Diagnosis and management of vascular complications after renal transplantation - 15 years of experience.

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Aims and objectives

Kidney transplantation is a cost-effective method of treatment suited for patients with end-stage chronic kidney disease (CKD). It provides high graft survival rate, increases quality-of-life and prolongs recipient’s lifetime [1-4]. Since the first fully successful renal homotransplantation in identical twins performed by Murray in 1954, an exponential growth in demand for kidney grafts has been noted worldwide, resulting in over 14,000 transplantations performed between 2001-2016 in Poland alone.

Refined surgery techniques, adequate antimicrobial therapy and improved rejection management with immunosuppressive agents have led vascular pathologies to be at the forefront of ailments following kidney transplantation and potentially causing graft dysfunction [5,6]. With the incidence of approximately 3-15% among all transplant recipients [5,7,8], vascular complications may be classified as early, comprising arterial and venous graft thrombosis or late, i.e. transplant artery stenosis (TRAS), arteriovenous fistulae (AVF) and pseudoaneurysms after renal biopsy [1,5,7].

Several suspected underlying factors have been identified for each of the above mentioned pathologies, regarding kidney donor and recipient, graft anatomy and surgical procedure. Risk factors for development of graft thrombosis include atherosclerosis, intimal rupture, faulty anastomosis, longer graft artery than vein, multiple arteries [1], deep vein thrombosis and external compression of the vessel [7]. Deceased donor, donor and recipient age, recipient's haemodynamic state, expanded criteria donor, delayed graft function, ischemic heart disease, cytomegalovirus infection as well as induction immunosuppression are listed among possible causes of the most prevalent vascular complication - TRAS [1,7-10]. Mainly iatrogenic nature of AVF implies graft biopsy to be its predominant cause [5,7,11].

The age-related factors, including atherosclerosis and expanded criteria donor, are of substantial meaning. As relatively steady yearly numbers of renal grafts could not meet the growing demands for kidney transplantation of the aging societies, expanded criteria donor were established allowing elder kidney donors and grafts with compromised vasculature to be transplanted. Such occurrence created conditions for higher incidence of vascular complications, TRAS and thrombosis in particular [1,7,12,13].

In addition to growing transplantation demands, preservation of graft function became even more pivotal, with thorough radiographic evaluation being crucial in decision-making regarding treatment of vascular complications. Ultrasound and Doppler ultrasound proved to be satisfactory screening methods in terms of sensitivity and specificity [2,5,12,14,15,17]. In uncertain cases, further confirmation of diagnosis may be obtained whether by standard invasive means of angiography (which offers immediate treatment options) [5,7,9,12] or non-invasive methods offered by computed tomography (CTA) or
magnetic resonance (MRA) angiography [5,6]. Although prompt diagnosis is essential for implementation of treatment, it also has to be remembered, that iodide-based contrast media applied in angiography and CTA may exacerbate renal insufficiency by exerting nephrotoxic effects, whereas gadolinium-based contrast media have been reported to cause nephrogenic systemic fibrosis [6,8].

With development of minimally-invasive surgery, invasive radiological procedures became method of choice to treat the majority of TRAS (with percutaneous transluminal angioplasty - PTA with or without stenting) [5,7,9,16,17] and large or symptomatic AVFs (via selective and superselective coil embolization) [5,7,11,17,18]. On the contrary, most of the thrombotic complications still require open surgery procedures; excluding cases of partial and early-detected thrombosis which may benefit from immediate direct catheter-guided thrombolysis [9].

The aim of this study is to present a single-center, 15-year (2001-2016) experience in ultrasound diagnosis and interventional radiology treatment of vascular complications after renal transplantation.
Methods and materials

470 adult patients - 162 women (34.5%) and 308 men (65.5%), after renal transplantation from deceased donor were included in a retrospective observational study. The mean age of graft recipients equaled 46.1 ± 13.8 years (detailed demographic data are presented in Table 1.) on the day of transplantation procedure. The median of follow-up period equaled 25 days (range: 1-3507; mean: 387 ± 682). All patients underwent full graft ultrasound examination immediately after operation (1-3 days after procedure) and subsequently, if applicable, at regular scheduled intervals or in presence of clinical indicators of worsened kidney function.

