The Effect of Hyperfiltration on Kidney Function in Living Donor Kidney Transplantation: A Prospective Cohort Study

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ABSTRAK

Latar belakang: *donasi ginjal dengan donor hidup merupakan prosedur medis yang aman. Kualitas hidup donor merupakan luaran utama dan dicapai melalui hiperfiltrasi ginjal yaitu mekanisme kompensasi untuk mempertahankan fungsi ginjal setelah nefrektomi unilateral. Penelitian mengenai hiperfiltrasi ginjal pada donor hidup masih terbatas. Penelitian ini bertujuan untuk menjelaskan mekanisme hiperfiltrasi ginjal termasuk dampaknya terhadap fungsi ginjal dalam 30 hari setelah nefrektomi, serta mengevaluasi keamanan donasi ginjal.* ***Metode:*** *desain penelitian ini adalah kohort prospektif yang diikuti oleh 46 orang donor hidup pada April hingga Desember 2019. Fungsi ginjal 30 hari setelah nefrektomi dievaluasi melalui estimasi laju filtrasi glomerulus (LFG) dan rasio albumin-kreatinin. Subjek penelitian dikelompokkan berdasarkan luaran pada hari ke-30, menjadi kelompok adaptif (LFG > 60 mL/menit/1,73 m^2) dan maladaptif (LFG < 60 mL/menit/1,73 m^2). Pemeriksaan resistive index (RI) ginjal, vascular endothelial growth factor (VEGF), neutrophil gelatinase-associated lipocalin (NGAL) dan heparan sulfat (HS) dilakukan secara serial sejak sebelum nefrektomi hingga 30 hari setelahnya. Luaran dianalisis dengan analisis multivariat.* ***Hasil:*** *empat puluh orang donor dianalisis hingga akhir, sebagian besar merupakan perempuan (67,5%). Rerata usia dan indeks massa tubuh (IMT) subjek berturut-turut adalah 45,85 (SB 9,74) tahun dan 24,36 (SB 3,73) kg/m^2. Sembilan belas donor (47,5%) mengalami hiperfiltrasi maladaptif. Proses hiperfiltrasi ditunjukkan oleh perubahan bermakna pada RI arteri ginjal serta kadar VEGF, NGAL dan HS urin (p<0,005). Tidak ada perbedaan bermakna masing-masing parameter antara kelompok adaptif dan maladaptif. Faktor perancu (IMT > 25 kg/m^2, hubungan donor-resipien, usia > 40 tahun dan kekakuan arteri) secara bermakna memengaruhi hiperfiltrasi ginjal (p<0,05).* ***Kesimpulan:*** *proses hiperfiltrasi tidak memengaruhi fungsi ginjal donor 30 hari pascanefrektomi. Berbagai faktor lain dapat memengaruhi proses hiperfiltrasi dan fungsi ginjal. Penelitian lebih lanjut diperlukan untuk mengevaluasi fungsi ginjal dalam jangka waktu yang lebih panjang.*

Kata kunci: *donor Hidup, heparan sulfat, hiperfiltrasi, neutrophil gelatinase-associated lipocalin, resistive index, transplantasi ginjal, vascular endothelial growth factor.*

