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Detection of transplant renal artery stenosis: determining normal velocities at the renal artery anastomosis

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Abstract

Purpose: Renal artery anastomosis peak systolic velocity (RAA PSV) exceeding 250 cm/s and a ratio of the renal artery to the adjacent external iliac artery (RAA:EIA) exceeding 1.8 historically suggest significant transplant renal artery stenosis (TRAS). However, the range of RAA PSV in transplants without TRAS has not been established.

Methods: A retrospective review of renal transplants at a single institution over 5 years was performed identifying patients without graft dysfunction, failure, or refractory hypertension. RAA PSV obtained during interval post-operative sonograms was recorded.

Results: Of 1141 patients, 844 met the inclusion criteria. Mean RAA PSV for 377 patients evaluated within 2 days of transplant measured 195 cm/s; RAA PSV exceeded 250 cm/s in 97 patients (26%). Mean RAA PSV for 820 patients evaluated 1-month post-transplant measured 206 cm/s; RAA PSV exceeded 250 cm/s in 224 patients (27%). Mean RAA PSV for 785 patients evaluated 4-month post-transplant measured 203 cm/s; RAA PSV exceeded 250 cm/s in 201 patients (26%). Mean RAA PSV for 766 patients evaluated 1-year post-transplant measured 189 cm/s; RAA PSV exceeded 250 cm/s in 141 patients (18%). At each of the given time points, 24%–34% of normal patients had RAA-to-EIA ratios greater than 1.8.

Conclusion: Approximately, 26% of patients without TRAS have RAA PSV $>$ 250 cm/s in the first 9 months, and 18% do at 1 year. Similar findings also occurred with regards to the RAA-to-EIA ratio threshold of 1.8. In isolation, a PSV over 250 cm/s or 1.8 ratio threshold for suspicion of TRAS will lead to a large number of false-positive assessments.

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Transplant renal artery stenosis (TRAS) is a vascular complication previously thought to occur in up to 23% of transplant kidneys [1, 2], with recent evidence from larger studies suggesting a much lower incidence of 1%–3% [3–6]. Clinically, TRAS may present with medically refractory hypertension, graft dysfunction, and graft failure [7–9]. Risk factors for developing TRAS include but are not limited to CMV infection, de novo donor-specific antibodies, delayed graft function, older recipient and donor age, and use of extended criteria donors [3, 10].

The color and spectral Doppler parameters considered suspicious for the diagnosis of TRAS were a topic of considerable interest in a number of studies published from 1987–1995 [2, 7, 11–14]. Baxter et al. suggested that peak systolic velocities (PSV) over 250 cm/s were suspicious for 50% or greater stenosis in the renal artery based on 31 patients (10 with TRAS, 21 without TRAS) [7]. Most review articles published since this work continue to promote 250 cm/s as a threshold for concern for TRAS [15]. The ratio of PSV in the renal artery to the adjacent external iliac artery (RAA-to-EIA) of 1.8 or greater is also a proposed Doppler parameter to suspect TRAS, although much less studied [16].

A major limitation of these studies is that the "normal range" of PSV in renal transplants without long-term clinical suspicion for TRAS has not been well established. Knowledge of the mean and distribution of anastomotic peak systolic velocities and RAA-to-EIA ratios in patients with normal graft function and no clinical evidence of TRAS would delineate the percentage

of patients with renal artery PSV exceeding current velocity and ratio thresholds that do not require any intervention. The aim of this investigation is to better establish the range of renal artery anastomosis PSV in patients with normal graft function and no clinical manifestations of renal artery stenosis.

