

Color Doppler Ultrasonography in the Diagnostic Evaluation of Renal Allografts

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Key Words

Color Doppler ultrasonography · Contrast-enhanced sonography · Chronic allograft nephropathy · Renal transplantation

Abstract

Color Doppler ultrasonography of large allograft vessels and renal parenchyma is established firmly in the diagnosis of renal allograft perfusion. While conventional color Doppler ultrasonography has proven itself to be an indispensable, rapid, highly valid and practicable method, e.g. in the diagnosis of allograft artery stenosis or allograft vein thrombosis, the diagnostic usefulness of this method with regard to allograft perfusion is considerably limited. With contrast-enhanced sonography, a simple and readily implementable method that enables the early diagnosis of chronic allograft nephropathy is now available. The timely diagnosis of vascular damage prior to a rise in S-creatinine offers the possibility of early therapeutic intervention and thus at least the potential for the improvement of allograft survival.

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Conventional Color Doppler Ultrasonography of Kidney Allografts

Color Doppler Ultrasonography of the Large Vessels of Renal Allografts

Color Doppler ultrasonography of kidney allografts is a standard procedure in the routine diagnosis of renal allografts [1]. Particularly in the early postoperative period, suspected vascular problems such as allograft artery occlusion (fig. 1) or allograft artery thrombosis (fig. 2) are detectable early by color Doppler ultrasonography and allograft function can be preserved.

It should be noted, for example, that in the evaluation of the allograft artery for stenosis, as opposed to the native kidneys, the renal inflow may depend significantly upon renal function, i.e. the flow velocity in the entire length of the non-stenotic artery may exceed 200 cm/s [2, 3]. On the other hand, a regional flow acceleration may already indicate a relevant renal artery stenosis if the flow velocity ratio in the other areas of the main artery is only one-third or one-fourth. Direct criteria for stenosis of the allograft arteries are localized flow accelerations of more than 1.5-fold compared with pre- or post-stenotic velocities. In this case the sensitivity and specificity of color Doppler ultrasonography are approximately 90% [2].

Color Doppler ultrasonography is essential, particularly postoperatively, in the evaluation of the allograft

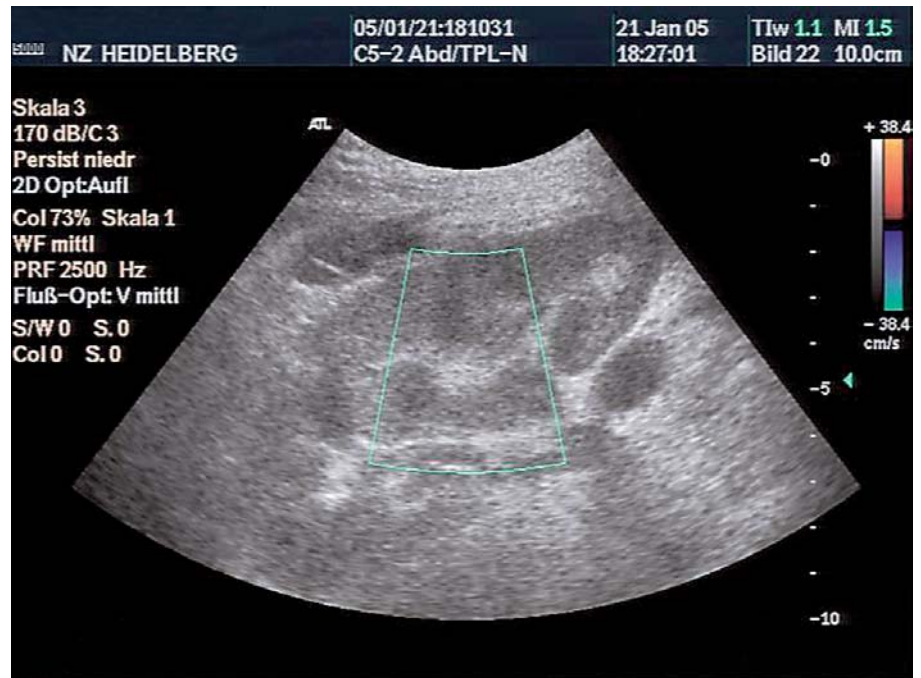


Fig. 1. Color Doppler ultrasonography absence of perfusion in the kidney allograft during complete arterial occlusion (by courtesy of Springer Verlag, Heidelberg, Germany).