ABSTRACT

Background: *living kidney donation is a safe medical procedure. Kidney function after donation is crucial for donors' health and quality of life. Kidney hyperfiltration is a compensatory mechanism, which will preserve kidney function after unilateral nephrectomy. The number of studies regarding hyperfiltration in living kidney donors is limited. Our study aimed to explain kidney hyperfiltration mechanism and evaluate its effect on the kidney function within 30 days after surgery.* ***Methods:*** *our study was a prospective cohort study with 46 living-kidney donors participating in the study between April and December 2019. We evaluated main outcomes, the 30-day post-surgery kidney function, which was evaluated by calculating estimated glomerular filtration rate (eGFR) and Urinary Albumin to Creatinine Ratio (ACR). The subjects were categorized into two groups based on their 30-day outcomes, which were the adaptive (eGFR > 60 mL/min/1.73 m^2 and/or ACR > 30 mg/g) and maladaptive (eGFR < 60 mL/min/1.73 m^2 and/or ACR > 30 mg/g) groups. A series of evaluation including calculating the renal arterial resistive index (RI) and measuring urinary vascular endothelial growth factor (VEGF), neutrophil gelatinase-associated lipocalin (NGAL), and heparan sulfate (HS) levels were performed before surgery and serially until 30 days after surgery. Multivariate analysis with adjustments for confounding factors was done.* ***Results:*** *forty donors were included and mostly were female (67.5%). The average age and body mass index (BMI) were 45.85 (SD 9.74) years old and 24.36 (SD 3.73) kg/m^2, respectively. Nineteen donors (47.5%) had maladaptive hyperfiltration outcomes. The hyperfiltration process was demonstrated by significant changes in renal arterial RI, urinary VEGF, NGAL, and HS levels ($p<0.005$). There was no significant difference regarding RI, urinary VEGF, NGAL, and HS levels between both groups. Several confounding factors (BMI over 25 kg/m^2, familial relationship, age over 40 years old, and arterial stiffness) were significantly influenced by kidney hyperfiltration and outcomes ($p<0.05$).* ***Conclusion:*** *the hyperfiltration process does not affect the 30-day post-nephrectomy kidney function of the donors. Several other factors may influence the hyperfiltration process and kidney function. Further study is necessary to evaluate kidney function and its other related variables with a longer period of time study duration.*

Keywords: *heparan sulfate, hyperfiltration, living-donor, neutrophil gelatinase-associated lipocalin, resistive index, kidney transplantation, vascular endothelial growth factor.*

INTRODUCTION

Kidney transplantation is an ideal treatment of choice for patients with end-stage renal disease (ESRD). Compared to lifetime dialysis, kidney transplant is associated with lower mortality and better quality of life.[1] Living kidney donation is considered to be a relatively safe procedure that does not harm donors in the long-term.[2-4] A compensating mechanism attempted by the remaining kidney is called hyperfiltration.[5] It occurs post-nephrectomy and will increase renal blood flow. Such mechanism is expected to preserve donor's kidney function.[6] However, the mechanism is not always successful. A failed hyperfiltration process is known as maladaptive hyperfiltration.[7] A study conducted by Choi[6] and Kwon.[8] reported that there were 40.38% and 55.8% donors, respectively, who developed chronic kidney disease (CKD) in 6 months period after kidney donation procedure. Unfortunately, none of these studies investigated the factors that affect the decreasing kidney function.

Adaptive and maladaptive hyperfiltration mechanisms are associated with renal blood flow and glomerular hypertrophy.[9,10] Renal blood flow is evaluated by using resistive index (RI)[11]; while glomerular hypertrophy is characterized by an increase in vascular endothelial growth factor (VEGF) level. VEGF is an important mediator in angiogenesis and a survival factor to maintain endothelial cells.[12] Nevertheless, it is still unclear whether changes in these parameters can significantly affect adaptive and maladaptive hyperfiltration. Schrijvers et al.[13] have reported that VEGF is related to glomerular and peritubular endothelial cells proliferation post-nephrectomy in animal models. To date, no study has been conducted on human urinary VEGF level in relation to post-uninephrectomy kidney hyperfiltration and its effects on adaptive and maladaptive hyperfiltration.

Renal function has also been associated with other factors related to nephrectomy including ischemic reperfusion injury and renal

cell hypoxia. Both of these conditions promote increased renal ischemic biomarkers levels such as neutrophil gelatinase-associated lipocalin (NGAL) and heparan sulfate proteoglycan.[14-16] These two biomarkers are also necessary to be tested in our study since changes in their levels can alter VEGF level.

Our study aimed to determine the incidence of maladaptive hyperfiltration in kidney donors within 30 days after nephrectomy. The study also aimed to compare RI, urinary VEGF, urinary NGAL, and urinary heparan sulfate proteoglycan levels between donors with adaptive and maladaptive hyperfiltration. Moreover, our research may provide basic profile of Indonesian living kidney donor transplantation that can be further utilized to develop kidney transplantation programs in Indonesia.

