

# Role of heterotopic kidney auto-transplantation for renal artery aneurysms

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## Abstract

To assess the applicability and surgical outcomes of ex vivo repair with heterotopic kidney auto-transplantation (HKA) for the treatment of renal artery aneurysms (RAA).

We retrospectively examined 36 cases presenting with RAA from September 2005 to June 2016. Patient demographics, estimated glomerular filtration rate (eGFR), and common vascular risk factors were evaluated. Patients were classified into 3 groups: those who received endovascular treatment, in situ open surgical repair, or ex vivo repair with HKA. The findings were compared among the groups.

The endovascular repair, in situ open repair, and ex vivo repair with HKA groups included 14, 9, and 13 patients, respectively (mean follow-up, 30.42 ± 30.54 months). The eGFR ( $P = .32$ ) and number of anti-hypertension medications ( $P = .33$ ) did not significantly differ among the groups. Moreover, 3 renal infarctions were detected in the endovascular group and only 1 was detected in the in situ repair group. One patient in the endovascular repair group required dialysis due to renal failure. Patients in the ex vivo repair with HKA group did not exhibit any complications.

With safety and effectiveness comparable to other RAA treatment methods, ex vivo repair with HKA for RAA treatment appears suitable particularly in cases with complicated renal artery branch aneurysm and marginal renal function.

**Abbreviations:** CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CT = computer tomography, HALN = hand-assisted laparoscopic nephrectomy, HKA = heterotopic kidney auto-transplantation, HTK = histidine-tryptophan-ketoglutarate, OKA = orthotopic kidney auto-transplantation, RAA = renal artery aneurysm.

**Keywords:** ex vivo repair, renal artery aneurysm, renal auto-transplantation

## 1. Introduction

Renal artery aneurysm (RAA) is a rare condition, with an prevalence rate of 0.09%,<sup>[1]</sup> but can nevertheless lead to fatal complications such as aneurysm rupture or renal failure due to renal artery thrombus that require immediate and aggressive treatment. No consensus on the treatment indications has been reached to date. However, it is generally accepted that treatment should be administered in cases with RAA diameter of > 2 cm, female patients of childbearing age, those with uncontrolled hypertension, and those presenting with symptoms of flank pain and increasing RAA size.<sup>[2]</sup> Similar to the indications for RAA treatment, there is no consensus on the ideal RAA treatment method either. Usually, endovascular treatment or in situ open surgical repair is used to treat RAA.<sup>[3]</sup> However, some cases of

aneurysms lack an appropriate indication of these methods due to the anatomical difficulty of the aneurysms. In this situation, heterotopic kidney auto-transplantation (HKA) is one of the available methods as an alternative to endovascular treatment or in situ open surgical repair methods. To our knowledge, no study to date has compared the results of ex vivo repair with HKA for RAA treatment with those of other methods. We therefore aimed to assess the utility of HKA as a treatment method for RAA.

## 2. Methods

### 2.1. Patients

Prospectively collected data were retrospectively analyzed, and the study protocol was approved by our institutional review board (approval number: 2016–0961). From September 2005 to June 2016, patients diagnosed with RAA were enrolled, excluding those who received nephrectomy or those undergoing follow-up without any procedures. A total of 35 patients with 36 RAAs were included.

RAA was diagnosed using computer tomography (CT) angiography in cases where 3-dimensional reconstruction was possible. After the CT scan was performed, an angiogram was performed when it was difficult to determine the involvement of distal or segmental branches and precise information on the shape and location of aneurysms. Angiograms were not routinely performed in all cases with involvement of distal or segmental branches. When open surgical repair was deemed necessary due to the involvement of distal or segmental branch as confirmed by CT scan, angiogram was not performed.

Generally, procedures were determined by the character of the aneurysms. The surgeon considered the shape and location of the aneurysms. Aneurysms with anatomy favorable to endovascular

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treatment were treated using this method, but aneurysms that were inappropriate for endovascular treatment, such as those with short and wide necks or those situated in bifurcation or trifurcation sites, were treated by in situ open repair. In cases during which a prolonged ischemic time was anticipated, HKA was conducted. Two surgeons performed all 13 HKAs: including laparoscopic procedures, 1 surgeon conducted 9 cases in succession, and the other performed 4 recent cases.

