# Comparation Of Bovine Mesenteric Artery With Bovine

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# Comparation Of Bovine Mesenteric Artery With Bovine Mesenteric Vein Patency As Xenograft In *Oryctolagus Cuniculus* Carotid Artery

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***Abstract:*** ***Cardiovascular diseases include coronary and peripheral arteries increase every year. Estimated mortality rates for cardiovascular diseases is up to 23.3 million in 2030 and more than 2 million patients will need hemodialysis access in 2030. Gold standard of vascular graft for bypass surgery is autologous artery or vein but sometimes unavailable. Because of limited availability, researchers encourage to search for another vascular graft in biological graft which has characteristics as good as autograft. This study aims to determine which one is better between bovine mesenteric artery and vein as xenograft by comparing each patency. We performed an in vivo test evaluating the patency of mesenteric artery compared to mesenteric vein as xenograft for four weeks. Each group, both artery and vein, consists of 16 grafts implanted in New Zealand rabbit carotid artery. Xenograft patency was evaluated by observing histopathology of intimal layer thickness, thrombosis events, amount of graft stenosis and number needed to treat (NNT). The result showed a statistically significant increasing in the thickness of the tunica intima of both groups. There was no histopathologic thrombus in the arterial and venous groups. Stenosis in the arterial and venous groups was 12.5% and 50% with an NNT value of 3. The conclusion was bovine mesenteric artery xenograft had better patency than bovine mesenteric vein xenograft.***

***Keywords:*** ***bovine mesenteric artery, bovine mesenteric vein, graft patency, vascular graft, xenograft***

## 1. INTRODUCTION

Bypass surgery using conduit from vein (homograft) is the most frequent, but often a vein in good condition is not found [1]. Apart from patients with peripheral vascular disease, many patients with end stage renal disease who require safe, long-lasting vascular access to dialysis are a major concern. Endogenous arteriovenous fistula is made when there is no autologous vein in good condition. In some countries, synthetic grafts, instead of autologous graft are used as access to vascular dialysis due to limited availibility. Synthetic graft has to be met

some requirements for the ideal graft which are resistant to infection, stimulate neo-endothelialization and a low risk of thrombosis, but until now there is still no graft that meets all the requirements above. [2, 3].

Several alternatives biological materials have been developed including human umbilical vein, bovine carotid artery, autologous vein with cryopreservation. Although it has biological characteristics, its use is still limited due to some unsatisfactory results such as structural degeneration and a high rate of postoperative thrombosis [4].

New research on the bovine mesenteric vein is being developed because it has high elastin content that allows the graft to maintain a good pulsation flow, sufficient thickness of the vessel wall and more resistant to aneurysmatic degradation [3]. Beside the vein, the bovine mesenteric artery also can be used as xenograft. The bovine artery xenograft has subsequently been used as a peripheral artery bypass conduit in peripheral artery disease with an overall success rate of 83% graft implantation and a 77% success rate in femoro-popliteal bypass [5].

From those research results, there is possibility that a better vascular graft material can be obtained from other living thing, for example bovine, so that it can be further developed as the material of choice for making vascular grafts with tissue engineering (TEVG) into an ideal vascular graft. The aim of this study was to determine which one is better patency between bovine mesenteric artery xenografts and bovine mesenteric vein xenografts preserved by freeze-drying technique and implanted in the New Zealand Rabbit (*Oryctolagus cuniculus*) carotid artery.

## 2. MATERIAL AND METHODS

This research was conducted by using in vivo experimental study which was done on *Oryctolagus cuniculus*, a species of New Zealand rabbit. The research protocol was assessed by the Animal Care and Use Committee (ACUC) Universitas Airlangga and registered on number 2.KE.161.07.2019. We performed a prospective *in vivo* test evaluating the histopathological thickness of intimal layer, thrombosis events, amount of stenosis, and NNT of mesenteric artery compared to mesenteric vein as xenografts for four weeks. There were 32 rabbits which were divided into two groups double blindly, bovine mesenteric artery group and bovine mesenteric vein group. Each group consists of 16 grafts, implanted to *Oryctolagus cuniculus* carotid artery. This study inclusion criteria were rabbit with the species New Zealand Rabbit (*Oryctolagus cuniculus*), gender of male rabbits, about 6 months old rabbit, healthy rabbits (weight 3-4 kg). Exclusion criteria was test animals that die before starting the treatment process. The research design as following diagram in figure 1.

The histopathology of intimal layer thickness, thrombosis events, and amount of graft stenosis were evaluated four weeks later and was measured statistically by using SPSS.