METHODS

Our study was a prospective cohort study, which was based on prognostic research program. The study was conducted at Cipto Mangunkusumo Hospital in Jakarta between November 2018 and February 2020. The inclusion criteria were living kidney donor patients aged older than 18 years old, who had agreed to participate in the study and had signed informed consent form; while the exclusion criteria were consistent with the National Consensus of Indonesian Society of Nephrology (InaSN) consist of functional or structural abnormality of kidney, uncontrolled hypertension, chronic diseases, alcohol and drugs abuse, viral infections, malignancy, pregnancy, psychosis or mental retardation, severe neurological deficiency or impairment, and other rare and or severe health condition. Total sampling method was used.

This study has been approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia on March 25th, 2019 (reference number KET-292/UN2.F1/ETIK/PPM.00.02/2019).

Serial examinations of calculating RI and measuring urinary VEGF, urinary heparan sulfate proteoglycan levels as well as performing routine blood test and urinalysis were carried out before nephrectomy and on day 1, 2, 3, 7 and 30 after nephrectomy. Urinary NGAL level was measured before and within 6 hours after nephrectomy. Renal resistive index (RI) was assessed using doppler ultrasonography (USG). Four main arteries were evaluated in our study, i.e. the renal artery, segmental artery, interlobar artery, and arcuate artery. Pulse wave velocity (PWV) measured using SphygmoCor® at the same time with initial measurement of blood pressure, height and weight. Samples for routine blood tests were obtained by phlebotomy; while samples for routine urinalysis were taken using mid-stream technique. Modification of diet in renal disease (MDRD) formula was used to determine donors' estimated glomerular filtration rate (eGFR). Measurement for urine biomarkers (VEGF, NGAL and heparan sulfate [HS]) levels were done using ELISA method with R&D Quantikine ELISA kit (Minnesota, USA) for urinary VEGF and NGAL, Cusabio ELISA kit (Wuhan, China) for urinary HS level. Subjects were then categorized into two groups, which were the adaptive group (subjects with eGFR >60 mL/min/1.73 m^2 and ACR <30 mg/g on day 30) and maladaptive group (subjects with eGFR <60 ml/min/1.73 m^2 and ACR >30 mg/g on day 30).

Shapiro Wilk test was used to determine data distribution. Numerical data were presented in average with standard deviation or median with minimum and maximum range. Categorical data were presented in frequency and percentage. Changes of RI, urinary VEGF, NGAL, heparan sulfate and also eGFR and ACR within both groups before and after nephrectomy were compared using paired T test for data with normal distribution and Wilcoxon test for non-normally distributed data. Values of each parameters between the two groups were compared using independent T test or Mann Whitney test. Subgroup analysis was performed to evaluate possible confounding factors including age of >40 years, BMI >25 kg/m^2, biological relationship to recipients and PWV of >8.33 m/s (50^{th} percentile). All statistical analyses were processed using SPSS software program version 20.0. Interim analysis was performed after six months of data collection. 25 subjects were included.

RESULTS

Forty-six living kidney donors were included. During the study, one patient refused to enroll

in the study and five patients were excluded due to lost to follow-up. Forty subjects, who were mostly female (27 donors, 67.5%), were included in the final analysis with average age of 45.85 years. Most donors were not biologically related to their recipients (55%). (**Table 1)**

Table 1. Donors' demographic, clinical and laboratory characteristics

Characteristics	Value (N=40)
Donor-recipient relationship, n (%)	
- Related	18 (45)
- Unrelated	22 (55)
Sex, n (%)	
- Male	13 (32.5)
- Female	27 (67.5)
Age (years), mean (SD)	45.85 (9.74)
Age group, n (%)	
- < 30 years old	1 (2.5)
- 30 – 39 years old	11 (27.5)
- 40 – 49 years old	14 (35)
- 50 – 59 years old	10 (25)
- > 60 years old	4 (10)
BMI (kg/m^2), mean (SD)	24.36 (3.73)
BMI group, n (%)	
- Underweight (<18.5)	1 (2.5)
- Normal (18.5 – 22.9)	16 (40)
- Overweight (23.0 – 24.9)	5 (12.5)
- Obese I (25.0 – 29.9)	14 (35)
- Obese II (> 30)	4 (10)
Systolic blood pressure (mmHg), median (min-max)	120 (90 - 145)
Diastolic blood pressure (mmHg), median (min-max)	80 (60 - 90)
Pulse wave velocity, (m/s), mean (SD)	8.52 (1.14)