Methods

After approval by the Institutional Review Board, a retrospective analysis of a prospectively maintained database of patients undergoing renal transplantation at Mayo Clinic, Arizona from 2009 to 2013 was performed. All patients who underwent renal transplant during the 5-year period were included in the initial database. Demographic and clinical data were collected, including age at the time of transplant, gender, donor type, delayed function/acute rejection, graft failure and/or loss, complications, and patient clinical status at the time of study. In order to define the range of renal artery PSV in patients without clinical evidence of TRAS, patients needed to have 1 year of documented clinical follow-up without evidence of clinically suspected graft dysfunction, failure, or medically refractory hypertension. Patients with more than one renal artery anastomosis were excluded. Any patient who had clinical evidence or confirmed renal artery stenosis, graft dysfunction or failure, or patients who died during the follow-up period were excluded.

As part of the standard transplant protocol, renal transplant patients underwent sonographic Doppler evaluation at varying time points in the postoperative period. All examinations were performed by Registered Diagnostic Medical Sonographers (RDMS) using a correction of less than 60°. Sonograms were retrospectively reviewed to record renal artery anastomosis PSV on studies performed in the immediate postoperative period (0–2 days), closest to 1 month (≥3 days–2 months), closest to 4 months (>2–6 months), and >11 months (9 months or later) after transplantation. Velocities in the ipsilateral external iliac artery were also recorded.

Descriptive statistics, including frequencies and proportions for categorical variables, mean, median, standard deviation (SD), first and third quartile, and range for continuous variables, were performed. Density plots were produced using the density plot function based on kernel density estimation in R. Statistical analyses were performed using the statistical software packages SAS Studio version 9.3 (SAS Institute, Cary, NC), and R version 3.1.2.

Results

There were 1141 patients who underwent renal transplant in the 5-year period with at least 1 year of clinical follow-up. Of these, 127 were excluded for graft dysfunction, failure, or death. More than one renal artery anastomosis was present in 157 patients, who were excluded. Of the remaining 857 patients, 13 had clinically possible, suspected, or confirmed TRAS and were excluded. This included patients with acceleration time (AT) >0.1 s and those with a significant tardus-parvus appearance. Thus, 844 patients meeting the inclusion criteria were included in subsequent analysis (age range 18–83 years, 489 males).

In the immediate postoperative period (mean 1-day post-transplant, range 0–2), 377 patients underwent sonographic evaluation (Table 1). The mean renal artery anastomosis PSV for this cohort measured 195 cm/s (range 20–676 cm/s). At this time interval, 26% (97

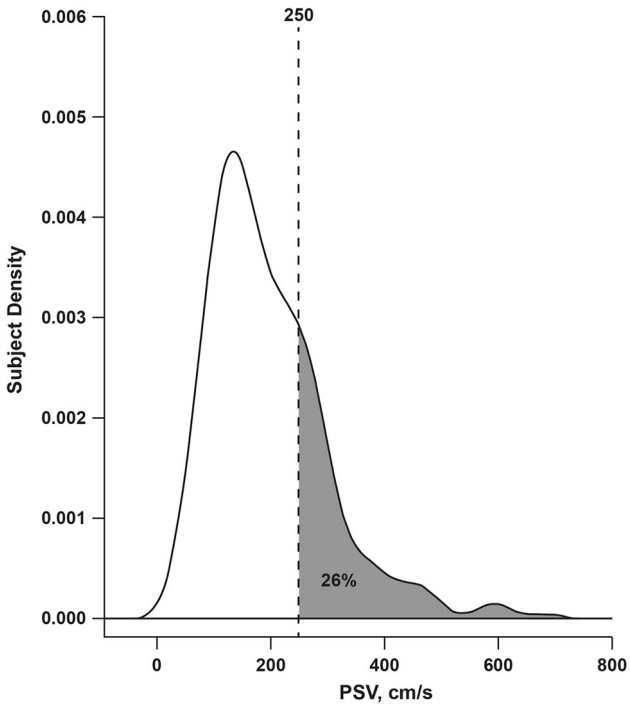

Fig. 1. Immediate postoperative period percent of patients with PSV greater than the current velocity threshold.

