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Surgical prevention and management of vascular complications of kidney transplantation

Thomas Bessede,[1,2] Stephane Droupy,[3] Yacine Hammoudi,[1] Dina Bedretdinova,[4] Antoine Durrbach,[5,6] Bernard Charpentier[5,6] and Gerard Benoit[2]

1 Urology department, University Hospital of Bicetre, Le Kremlin Bicetre, France
2 EA 4122, University Paris South, Le Kremlin Bicetre, France
3 Urology and Andrology department, University Hospital Caremeau, Nimes, France
4 INSERM U1018, CESP, University Paris South, Le Kremlin Bicetre, France
5 Nephrology Department, University Hospital of Bicetre, Le Kremlin Bicetre, France
6 UMR 1014 INSERM University Paris South, Villejuif, France

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Correspondence
Dr Thomas Bessede, Bicetre Hospital, Department of Urology, 78 rue du General Leclerc, 94270 Le Kremlin Bicetre, France.
Tel.: +33145214455;
fax: +33145212170;
e-mail: thomas.bessede@gmail.com

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Summary

The main surgical changes in kidney procurement, preparation, and transplantation procedures occurred 20 years ago and were undertaken despite the inability to design randomized studies. The objective was to assess the evolution of vascular complications after kidney transplantation in a setting of surgical preventive measures in a historical series. A monocentric series of 3129 consecutive kidney transplantations performed over 3 decades was reviewed. The occurrence of arterial or venous thromboses, stenoses, and aneurysms was analyzed in relation with kidney procurement, preparation, and transplantation techniques. Vascular complications occurred in 13.5% of the recipients with a mean 3-year decrease in kidney graft function. The transplantation of a right kidney without renal vein extension, multiple renal arteries, *ex vivo* vascular repairs, and end-to-end arterial anastomoses were the unfavorable surgical vascular factors. It was possible to manage Transplant Renal Artery Stenosis (TRAS) nonsurgically in 80% of the cases. The prevention of vascular complications begins from the time of organ procurement by skilled surgeons. The aims of organ preparation are to evaluate the vascular risk, select the organs, and to simplify the anatomical constraints of vascular implantations. The three surgical steps of kidney transplantation are determinant in postoperative vascular complications and the duration of graft function.

Introduction

The original surgical technique of kidney transplantation was described in 1951 and has only evolved slightly over 60 years [1]. The gold standard surgical procedure is still open and still in the right iliac fossa, even if an end-to-side anastomosis to the external iliac artery is now being preferred to the original end-to-end internal iliac artery anastomosis [2]. The main surgical evolutions have chiefly concerned the organ procurement strategy. It has evolved with time, experience, and technical improvements and has mainly consisted in *in situ* perfusion, the choice of the graft conservation solution, the procurement of aortic cuffs, and extension of the right renal vein using the inferior vena cava [3–5].

Management of recipients has also been optimized by treating hyperthyroidism, decreasing the transplant cold ischemia time and scheduling transplantations in the predialysis period. These measures aim to limit the development of atherosclerotic lesions in the recipients. However, after decades of medical and surgical progress, vascular complications in kidney grafts continue to carry a poor prognosis and compromise function and the lifetime of the graft [6–10]. The analysis of a large transplantation register has identified older recipients and donor age, extended donor criteria, immunosuppression, delayed graft function, and

ischemic heart disease as the medical determinants of Transplant Renal Artery Stenosis (TRAS) [6]. The surgical determinants are still under debate and more difficult to evaluate in prospective studies.

The aim of this study was to investigate the evolution of vascular complications of kidney transplantation in the setting of surgical prevention measures in a large monocentric historical series and to identify their surgical determinants.

Patients and methods

Three thousand kidney transplantations were consecutively performed in a single center from 1971 to 2010. The organs were locally procured from deceased donors (encephalic or cardiac death), living donors, or were attributed according to the national distribution rules. The kidneys were recovered without aortic cuffs in living donors, and in deceased donors before 1977. After 1984, the right kidneys were recovered in deceased donors with the inferior vena cava to extend the right renal vein [11].

