



THE EFFECT OF VERAPAMIL ADDED TO THE INSUFFLATION SYSTEM USED IN OFF-PUMP CORONARY ARTERY BYPASS SURGERY ON ENDOTHELIAL DAMAGE

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ABSTRACT

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Coronary artery disease is one of the leading causes of death worldwide. In addition to the medical options in the treatment, surgical intervention options such as percutaneous cardiac interventions and coronary artery bypass graft surgery have also taken place in treatment protocols. Performing surgery using a heart-lung machine in coronary artery bypass surgery has been a significant improvement in terms of anastomosis comfort for surgeons. However, the observation of the complications that may develop due to this machine has led to the birth of off-pump coronary artery bypass surgery, which allows the application of coronary artery bypass surgery without the use of a heart-lung machine in appropriate cases. However, while using this technique, the washing solution, which is a mixture of gas and serum, must be insufflated with pressure to the field for keeping the surgical field blood free. This insufflation itself can cause premature occlusion of anastomoses by causing endothelial damage.

In this study, we planned to investigate the protective effects of adding verapamil to the insufflation solution on the endothelium in off-pump coronary bypass.

Introduction

Coronary artery disease is one of the leading causes of death worldwide. Coronary artery disease (CAD) is the leading cause of death in our country, and it is known that we share the first places among European countries in this regard. (1,2,3).

In addition to the medical options in the treatment, intervention options such as percutaneous cardiac interventions which have developed in recent years (eg percutaneous intracoronary angioplasty) and coronary artery bypass surgery have also taken place in the treatment of coronary artery disease (4).

Revascularization of the coronary artery system is still a basic application of cardiac surgery practice (5).

Direct surgical intervention for coronary arteries was first applied on laboratory animals by Alexis Carrel (6). Carrel, who conducted experimental studies on anastomosis techniques and vascular grafts between 1902-1939 and received the Nobel Prize for these studies, performed coronary artery bypass operation in the form of the implantation of the autogenous carotid artery segment between the descending aorta and the circumflex coronary artery on dogs. The implantation of the Internal Thoracic Artery (ITA) into the heart muscle was performed by Vineberg in 1949 and it was called "Vineberg Surgery". Aortic coronary bypass with saphenous vein was first performed by Sabiston in the right coronary artery (RCA) in 1962 and by Garrett in the left anterior descending artery (LAD) in 1964. Direct coronary artery revascularization was

successfully performed in the laboratory (for the first time) by Demikhov in 1953 by anastomosing the ITA to the coronary artery with the help of a metal tube, and it was performed successfully in humans for the first time by Robert Goetze in 1961 (7,8).

The first artificial heart-lung machine was made by Von Frey and Gruber in 1885. Although the idea and first laboratory trials of extracorporeal circulation (ECC) methods are quite old, the first successful open-heart operation with the help of the heart-lung pump was performed in 1953 (9). Coronary surgery has become widespread with the development of ECC and myocardial protection techniques. However, artificial circulation negatively affects many physiological mechanisms, especially in long operations. During ECC, contact of blood with artificial surfaces triggers many protection mechanisms by activating blood cells and humoral systems, and causes systemic inflammatory response (10-15). Up to the present, by benefiting from many technical developments, it is tried to minimize the negative effects of ECC on the organism and to provide sufficient safety. However, ECC is still considered as an application that increases morbidity and mortality (16-17). Coronary artery surgery was initially applied in the clinic without ECC, it developed and became widespread with the help of ECC. Considering total number in a year, it was observed that coronary artery bypass graft (CABG) operations still constitute a large part of open-heart interventions. Except for new techniques to improve myocardial protection, the technical details of the procedure have remained unchanged for years. Contrary to the fact that the techniques that are essential in other branches have changed in parallel with the developing technology, standard bypass graft operation techniques have resisted to change to a great extent. The CABG technique owes its permanence to the historically proven reliability and efficiency parameters (18-20). In addition to these, it has been a technique which can be easily applied by many surgeons regardless of their clinical experience and with which remarkably successful results are obtained. Due to the successful catheter interventions