Table 1. Summary of data results for the entire cohort at varying time points post-transplant

Time of evaluation	Mean (range)	No of patients	Mean RAA PSV ± SD (cm/s)	RAA PSV range (cm/s)	Mean RAA:EIA ± SD	RAA:EIA range
Immediate postoperative period	1 (0–2)	377	195 ± 104	20–676	1.4 ± 0.9	0.2–8.0
1 month	34 (3–60)	820	206 ± 91	40–683	1.7 ± 0.8	0.2–5.7
4 months	131 (90–273)	785	203 ± 86	35–556	1.7 ± 0.8	0.3 ± 4.8
≥11 months	394 (≥330)	766	189 ± 76	51–598	1.6 ± 0.7	0.4–7.3

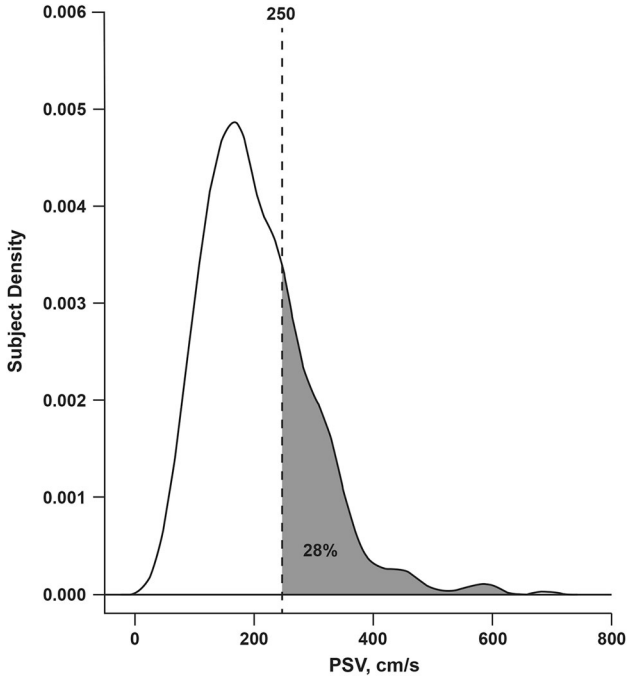

Fig. 2. Percent of patients 1 month post-transplant with PSV greater than the current velocity threshold.

patients) had renal artery anastomosis PSV > 250 cm/s with 5% (18 patients) exhibiting renal artery anastomosis PSV greater than 401 cm/s (>mean + 2 SD) (Fig. 1). The mean RAA-to-EIA ratio was 1.4, and 24% (88/369) of renal transplants had a RAA-to-EIA ratio > 1.8.

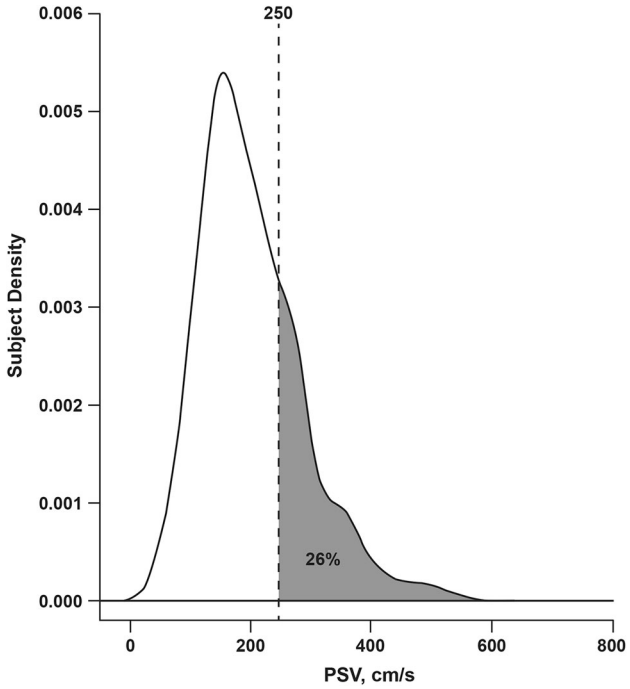

Fig. 3. Percent of patients 4-months post-transplant with PSV greater than the current velocity threshold.