Patient demographics and common vascular risk factors were assessed, including age, sex, symptoms, hypertension, hypercholesterolemia, diabetes mellitus, estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD), smoking, and the number of hypertension medications. Hypertension was defined as a systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, which was confirmed by multiple separate blood pressure recordings or current use of anti-hypertensive medications. Hypercholesterolemia was defined as total cholesterol level of > 240 mg/dL or current use of cholesterol lowering medications. Diabetes mellitus was defined as a fasting glucose > 126 mg/dL or current use of hypoglycemic medications (including insulin). eGFR was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>[41]</sup> CKD was defined as eGFR < 60 mL/min/1.73 m<sup>2</sup>. Smoking status was defined as current smokers, which also included former smokers. Post-procedural data, including the length of hospital stay, and complications were recorded.

## 2.2. Analysis

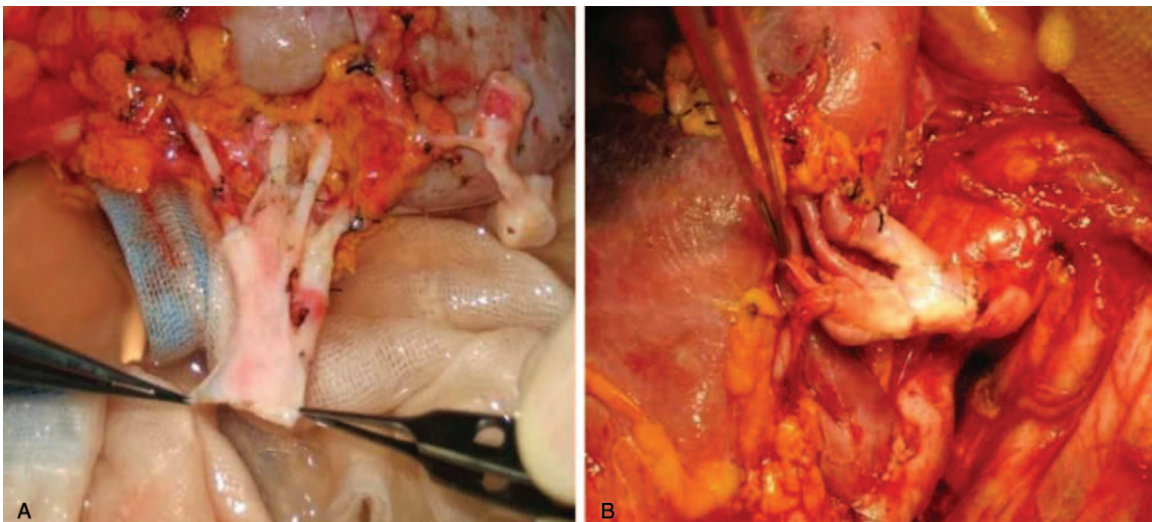
Patients were classified into 3 groups: those who received endovascular treatment, in situ open surgical repair, or ex vivo repair with HKA. The findings were compared among the groups. To determine the influence of renal function, the pre- and post-CKD stages, and eGFR were compared. Moreover, in cases receiving treatment for hypertension, the number of anti-hypertensive medications prescribed before and after the procedure was compared. Post-procedural follow-up CT angiography was conducted prior to discharge to assess renal artery patency and the presence of complications. Additional follow-up was performed at 6-month intervals. If follow-up CT did not indicate significant results, blood sample collection, and clinical examinations were performed.

