechanical properties, the delivery pressure of the cardioplegic solution in neonatal coronary arteries should not exceed 100 mmHg, because higher pressure increases the risk of structural damage of the vascular wall leading to the injury of myocardium. Our research is going to be continued, including additional investigations of morphology of arterial wall of neonates and adults.

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