Nineteen subjects (47.5%) were found to have maladaptive kidney function within 30 days after nephrectomy. GFR of both groups were more likely to decrease in day 1 and day 2 before rising on day 3 onwards. However, in subjects of maladaptive group, the increase in GFR was not at the same pace, which then resulted in failure of kidney function. There was a significant difference of GFR between adaptive and maladaptive groups (57.00 mL/min/1.73 m^2 vs. 70.10 mL/min/1.73 m^2; p< 0.001). In contrast, the ACR was not significantly different between both groups (18.46 vs. 10.10; p 0.055) (**Table 2**).

The cut-off value for GFR before the subjects underwent nephrectomy between adaptive and maladaptive group was 104.60 (76.2% sensitivity, 72.3% specificity) with Area Under Curve of 85.7% (CI 95% 74.3 – 97.1).

Despite several insignificant results of RI, there was a consistent trend found in renal, segmental, interlobar and arcuate arteries. (**Figure 1**)

The RI increased on day 2 following the nephrectomy before decreasing on day 7 and day 30. **Figure 2** shows significant RI difference of arcuate arteries between day 2 and day 30, which was found only in the adaptive group.

Our study found no significant difference regarding RI between adaptive and maladaptive groups as shown in **Table 3**.

Several results of factors affecting hyperfiltration mechanism are presented in

Tabel 2. Changes in eGFR and ACR between maladaptive and adaptive groups

Variables	Day	Maladaptive (n=19)	Adaptive (n=21)	p
eGFR (mL/min/1.73 m^2)	Dpreop, mean (SD)	92.94 (13.21)	111.17 (11.38)	<0.001
	D1, mean (SD)	64.06 (14.54)	80.20 (17.27)	0.003
	D2, median (min-max)	51.70 (27.10–74.80)	62.10 (49.70–131.00)	0.002
	D3, median (min-max)	55.80 (30.10–74.80)	64.30 (51.00–104.90)	<0.001*
	D7, mean (SD)	54.17 (9.37)	74.55 (15.23)	<0.001
	D30, median (min-max)	57.00 (41.10–71.10)	70.10 (60.10–119.10)	<0.001*
ACR	Dpreop, median (min-max)	16.50 (1.50–218.30)	9.10 (1.20–38.20)	0.062*
	D1, median (min-max)	72.05 (17.80–661.60)	49.10 (9.80–96.70)	0.114*
	D2, median (min-max)	58.90 (10.22–174.00)	39.70 (13.40–109.40)	0.020*
	D3, median (min-max)	41.95 (10.22–268.30)	38.10 (4.00–125.00)	0.465*
	D7, median (min-max)	31.90 (3.70–265.10)	12.50 (3.60–96.80)	0.186*
	D30, median (min-max)	18.46 (3.50–555.60)	10.10 (3.00–25.60)	0.055*

*Mann-Whitney Test

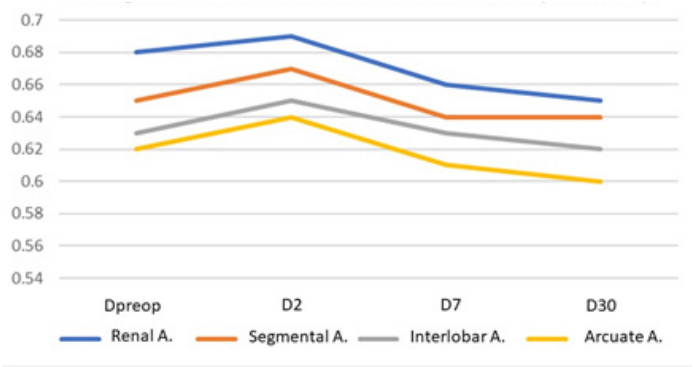

Figure 1. Changes in resistive index before and after nephrectomy.