## 2.3. Procedure

There were changes in the surgical methods used during the research period. Initially, open surgical nephrectomy was performed through midline incision; however, after 2014, hand-assisted laparoscopic nephrectomy (HALN) was preferred. After HALN, a Gibson incision was made for HKA in the iliac fossa. There were no changes in the surgical techniques for kidney transplantation after harvesting. Before the transplantation, we performed aneurysm resection and patch angioplasty repair using saphenous vein conduit on the back table bench procedures. For bench procedures, first, local cooling and perfusion of the kidney were needed for protection during the harvest of the kidney. For the cold perfusion, 4°C histidine-tryptophan-ketoglutarate (HTK) solution or Euro-Collins solution was used. After the cold perfusion, angioplasty was performed to repair the aneurysm. We used previously-prepared saphenous vein for aneurysm resection and patch angioplasty. This anastomosis is carried out with continuous 8–0 monofilament non-absorbable sutures. After the bench procedures, the kidney was then placed on the iliac fossa, and the internal iliac artery or external iliac artery was connected to the renal artery. Depending on the operator's preference, end-to-end anastomosis was carried out for internal iliac artery anastomosis, and end-to-side anastomosis was carried out for external iliac artery anastomosis. All renal veins were connected to the external iliac vein by end-to-side anastomosis. These vessel anastomoses were conducted with continuous 7–0 monofilament non-absorbable sutures (Fig. 1). Ureteroneocystostomy was performed with continuous 6–0 monofilament absorbable sutures for mucosa anastomosis and interrupted 4–0 multifilament absorbable suture was used to repair the bladder muscle layer. Double J stents were inserted in all ureteroneocystostomies and removed after 4 weeks.

## 2.4. Statistical analysis

Quantitative variables are expressed as mean and standard deviation for normal distribution, and as median and range for non-normal distribution. The differences among the 3 groups were analyzed using 2 statistical tests. Categorical data were analyzed using Fisher exact tests, whereas continuous data were assessed using Kruskal-Wallis tests. All statistical analyses were



**Figure 1.** Angioplasty with resection of aneurysms using patient's saphenous vein. After re-perfusion between reconstructed renal artery and internal iliac artery.

**Table 1**  
Patient characteristics and indications for repair at diagnosis.

	Endovascular repair (n=14)	In situ repair (n=9)	Ex vivo repair with heterotopic auto-transplantation (n=13)	P
Age, y	52 (35–73)	55 (41–68)	58 (32–64)	.54
Male sex	7 (50)	2 (22)	4 (30)	.41
Right sided aneurysm	7 (50)	2 (22)	10 (76)	.04
DM	1 (7)	2 (22)	0 (0)	.23
HTN	5 (35)	3 (50)	6 (46)	.79
Smoking	5 (35)	0	3 (23)	.14
CKD (eGFR* <60)	2 (14)	0	0	.19
Hyperlipidemia	0	0	0	1.00
Indications for repair				
Aneurysm size > 2 cm	9 (64)	6 (66)	6 (46)	
Difficult to control hypertension	1 (7)	2 (22)	1 (7)	
Hematuria	1 (7)	1 (11)	4 (30)	
Flank pain	3 (21)	3 (33)	2 (15)	

CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HTN = hypertension.  
\* eGFR calculated by CKD-EPI equation.

performed using SPSS software (version 18.0; SPSS, Chicago, IL), with  $P \leq .05$  considered statistically significant.

### 3. Results

#### 3.1. Outcomes

A total of 36 cases were examined (23 women and 13 men; median age, 55 years [range, 32–73 years]), which included 14 in the endovascular treatment group, 9 in the in situ repair group, and 13 in the ex vivo repair with HKA group. No patient characteristic other than aneurysm laterality was significantly different among the groups (Table 1).

The mean aneurysm size was  $1.97 \pm 0.82$  cm. Saccular shape aneurysm was more common than fusiform shape, and main renal artery bifurcation was the most common location of aneurysm (Table 2).

Coil embolization, stent graft insertion, and stent-assisted coiling were used for endovascular treatment. Coil embolization was carried out on narrow neck aneurysms of saccular shape. Stent-assisted coiling was applied to relatively wide or short neck aneurysms compared to those in coil embolization cases.

