# SKIN MICROVASCULAR PERFUSION CHANGE WITH ARTERIOVENOUS FISTULA CREATION IN CHRONIC KIDNEY DISEASE

**BY**
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# ABSTRACT
# ABSTRAK

# Abstract

Introduction:

Matured native arteriovenous fistula (AVF) is an optimal vascular access for supporting the haemodialysis blood circuit. Maturation of AVF involved complex vascular remodeling including shunting of blood flow from arterial system toward the low resistance venous limb. In this study, we would like to evaluate the change of skin microvascular perfusion over the extremity with AVF maturation by using laser doppler flowmetry.

Method:

Total of 45 consented patients with chronic kidney disease (CKD) Stage IV-V who underwent AVF creation over upper extremity from July 2014 to Jun 2016 at Hospital Universiti Sains Malaysia were included in this study. The measurement of skin microvascular perfusion was done with laser doppler flowmetry pre-operative and post operative day 1, week 2, week 6 and week 12. Assessment of AVF maturation was done by 6 weeks.

Result:

Thirty-two patients with mean age of 55.6 (20 male, 12 female) had achieved AVF maturation. There were 13 (40.6%) radial-based and 19 (59.4%) brachial-based AVF. There was 32.8% reduction of mean skin perfusion distal to the fistula by day 1 compare to baseline perfusion but perfusion increased back by 47% by Week 2 compare to day 1 and no dramatic change upon AVF maturation. At the area proximal to anastomosis AVF, there was increasement of

mean skin perfusion over 12 weeks with 35.8% at day 1 from baseline. However, the change of mean skin perfusion was not statistically significant. There was also no significant relation of skin perfusion change with the type of fistula, diabetes mellitus, hypertension and hyperlipidemia.

Conclusion:

Laser doppler flowmetry successfully detected the subclinical change of skin microvascular perfusion relation with AVF creation and maturation. Reduction of skin perfusion distal to the fistula suggested that in patients with existing perfusion inadequacy of extremities may experiences ischemic symptom as early as day 1 post operation and need close monitoring for distal limb ischemic-related complications.

# Abstrak

Pengenalan

Arteriovenous fistula (AVF) adalah akses vaskular optimum untuk menyokong proses hemodialisis. Kematangan AVF melibatkan perubahan kompleks kepada salur darah termasuk pengaliran darah daripada sistem arteri yang bertekanan tinggi ke sistem vena yang mempunyai rintangan yang rendah. Dalam kajian ini, kami ingin menilai perubahan perfusi mikrovaskular kulit di bahagian tangan berhubungan dengan kematangan AVF dengan menggunakan laser doppler flowmetry .

Metodologi

Seramai 45 pesakit dengan penyakit buah pinggang kronik ( CKD ) peringkat IV- V yang menjalani pembedahan AVF dari Julai 2014 hingga Jun 2016 di Hospital Universiti Sains Malaysia telah dimasukkan dalam kajian ini. Pengukuran perfusi mikrovaskular kulit telah dilakukan dengan laser doppler flowmetry pra-pembedahan dan selepas pembedahan pada hari pertama , minggu ke-2, minggu ke-6 dan minggu ke-12. Kematangan AVF telah dinilai pada minggu ke-6 selepas pembedahan.

Tiga puluh dua pesakit dengan purata umur 55.6 (20 lelaki, 12 perempuan) telah mencapai kematangan AVF. Terdapat 13 (40.6 %) AVF berdasarkan radial arteri dan 19 (59.4 %) AVF berdasarkan brachial arteri. Penurunan sebanyak 32.8% perfusi kulit distal pada fistula pada hari pertama selepas pembedahan berbanding dengan perfusi pra-pembedahan, tetapi perfusi meningkat semula sebanyak 47% pada minggu

ke-2 berbanding dengan hari pertama dan didapati tiada perubahan dramatik apabila AVF mecapai kematangan. Di bahagian kulit proksimal dari anastomosis AVF, terdapat peningkatan perfusi kulit sepanjang 12 minggu dengan 35.8 % penigkatan pada hari pertama berbanding dengan pra-pembedahan. Walau bagaimanapun, perubahan perfusi kulit tidak signifikasi secara statistik. Perubahan perfusi kulit dengan jenis fistula , kencing manis , darah tinggi dan hyperlipidemia tidak signifikan secara pengiraan.