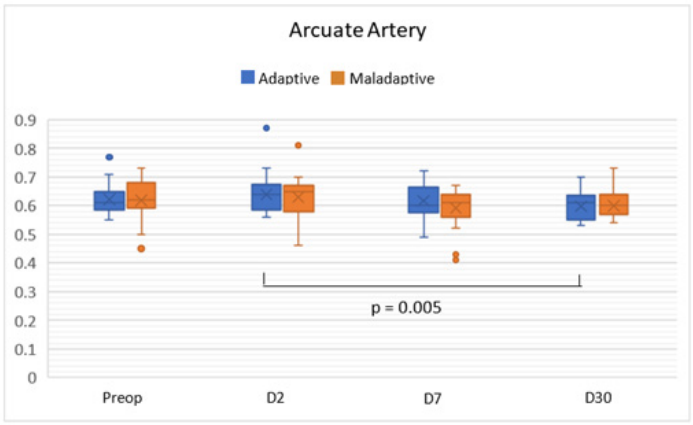

Figure 2. RI difference of arcuate arteries between day 2 and day 30.

Table 3. Changes in resistive index between adaptive and maladaptive groups

Resistive Index	Adaptive Hyperfiltration (n=20)	Maladaptive Hyperfiltration (n=19)	P
Pre-op, mean (SD)			
- A. Renal	0.68 (0.03)	0.68 (0.07)	0.91
- A. Segmental	0.65 (0.05)	0.65 (0.06)	0.89
- A. Interlobar	0.63 (0.05)	0.62 (0.06)	0.67
- A. Arcuate	0.62 (0.05)	0.62 (0.07)	0.89
D2			
- A. Renal	0.67 (0.63 – 0.80)	0.70 (0.06)	0.73*
- A. Segmental, mean (SD)	0.66 (0.06)	0.67 (0.07)	0.53
- A. Interlobar, mean (SD)	0.64 (0.06)	0.66 (0.07)	0.41
- A. Arcuate	0.64 (0.56 – 0.87)	0.63 (0.07)	0.65*
D7			
- A. Renal, mean (SD)	0.67 (0.06)	0.65 (0.05)	0.32
- A. Segmental, mean (SD)	0.64 (0.04)	0.63 (0.05)	0.46
- A. Interlobar, mean (SD)	0.64 (0.06)	0.62 (0.05)	0.37
- A. Arcuate	0.62 (0.06)	0.61 (0.41 – 0.67)	0.23*
D30			
- A. Renal, mean (SD)	0.66 (0.05)	0.65 (0.08)	0.45
- A. Segmental, mean (SD)	0.64 (0.04)	0.63 (0.07)	0.31
- A. Interlobar, mean (SD)	0.61 (0.06)	0.62 (0.07)	0.78
- A. Arcuate	0.60 (0.05)	0.60 (0.06)	0.88

*Mann-Whitney Test

Tabel 4. Changes in urinary VEGF, NGAL, and heparan sulfate levels in maladaptive and adaptive groups.

Biomarker	Adaptive (n = 21)	Maladaptive (n = 19)	p
VEGF (pg/mL), median (min-max)			
- Prenephrectomy	20.31 (8.67–112.20)	26.91 (9.54 – 298.60)	0.371
- D22	173.40 (20.98–670.15)	221.40 (30.84 – 970.86)	0.250
- D7	31.25 (9.05–299.35)	45.39 (7.85 – 414.55)	0.147
- D30	19.67 (4.76–1051.44)	62.50 (8.01 – 2244.5)	0.129
NGAL (ng/mL), median (min-max)			
- Prenephrectomy	4.5 (0.80–43.30)	4.9 (1.00–68.50)	0.809
- D1	9.40 (1.20–214.90)	11.20 (0.90–46.30)	0.450
Heparan Sulfat (ng/mL), median (min-max)			
- Prenephrectomy	13.30 (5.53 – 400.00)	11.52 (5.76 – 82.14)	0.461
- D2	12.148.84 (294.16 – 3.2745.52)	14.287.96 (1136.22 – 28.801.69)	0.425
- D7	193.94 (9.69 – 8.379.05)	122.66 (11.56 – 9.020.03)	0.857
- D30	33.71 (6.67 – 916.35)	58.45 (6.45 – 468.46)	0.881