<table>
<thead>
<tr>
<th>number of patients</th>
<th>Total (%)</th>
<th>470 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>308</td>
<td>65.5%</td>
</tr>
<tr>
<td>Female (%)</td>
<td>162</td>
<td>35.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>age (years)</th>
<th>overall</th>
<th>mean ± SD</th>
<th>46.1 ± 13.8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>minimal</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>maximal</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

| male | mean ± SD | 45.5 ± 13.6 |
|      | minimal   | 18          |
|      | maximal   | 73          |

| female | mean ± SD | 47.4 ± 14.0 |
|        | minimal   | 19          |
|        | maximal   | 72          |

Table 1: Patients' detailed demographics.
References: - Lublin/PL

The ultrasound examination of the transplanted kidney was performed with 3.5-5MHz convex or if applicable, additional 6-10MHz linear transducer, and comprised: greyscale measurement of the graft size in longitudinal and transverse projections; greyscale assessment of graft morphology - corticomedullary differentiation, presence of urinary collecting system dilatation and measurement of dilated collecting duct diameter; greyscale assessment of possible presence of perirenal fluid collections; triplex Doppler - B-mode, color-Doppler and spectral mode assessment of the global graft perfusion (examination of the graft artery and vein at the hilum and interlobar vessels in the upper
and lower pole), graft artery and vein from the level of anastomosis to the hilum, as well as adjacent iliac vessels. Triplex Doppler assessments included measurements of peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility (PI) and resistive (RI) indices, renal-iliac ratio (RIR) and acceleration time (AT).

Cut-off values and image characteristics that led to diagnosis of particular vascular complications are stated in Table 2.

<table>
<thead>
<tr>
<th>TYPE OF VASCULAR COMPLICATION</th>
<th>ULTRASOUND AND DOPPLER ULTRASOUND DIAGNOSTIC CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGT</td>
<td>• complete absence of flow over intrarenal vessels on color flow (including B-flow) and spectral analysis</td>
</tr>
</tbody>
</table>
| VGT                           | • absence of renal venous flow  
• renal enlargement and hypoechoicity  
• reversal of flow in the renal artery in diastole |
| TRAS (>60%)                   | • PSV > 1.8 m/s  
• EDV > 1.5 m/s  
• AT > 0.08 s  
• AI > 3 m/s²  
• RIR > 3.5  
• tardus-parvus waveforms |
| AVF                           | • focal mosaic appearance on color Doppler  
• high-velocity, low-resistance waveform of the feeding artery on spectral Doppler  
• pulsatile or ‘arterialized’ waveform over draining vein |
| PA                            | • simple or minimally complex cyst on B-mode  
• ‘yin-yang’ flow pattern within the body of the PA on color Doppler  
• to-and-fro flow in the neck of PA on spectral Doppler |

Table 2: Vascular complications diagnostic parameters. AGT - arterial graft thrombosis, VGT - venous graft thrombosis, PA - pseudoaneurysm, PSV - peak systolic velocity, EDV - end diastolic velocity, AT - acceleration time, AI - acceleration index, RIR - renal-iliac ratio

References: - Lublin/PL

If applicable, interventional radiology treatment was introduced after consultation with transplantation surgery department and additional radiographic confirmation of the pathology. For TRAS, PTA alone (with use of conventional balloon or drug-eluting balloon - DEB) or PTA with stenting were performed depending on individual indications based on patient's clinical characteristics, stenosis degree and morphology, as well as
procedure course and possible residual stenosis or immediate complications. In case of symptomatic AVF, selective coil embolization was implemented.
Results

Vascular complications were observed in total of 1.7% patients (n=8), and comprised: arterial stenosis at the site of anastomosis in 1.1% (n=5), renal vein thrombosis in 0.4% (n=2) and formation of arteriovenous fistula after graft biopsy in 0.2% (n=1) of patients. No cases of renal artery thrombosis, aneurysms or pseudoaneurysms were noted.