Kesimpulan

Laser doppler flowmetry telah berjaya mengesan perubahan perfusi mikrovaskular kulit yang subklinikal berhubung dengan penciptaan dan kematangan AVF. Pengurangan perfusi kulit distal pada fistula mencadangkan bahawa golongan pesakit yang mempunyai kekurangan perfusi pada bahagian tangan sebelum pembedahan boleh mengalami gejala iskemia seawal hari pertama selepas pembedahan dan pemerhatian rapi diperlukan untuk mengelakkan komplikasi iskemia yang berkaitan dengan AVF.

# 1.0

# INTRODUCTION

# 1.0 Introduction

## 1.1 Chronic kidney disease and arteriovenous fistula

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## 1.1 **Chronic kidney disease and arteriovenous fistula**

### *1.11 Chronic kidney disease – Epidemiology & classification*

Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate lower than 60 mL/min per 1·73 m2 for 3 months or longer, and proposed a classification scheme based on glomerular filtration rate.(NKF-DOQI 2002) End-stage renal disease (ESRD) can be defined by the requirement for life-saving dialysis or kidney transplantation. Worldwide, the number receiving renal replacement therapy (RRT) is estimated at more than 1.4 million, with incidence growing by approximately 8% annually.(Aileen *et al*, 2005) In Malaysia, the intake of new dialysis patients from 1993 to 2012 showed exponential increase from 358 in 1993 to at least 5830 in 2012. In 2012, the total number of patients receiving dialysis was 28590, and reported that number of hemodialysis patients was 26067 including 5121 new cases.(Lim YN *et al.*, 2012) Diabetic mellitus and hypertension remained as the main causes of primary renal disease accounting for 58% and 11% of new dialysis patients respectively in 2012.(Lim YN *et al.*, 2012)

For the staging of CKD, NKF-KDOQI (National Kidney Foundation – Kidney Disease Outcomes Quality Initiative) classification is commonly practice. There are Stage 1 to Stage 5 CKD. The classification (Table 1) is based on GFR (level of kidney function), pathological changes (kidney damage) and presence of abnormality for at least three months.

Table 1 Staging of Chronic Kidney Disease

| Stages of CKD | | |
|---|---|---|
| Stage | GFR (ml/min/1.73m$^2$) | Description |
| 1 | ≥ 90 | Normal or increased GFR with other evidence of kidney damage |
| 2 | 60-89 | Slight decrease in GFR, with other evidence of kidney damage |
| 3A | 45-59 | Moderate decrease in GFR, with or without other evidence of kidney damage |
| 3B | 30-44 | |
| 4 | 15-29 | Severe decrease in GFR, with or without other evidence of kidney damage |
| 5 | <15 | Established renal failure |

The respective suffices should be added:

- Suffix 'p' if overt proteinuria present
- Suffix 'd' if patients on dialysis
- Suffix 't' if patients has been transplanted

(Adapted from National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S000, 2002.)

*1.12 Autologous arteriovenous fistula in chronic kidney disease*

Vascular access remains as the key component to achieve safe and effective haemodialysis. There are three principles form of vascular access including autogenous arteriovenous fistula (AVF), prosthetic arterivenous graft and central venous catheter insertion. The autogenous arteriovenous access for dialysis had been showed to be superior to prosthetic graft or catheter access in term of patient's morbidity and mortality.(Ascher E *et al.*, 2000; Murphy GJ *et al.*, 2000)

An autologues arteriovenous fistula creation is a surgical procedure involving the anastomosis of adjacent artery (high pressure system) and vein (low pressure

system). The techniques of anastomosis are either side-to-side, end-to-end and side-to-end depending on its suitability and surgeons' preference. Once the arterivenous fistula is created, fistula need to be matured before it can be used for haemodialysis. Process of fistula maturation will be further discussed.

According to guidelines, patient should be referred for creation of AVF when the serum creatinine concentration exceeds 4mg/dl and estimated GFR is ≤ 25ml/min. ((NKF-DOQI, 1997; 2006). Prior to creation of arterivenous fistula (AVF), patients will be access clinically and intructed to preserve the vein over the forearn by surgeons. Preoperative Duplex sonography for venous mapping is gaining its popularity. Silva (Silva MB Jr *et al.*, 2000) reported that preoperative measurement of arterial diameter, resistance index and venous diameter would help in predicting the outcome of the AVF.