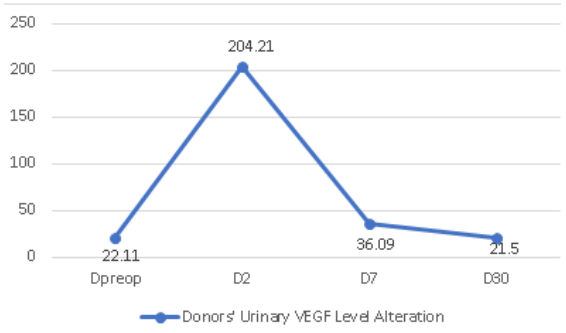

Figure 3. Changes in urinary VEGF levels before and after nephrectomy.

the following tables. A surge of urinary VEGF level on the second day after nephrectomy is demonstrated in **Figure 3**.

VEGF levels rose significantly on day 2 following the nephrectomy ($p<0.001$) before decreasing on day 7 and day 30 nearly to the baseline. Not with standing the statistically insignificant results (**Table 4**), urinary VEGF levels in maladaptive group were likely to be higher compared to those in the adaptive group.

Urinary NGAL and HS levels significantly increased after nephrectomy in both groups ($p<0.001$). Urinary NGAL level was insignificantly higher in maladaptive group. The median of urinary NGAL level before nephrectomy was 4.5 mg/mL and the level significantly rose ($p <0,001$) within four to six hours after nephrectomy (up to 11.00 mg/mL). The median urinary HS level was 12.41 ng/mL. Urinary heparan sulfate levels on day 2, 7 and 30 were found to be significantly higher compared to initial pre- nephrectomy level ($p<0,001$). Changes in urinary NGAL and HS levels. (**Table 4)**

Using a subgroup analysis method, there were four adjustments that had been made based on possible confounding factors (age, donor-recipient relationship, arterial stiffness and BMI). These factors were adjusted to the following parameters below in order to evaluate their correlations ($p<0.05$):

1. Renal artery resistive index before and after nephrectomy
2. Urinary VEGF level before and after nephrectomy
3. Urinary NGAL level before and after nephrectomy
4. Urinary HS level before and after nephrectomy
5. eGFR prior to surgery and after 30 days post nephrectomy
6. ACR prior to surgery and after 30 days post nephrectomy.

BMI >25 kg/m^2 is associated with lower VEGF level on day 7 post surgery. Age over 40 years old, Biological relation related to their recipients and higher PWV are several factors that give rise to lower kidney function. Higher PWV is related to renal artery RI on day 1 and day 7 post-nephrectomy.

DISCUSSION

Based on the donor's characteristics, the proportion of biologically-related donor is lower compared to unrelated donor (45% and 55%, respectively). Our findings differ from previous studies.[17,18] The average age of donors in our study was 45.85 years (SD 9.74). There were 13 donors (32.5%) aged over 50 years old. Older donor age is correlated to strict evaluation and comorbidities.[18]

Subjects in this study are dominated by female donors (67.5%). A study by Bloembergen, et al.[19] reported the same finding in which living kidney donors were dominated by female (RR 1,28, $p < 0.001$). Several underlying reasons that may affect one's decision in organ donations are socioeconomic status, various understanding levels of organ donation, family background and psychological ties, influences from family opinions, religion, culture, and belief in medical procedures for organ donation affect.[19]

The average BMI of our subjects was relatively high, i.e. 24.36 kg/m^2 (SD 3.73), which fell in the overweight category based on the Asia-Pacific WHO BMI classification.[20] Living donors with obesity tend to have higher risk of post surgery complications, longer inpatient recovery time, infection, hypertension and lower kidney function. Donors with BMI >35 kg/m^2 are not recommended to proceed undergoing transplantation procedure.[21]

Arterial stiffness was measured using PWV and it was concluded that average PWV in donors of our study was higher than normal population (7.2 m/s). Cited from Fesler et al.[22], we know that living kidney donors with higher PWV tend to show lower chance of successful adaptive hyperfiltration process after uninephrectomy.