<table>
<thead>
<tr>
<th>Complication type</th>
<th>No. days from RTX</th>
<th>Invasive radiology treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. TRAS loco typico</td>
<td>757</td>
<td>PTA + carbon-coated stent deployment</td>
</tr>
<tr>
<td>2. TRAS loco typico</td>
<td>227</td>
<td>PTA + carbon-coated stent deployment</td>
</tr>
<tr>
<td>3. TRAS loco typico</td>
<td>121</td>
<td>PTA + DEB</td>
</tr>
<tr>
<td>4. TRAS loco typico</td>
<td>200</td>
<td>PTA + DEB</td>
</tr>
<tr>
<td>5. TRAS loco typico</td>
<td>178</td>
<td>PTA + non-drug eluting balloon</td>
</tr>
<tr>
<td>6. RVT</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>7. RVT with extensive ilio-femoral DVT, popliteal DVT</td>
<td>7</td>
<td>Filter implantation to IVC</td>
</tr>
<tr>
<td>8. AVF</td>
<td>17</td>
<td>Coil embolization (Interlocking coil)</td>
</tr>
</tbody>
</table>

Table 3: Vascular complications detected during ultrasound follow-up and employed treatment. RVT - renal vein thrombosis, DVT - deep vein thrombosis, AVF - arteriovenous fistula, TRAS - transplanted renal artery stenosis, PTA - percutaneous transluminal angioplasty, DEB - drug eluting balloon, IVC - inferior vena cava

References: - Lublin/PL

All stenotic patients (n=5) were qualified for endovascular treatment as graft-saving procedure. Drug-eluting balloon (DEB) angioplasty was performed in 2 patients, uncoated balloon angioplasty in 1 patient, and balloon angioplasty with carbon-coated stent deployment due to residual stenosis was implemented in the remaining 2 patients. The immediate technical success rates, defined as complete reperfusion of the renal artery, reached 100% (n=5).

Each of the angioplasty procedures was conducted under local anesthesia at the site of puncture. Seldinger technique was employed to obtain ipsilateral, contralateral or mixed arterial access, through which a 5-5.5F vascular sheath was then introduced (with a cross-over technique if applicable) to reach the level of common femoral
artery. Angiography was then performed in order to visualize localization of the stenosis. In the following step, a 0.014”-0.035” catheter was employed to pass through the stenotic fragment. Subsequently, balloon angioplasty was performed with use of either conventional balloon or DEB (Fig. 1). In the two cases of stenting, carbon-coated stents were deployed following balloon angioplasty, due to presence of residual stenosis (Fig. 2-3). Control angiographies demonstrated adequate degree of renal graft arteries dilatation. The technical success rates equaled 100%. No procedure-related complications were observed.
Fig. 1: Consecutive steps of PTA procedure with use of drug-eluting balloon are pictured. Selective graft arteriography depicts the localization of stenosis. Post-procedural control angiography presents full resolution of the stenosis.

References: Department of Interventional Radiology and Neuroradiology, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, Lublin/PL

Fig. 2: A pre-procedural ultrasound examination of the patient who undergone PTA with stent deployment due to TRAS. (A) Greyscale measurements of the kidney size. (B) Post-stenotic flow waveform within intrarenal arteries. (C) and (D) PSV>400 m/s at the main renal artery suggestive of TRAS. (E) Duplex evaluation of the TRAS at the anastomosis in a longitudinal projection.

References: Department of Interventional Radiology and Neuroradiology, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, Lublin/PL
**Fig. 3:** PTA plus carbon-coated stent deployment in patient with TRAS. Consecutive steps of the procedure are shown. (A) Pre-procedural arteriography from the level of abdominal aorta. (B) After catheterization of left external iliac artery an arteriography was made, depicting TRAS at the site of anastomosis. (C) Additional ipsilateral access was obtained due to angulation of graft artery origin. (D) Balloon angioplasty was first performed in order to dilate stenotic fragment of renal artery. (E) Residual post-PTA stenosis is well-visible. (F) A full flow restoration had been achieved after stent insertion.