At the time period closest to one-month post-transplant, 820 patients underwent routine sonographic evaluation (mean 34 days, range 3–60) (Table 1). The mean renal artery anastomosis PSV for this cohort measured 206 cm/s (range 40–683 cm/s). Twenty-eight percent (224 patients) had renal artery anastomosis PSV > 250 cm/s (Fig. 2). Four percent (29 patients) exhibited PSV greater than 388 cm/s (>mean + 2 SD). The mean RAA-to-EIA ratio was 1.7, and 33% (273/819) of patients had a RAA-to-EIA ratio > 1.8.

At the time period closest to four-months post-transplant, 785 patients underwent sonographic evaluation (mean 131 days, range 90–273) (Table 1). The mean renal artery anastomosis PSV for these patients measured 203 cm/s (range 35–556 cm/s). Twenty-six percent (201 patients) at this time interval exhibited renal artery anastomosis PSV > 250 cm/s (Fig. 3), and 4% (32 patients) demonstrated renal artery anastomosis PSV greater than 375 cm/s (>mean + 2 SD). The mean RAA-to-EIA ratio was 1.7 (range 0.3–4.8), and 34% (264/782) of the patients had a RAA-to-EIA ratio > 1.8. Collectively, within the first nine-months post-transplant, 26% (522/1982) of these 847 patients showed renal artery anastomosis PSV greater than 250 cm/s (Fig. 4).

The final cohort evaluated 766 patients 11 months or more post-transplant (mean 394 days, range 330–766 days) (Table 1). The mean renal artery anastomosis PSV measured 189 cm/s (range 51–598 cm/s). At this

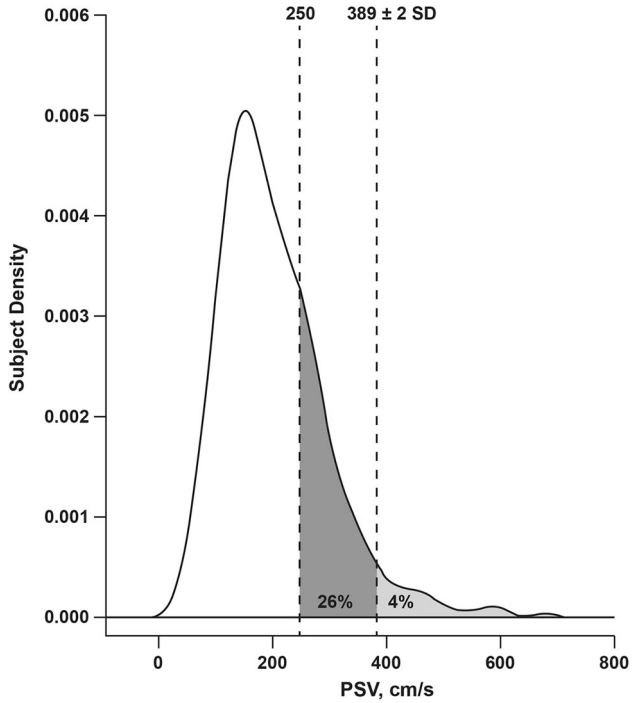

Fig. 4. Cumulative percentage of patients within the first year post-transplant with PSV velocities greater than 250 cm/s and 2 SD above the time period mean.