## 3. RESULTS

The patency of bovine mesenteric artery and vein was collected by measuring the thickness of intimal layer, thrombosis events and amount of stenosis. The thickness of intimal layer of bovine mesenteric artery was increased significantly after four weeks implantation ($p<0.00$) and so was bovine mesenteric vein ($p<0.00$). The histopathology of bovine mesenteric artery and vein could be seen in figure 2 and 3 below. But there was no significant different comparing to bovine mesenteric artery and vein after four weeks ($p=0.083$) (Table 1.)There was no thrombosis formation in bovine mesenteric artery and vein xenograft. Bovine mesenteric artery graft tend to less become stenose, compared to bovine mesenteric vein (87,5% vs 50%) but there is no significant different statistically ($p=0.054$) (Table 2.)

Then, the researcher also calculated the risk of stenosis between bovine mesenteric artery and vein by using Number Needed to Treat (NNT). The formula of NNT as follow :

**NNT = 1/ARR**

**ARR = % of vein stenosis - % of artery stenosis**
**ARR = Absolute Risk Reduction**

From that formula, the researcher obtained that bovine mesenteric vein xenograft has a risk of stenosis 3 times greater than bovine mesenteric artery xenograft.

## 4. DISCUSSIONS

The use of vascular bioprosthesis graft has been started in 1970s by using bovine pericardium preserved with glutaraldehyde. The result of first attempt was unsatisfied because it formed some complications such as massive neointimal hyperplasia and degeneration of the tissue. Other researchers used bovine carotid artery, replacing bovine pericardium as xenograft with the same result. Then, the research of vascular bioprosthesis especially in bovine vascular developed in advance [6].

From this study's result, the bovine mesenteric vein seemed to have more thicken intimal layer than the artery but there is no significant different statistically. This was probably due to different mechanism. In vein, the thickening of the intimal layer was thought by increasing shear stress which led more trauma on the intimal layer. The traumatic venous intimal layer reduced prostacyclin and heparin sulphate, which could inhibit vascular smooth muscle cell (VSMC), produced by tunica media of the vessel. The proliferation of VSMC became exaggerated and then migrated and accumulated in the intimal layer. The accumulation of VSMC in intimal layer gave signal to the intimal cell to produce more extracellular matrix which was more thickened the intimal layer and ultimately could block the lumen of the vein [7]. In this study, we found there was no any thrombus formation in both bovine mesenteric artery and vein xenograft group. This result was in line with Manduz et al, which stated that only two of seven bovine mesenteric vein xenograft had thrombus. It was probably due to technical error in anastomosis site or lack of distal run-off [8]. It was also consistent with Knapp et al that bovine xenograft was lesser had thrombus formation than synthetic graft [9].

In artery, the mechanism of thickening intimal was little bit different from vein and was thought due to destruction of some parts of the endothelium by accumulation of lipid which led to atherosclerosis so that the proliferation of VSMC was not as much as vein[10]. Beside atherosclerosis, the other factors could be considered. In the study conducted by Morrison et al in Brazil showed that bovine mesenteric artery was lesser to form some complications such as thrombosis and neointimal hyperplasia. It was thought there were multifactorial mechanical stress that induced the formation of thrombosis and intimal hyperplasia. If the vessel became more stiffness, it would increase the shear stress to the endothelial cell and made a site of injury so that thrombosis would develop. Beside the stiffness of the vessel wall, the changing of blood flow should be considered because if the blood flow became turbulent, it would also make more shear stress to the wall and ultimately the formation of neointimal would happen.

This research also showed bovine mesenteric vein was more likely to become stenose than bovine mesenteric artery. The hemodynamic different between artery and vein played important role to the intimal wall. Naturally, intimal vein wall subjected to low flow with low shear stress. In this research, the vein was used as graft implanted to carotid artery which was

high flow. After implantation, blood flowed from artery to the vein, then intimal wall of the vein received high pressure blood flow circumferentially and made more shear stress which generated the intimal wall hyperplasia [11].

## 5. CONCLUSION

The conclusion of this study was bovine mesenteric artery vascular graft had better patency than bovine mesenteric vein vascular graft. Further research should be done in bovine mesenteric artery with decellularized process continued with cellularization process by seeding endothelial cell (ECs) and vascular smooth muscle cells (VSMCs) to get better characteristics of intraluminal layer and vascular wall.