**References:** Department of Interventional Radiology and Neuroradiology, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, Lublin/PL

The symptomatic AVF was treated under local anesthesia by means of superselective coil embolization with use of interlocking coil. Arterial access was obtained with Seldinger technique by puncturing contralateral common femoral artery. To reach the
level of renal graft artery (anastomosed with left external iliac artery), a catheter was introduced over a J-wire by means of cross-over technique. Selective angiography was then performed, which pictured an AVF originating from lower pole interlobar artery. Subsequently, a microcatheter was introduced to the AVF feeding artery to perform superselective angiography. The AVF embolization with a single 3x60 mm interlocking coil was implemented. Control angiography depicted complete closure of the AVF. Both immediate technical and clinical successes were achieved in this particular case. (Fig. 4-5).

**Fig. 4:** Pre-procedural ultrasound examination of a patient with diagnosis of AVF. (A) and (B) A residual flow has been depicted despite high PRF values, which is suggestive of AVF presence. (C) Low RI and PI indices measured within renal artery - typical for AVF. (D) Increased PSV at the location of AVF. (E) and (F) Undisrupted flow pattern over main renal artery.

**References:** Department of Interventional Radiology and Neuroradiology, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, Lublin/PL
Fig. 5: Selective coil embolization of the AVF. (A) Selective arteriography depicts nearly simultaneous contrast enhancement over AVF feeding artery and draining vein. (B) Superselective arteriography of the feeding artery allowed for exact localization of the fistula. (C) Single interlocking coil was deployed in the feeding artery. (D) Control arteriography depicts successful closure of the AVF.

References: Department of Interventional Radiology and Neuroradiology, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, Lublin/PL

An inferior vena cava filter had been implanted as an emergency procedure in the patient with extensive thrombotic complications comprising RVT, ilio-femoral DVT and popliteal DVT. (Fig.6-7) Both patients diagnosed with RVT were lost to radiological follow-up.
Fig. 6: Pre-procedural ultrasound examination of the patient with extensive venous thrombotic complications. (A) No color signal had been noted over renal artery of the graft. (B) Color-Doppler imaging shows arterial flow and no signs of venous flow over iliac vessels. (C) Color aliasing in a patent artery due to very low PRF values. (D) Subtle flow wave reversion over renal artery.

References: Department of Interventional Radiology and Neuroradiology, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, Lublin/PL
**Fig. 7**: Temporary filter inserted into inferior vena cava of the patient with extensive thrombotic complications.

**References**: Department of Interventional Radiology and Neuroradiology, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, Lublin/PL
Conclusion

Vascular complications are relatively rare occurrences in patients after renal transplantation, with reported incidence rates of approximately 2.5-15% [5-8]. However, they pose a significant risk of graft malfunction or rejection [5,6,12]. Therefore, there exists a need for sufficient, non-invasive monitoring and screening tool.

According to the literature, ultrasound and Doppler ultrasound modalities proved to be reliable diagnostic means by fulfilling the above-mentioned criteria in terms of sensitivity (87-94%) and specificity (86-100%) [12,15]. They are successfully employed in the early post-operative period, as well as used for long-term follow-up [5]. However, the use of unenhanced ultrasound examination is limited with respect to discrimination between causes of early graft dysfunction, i.e. acute tubular necrosis, rejection and toxicity attributed to immunosuppressants [2]. In addition, patient-related factors, e.g. flatulence, excessive peristalsis, intraabdominal inflammation, free abdominal fluid may obscure the classical ultrasound image. Due to this fact, some researchers postulate implementation of contrast-enhanced ultrasound (CE-US) to the radiographic routine of graft monitoring. CE-US allows for better visualization of anastomotic region, even in unfavorable examination conditions, and there exists a strong positive correlation between the degree of stenosis at the anastomosis and the prolonged graft parenchymal perfusion time in CE-US [12,14].

In our study, combined methods of greyscale, color and spectral Doppler ultrasound allowed for detection of vascular complications in 1.7% (n=8) patients in the studied population of 470 renal graft recipients.