**Table 2**  
Characteristics of renal artery aneurysm.

	Endovascular repair (n=14)	In situ repair (n=9)	Ex vivo repair with heterotopic auto-transplantation (n=13)
Aneurysm size, mean $\pm$ SD	2.06 $\pm$ 0.78	2.08 $\pm$ 0.53	1.82 $\pm$ 0.85
Shape			
Saccular 29 (81)	11 (79)	6 (66)	12 (92)
Fusiform 7 (19)	3 (21)	3 (33)	1 (8)
Location			
Proximal of main renal artery bifurcation (Henke classification* 1–3) 10 (28)	6 (43)	4 (44)	0
Main renal artery bifurcation (Henke classification 4) 14 (39)	0	5 (55)	9 (69)
Distal of main renal artery bifurcation (Henke classification 5–7) 12 (33)	8 (57)	0	4 (31)

\* Henke classification.<sup>[24]</sup>

**Table 3**  
Procedures used for renal artery aneurysm repair.

Technique of repair	N (%)
Endovascular repair	14
Coil embolization	9 (64)
Stent grafting	3 (21)
Stent-assisted coiling	2 (14)
In situ repair	9
Segmental resection with primary anastomosis	1 (11)
Aneurysm resection with patch angioplasty	2 (22)
Interposition by great saphenous vein	6 (66)
Ex vivo repair with heterotopic auto-transplantation	13
Ex vivo repair with open surgical nephrectomy	10 (76)
Ex vivo repair with hand-assisted laparoscopic nephrectomy	3 (23)

Uncovered stents were used to prevent distal embolization and coil protrusion. Stent grafts were also used as endovascular treatments. This covered stent only applied to main artery aneurysms and cases in which appropriate landing zones were secured, as it is capable of treating fusiform aneurysms that cannot be treated with coil embolization or stent-assisted coiling (Table 3).

Changes in the CKD stages and eGFR before and after 1 year the procedures were not statistically different among the groups ( $P = .46$ ,  $P = .11$ ), and the number of anti-hypertensive medications also did not significantly differ before and after 1 year the procedures ( $P = .32$ ) (Table 4). Four patients underwent procedure to treat difficult-to-control hypertension. No apparent renal artery stenosis was observed; however, these patients' renin and aldosterone levels were elevated as is usually observed in renovascular hypertension. After the procedures, all 4 patients' hypertension status improved (Table 5).

#### 3.2. Complication and follow up

After coil embolization, 1 patient required dialysis due to renal failure. This patient was diagnosed with angiomyolipoma involving both kidneys: after the right kidney procedure, a right kidney nephrectomy was performed 8 days after the procedure due to renal infarction with severe pain. In addition to this patient, 4 other patients were diagnosed with embolic partial renal infarction by follow-up CT angiography during hospitalization. One of these patients showed a decrease in eGFR from 108.8 mL/min/1.73 m<sup>2</sup> to 78 mL/min/1.73 m<sup>2</sup> (Fig. 2). One case exhibited bleeding of the renal artery due to guide wire injury

**Table 4****Changes in the CKD stage, eGFR, and the number of antihypertensive drugs prescribed before and after 1 year the procedure.**

	Endovascular repair	In situ repair	Ex vivo repair with heterotopic auto-transplantation	P
Change in the CKD stage*	0.38 ± 0.69	0.25 ± 0.52	0.1 ± 0.68	0.46
Change in the eGFR	15.51 ± 13.21	6.5 ± 10.45	4.31 ± 10.32	0.11
Change in the number of antihypertensive drugs	-1.2 ± 0.83	-1 ± 1.0	-0.5 ± 0.54	0.32

\* CKD stage: stage 1 (GFR ≥ 90 mL/min/1.73 m<sup>2</sup>), stage 2 (GFR, 60–89 mL/min/1.73 m<sup>2</sup>), stage 3 (GFR, 30–59 mL/min/1.73 m<sup>2</sup>), stage 4 (GFR, 15–29 mL/min/1.73 m<sup>2</sup>), stage 5 (GFR < 15 mL/min/1.73 m<sup>2</sup>).  
CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate.