Regarding changes in eGFR and ACR, at the end of our study, we found that there were significant difference between the two groups. Significant difference was only found in eGFR (57.00 mL/min/1.73 m^2 vs. 70.10 mL/min/1.73 m^2) with $p < 0.001$. On the other hand, ACR was not significantly different between both groups (18.46 vs. 10.10; $p = 0.055$). Our result is in line with results demonstrated by Yoon et al.[23] study.

The hyperfiltration mechanism was evaluated by calculating 30-day post-surgery eGFR and ACR. Donors who had eGFR < 60 mL/min/1.72 m^2 and/or ACR > 30 were categorized as having maladaptive hyperfiltration. Prior to nephrectomy, eGFR level in maladaptive group was significantly lower compared to the adaptive group. Therefore, initial kidney function is a key factor to determine success of hyperfiltration process. The cut-off point for initial kidney function in our study was 104.60 ml/min/1.73 m^2. Donors who initially had lower eGFR than the cut-off point would develop higher risk for having eGFR < 60 mL/min/1.73 m^2 within 30 days after nephrectomy. Such findings are in line with results of a study conducted by Kwon et al.[8] Moreover, Kwon et al mentioned that the results from 30 days after nephrectomy will predict long-term kidney function. Donors with low kidney function within a month after surgery tend to develop CKD.

The increase in RI on day 2 after nephrectomy, which was then followed by reduction on day 7 and day 30 after nephrectomy in our study, showed that there were changes in blood flow following the nephrectomy.[24] Increase of RI on day 2 after surgery was caused by increase of renal blood; while renal vascular resistance dominantly decreased in systolic compared to diastolic components.[25] This mechanism is caused by vascular relaxation triggered by nitric oxide (NO), a vasodilator which is increasing on day 2 after nephrectomy and decreasing after the first week.[26,27] There was no significant difference regarding RI between adaptive and maladaptive groups, which suggests that RI has no effect on kidney function within 30 days after nephrectomy. However, a significant difference of RI of arcuate artery between day 2 and day 30 in adaptive group suggests that prolonged increased of RI may be associated with lower kidney function.

Arcuate artery is the ideal location to evaluate alteration of RI in donors after nephrectomy. Anatomically, arcuate artery is closest to glomerulus; therefore, any disturbance in glomerulus will be reflected better in arcuate artery than in any other location.[28] However, there was a statistically insignificant trend of RI alteration in both groups, which then lead to a conclusion that RI does not affect kidney function within 30 days after nephrectomy.

The alteration of urinary VEGF level after nephrectomy is considered to be associated with ischemic injury and renal cells hypoxia, as well as hypertrophic response of renal cells. Ischemic-related surge of VEGF may take place within 1-2 hours; while hypertrophy-related surge of VEGF normally takes place during the first two days.[29-31]

Our study could not provide evidences that the increase of VEGF level was caused by ischemia. However, the increase was probably related to hypertrophic response of renal cells.[13,32] Moreover, there was no significant difference of urinary VEGF levels between adaptive and maladaptive group. The result suggests that urinary VEGF level as a marker of hyperfiltration does not affect kidney function within 30 days after nephrectomy.

The increase in urinary NGAL level after nephrectomy suggests that there is hyperfiltration-related acute kidney injury;[33] however, it has no association to kidney function within 30 days after nephrectomy. Heparan sulfate proteoglycan level, which increased on day 2 after nephrectomy, is associated with ischemia. However, as there were no significant differences between the adaptive and maladaptive groups, the surge was hypothesized to be a physiologic response and did not cause any decline in kidney function.