The transplantation site was the right iliac fossa for a first or a third kidney graft and the left iliac fossa for a second graft or a simultaneous kidney–pancreas graft. At the beginning of our experience, the renal artery was end-to-end anastomosed to the internal iliac artery and the renal vein end-to-side to the inferior vena cava. Since the mid-1980s until now, arterial anastomoses have been end-to-side to the external iliac artery using aortic cuffs and venous anastomoses to the external iliac vein. In case of multiple renal arteries without aortic cuffs, an *ex vivo* reconstruction could be performed [12], if not, the anastomoses were separate. In case of a third graft, the kidney was transplanted in a high position with caval, common iliac, and ureteral anastomoses.

The transplantation database was prospectively filled: it included procurement, transplantation, postoperative and long-term follow-up data. The procurement details were: kidney side, status of the donor, number of arteries, the presence of an aortic cuff, atheroma, section of a polar artery, right vein extension, and *ex vivo* repair. The transplantation data were: recipient gender, type, number and site of transplantation, number and site of anastomoses, iliac atheroma, eventual endarterectomy, and vascular prosthesis. The postoperative information included: diuresis, creatininemia, blood pressure, drainage, arterial resistance index at Doppler examination, vascular stenosis or thrombosis and their eventual medical, radiological or surgical treatment. In case of suspicion of a vascular complication at the postoperative Doppler examination, angiographic imaging of the anastomosis was performed with different technologies during the study period (angiography, angio-CT scan or angio-MRI).

In case of multiple arteries or veins, the diagnosis of thrombosis was made if one of the vessels was found to be occluded at the Doppler examination. A diagnosis of a stenosis had to be confirmed using angiography imaging. All the radiologically depicted stenoses were analyzed in the study without any distinction regarding the percentage of stenosis and even stenoses not requiring either medical or surgical treatment were included. Patients with early arterial or venous thrombosis underwent a renal transplantatectomy, whereas the late cases were to be managed conservatively. The treatment of arterial stenoses combined an antihypertensive treatment followed by surgical repair before 1986 (anastomosis resection and reimplantation, or interposition of a vascular graft) or percutaneous dilatation of stenoses after 1986 [13–17].

Early surgical complications were defined as time to onset within 3 months of surgery and late surgical complications as time to onset beyond 3 months post surgery. An amount of 20 procedures previously performed by a surgeon in our center was the threshold to define the surgeon's experience. The duration of overall graft function was evaluated in the group of vascular complications and compared with the population of uncomplicated kidney grafts. There were missing values due to the retrospective methodology of the study. As some of the patients had more than one complication, the binary variable ''total vascular complications'' was created thus to distinguish, which had at least one complication. The statistical analysis was performed using the Statistical Analysis Software, version 9.2. The Pearson Chi-2 test was used to compare qualitative data of different types of vascular anastomoses: the nonpaired *t*-test was used for quantitative data. For further analysis, all estimated parameters were presented in binary variables. The univariate analysis of all types of complications was performed using a Pearson Chi-2 test, logistic regression was used for analysis adjusted for age and for multivariate analysis. Two additional multivariate analysis were performed in subgroup of patients with right kidney to check the effect of right vein extension and in subgroup of patients with end-to-side anastamosis to check the effect of aortic cuff.

Results

Three thousand one hundred and twenty-nine kidney transplantations were performed. Thirty-one surgeons participated in the transplantation program and each of them performed from 1 to 986 procedures. Procurement, recipient, and transplantation characteristics are presented in Table 1. The series comprised a majority of transplants from deceased donor (93%) with a single artery (77%) and an aortic cuff (83%). They were typically

transplanted in young (90%), male (63%) recipients with end-to-side external iliac anastomoses (85%). Overall vascular morbidity in the series was 13.5% (421 events). TRAS was the most frequent vascular complication and occurred 328 times (78%), usually in the late postoperative period (87%). In contrast, thrombotic events mostly occurred in the early postoperative period (70%), in particular venous thrombosis (97%).