## 6. ACKNOWLEDGMENT

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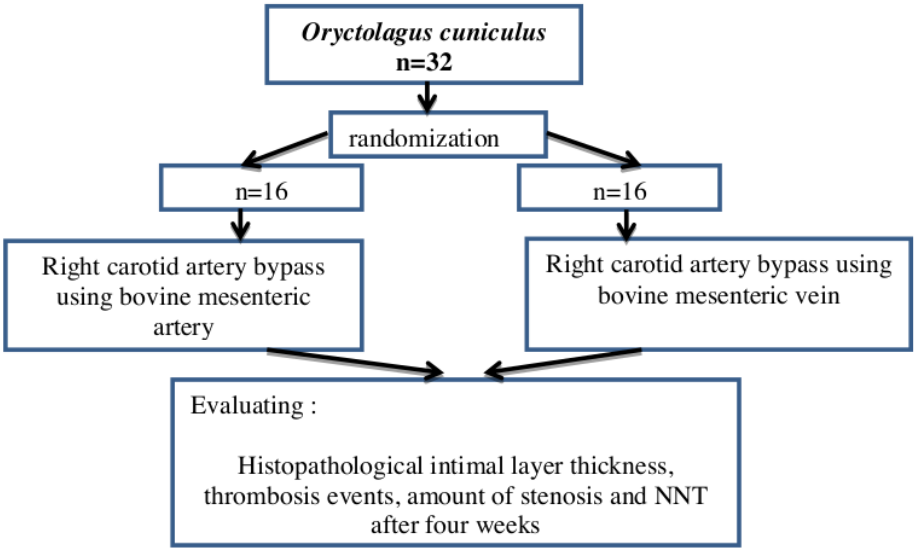


Figure 1. Experimental study design of bovine mesenteric artery and vein as xenograft

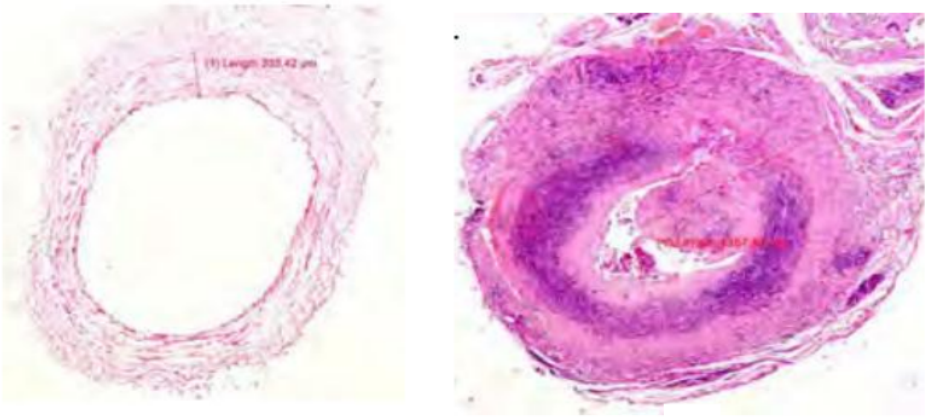

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Figure 2. The histopathology of bovine mesenteric artery (a) before and (b) after four weeks implantation

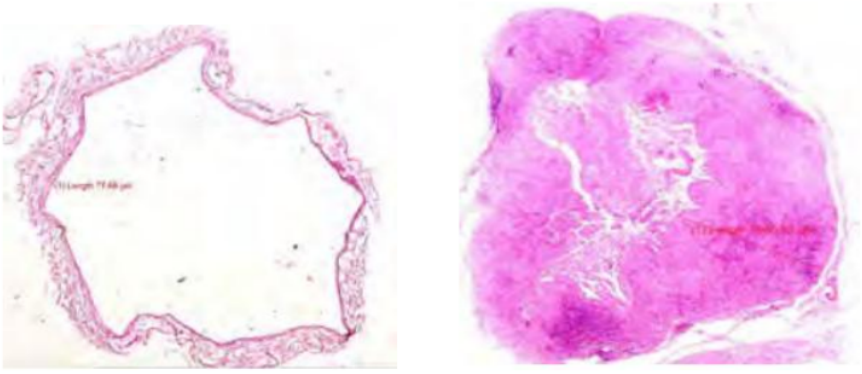

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Figure 3. The histopathology of bovine mesenteric vein (a) before and (b) after four weeks implantation.

Table 1. Thickness of Intimal Layer Results

| | **Thickness of intimal layer ($\mu$m)** | | **p value** | **p value** |
|---|---|---|---|---|
| | **Before implantation** | **After implantation** | | |
| **Bovine mesenteric artery** | 245.0±67.9 | 971.2±474.4 | p<0.00 | p=0.083 |
| **Bovine mesenteric vein** | 77.0±22.6 | 709.2±339.7 | p<0.00 | |

Table 2. Amount of Stenotic Results

| | **Variables** | **Bovine mesenteric artery** | **Bovine mesenteric vein** | **p value** |
|---|---|---|---|---|
| **Stenosis** | Stenosis (%) | 2/16 (12.5) | 8/16 (50) | 0.054 |
| | Patent (%) | 14/16 (87.5) | 8/16 (50) | |

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