applied in the treatment of ischemic coronary syndromes and the application of less invasive interventions in other surgical branches, and also the negative effects of artificial circulatory systems, such as causing systemic inflammatory response especially in long-term applications by activating many cellular and humoral protection systems due to the contact of blood with foreign surfaces (21-22), interest in surgery methods with less invasive methods including off-pump CABG (OPCAB) has gradually increased. First of all, attempts related to the different location of the incision and to reduce its size have been made in the intervention performed on the cardiac patient. Revascularization was performed either in the arrested heart by peripheral cannulation or by minimally invasive direct coronary artery bypass (MIDCAB). Successful results of the surgical intervention performed in selected patients by eliminating cardiopulmonary bypass (CPB) enabled the development of beating heart CABG operation (23-25). In order to avoid the negative effects of ECC and especially considering its economic advantages in South American countries, studies on bypass surgery on beating heart have been continued. In parallel with the developments in the world, CABG applications on the beating heart were previously mostly limited to LAD and RCA and performed without the use of myocardial stabilizers in a small percentage (approximately 5-15%) of patients (30-33). Providing "Local Stabilization" in the anastomosis area with techniques and tools developed with very simple basic principles played the most important role in the development and the state of becoming widespread of coronary surgery on the beating heart without the help of ECC (10,34-37). With the introduction of myocardial stabilizers in 1997-98, increasing coronary surgery applications on the beating heart without the use of ECC have become routine applications covering all coronary surgery interventions, except for rare contraindications in some centers (36,38-40). In a recently published article including all isolated CABG operations performed in 76 hospitals within the HCA National Hospital Systems, it was stated that 3672 (21.6%) cases were performed with off-pump coronary

artery bypass (OPCAB) (36). As experience progresses, it will be inevitable to observe an increase in the number of cases and success with OPCAB. The transformation of this technique from being just an intellectual or alternative technique into a central belief and applicable technique is based on the following scientific proofs:

- i. Graft patency is equal or the same compared to conventional techniques
- ii. Mortality and morbidity are significantly low, especially in the high-risk group.
- iii. A rapid return to normal functional capacity is provided.
- iv. It is economically more profitable.

In addition to the need for stabilization devices in order to perform the OPCAB operation, disposing the blood from the operation area is extremely important as it will determine the surgical comfort during bypass. Since the beginning of OPCAB surgery, researchers have focused their attention on determining the blood free operation area, effective and comfortable bypass, and performing the same graft patency as with the operations performed with CPB. Especially in the studies conducted by Ip et al. (41) in the 1990s, they study the damage that caused by the slings used to suspend the coronary arteries and classified it into 3 groups as Type 1, Type 2, and Type 3 damage. The classification made by Ip et al. is used for the expression of the damage. In this classification the types are defined as follows:

Type 1: Normal morphology despite functional change in the endothelial layer,

Type 2: Internal elastic lamina and media layer remain intact despite peeling of the endothelial layer and intimal damage,

Type 3: Intimal and medial damage with peeling of the endothelial layer.

The high-flow insufflation technique to the anastomosis site is also the most effective method in keeping the surgical area bloodless; however, this technique has various risks, both hypothetical and experimental. These possible risks can be classified as

risks related to the gas used and damage to the coronary endothelium. Among the possible risks related to gas are; The flammability of Oxygen, the filtered air causing embolism and risk of the coronary endothelium damage as a result of these risks (42). It has been reported that Carbon Dioxide (CO₂) gas can also directly damage the endothelium (42,43).

Although many studies explain the effects of the slings and insufflation used to remove blood from the bleeding area, there is no study on whether adding different vasoactive solutions to the insufflation solution has a protective effect on the endothelium. Since trying to reduce endothelial damage as much as possible will make these applications widespread, we tried to investigate whether the addition of vasoactive substances known to have endothelial protective effects to the insufflation solution has an effect of reducing coronary endothelial damage.

The aim of our study is to determine whether the effect of the insufflation system, which cleans the surgical site from blood, on the endothelial changes according to the characteristics of the washing solution depending on the stabilizer systems used in OPCAB surgery.

Material and Method

14 Wistar-Albino rats weighing 230-260 g were included in the study. The rats were randomly divided into 2 groups, one as the control group (Group 1) and the other as the study group (Group 2).