In general, the results from our investigation indicate lower rates of vascular complications occurrence than had been previously reported in the literature, possibly because relatively extensive criteria were applied in the ultrasound diagnostic protocol proposed for this study (as mentioned in the Methods and Materials section). Numerous publications pointed TRAS to be the most prevalent ailment among vascular complication in transplanted kidneys, with incidence rates at the level of 3-23% [5,7,8,14]. However, in our study TRAS was detected in 5 out of 470 patients, which merely account for 1.1% of the screened population. All of the diagnoses were further confirmed with pre-procedural angiography. A single AVF was diagnosed in the study population, which accounted for 0.2% of all renal grafts, whereas the incidence of 8.3% in post-biopsy allografts have been described by Schwartz et al. [11] and can be as high as 18% as reported in other studies [9]. Finally, the contrast between incidence of RVT among our patients: 0.4% (2 cases) and rates reported in literature, which oscillate between 0.3-18% of allograft biopsies [7,10,17], seems to be the lowest.

Nonetheless, time references for pathology occurrence seem to be consistent with the results of previously reported investigations. Although TRAS may occur at any post-transplantation time, the significant majority of cases are observed within 3-24 months.
The onset time range of 121 to 757 days [4 to 25 months] presented in our series is coherent with these findings. On the contrary, thrombotic events are known for their sudden development in the very first week [5] or even hours [20] after kidney transplantation. Both of the patients diagnosed with RVT developed the pathology within 7 or less days counting from the date of transplantation, thus supporting the above-mentioned information. In case of AVF, the ailment’s onset is closely-related to performed biopsy, therefore no specific time ranges can be set strictly. Nonetheless, it had been observed that allografts are more prone to the AVF development, if the biopsy occurred within first 6 weeks after surgery. The authors of this particular observation postulate that such circumstance may be explained with greater vulnerability and susceptibility of the graft at early post-transplantation stages [11]. The only symptomatic AVF included in our series arose after 17 days from transplantation procedure.

The emphasis should be put on graft-saving procedures which may be implemented after stating ultrasound diagnosis of vascular complications. This is of particular importance, especially given the tendency of growing demands for renal transplantation in older populations, which is not associated with an increase in the number of available grafts [13].

Interventional radiology offers a selection of procedures applicable to treat post-transplantation vascular complications in renal allografts. Due to the low periprocedural morbidity rates and minimally invasive nature, radiologic methods became the first line of therapy, especially that it does not exclude future surgical procedures [7,8].

Out of 5 TRAS cases presented in this investigation, all were treated by means of PTA with optional stenting procedure, depending on presence of residual stenosis. The immediate technical success rates equaled 100%, as the proper blood flow has been established through the previously stenotic region of the vessel. The longest, 2-year radiologic follow-up of the patient with TRAS showed no long-term complications of the procedure and proper graft function. Such results are consistent with the outcomes of previously reported series comparing treatment with PTA alone and PTA with stenting in patients with TRAS. In the majority of studies, technical success rates of PTA approximated 60-90% and clinical success rates of the procedure exceeded 80% [8,9]. The clinical success was considered as relieve in TRAS-related symptoms, i.e. refractory hypertension and deteriorating graft function represented by high serum creatinine levels. The reported results for PTA with stenting comprised blood pressure improvement in over 65% of patients and the initial graft function improvement in almost 45% patients, as described by Peregrin et al. However, in the same series not a single patient became normotensive and medication-free [17].

Although more than 75% of biopsy-related AVFs resolve spontaneously within 24 months, the large and/or symptomatic ones require proper medical care and the embolization has become the treatment of choice [7,11,17]. Selective or superselective transcatheter coil embolization proved to be a safe and highly-effective therapeutic method, leading to improvement in renal graft function and minimizing the loss of allograft tissue, as
compared to surgery [17,18]. This particular treatment was successfully implemented in the single reported case of AVF in our series, resulting in both technical and clinical successes.

There exists a well-recognized relationship between renal and ileo-femoral thrombosis with the extension of the latter being risk factor for the occurrence of thromboembolic adverse event in renal graft recipients [10,20]. Regarding this, a decision was made to insert a temporary filter inside inferior vena cava of the patient with extensive ileo-femoral, popliteal and renal vein thrombosis, on emergency basis. Unfortunately, this patient had been lost to radiologic follow-up and no further information on his medical condition are known to the authors of this presentation.

Vascular complications are rare occurrences in patients after renal transplantation. However, they pose a significant risk of graft malfunction or rejection. Endovascular minimally-invasive radiologic procedures demonstrated to be sufficient, highly-effective treatment technique of these pathologies.
References