Using subgroup analysis to adjust the results based on several confounding factors, the donors who are over 40 years old tend to have lower kidney function. The result might be associated with age-related decline of vascular compliance, which in turn affects hypertrophic response.[34,35] Donors who are biologically related to the recipients also show lower kidney functions. However, it is unknown whether the etiology of declining kidney functions in those donors is hereditary.[36,37] In addition to those facts, we have found that donors with higher PWV tend to have lower GFR. Moreover, BMI of over 25 kg/m^2 is correlated with lower GFR pre- and post-nephrectomy. Obese donors have underwent hyperfiltration for years for years in order to meet higher metabolic demand. After nephrectomy, kidney needs to do further compensation, which may result in lower kidney function. Chronic hyperfiltration will also affect changes in blood vessels and blood flow.[38]

Our study has provided evidences about hyperfiltration process as a renal compensatory mechanism in living kidney donor post-nephrectomy (**Figure 4**). The kidney hyperfiltration is characterized by alteration in RI, which reflects altered renal blood flow. A trend of changes in every renal artery, which

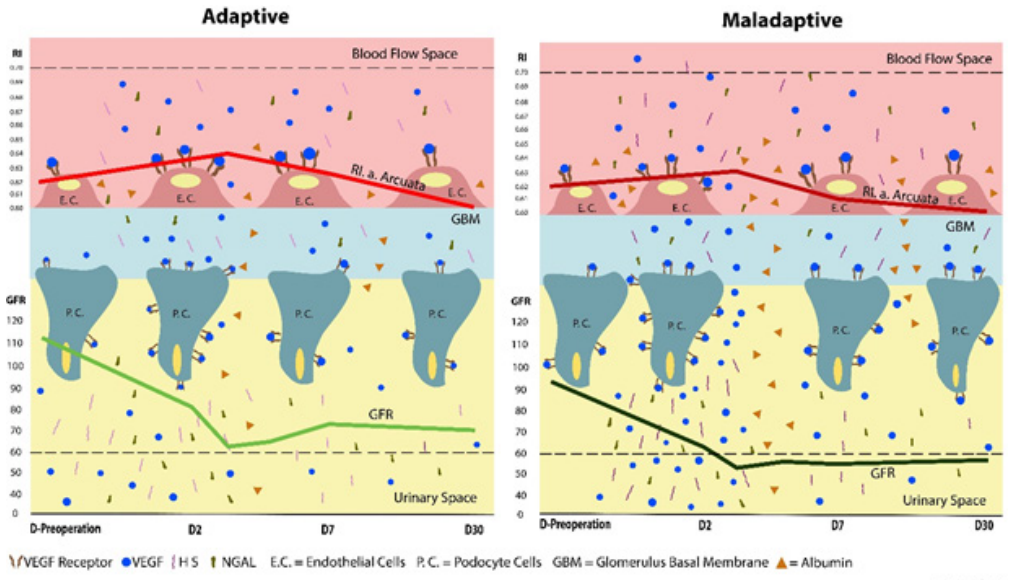

Figure 4. Hyperfiltration is marked by changes in RI, VEGF, HS and NGAL. RI of Arcuate Artery increases more prominently and decline more rapidly in adaptive group (left). VEGF contributes to widening of filtration slit, resulting in worse albuminuria and hence, kidney function. HS promotes VEGF migration from podocytes to endothelial cells. Both VEGF and HS increase dramatically on day 2, and more prominently in maladaptive group. NGAL is produced to a greater extent by maladaptive group, suggesting more severe tubular injury.

flatten back to nearly pre-nephrectomy RI is obvious on the 30th day post-uninephrectomy. Arcuate artery is the most ideal location to assess renal RI in living kidney donation. In addition to that, the kidney hyperfiltration process is also characterized by changes in urinary VEGF level, which reflects compensated kidney hypertrophy. The increase in both urinary NGAL and HS levels may suggest the ischemic and hypoxic condition of remaining kidney tissue due to nephrectomy.

CONCLUSION

The hyperfiltration process does not affect the 30-day post-uninephrectomy kidney function of the donors. The incidence of maladaptive hyperfiltration in kidney living donors within 30 days after nephrectomy is 47.5%. RI, urinary VEGF, NGAL and heparan sulfate proteoglycan levels of donors with adaptive hyperfiltration are not different compared to the results of those with maladaptive hyperfiltration. Several other factors are suggested to have some influences on hyperfiltration process and kidney function. Further studies should include evaluation on the role of genes in hyperfiltration, the role ischemic marker such as KIM-1 and changes in kidney volume within a longer period of monitoring in order to evaluate donors' kidney function and its other related variables.

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