**Table 5****Pre- and Post-operative anti-hypertensive medication of patients who underwent procedure for medically difficult-to-control HTN.**

	Endovascular repair (n = 1)	In situ repair (n = 2)	Ex vivo repair with heterotopic auto-transplantation (n = 1)
Pre-operative anti-hypertensive drugs	Alpha adrenergic blocker, calcium channel blocker, diuretics	Calcium channel blocker, diuretics Beta adrenergic blocker, calcium channel blocker, diuretics	Beta adrenergic blocker, calcium channel blocker
Post-operative anti-hypertensive drugs	Calcium channel blocker	None None	Calcium channel blocker

HTN = hypertension.

during stent graft insertion. One patient had large hematoma due to puncture site bleeding. Pneumonia occurred on post-operative day 5 in 1 in situ open repair patient. One patient who underwent HKA was later diagnosed with urinary tract infection prior to removal of the double J stent; this patient also presented with lymphocele 2 months after the surgery. The post-procedural length of hospital stay in the ex vivo repair with HKA group was significantly longer than those in the other groups ( $10.92 \pm 3.52$  days,  $P < .001$ ). No other complications or cases of mortality were noted during the follow-up period (mean follow-up period,  $30.42 \pm 30.54$  months) (Table 6).

#### 4. Discussion

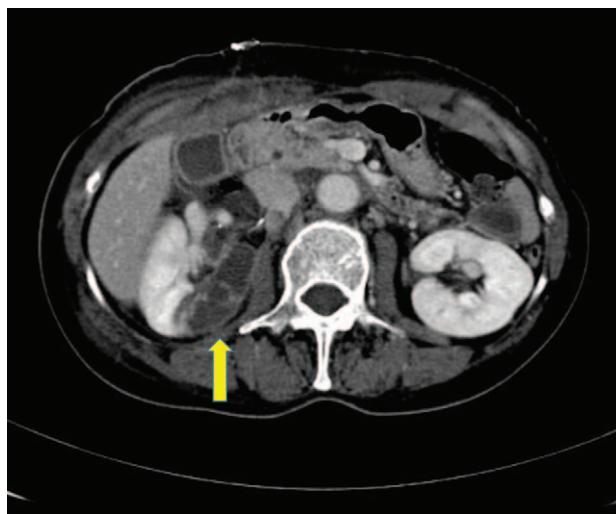
In the treatment of RAA, ex vivo repair using HKA was comparable to other procedures in terms of safety, effectiveness, and overall surgical outcome. Hence, HKA is a viable option for

the treatment of RAA, especially in patients with complicated renal artery branch aneurysms and marginal renal function. Although endovascular treatment has advantages such as short post-procedural hospital stay and minimal invasiveness,<sup>[5]</sup> it may not be appropriate in certain cases with RAA located in renal artery bifurcation or with RAA in large fusiform shape.<sup>[6]</sup> Also, our results indicate that HKA does not have higher chance of complications compared to other methods.

The outcomes of in situ open repair were not inferior to those of endovascular treatment,<sup>[7]</sup> and it could thus serve as an alternative treatment for RAA. However, due to the risk of nephron injury, it cannot be appropriately applied in cases where a cold ischemic time of > 35 minutes during in situ procedure is required.<sup>[8]</sup> Furthermore, in situ repair of right mid renal artery lesions may be more technically challenging; nevertheless, because the inferior vena cava runs between the aorta and the kidney, cases of aortorenal bypass simply require conduit tunneling through the retrocaval space.

Hence, ex vivo repair with HKA may be ideal for RAA treatment in patients with complicated renal artery branch aneurysms, wherein endovascular treatment or in situ repair (due to longer ischemic time) cannot be performed. This is also applicable to patients with marginal renal functions or a solitary kidney, wherein the outcomes do not significantly differ but ex vivo repair with HKA exhibits better preservation of renal function. In fact, some studies of ex vivo repair with auto-transplantation showed positive outcomes for the treatment of RAA without any renal dysfunction in cases with a solitary kidney.<sup>[9–11]</sup>

There has yet to be a consensus on the mechanical relationship between renal artery aneurysms and hypertension.<sup>[12–14]</sup> In our current study, 9 out of the 14 patients on anti-hypertensive medications had reduced or discontinued their medication after any procedures. We had 4 patients who underwent a procedure to treat difficult-to-control hypertension and while there was no observed apparent renal artery stenosis, these patients' renin and aldosterone levels were elevated as in cases of reno-vascular hypertension. After the procedures, all 4 patients' hypertension improved. Without an apparent artery stenotic region, we suspect that turbulent renal blood flow was the cause of renin-dependent



**Figure 2.** Post-operative renal infarction (yellow arrow) after the interposition of autogenous saphenous vein with segmental resection of involved main renal artery.