Sternotomy was performed on rats under intramuscular ketamine anesthesia at a dose of 10 mg / kg. Following the sternotomy, aortotomy was performed in the ascending aorta, by placing a clamp 0.5 cm above the aortic valve. Following the aortotomy, in Group 1, room temperatured physiological saline was insufflated into the aortotomy at a speed of 5 lt / min from a distance of 15 cm for 20 minutes. In group 2, the solution formed by adding 10 mg of verapamil (Isoptin, 2 ampoules) into 500 cc physiological saline was insufflated at a speed of 5 lt /

min at a distance of 15 cm for 20 minutes.

Later, the treated aortic segments were excised, fixed with 10% formol and allocated for histopathological study. Sections were prepared with paraffin in 5µm pieces.

Histopathological Evaluation

Sections were stained with hematoxylin-eosin and Verhoeff's elastic stain. Sections were evaluated under a light microscope (Eclipse Nikon E400, Japan) as double blind by two separate pathologists.

Results

We evaluate no evaluation for protection of endothelium in histopathologic microscopic views that indicating the protective effects of adding verapamil to the insufflation solution. Histopatologic evaluation on light microscope could be seen in Figure-1 and Figure-2 .

Discussion

Definite and effective coronary artery anastomosis is the main goal in the treatment of coronary artery disease. The increase in CABG surgeries on the beating heart, which has gained popularity in recent years, cannot cause us to ignore this fact. Although coronary artery bypass surgery using ECC seems technically easier, the immune response activated as

a result of the contact of the patient's blood with the foreign surface and the more severe course of this response, especially in people with underlying diseases such as chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM), and also the fact that the patient group mostly consists of such people in recent years parallel to the developments in interventional cardiology contribute to the popularity of the OPCAB surgery.

In order to technically facilitate OPCAB surgery, stabilization of the surgical site and prevention of blood flow from the anastomosis area is required. Especially an effective and safe anastomosis, so the success of the surgery depends on the adequate clearance of the anostomosis area from blood. For this purpose, drying the arteriotomy area with an absorbent material, washing intermittently with saline solution, intraluminal coronary shunts, and high flow gas insufflation techniques are applied (44).

The main problem in these methods used to remove blood from the arteriotomy site is the amount of damage given to the coronary endothelium in the bypass area by each method. The size of the intraluminal coronary shunts is important. While shunts that are fully compatible with the coronary diameter may cause damage to the endothelium, small-sized shunts that are thought to cause less damage to the endothelium cannot completely

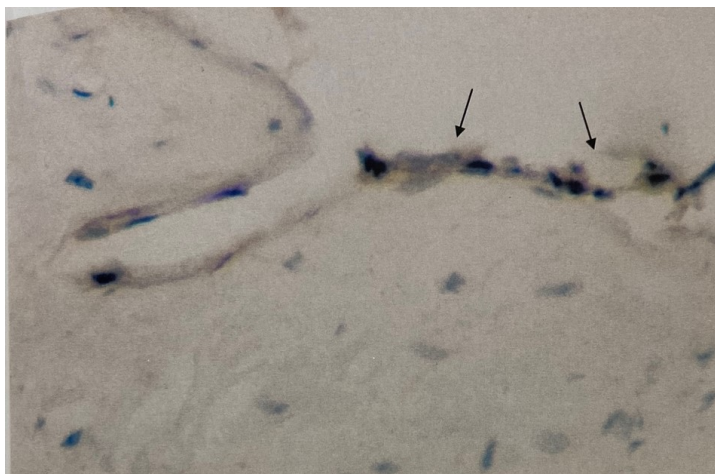


Figure 1: Control Group; Endothelial damage due to physiological saline insufflation applied to the aorta is shown with arrows.

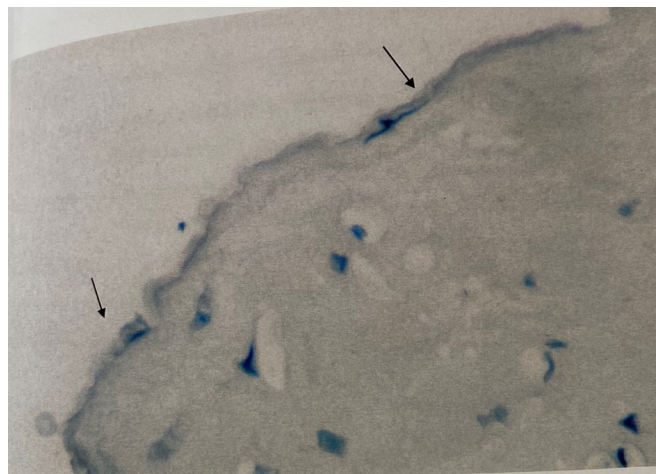


Figure 2: Study Group; The endothelial damage seen in the aortic segments examined in the study group as a result of the application of physiological saline insufflation prepared with the vasoactive agent verapamil is shown with arrows.

