The closer the shield, the higher the score: timing of resistance index measurement and its prognostic impact in kidney transplant recipients

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Doppler ultrasound is a non-invasive imaging method, widely used in kidney transplant recipients. In the very early period after transplantation, the measurement of blood flow in the main vessels of kidney grafts helps to verify the patency of vascular anastomoses and to exclude thrombotic complications. Simultaneously, the spectrum of Doppler blood flow is routinely measured within the kidney graft’s segmental arteries and is described with two parameters of vascular resistance: the pulsatility and resistance indices, calculated based on systolic peak velocity and end-diastolic velocity. Of note, the values of resistance indices are particularly elevated in patients with delayed graft function (DGF), which is mostly the consequence of acute tubular necrosis (ATN) and/or acute rejection [1]. When measured repeatedly, resistance indices help to detect those complications more effectively [2, 3]. On the other hand, parameters of vascular resistance may also predict the severity and duration of ATN [1, 4]. In the immediate post-transplant period, Doppler ultrasound is a first-line diagnostic measure in routine daily clinical practice in case of kidney graft dysfunction without an evident cause.
The prognostic value of resistance index (RI) for long-term graft and recipient survival after kidney transplantation was thoroughly evaluated. In the seminal prospective trial performed in 601 stable kidney transplant recipients, Radermacher et al. [5] demonstrated that RI >0.8 was associated with poor subsequent allograft performance or death. However, the time frame of RI measurements analysed in this study was extensive and included longer time points of the post-transplant follow-up period, with a median of 40 months, ranging from 3 to 317 months. This extreme range caused the Aachen group to hypothesize that the predictive value of RI may differ substantially depending on the time of the RI measurement after transplantation. In this issue of NDT, Kramann et al. [6] published the results of a retrospective analysis of RI values measured in 88 kidney transplant recipients in three different time spans: 0–3, 3–6 and 12–18 months after transplantation and of their power to predict renal allograft survival. The authors found that only RI measured between 12 and 18 months after transplantation, in contrast to earlier measurements, had a significant predictive value for renal allograft failure or recipient death. The multivariate analysis confirmed this finding with the highest hazard ratio for combined end point (allograft failure with a return to dialysis or death) for RI measured at the last time span, i.e. between 12 and 18 months [6]. The authors’ final conclusion pointed out the relationship between the timing of the RI measurement after transplantation and RI predictive value for graft failure or death, simultaneously denying such a value for the RI measured within the first 6 months post-transplantation.

The observation about the higher predictive impact of RI measured later in comparison with its earlier measurements in the same patient is original in the transplant literature, although it is not quite surprising. The later the measurement, the shorter the time is left to foresee the long-term transplant outcomes, and so the narrower the inaccuracy margin becomes for prognosis. It works exactly like a weather forecast, we would say. However, in our opinion, the lack of predictive value of RI measured within the first 6 post-transplant months in this study seems not to be universal. Regarding the first 3 months, there are several reports confirming the predictive value of RI measured in the segmental arteries of the kidney graft for such end points like 1-month and 1-year allograft function [7], serum creatinine increase >50% during a mean follow-up of 49 months [8], graft failure during a mean follow-up of 63 months [9] or serum creatinine increase >30% or death-censored graft loss during a mean follow-up of 54 months [10]. Unfortunately, the first three analyses did not include the kidney transplant recipients with post-transplant complications, and three of four had relatively small number of participants [7, 8, 10]. Even so, four other reports with RI measured shortly after transplantation in a large consecutive cohort of patients were published recently. In the work of McArthur et al. [11], RI measured within the first week after transplantation revealed no significant association with death-censored graft survival, whereas the RI measured between 1 week and 3 months after transplantation was independently correlated with death-censored graft survival at multivariate analysis. This observation, to some extent, harmonizes with our theory of forecast accuracy. On the contrary, however, according to the work of Loock et al. [12] neither 4-month nor 12-month RI predicted graft loss, whereas patients with ΔRI4–12 ≥ 10% revealed an increased risk of graft loss with a hazard ratio of 6.21. This remark corresponds well with the previously reported higher clinical impact of Doppler parameters’ based on their serial measurement [2, 3], thus confirming the dynamic nature of this diagnostic tool. Nevertheless, in our recent work [13], we demonstrated that high RI values measured in segmental arteries of the kidney graft in the early post-transplant period are the predictor of worse kidney graft function and all-cause graft loss, including the patient death. We have also observed the significant trend for death and for combined outcome in three subsequent initial RI tertile groups, aligned according to increasing RI value. Finally, Barba et al. [14] found that RI measured as early as 24 h after surgery yields information that can help to predict long-term graft survival. In multivariate analysis, RI >0.7 and an absence of normal orthograde flow within the graft’s vasculature were the only factors, independently associated with graft survival.