**Table 6****Outcomes of renal artery aneurysm repair.**

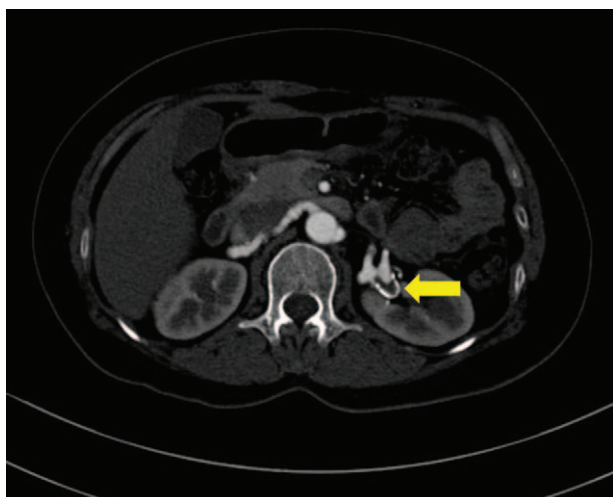
	Endovascular repair (n = 14)	In situ repair (n = 9)	Ex vivo repair with heterotopic auto-transplantation (n = 13)	P
Renal infarction	3	2	0	
Dialysis due to renal failure	1	0	0	
Bleeding of renal artery	1	0	0	
Pneumonia		1		
Urinary tract infection			1	
Lymphocele			1	
Bleeding of puncture site	1			
Post-procedural length of hospital stay, d	5.07 ± 7.71	6.89 ± 2.57	10.92 ± 3.52	< .001
Follow-up period, mean ± SD, mo	32.50 ± 33.99	30.56 ± 28.28	28.08 ± 30.4	.91

hypertension. Hemodynamic changes from turbulent blood flow within the aneurysm has been shown to result in decreased distal renal artery perfusion.<sup>[15]</sup> Flank pain is also controversial to regard it as an indication of aneurysm treatment, and Cowan et al<sup>[16]</sup> postulated that a microvascular etiology is likely. In our study, we could not find the exact relationship between flank pain and renal artery aneurysms. Seven patients underwent procedures due to flank pain, but they did not have pre-operative leukocytosis or fever. We presume that microinfarctions derived from thrombus in the aneurysm could have been a cause of flank pain, since 5 patients had thrombosis in their aneurysms (Fig. 3).

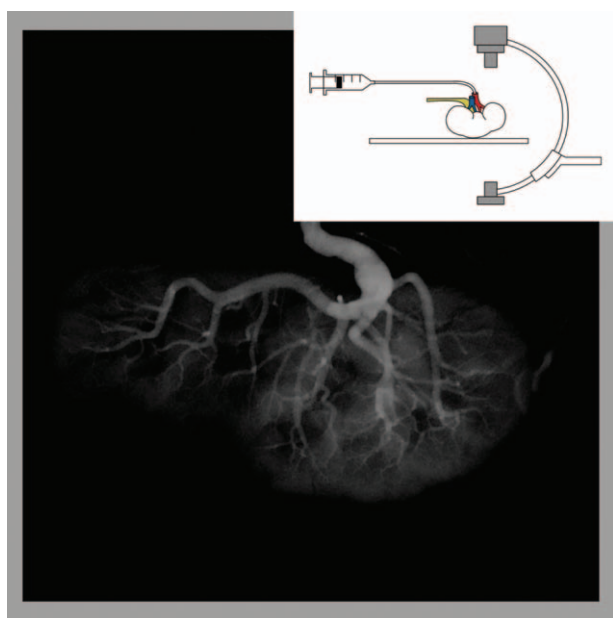
Ex vivo repair with orthotopic kidney auto-transplantation (OKA) is another technique of note, in which the vessels in the renal fossa are reconnected with the un-resected ureter. Some studies have assessed the outcomes of ex vivo repair with OKA<sup>[14,17]</sup> and found that it is superior to HKA.<sup>[14,18]</sup> First, the OKA method avoids the complications associated with ureteroneocystostomy. However, ureteroneocystostomy-related complications are not common,<sup>[19]</sup> and none were found in the present study. Second, in cases with atherosclerotic peripheral arterial disease in the iliac artery, perfusion to the transplanted kidney decreases and an intervention for iliac artery stenosis is difficult due to renal artery anastomosis. However, our current patients who underwent ex vivo repair with HKA had 0.75 ± 0.73 risk factors, including those for peripheral arterial disease