The statistical analyses are presented in Table 2. The rate of postoperative vascular complications was lower with left versus right kidneys (10.8 vs. 16.4%, $P < 0.0001$), or with kidneys with a single artery (12.7 vs. 16.3%, $P < 0.05$). When a right kidney was transplanted, a prior renal vein extension using the donor's inferior vena cava was associated with significantly lower rates of arterial complications (thrombosis and stenosis). Higher rates of arterial complications occurred when the kidney vessels had required *ex vivo* repair (22.0 vs. 13.1%, $P < 0.005$), whereas the origin of the kidney (living or deceased donor) and the presence of an atheroma in the donor or recipient were not significant determinants of overall vascular complications. Multiple arteries (4.0 vs. 1.3%, $P < 0.05$) and *ex vivo* repairs (6.1 vs. 1.7%, $P < 0.05$) were associated with high rates of arterial thrombosis. The recipient's age was significantly, but negatively correlated with the rate of vascular complications. With the end-to-end anastomoses to the internal iliac artery, the rates of arterial stenoses, arterial thrombosis, and venous thrombosis were twofold higher than with the end-to-side anastomoses to the external iliac artery ($P < 0.001$). The presence or absence of an aortic cuff on the artery was not a statistically significant factor for vascular complications following renal transplantation. The surgeon's experience was also not a significant predictor for vascular complications.

The management of the cases and the duration of graft function are presented in Table 3. Overall vascular events were a significant factor in the decreased duration of graft function (7.2 vs. 10.4 years, $P < 0.001$) and the type of vascular complication was significantly associated with the duration of graft function. Of the 138 medically managed TRAS, seven cases required a complementary percutaneous intervention and a total of nine graft failures was observed for an overall mean function duration of 8.4 years. The 57 surgeries performed for a TRAS had an 82% success rate (two thromboses, seven restenoses, and one postoperative aneurysm) and provided blood pressure control in 91% of cases with a mean function duration of 9.3 years. As a third option ($n = 128$), percutaneous dilatation yielded a similar 82% success rate (13 interventional failures, 3 ruptured anastomoses, 10 per-procedure thromboses, 10 restenoses, 1 arterio-venous fistula, and 2 aneurysms) with a mean function duration of 9.3 years.

Table 1. Transplantation characteristics. Main characteristics of transplantations and patients.

Total		*n* = 3129	
Kidney	Left	1534	49.8%
	Right	1546	50.2%
	Right renal vein extension	847	54.8%
Donor	Deceased donor	2879	92.5%
	Cardiac death	102	3.3%
	Living donor	235	7.5%
Aortic cuff	None	457	17.4%
	Present	2176	82.6%
Recovery difficulties	Multiple arteries	728	23.3%
	Without cuff	121	16.6%
	With cuff	607	83.4%
	Atheroma	245	7.8%
	Inferior polar artery section	27	0.9%
	Ex vivo repair	164	5.2%
Recipient	Male	1971	63.0%
	Female	1158	37.0%
No. of transpl.	First	2682	89.4%
	Second	293	9.8%
	Third	22	0.7%
Type of transpl.	Isolated kidney	2688	88.3%
	Liver-kidney	131	4.3%
	Pancreas-kidney	126	4.1%
	Kidney bi-transplantation	50 (x2)	3.3%
Recipient	Age >60	306	9.8%
	Iliac atheroma	228	7.3%
	Endarterectomy	54	1.7%
	Arterial prosthesis	15	0.5%
Arterial anast.	End-to-end in intern iliac artery	457	14.8%
	End-to-side in extern iliac artery	2639	85.2%
Venous anast.	Inferior vena cava	223	7.1%
	Iliac extern vein	2850	92.9%
Vascular complications		421	13.5%
	Early (<3 months)	91	22.0%
	Late (>3 months)	322	78.0%
Thrombosis	Arterial	61	1.9%
	Early (<3 months)	36	59.0%
	Late (>3 months)	25	41.0%
	Venous	31	1.0%
	Early (<3 months)	30	96.8%
	Late (>3 months)	1	3.2%
Transplant Renal Artery Stenosis (TRAS)		328	10.5%
	Early (<3 months)	43	13.3%
	Late (>3 months)	280	86.7%
	Surveillance	138	42.7%
	Percutaneous treatment	128	39.6%
	Surgical treatment	57	17.6%
Anastomotic aneurysm		9	0.3%

Table 2. Surgical determinants of vascular complications of kidney transplantation.