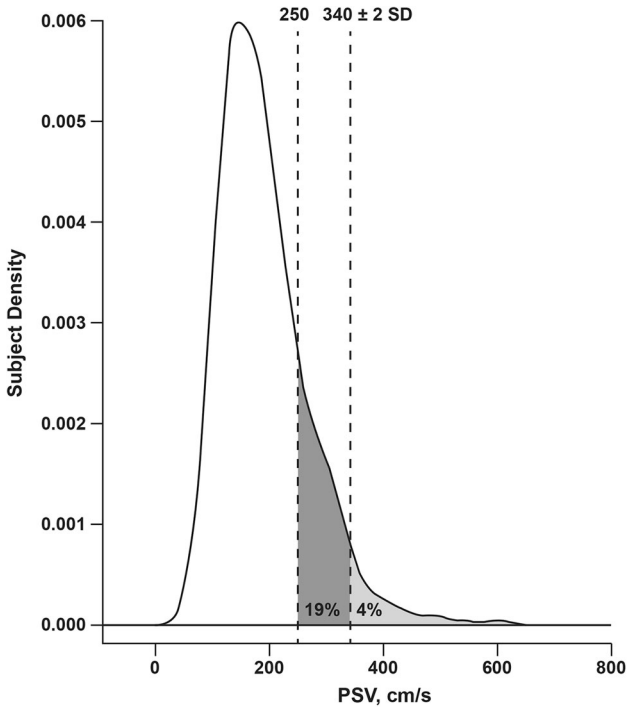

Fig. 5. Cumulative percentage of patients after the first year post-transplant with PSV velocities greater than 250 cm/s and 2 SD above the time period mean.

time point, 19% (141 patients) had renal artery anastomosis PSV greater than 250 cm/s, and 4% (26 patients) exhibited renal artery anastomosis PSV > 340 cm/s (>mean + 2 SD) (Fig. 5). The mean RAA-to-EIA ratio was 1.6 (range 0.4–7.3), and 28% (216/766) of the patients had a RAA-to-EIA ratio > 1.8.

Discussion

Transplant renal artery stenosis (TRAS) is uncommon; evidence from the most recent studies with the largest patient cohorts suggests an incidence of 1%–3%. Literature originating from the 1970s and 1980s showed a wider range of occurrence varying between 1% and 12% [2], with an outlier incidence of 23% reported by Lacombe [1].This range up to 23% is often still referenced as the incidence range for TRAS in reviews [8]. However, in a large registry of over 40,000 patients in the United States, the incidence of TRAS from 2000 to 2005 was only 2% [3]. The three largest studies after 2000 from single centers showed a TRAS incidence of 1.7% in 1500 allografts in 2009 [6], 0.9% in 793 allografts in 2006 [5], and 3.1% in 831 allografts in 2001 [17]. The low incidence of this disorder is an important factor to consider when considering how to manage higher than average velocity measurements in the renal artery on Doppler.

TRAS is associated with diminished graft function and survival [18]. Detection of this complication is important, as outcomes for patients with successfully treated TRAS show no significant difference to outcomes for patients without TRAS and better outcomes than patients with untreated TRAS [18]. Since hypertension is common in patients with end-stage renal disease, the mere presence of hypertension in a patient with a renal transplant is not a sufficient predictor for stenosis. The clinical suspicion for TRAS is often reserved for patients with severe or worsening hypertension refractory to medical therapy or patients with unexpected graft dysfunction [19]. Furthermore, evidence now shows that patients with certain cardiovascular and immunologic risk factors, including patients with CMV infection and patients who develop certain donor-specific antibodies, are at elevated risk for developing TRAS [10, 18, 20, 21].

Ultrasound and Doppler evaluation of renal transplants is the standard of care when transplant dysfunction or complication is clinically suspected, but sonographic and Doppler evaluation are also often performed as part of routine post-transplant evaluations. Based on 31 patients (10 with TRAS, 21 without TRAS) reported by Baxter et al. in 1995, 250 cm/s was established as a threshold for suspicion of 50% or greater stenosis. Most review articles published since this work continued to promote 250 cm/s as a threshold for concern [15]. A subsequent investigation in 2003 by Patel et al. based on 117 patients (5 with TRAS, 112 without TRAS) suggested that 300 cm/s had better diagnostic performance as a threshold, albeit with a low positive predictive value of only 33%. The ratio of renal artery anastomosis PSV to external iliac artery PSV has also been suggested as a method for identifying patients with TRAS, although less well studied, with proposed threshold as low as 1.8 [16].