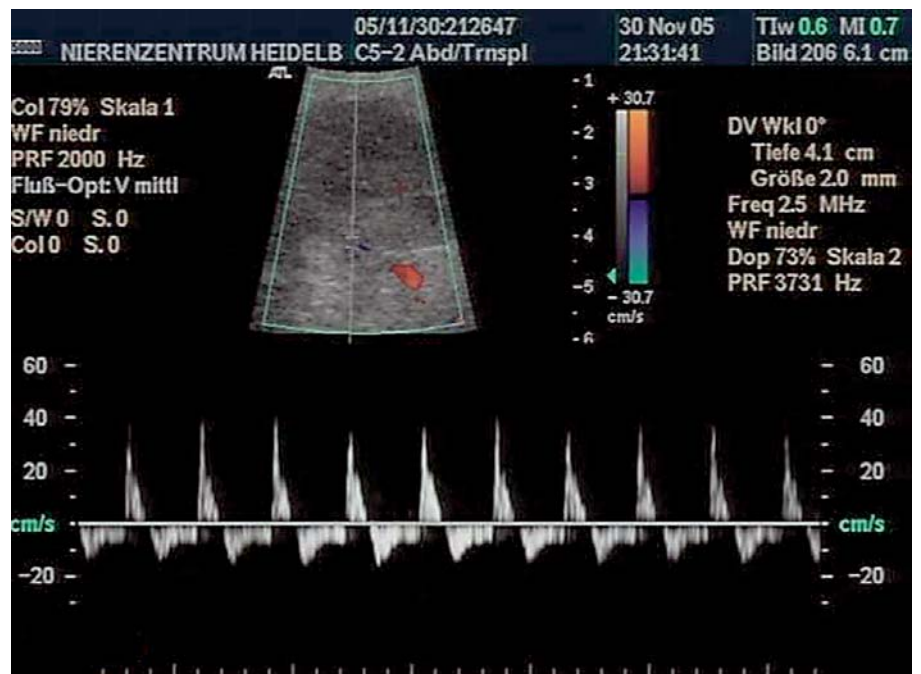


Fig. 2. Color Doppler ultrasonography evidence of a kidney allograft vein thrombosis with arterial reverse diastolic flow (by courtesy of Springer Verlag, Heidelberg, Germany).

vein. Complete allograft vein thrombosis can be reliably identified with color Doppler ultrasonography if no veins are educible intrarenally, or if pathognomic reversed diastolic flow exists in the arteries (!). This reversed diastolic flow results from the maximal increase in flow resistance during complete renal vein thrombosis, i.e. the re-

trograde blood flow during diastole. The diagnosis may be more difficult in the event of incomplete renal vein thrombosis. In addition, evidence of arteriovenous fistulae of the allograft, particularly following renal biopsies, is highly visible via the use of color Doppler ultrasonography due to an aliasing phenomenon.

Determination of Resistance Index

In addition to B-mode ultrasonography and the evaluation of the large vessels of the renal allograft, the determination of the resistance index (RI) [1] is considered a standard practice in clinical monitoring. A prospective study [4] postulated that a RI of >0.8 predicts not only the survival of the allograft but also patient survival. Although this study emphasizes the value of color Doppler ultrasonography of allograft kidneys for the first time, uncertainties in everyday clinical practice nevertheless persist. For example, the high RI of over 0.8 did not correlate significantly with the findings of the 6-month protocol biopsy. Furthermore, it was not the age of the donor (and therefore the kidney) but rather the age of the recipient and the blood pressure amplitude that most strongly correlated with the RI. It is worth noting that in this method the RI, as shown by Heine et al. [5] and us [6], assesses not only the renal vessel situation in the allograft, but also indirectly the elasticity of the large upstream vessels. Based on this substantial prospective study [4], it appears highly advisable to incorporate color Doppler ultrasonography into the routine examination of kidney allografts. However, in the interpretation of high RI values, the intima medial thickness (as an indicator of vascular damage), pulse pressure or preferably, if possible, pulse wave velocity should be ascertained. It has not yet been determined to what extent the threshold value of 0.8 truly indicates a good cut-off point, as it was arbitrarily selected (at least for the kidney allograft).

It has been demonstrated in several studies that the diagnostic value and interpretation of the RI is very limited, for example in the event of acute allograft dysfunction or rejections [7, 8]. For an assessment of allograft rejection, the order of RIs, i.e. the increase of the RI, is important and not the individual value. It is not possible to interpret an isolated elevated RI and to differentiate whether this is the result of decreased renal function, acute tubular necrosis, calcineurin inhibitor toxicity or rejection. For the reasons mentioned, the evaluation of the RI in the case of chronic allograft dysfunction is likewise very limited.