The latter finding compels us to further highlight the nature of RI and its ability to reflect graft and recipient outcome after kidney transplantation. First, it has long been generally assumed that parameters of vascular resistance measured in the segmental arteries of transplanted kidneys reflect the degree of interstitial oedema within the graft, developed as a consequence of ischaemia–reperfusion injury. Recently, an experimental study by Herrler et al. [15] finally validated this hypothesis, hence allowing us to explain the markedly elevated pulsatility index and RI values observed in patients with DGF and/or acute rejection. Noteworthy, as those early post-transplant complications were shown to be independently related to worse allograft survival [16, 17], with the worst outcome in patients with both DGF and rejection, thus, the negative prognostic impact of significantly higher RI values on long-term kidney transplant outcomes probably, at least in part, reflects the influence of DGF or rejection itself.

Secondly, it has been shown in stable transplant recipients that RI values measured within the kidney graft were associated with systemic atherosclerosis [RI correlated with common carotid intima-media thickness (IMT) and was increased in patients with abnormal ankle-brachial index [18]]. Additionally, intrarenal RI values were significantly different between the three groups based on the Framingham risk score (FRS) for coronary heart disease, and high-risk patients had significantly higher RI than low-risk ones. In the same group of patients, Gerhart et al. [19] have shown that after 5 years, both increased IMT and high FRS were positive predictors of the combined outcome (>50% increase of serum creatinine, graft loss or death). In contrast, increased RI was associated with allograft loss only in a subgroup of low-risk patients, not in the entire cohort. In line with this observation, Schwenger et al. [20] found that in patients with a stable kidney transplant, graft RI depends on vascular stiffness, characterized by pulse wave velocity, pulse pressure and IMT. Finally, a majority of studies in patients with stable kidney transplant clearly show a correlation between RI value and age...
of the recipient, but not of the donor. On the other hand, in those recipients who were 10 or more years younger than their living donors, Aschwanden et al. [21] reported a rapid and significant decrease of kidney graft RI in comparison with the same kidney RI measured in living donor before transplantation. When analysing resistance indices in stable kidney graft recipients, Krumme et al. [22] found no correlation with numerous parameters of kidney function, such as serum creatinine concentration, creatinine clearance rate and proteinuria. All the above-mentioned observations strongly support the hypothesis that kidney graft RI is rather a haemodynamic index that reflects the complex integration of arterial compliance, pulsatility and peripheral resistance of a whole vasculature of the recipient, than a specific marker of kidney damage.

In conclusion, the main finding of Kramann et al. [6] confirming the dependency of RI predictive value on the post-transplant period of analysed RI measurement seems to be a valuable observation, which would further improve the accuracy of RI interpretation. However, taking into account the results of already-published studies, as well as some limitations of Kramann’s work, it seems that the time point of RI measurement after kidney transplantation might not to be a crucial factor determining its prognostic value for the long-term post-transplant outcomes. It is worth bearing in mind that even very early Doppler examination of kidney grafts is helpful in identifying the patients with high risk of post-transplant complications and, hence, worse long-term prognosis, offering us the opportunity for closer diagnosis and treatment of such patients. Nevertheless, we should remember that RI is a semiquantitative, operator-dependent haemodynamic parameter, primarily related to haemodynamic conditions within the kidney graft, and therefore, it can provide reliable information particularly when monitored repeatedly in the same patient.

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References


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