such as hypertension, diabetes mellitus, smoking, hypercholesterolemia, and CKD. Based on this finding, it can be assumed that these cases would have a very low incidence of peripheral arterial disease.<sup>[20,21]</sup> It must be noted, however, that HKA also has some advantages over OKA: HKA requires only iliac artery to be clamped and thus avoids the need for aortic cross-clamping. This is beneficial in that aortic cross-clamping is likely to increase the risk of complications and places greater stress on cardiac function, as 55% of blood flow occurs above the renal artery level and blockage of this flow leads to a marked increase in cardiac afterload. Ischemia and reperfusion injury are also examples of serious complications of aortic cross-clamping that can lead to bleeding tendency, and consequently result in consumption coagulopathy and decreased fibrinolytic activity.<sup>[22]</sup> Moreover, cooling of the graft and angioplasty are easier with HKA, as these procedures are conducted on the back table. In contrast, cooling of the kidney after HTK solution reperfusion and angioplasty are difficult with the OKA method in which these procedures have to be performed on the patient's body wall due to the presence of un-resected ureter. To confirm the patency of the conduit, the surgeon can also perform angiography with ease on the back table (Fig. 4). Three recent cases in the present study underwent HALN, which differs from the previous open surgical nephrectomy method. In particular, HALN can reduce the length of the post-procedural hospital stay, which is the only disadvantage of ex vivo repair with HKA. Moreover, HALN is associated with reduced incisional morbidity, whereas OKA requires a midline or extended flank incision; HKA with HALN only requires a Gibson incision with laparoscopic incisions. To our knowledge, no studies to date have compared the complication rate of ex vivo repair with HKA and OKA; some reports have indicated that the complication rates of OKA range from 12% to 18%,<sup>[17,23]</sup> which is a similar complication rate as that of HKA found in our present study (15%).

The present study has some significant limitations of note. First, selection bias is the most serious limitation in this study. It is a study to prove the hypothesis that the HKA method's outcome is not inferior to the other options. For this purpose, we inevitably compared the results of HKA and other options. However, this comparison has a selection bias from the outset because HKA can only be used in complicated situations in which other options are not feasible. Second, the results of this study are limited to only short-term results. More long-term follow up data, especially with regard to complications, are desired. In particular, ureteroneocystostomy-related complications such as urethral stricture usually occur much later. In a follow up period of 30 months, we could not confirm the true incidence rates of complications.



**Figure 3.** Thrombosis (yellow arrow) in aneurysmal sac before procedure.



**Figure 4.** Intra-operative renal angiogram on the back table after bench procedure.

Third, the small sample size may limit the statistical validity of our results. In particular, we only examined 13 cases involving ex vivo repair with HKA. Nevertheless, given the rare nature of the disease, it is difficult to enroll a large number of patients, and a multi-center study in the future would be valuable. Fourth, this study includes the data on the changes in eGFR and the presence of hematuria after HKA and the secondary data on the changes in blood pressure by documenting the antihypertensive drugs. However this is not enough evidence to support the safety of the kidney due to lack of data on proteinuria and direct blood pressure records. Fifth, it is reasonable that the HKA procedure should be performed only if there is a well-trained vascular and renal transplant surgeon with the well supported medical environment, because of the high degree of operative difficulty and the risky complications.

## 5. Conclusions

Ex vivo repair with HKA is not necessarily superior to other procedures in terms of overall surgical outcome. However, with safety and effectiveness comparable to other RAA treatment methods, ex vivo repair with HKA is a viable option for the treatment of RAA in patients with complicated renal artery branch aneurysms and marginal renal function.

## Author contributions

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**Writing – original draft:** Jun G. Gwon.

**Writing – review & editing:** Tae W. Kwon.

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