Color Doppler Ultrasonography in Chronic Allograft Nephropathy (CAN)

Non-immunological factors [9, 10], among other reasons, lead to CAN and are particularly important in the long-term medical management of renal allograft recipients [11]. In particular, early diagnosis and potential treatment plays an important role for long-term allograft function. CAN is characterized by chronic interstitial fi-

brosis, tubular atrophy and vascular fibrointimal hyperplasia and represents one of the primary causes of allograft loss [12].

CAN is difficult to diagnose by non-invasive techniques. The calculation of the RI is not reliable for the diagnosis of CAN [13, 14]. Modern color Doppler ultrasonography techniques for the early diagnosis of CAN are thus especially important. The difficulty in the interpretation of new methods is that the results require comparison to allograft histology. Most recent ultrasound techniques have not yet been validated due to a highly inhomogeneous patient population and the lack of histological data [15]. In the meantime, at least two biopsy-proven and promising color Doppler ultrasonography techniques are available with a distinctly higher sensitivity and specificity than conventional color Doppler ultrasonography [16, 17].

Modern Color Doppler Ultrasonography Techniques of Kidney Allografts

Determination of the Maximal Fractional Area (MFA)

Nankivell et al. [17] were able to demonstrate the advantages of their technique with the cineloop technique (Philips Medical Systems) in a pilot study involving 13 patients and prospectively in 67 patients with biopsy-proven CAN. Two 5-s color Doppler cineloop images in longitudinal sections were evaluated independently of each other. A histogram was plotted in which the median blood flow velocity within a region of interest (ROI) was measured. The maximum and minimum values were analyzed and the fractional area was calculated as a percentage ratio of the color pixels in this area in relation to the entire ROI (maximal divided by minimal fractional area). Of the 67 kidney allograft patients examined, 32 exhibited no CAN, 20 patients had grade I (1°) CAN and 15 patients exhibited grade II (2°) CAN. The RIs determined were comparable in all three groups; the diagnosis of CAN was therefore not possible via color Doppler ultrasonography determination of the RI (table 1). When the MFA (MFA) was utilized, patients without CAN (according to the BANFF criteria) differed significantly from patients with CAN 1° ($p < 0.01$) and CAN 2° ($p < 0.001$). The MFA was higher in patients without CAN than in patients with CAN 1° , and higher than in patients with CAN 2° ($p < 0.01$) (table 1). In patients with calcineurin inhibitor toxicity, the MFA was likewise reduced (18.0 ± 9.3 vs. $26.9 \pm 10.7\%$; $p < 0.01$). When the distance between

Table 1. Significance of the maximal fractional area (MFA) in the diagnosis of chronic allograft nephropathy (according to Nankivell et al. [17])

	CAN 0° (n = 32)	CAN 1° (n = 20)	CAN 2° (n = 15)
RI	0.66 ± 0.07	0.70 ± 0.06	0.69 ± 0.08
MFA	28.5 ± 9.7	18.0 ± 8.0*	12.5 ± 6.4**

RI = Resistance index; MFA = maximal fractional area; CAN = chronic allograft nephropathy.

* p < 0.01 (compared to CAN 0°). ** p < 0.001 (compared to CAN 1°).

peripheral color pixel accumulation and the renal capsule was additionally measured, it was demonstrated that the distance is greater in patients with CAN 2° in comparison to those without (6 ± 1.6 vs. 3.9 ± 1.0 mm; $p < 0.01$). With the MFA alone, CAN was diagnosed with a sensitivity of 69%, a specificity of 88% and a positive predictive value of 86%, and even in patients with severe CAN, with a sensitivity of 87%, a specificity of 71% and a positive predictive value of 46%. When a threshold value of 5 mm was taken for the collection of the peripheral color pixels up to the renal capsule, it was less sensitive on one hand (49%), though at 91% somewhat more specific. In the combination of the MFA and distance measurement, although the sensitivity falls to 46% for the accurate diagnosis of CAN, the specificity rises to 97% [17].

Although these data are preliminary, these studies are nonetheless very promising, and the MFA, alone or in combination with the distance measurement, is helpful, at least in the evaluation of severe allograft nephropathy. This technique is, however, far superior to the conventional color Doppler ultrasonography with regard not only to CAN 2° but also to CAN 1°. Moreover, in this investigation it was shown that an RI of 0.8 represents a poor discriminatory power [17].