Characteristic		No. of transplantions (n = 3129)	Arterial thrombosis (n = 61)		Venous thrombosis (n = 31)		Arterial stenosis (n = 328)		Anasto-motic aneurysm (n = 9)		Total vascular complications (n = 421)		Univariate	Univariate adjusted for age	Multivariate
Surgeon's experience	<20 Tx	436	8	1.8%	8	1.8%	39	8.9%	1	0.2%	55	12.6%	P = 0.58	P = 0.59	0.226
	>20 Tx	2693	53	2.0%	23	0.9%	289	10.7%	8	0.3%	366	13.6%			
Kidney	Left	1534	24	1.6%	14	0.9%	126	8.2%*	6	0.4%	166	10.8%	P < 0.0001	P < 0.0001	P < 0.0001
	Right	1546	37	2.4%	16	1.0%	201	13.0%*	3	0.2%	253	16.4%			
Right vein extension	Yes	847	15	1.8%	7	0.8%	85	10.0%*	2	0.2%	109	12.9%	P < 0.0001	P < 0.0009	P = 0.0002
	No	693	22	3.2%	9	1.3%	116	16.7%*	1	0.1%	144	20.8%			
Donor	Cadaveric	2879	59	2.0%	30	1.0%	303	10.5%	9	0.3%	393	13.7%	P = 0.20	P = 0.1889	P = 0.2288
	Living	235	2	0.9%	1	0.4%	24	10.2%	0	0.0%	27	11.5%			
Ex vivo repair	Yes	164	10	6.1%*	1	0.6%	25	15.2%*	0	0.0%	36	22.0%	P = 0.0013	P = 0.0012	P = 0.0653
	No	2936	51	1.7%*	30	1.0%	303	10.3%*	9	0.3%	385	13.1%			
Donor atheroma	Yes	245	7	2.9%	1	0.4%	23	9.4%	0	0.0%	30	12.2%	P = 0.12	P = 0.376	P = 0.2105
	No	2818	54	1.9%	30	1.1%	305	10.8%	9	0.3%	391	13.9%			
No. arteries	Unique	2341	31	1.3%*	22	0.9%	242	10.3%	6	0.3%	298	12.7%	P = 0.013	P = 0.0121	P = 0.016
	Multiple	728	29	4.0%*	9	1.2%	83	11.4%	3	0.4%	119	16.3%			
Recipient atheroma	Yes	228	9	3.9%*	2	0.9%	25	11.0%	0	0.0%	35	15.4%	P = 0.42	P = 0.0905	P = 0.3068
	No	2873	52	1.8%*	29	1.0%	303	10.5%	9	0.3%	386	13.4%			
Endarterectomy or Prosthesis	Yes	69	3	4.3%	0	0.0%	9	13.0%	0	0.0%	12	17.4%	P = 0.33	P = 0.16	P = 0.7614
	No	3060	58	1.9%	31	1.0%	319	10.4%	9	0.3%	409	13.4%			
Recipient age	>60	306	7	2.3%	0	0.0%	18	5.9%†	2	0.7%	26	8.5%	P = 0.007	N/A	P = 0.0379
	<60	2814	54	1.9%	31	1.1%	310	11.0%†	7	0.2%	395	14.0%			
Anastomosis	End-to-end	457	13	2.8%	9	2.0%†	86	18.8%*	1	0.2%	106	23.2%	P < 0.0001	P < 0.0001	P < 0.0001
	End-to-side	2639	47	1.8%	22	0.8%†	241	9.1%*	8	0.3%	313	11.9%			
Aortic cuff in end-to-side An.	Yes	2176	37	1.7%	18	0.8%	194	8.9%	7	0.3%	252	11.6%	P = 0.35	P = 0.5004	P = 0.7796
	No	457	9	2.0%	4	0.9%	47	10.3%	1	0.2%	60	13.1%			

*Significant difference in univariate analysis adjusted for age.
†Significant difference in univariate analysis.

Table 3. Duration of graft function (in years) by vascular complications.

Event	Duration (year)
Arterial thrombosis (n = 61)	3.6
Venous thrombosis (n = 31)	0.91
Arterial stenosis (n = 328)	8.7
Surgically managed (n = 57)	9.3
Percutaneously managed (n = 128)	9.3
Medically managed (n = 137)	8.4
Arterial aneurysm (n = 9)	4.5
No vascular complication (n = 2708)	10.4

There was no significant difference in the duration of renal function after the three management options (medical, percutaneous, and surgical) used for TRAS and the interventional techniques had the same success rate (82%).