### *1.13 Maturation of arteriovenous fistula*

Once the arterivenous fistula is created, fistula need to be matured before it can be used for haemodialysis. In most of studies, the clinical criterias are used to define fistula maturation. New vascular guideline from National Kidney Foundation-kidney Dialysis Outcomes Quality Initiative recommended that matured AVF should fullfilled some parameters which including a diameter of vein greater than 0.6cm, flow over the venous limb greater than 600ml/min and located 0.6cm from the skin surface. However, Beathard et al(Beathard *et al.*, 2003) and Dember et al defined that a matured AVF need to be used for dialysis for three months and 4 months respectively.

Fistula maturation is a complex vascular remodeling process that requires vessel dilation, marked increases in blood flow rates in the feeding artery and draining vein, and structural changes in the vessel walls (Asif *et al.*, 2006; Dixon, 2006). Maturation of fistula involved changes in haemodynamic, anatomical, molecular and functional level.

For the anatomical changes, vessels dilatation occurs as the response of increasing shear stress on the vessel wall post AVF creation. These changes were demonstrated by Corpataux JM et al (Corpataux *et al.*, 2002). The internal diameter of the cephalic vein post anastomosis was progressively increased from post op week 1 to week 12. Whereas, the shear stress was raised at initial phase postoperatively and inversely return to normal by 12 weeks by vessel remodelling. There was also a change in the wall cross sectional area of cephalic vein with excentric hyperthrophy (Mulvany, 1999). In addition, the feeding artery proximal and distal to anastomosis will be dilated too.

At biological level, high shear stress rate result in endothelial cell survival and alignment of endothelial cells. Secretion of substances such as nitric oxide (NO) and prostacyclin promotes vasodilatation and inhibit thrombosis (Joannides R *et al.*, 1995; Guzman RJ *et al.*, 1997; Ballerman BJ *et al.*, 1998). Endothelial cells up-regulated the gene for G protein and cytosolic calcium and increased phosphorylation of endothelial synthase (Guzman RJ *et al.*, 1997). The NO causes vascular smooth muscle cell (VSMC) relaxation and vascular dilatation by stimulating guanyl cyclase and

formation of cyclic guanosine mnophospahte (cGMP) (Konner *et al.*, 2003). Other mediators including matrix metalloproteinases (MMPs), transforming growth factor beta (TGF-B), platelet derived growth factor (PDGF) and basic fibroblast growth factor are also playing the role in shear test mediated vascular dilation(Singh TM *et al.*, 1998; Sho E *et al.*, 2002). MMPs cause matrix digestion and reorganization, achieving additional vessels dilatation (Guzman RJ *et al.*, 1997). Diabetes mellitus, hypertension and chronic kidney disease had been shown to have impair microvascular reactivity in previous study (E *et al.*, 1991; M *et al.*, 2006; M *et al.*, 2007).However, Korsheed reported that cases of successful created arteriovenous fistula in patients with endothelial dysfunction. (Korsheed *et al.*, 2013)

Once AVF created surgically, blood from the high pressure feeding artery will flow toward the low resistance vein. Kwun et al (Kwun BS *et al.*, 1979) reported that 73% of radiocephalic arteriovenous fistula (RCF) and 91 % of branchial-axillary with prosthetic graft (8mm) demonstrated reversed flow in the artery distal to fistula creation. The diversion of blood flow in AVF can be transient or prolonged and lead to tissue ischemia. Whereas, Sivanesan et al (Sivanesan *et al.*, 1998) showed that the blood flow in the distal radial artery based on measurement taken intraoperative and post-operative 1 day was retrograde in 77% (23 out of 30 RCF) and antegrade in 23% (7 out of 30 RCF). In the retrograde flow group, the contribution of blood flow to fistula was decreased from 31 ± 16% (intraoperative) to 26 ± 15% (Postoperative day 1). In the antegrade flow group, the blood flow from the proximal to distal radial artery decreased from 25 ± 14% to 19 ± 13% due to shunting of blood flow toward

low resistance venous limb. However, no patients was reported to experience ischeamic symptom regardless the direction of flow over the distal artery.

In this study, we are interested to evaluate the change of skin microvascular perfusion over proximal and distal extremity post arteriovenous fistula creation and maturation.