prevent blood flow from the surgical site. This makes the anastomosis difficult and directly affects the success of the surgery.

It is known that snares placed around the coronary arteries to remove blood from the arteriotomy site cause endothelial damage. For this reason, it should be avoided to place a snared suture to distal anastomosis, especially in the native vessel (41,45,46). However, in some studies, it has been shown that these snares have no effect on the endothelium (46).

In gas insufflation, oxygen, carbon dioxide and filtered room air are used; however, they pose a danger of causing intimal damage (47). In addition, coronary artery gas embolism is one of the feared problems (48).

Endothelial cells have particularly important roles in maintaining vascular endothelial homeostasis. In addition to their ability to manage membrane permeability, endothelial cells regulate vascular tonus by secreting nitric oxide (NO) and other endothelium-derived relaxants. Endothelial cells also synthesize growth and inhibitory factors that primarily affect vascular smooth muscle cells (44). As a result, endothelial cells are active cells that affect coagulation, fibrinolysis, vascular tonus, hence blood flow and pressure, and play a role in various physiological and pathological events with the mediators they secrete (49,50).

Occurred endothelial damage is the main factor determining mortality and morbidity in cases undergoing open heart surgery. It is also one of the determinants of damage, especially occurred in the post-bypass reperfusion phase. The damage caused is associated with calcium metabolism, mitochondrial dysfunction, and loss of purine nucleotides. As a result, lipid peroxidation develops, and cell damage occurs. All these lipid peroxidation products are cytotoxic (51). Lipid fragments such as oxidized low-density lipoproteins (LDL) show toxic effects on proliferating target cells such as fibroblasts and endothelial cells (51,52).

Calcium channel blockers (CCB) have an effect that regulates calcium flow to vascular cells (53). Various independent researchers have shown that these agents have dose-dependent antioxidant effects in studies in which various cellular and subcellular preparations are used along with commonly used hypertension and angina pectoris (54,55,56). Some researchers proved that these agents acts dose dependent antioxidant activity besides the effects on hypertension and angina pectoris (54,55,56). The antioxidant activity of these lipophilic agents may allow them to be used in the treatment of diseases caused by oxidative stress such as atherosclerosis (57,58,59). Thus, CCB inhibits the oxidation of LDL by oxygen radicals. Similar to antioxidants, CCB, which has different chemical structure, has a concentration-dependent effect against LDL oxidation (60,61,62). Studies have shown that, in a dose-dependant manner, verapamil and nifedipine significantly inhibit the peroxidation of lipids on LDL. At the same time, it was determined that various L-channel CCBs have membrane antioxidant effects (56,58,63-65).

In the light of these studies, we aimed to investigate whether putting verapamil from CCB, of which antioxidant effects and endothelial protective effects have been shown, in the coronary insufflation solution used during the bypass operation on the beating heart has a protective effect against endothelial damage that may occur during the procedure.

We conducted this study on non-atherosclerotic vessels. However, considering that our patient group we undergo surgery is atherosclerotic and the atherosclerotic vascular intima is less elastic than the non-atherosclerotic group, the damage we cause in practice is probably more than we showed in our study. We believe that considering this situation will bring surgical success with it and provide a more comfortable life for patients in the postoperative period.

In addition, we applied insufflation on the artery for only 20 minutes in our study. We believe that the importance of keeping the anastomosis time short will

be better understood, especially when multi-vessel patients are considered.

Conclusion

As a result, we observed that the endothelial damage did not change when the drug, which we know has vasoactive and antioxidant effects, is added to the insufflation solution. We conclude that more detailed studies must be performed to find an optimum endothelial protective material added to the insufflation solutions used in OPCAB operations in order to achieve long time graft patencies.

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