Discussion

The activity of kidney transplantation involves medico-surgical teams who manage various pre and postoperative decisions and complications. The medical determinants of renal allograft thrombosis and arterial stenosis are well established and prospective randomized studies have compared immunosuppressive treatments [18,19]. In contrast, the surgical factors have only been investigated in small series, the main surgical advances have mostly been empirical, only a few prospective studies have compared the surgical techniques and no study has evaluated the surgical vascular outcome of kidney transplantation [3–5,12,20,21]. In this context, a comparison of a large retrospective series proved to be determinant in our understanding and in the improvement of surgical results. The historical inclusions over 3 decades in a single center enabled us to focus on the different changes in the procedures. Our data contain the details of the three surgical steps (procurement, organ preparation, and transplantation) from the beginning of our experience. They provide crucial information allowing an appraisal of the effects of these evolutions.

With an overall vascular complication rate of 13.5%, our results are situated in the top part of the 2–23% range of frequencies reported in literature [22]. This wide range indeed reveals disparate inventories performed in retrospective studies. As presented in Table 4, most of the authors considered only one or a few predefined vascular complications, or did not exhaustively screen complications in their study populations [16,18,23–29]. Some authors included only the interventional cases retrospectively, which constitutes a selection bias. In our institution, our policy was to screen all vascular complications. This strategy has been demonstrated to increase the TRAS detection rate from 2.4% to 12.4% [30]. Moreover, the diagnosis of TRAS did not systematically lead to a treatment in our series: only half of these patients were surgically or radiologically treated, a proportion, which is comparable with that of cases requiring intervention in the literature [31]. Comparisons of our results period-by-period are also consistent with contemporary series. For example, during the 2000–2005 period, the TRAS rate was 6.5% in our study and 8.3% in a US registry of 41 867 recipients [6]. The analysis of graft function durations provided clinically relevant data that were not previously assessed. The 3-year shortening of renal function indicates the need to prevent vascular complications, in particular arterial and venous thromboses that usually require an emergency transplantectomy. Higher risk of graft loss or vascular have already been described complications with multiple renal graft arteries as well as short renal vein without extension of a donors vena cava [32].

In our study, a few anatomical and surgical parameters were significantly associated with the complication rate. The side of procurement determines the length of the vessels: with a longer artery and a shorter vein, right

Table 4. Review of the literature.

Author	Country	No. Patients	No. Cases	Incidence	All vascular complications	Systematic postop imaging
Lacombe [16]	France	100	23	23%	–	+
Basic *et al.* [24]	Serbia	463	25	5.4%	–	–
Dimitroulis *et al.* [25]	Greece	1367	57	4.2%	+	–
Krishnamoorthy *et al.* [28]	India	543	43	7.9%	–	+
Salehipour *et al.* [29]	Iran	1500	133	8.9%	+	+
Kamali *et al.* [27]	Iran	360	24	6.6%	–	–
Luna *et al.* [18]	Spain	577	35	6.0%	–	–
Aktas *et al.* [23]	Turkey	1843	47	2.6%	+	+
Eufrasio *et al.* [26]	Portugal	2000	54	2.7%	+	–
Present study		3129	421	13.5%	+	+
Means/Totals		11882	862	7.3%	–	–

kidneys run a higher risk of arterial kinking [23,33]. However, extension of the right renal vein enabled us to keep the two vascular implantations apart, to facilitate the two anastomoses, and to finally decrease the rate of arterial thrombosis and stenosis without increasing the rate of venous complications. This main change in our transplant preparation probably explains the decrease in the rate of thrombosis. Between 1980 and 2000, the arterial thrombosis rate decreased from 3% to 0.9% and the venous thrombosis rate from 1.8% to 0.5%. As vascular thromboses occur during the early postoperative period and are the main reason for transplantectomies, they exert major effects on the duration of graft function. Thus, this long monocentric survey clearly demonstrates the benefit of right vein extension during the transplant preparation procedure.