## 1.2 Skin microcirculation – Anatomy of skin blood supply

Skin microvascular perfusion is related to its vascular plexuses which included subepidermal plexus, dermal plexus and subdermal plexus. All these plexuses are receiving the blood supply from the deep vessels and via interconnecting vessels - fasciocutaneous vessels and musculocutaneous vessels. Blood flow to the skin can be affected by the intraluminal blood pressure based on the myogenic theory, neural innervation, humoral factors and temperature. Alteration of any of these factors in physiological or pathological states may lead to increase or decrease in the skin perfusion.

Many studies had been carried out to measure the skin perfusion via various methods including the dynamic capillaroscopy, isotope technique, percutaneous measurement of partial oxygen pressure, fluorescence videomicroscopy, skin temperature measurement, videodensitometry and laser Doppler flowmetry. All these studies had contributed to our knowledge of physiology of skin microcirculation and pathophysiology of various disease.(Bongard O *et al*., 1993)

In our study, laser Doppler fluximetry (LDF) will be used to measure the skin microvascular perfusion and function of patients post brachial –based or radial-based arteriovenous fistula creation. More details regarding the LDF will be discussed under section 3.0.

## 1.3 Laser Doppler fluximetry (LDF) – its development and clinical application

Laser Doppler fluximetry (LDF) is a non-invasive, safe and reliable method to assess the microvascular perfusion of skin. It can provide continuous or near-continuous record.(Yvonne-Tee *et al.*, 2005)

LDF applied the concept of Doppler effect. The Doppler effect was discovered by Christian Johann Doppler, an Austrian physicist and mathematician, is defined in Dorland's Medical dictionary as "the relationship of the apparent frequency of waves, as of sound, light and radio waves, to the relative motion of the source wave and the observer, the frequency increasing as the two approach each other and decreasing as they move apart." (Dorland, 1998) Therefore, the basic principles of LDF are as below: A beam laser light is directed by an optical fiber to the probe head. When the probe head is applied to the skin, the light will penetrate to a depth of skin approximately 1-2mm. The laser light is shifted in frequency when it is scattered by the static tissue and some scattered by moving red blood cells. The total backscattered light from tissue will be detected by the photodetector, and the voltage output, which contain the Doppler frequency information is obtained. The resulting photocurrent can be processed and expressed as flux, concentration and speed parameters relating to red blood cell.(Swiontkowski MF, 1991; Hee CE, 1995)

"Flux" is a parameter related to the products of velocity and concentration of red blood cells in the tissue sample volume. It is the most widely used parameter for laser publication. "Concentration" is the parameter reflected the number of moving red

blood cells in the tissue sample volume. “Speed” is the parameter for average velocity of the red blood cell. In addition, “temperature” of measured tissue can be recorded if a temperature probe is used.

Traditional laser Doppler flowmeters consist of helium-neon (He-Ne) laser of wavelength 632.8 nm.(Bircher A *et al.*, 1994) Nowadays, semiconductor laser diodes with near-infrared light of 780nm wavelength had been used as the light source. The differences are the laser diode flowmeter are available as multichannel instruments and the light can penetrate more deeply than He-Ne light which is about 1-2mm below the skin surface.(Vongsavan N *et al*., 1993) Optical arrangements also played as important role for sampling depth and accuracy.

The use of laser Doppler flowmetry for blood flow measurement in retinal vessels for rabbits was first presented by Riva et al,(Riva C *et al.*, 1972) subsequently in 1975, Stern demonstrated the laser Doppler technique for assessment of skin blood flow in human.(Stern, 1975) Nowadays, laser Doppler flowmetry/fluximetry is widely use in medical field especially in dermatopharmacological field for various purposes. In surgical field, lasser doppler flowmetry/fluximetry is well establised to be used to monitor flaps, replants, wound healing, burn depth and tissue expander monitoring.

In our study, laser Doppler flow monitor – Moor Instrument DRT4 will be used together with 2 skin probes – VP1T/7 for skin perfusion measurement. We believed that LDF would be able to detect the change of skin microvascular perfusion in relation with AVF creation and maturation.

# 2.0

# STUDY PROTOCOL

## 2.1 Document submitted for ethical approval

**DISSERTATION PROPOSAL**

# Microvascular Perfusion and Endothelial Function Changes with Arteriovenous Fistula Creation in Chronic Kidney Disease


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