Real-Time Contrast-Enhanced Sonography (CES)

A further possibility in the ultrasonography diagnosis of CAN is real-time CES. Numerous (in particular cardiologic) trials have verified the practicability of contrast-enhanced echocardiography, specifically in the determination of cardiac perfusion. The safety of these procedures was recently summarized in a review [18]. Data from animal experiments on safety likewise indicate that renal damage was unverifiable [19]. Allergic reactions to

the contrast agent are rare and are less than 1% according to the manufacturers' product information.

With real-time CES, the renal allograft is first displayed in B-mode. After alignment of the longitudinal axis, a switch is made to an ultrasonography contrast technique with a low mechanical index (MI), in accordance with international guidelines [20]. The ultrasonography contrast agent is administered intravenously as a bolus injection for 10–20 s. The image display is made in low MI color mode (MI = 0.1) at the rate of approximately 10 images/s. After about 15–25 s, the initial visualization of the kidney allograft appears through the ultrasonography contrast agent. When the peak of the contrast agent enhancement is reached after 35–45 s, a 0.3- to 0.5-second pulse with a high mechanical index (MI = 1.0) is emitted to destroy the tiny microbubbles from the ultrasonography contrast agent (fig. 3a). A powerful ultrasonography contrast signal is thereby emitted. We utilized an ultrasonography contrast agent consisting of perflutren-containing microspheres from heat-treated albumin (1% albumin solution) for this purpose. The concentration is $5\text{--}8 \times 10^8$ perflutren-containing microspheres per ml with a mean diameter of 2–4.5 μm . The average concentration of perflutren gas is 0.22 mg/ml ultrasonography contrast solution. After the emission of the high MI pulse, the display with the low MI is automatically reverted back to and the reinjection of the ultrasonography contrast agent is recorded over 10–15 s (fig. 3b–d).

For quantitative analysis of renal tissue perfusion, a ROI is placed in the renal cortex. For this purpose we chose a volume within the ROI of approximately 500 mm² (fig. 3d). The aa. interlobar and arcuate vessels must be excluded from the ROI. By means of a software tool developed for this device (Q-Lab Medical, Philips), the contrast agent concentration (maximum and increase over time according to an exponential function) was plotted (fig. 4). Blood flow was quantified by the product of the maximum signal intensity and elevation according to an exponential function [$y = A \cdot (1 - e^{-\beta t})$] and thus described in more detail [16]. It was demonstrated in 26 kidney allograft recipients [16] that the renal blood flow established using this method can diagnose CAN with a sensitivity of 91% and a specificity of 82%. In comparison, conventional color Doppler techniques achieved a sensitivity of 82% and a specificity of 64% [16]. Interestingly, as in Nankivell's study, a RI of 0.8 was not a reliable discriminatory power in the evaluation of allograft dysfunction [16, 17]. The RI obtained the highest sensitivity and specificity as a discriminatory power for CAN with