In case of a renal artery atheroma, the strategy in our center was to cancel the transplantation if the atheromatous infiltration was severe. In cases with a moderate atheroma, the cuff was sacrificed to enable an anastomosis to a nonatheromatous plaque. This strategy introduced a selection bias in our study and, as a consequence, the criterion ''atheroma in donor'' may appear to be irrelevant in the analysis. The absence of a difference between transplants with and without an atheroma retrospectively validates the fact that we did not transplant cases with severe atheromatous infiltration.

Hwang *et al.* concluded in a series with 25% of multiple arteries that the surgical strategy in the presence of polar arteries (single anastomosis, multiple anastomoses, ligation) and the type of anastomosis (end-to-end versus end-to-side) does not affect the long-term outcome [34]. With 29% of multiple-artery transplantations, our data contradicts these two statements after a multivariate analysis. The vascular anatomy significantly impair the surgical result, in particular for arterial thrombosis. However, it is important to precise that an arterial thrombosis was reported in or database even if it occurred in a polar artery. As a consequence, all arterial thromboses did not require a transplantectomy.

The end-to-end anastomoses were a risk factor for arterial and venous complications ($P < 0.0001$). However, these anastomoses were performed at the beginning of our experience. At that time, our reference technique was an implantation into the internal iliac artery, before Sutherland *et al.* showed that this artery gave rise to higher risks of atheroma and endarterectomy [2]. In our adult series, the absence of an effect of the aortic cuff was established by comparing the types of anastomoses. The analysis of living donor organs (also procured without a cuff) confirms this result. However, aortic cuffs are known to decrease the rate of arterial stenosis in pediatric transplantations [4]. We also still advocate procurement with aortic cuffs in case of multiple arteries. They facilitate vascular reconstruction and avoid *ex vivo* repairs because polar arteries are often identified after the aortic division.

With the increase in complications after an *ex vivo* transplant repair ($P = 0.001$ in univariate analysis, $P = 0.06$ in multivariate analysis), we have promoted several policies to prevent procurement accidents: educating new surgeons in the national ''procurement school'', supervision of the first procedures by a expert surgeon, atraumatic cannulation to avoid damaging the intima wall, the choice of the conservation solution, explantation without traction on vessels, and procurement with aortic cuffs.

The paradoxical role of the recipient's age in the occurrence of vascular complications remains uncertain. No other study has reported a protective effect of age over 60 years. This observation probably corresponds to a management bias for this category of patients: an iliac or a coronary stenosis was a contraindication in older potential recipients. The transplant kidneys were also selected more cautiously.

This series confirms that TRAS is the most frequent vascular complication and it decreased renal function by 20 months. How the lesion presents and time to onset are variable, which suggests a multifactorial origin: the procurement technique, extended criteria donors, transplantation technique, cold ischemia time, CMV infection, and delayed graft function can be hypothesized [35]. TRAS were treated radiologically exclusively after a medical failure, which occurred in 4% of all recipients. Indeed, the two strategies (medical and radiological i.e., percutaneous) previously provided similar results [31]. If interventional management was decided, the percutaneous and surgical techniques had similar success rates (82%). The likelihood of arterial kinking should therefore determine the choice of open surgery because this complication is refractory to balloon dilatation [23]. In case of restenosis, surgical reconstruction or arterial stenting are two options that provide durable results.

Conclusion

With a 13.5% incidence rate and a mean 3-year decrease in the duration of graft function, management of vascular complications of kidney transplantation was a significant challenge in a large historical study. As the medical procedures were advanced, the surgical steps (procurement, preparation, and transplantation) were gradually standardized. Education of the procurement surgeons, explantation of the kidney without undue traction on vessels, transplant selection, right vein extension, end-to-side anastomoses, and adhering to a surgical strategy for

determining the sites of the anastomoses on the receiving vessels were some of the actions implemented during the study period and most likely enabled a decrease in vascular complications. The management of the transplant renal artery stenosis was standardized with percutaneous interventions being restricted to the resistant medically treated cases.

Authorship

TB and GB: conception and design. GB, SD, BC and AD: acquisition of data. TB and GB: analysis and interpretation of data. TB: drafting of the manuscript. AD and GB: critical revision of the manuscript for important intellectual content. DB and TB: statistical analysis. Obtaining funding: None. Administrative, technical, or material support: None. GB and AD: supervision.

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