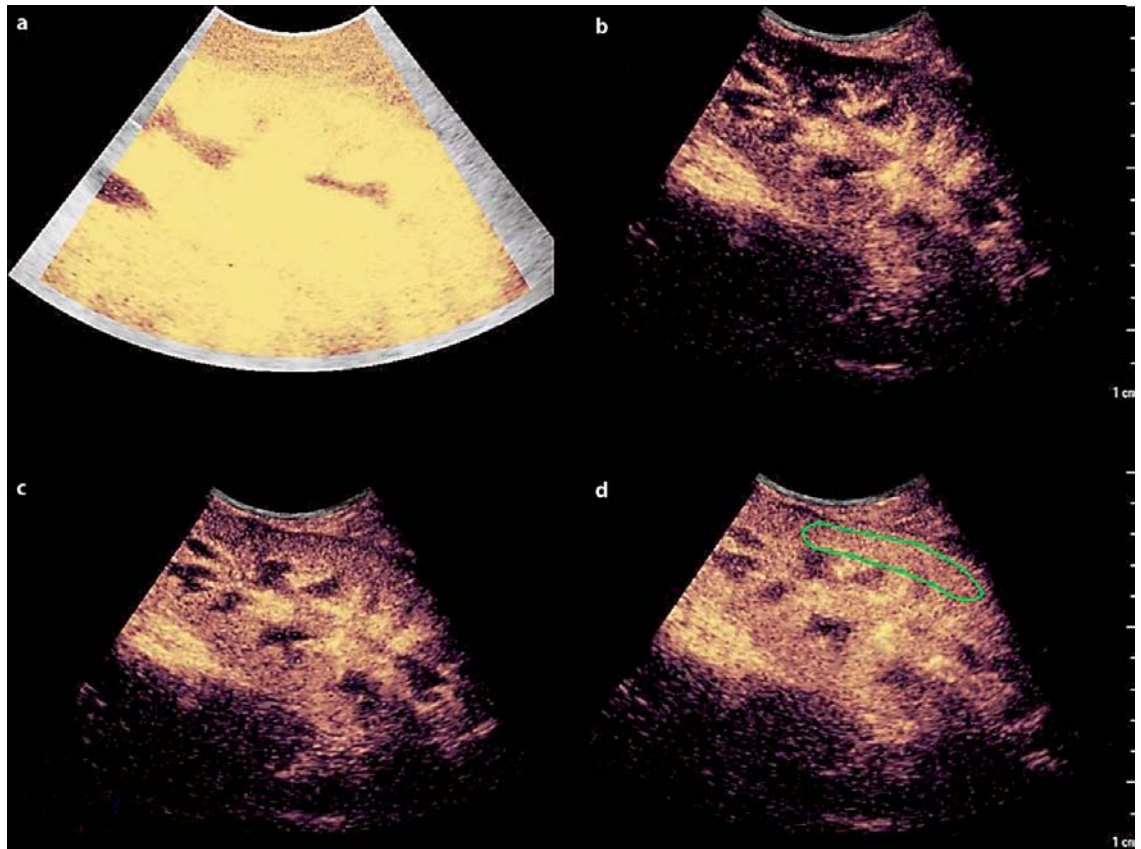


Fig. 3. Contrast-enhanced sonography of a kidney allograft. **a** Pulse with a high mechanical index (MI), which affects the eradication of the gas bubbles from the sonography contrast agent. **b–d** Replenishment of the ultrasonography contrast agent after the emission of a pulse with a high MI (1.0). **d** Placement of a ROI in the renal parenchyma (by courtesy of Springer Verlag, Heidelberg, Germany).

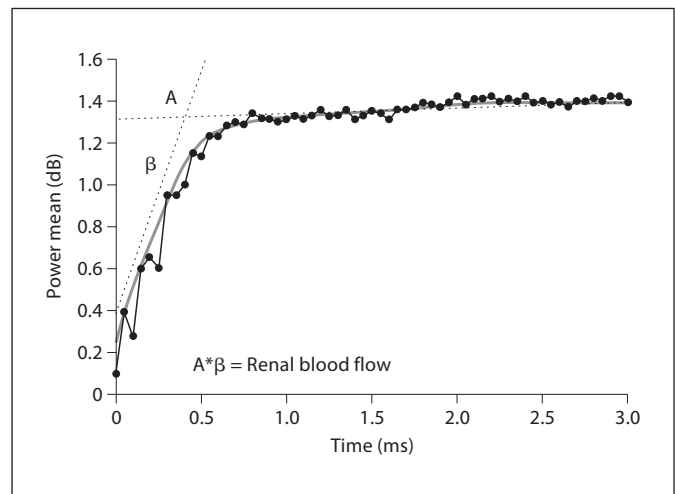


Fig. 4. Curve progression of the replenishment of the sonography contrast agent following the emission of a pulse with a high MI (1.0). Determination of perfusion from the product of the maximum and rise over time (by courtesy of Springer Verlag, Heidelberg, Germany).

a value of 0.68; for the renal perfusion measurement, the value was 5.79 dB/s [16]. Intraobserver variability was 4–7% and the pressure of the transducer on the allograft was almost only determined by the weight of the ultrasound array. Color gain settings were optimized and kept constant during the complete investigation period (color gain 75%).

As mentioned before, early diagnosis of CAN is especially important – that is before the onset of irreversible damage and an increase in S-creatinine has already taken place. Notably, in our study, 6 of 11 patients with biopsy-proven allograft nephropathy exhibited a serum creatinine level of <2 mg/dl [16]. By means of CES, these patients were identified earlier with only slightly elevated

serum creatinine levels. Therefore, CES is the first non-invasive ultrasound methodology to detect the onset of CAN even before S-creatinine increases. Further studies are certainly necessary in this area to confirm this pilot experiment, particularly to investigate other applications such as acute vascular rejection and calcineurin inhibitor toxicity.

In summary, color Doppler ultrasonography and the calculation of the RI alone in the diagnosis of CAN are afflicted with many uncertainties. Modern techniques, such as the calculation of the MFA and CES, are very promising procedures which enable the timely diagnosis of CAN.

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