To date, no investigation has attempted to define the range of renal transplant artery PSV or RAA-to-EIA ratio in patients who have no clinical suspicion of TRAS and who do not develop graft dysfunction—in other words, the "normal range" of renal transplant artery PSV and RAA-to-EIA ratio. The current data show that renal transplant artery PSV range widely in these patients with variation skewed to higher velocities than would be predicted by a normal distribution. In a normal distribution, approximately 2.2% of values exceed 2 SD above the mean—in the current report, at any given time point during the first year of transplantation, 4%–5% of renal transplants without clinical evidence of TRAS showed velocities greater than 2 SD above the mean. More importantly, the data show that 26%–28% of transplants without graft dysfunction or clinical concern for renal artery stenosis have renal transplant artery PSV over 250 cm/s when studied in the first year, and 19% have velocities over 250 cm/s after the first year post- transplant. The RAA-to-EIA ratio also varies widely, with 28%–34% of patients exceeding ratios of 1.8 when evaluated beyond the immediate postoperative period. This has profound implications for deciding if renal

transplant artery PSV or RAA-to-EIA "screening" is of value, and what velocity threshold, if any, should be used for suspecting stenosis in the absence of clinical suspicion or heightened risk factors.

For illustrative purposes, assume that 20% of normal renal transplants (defined as those without clinical evidence of TRAS and without any graft dysfunction at 1 year) have a renal transplant artery PSV over 250 cm/s. If the incidence of TRAS is 2% and all patients with TRAS have velocities over 250 cm/s, then among 1000 patients evaluated, 20 will have TRAS showing velocities over 250 cm/s. At the same time, of the 980 patients without TRAS, 196 patients (20%) will have velocities over 250 cm/s. Therefore, there will be 216 patients with renal transplant artery PSV over 250 cm/s, of which only 20 (9%) will have TRAS. Clearly, using 250 cm/s as the threshold for raising concern *in the absence of clinical concern or risk factors for TRAS* results in far too many false-positive assessments.

While this example is hypothetical, recent empirical data show this to be true. Willicombe et al. published a recent study aimed at understanding the association of donor-specific antibodies with renal artery stenosis. The study was not aimed at trying to analyze the incidence of TRAS or the effectiveness of standard Doppler criteria in identifying patients at risk for TRAS (presumably the 250 cm/s threshold was used but unspecified in their methods). In their protocol, all patients undergoing renal transplantation had Doppler evaluation in the perioperative period based on clinical concerns or routinely at 3 months following transplant. Based on their methods, 999 patients were identified as possibly having TRAS. For 152 patients, further workup was not initiated, and these patients were considered as not having TRAS. The other 847 patients underwent further evaluation with MR angiography [828 (97.8%)], CT angiography [14 (1.7%)], or digital subtraction angiography [5 (0.6%)], and some of the patients initially evaluated with MRA or CTA were further evaluated with DSA as needed. Among the 999 patients, only 137 (13.7%) proved to have TRAS at final evaluation. In other words, 86.3% of patients in their study who were identified as possibly having TRAS using Doppler did not have TRAS.

For illustrative purposes, if the Doppler threshold was set at 2 SD above the mean, between 340 and 400 cm/s, the current report suggests that up to 5% of normally functioning renal transplants will be misidentified as possibly having TRAS based on Doppler. Assuming the incidence of TRAS is 2%, and if all patients with TRAS have velocities over the threshold (which may not be true), then among 1000 patients evaluated, 49 patients without TRAS and 20 patients with TRAS would exceed the threshold. In this scenario, 29% (20/69) of the patients identified by the 2 SD threshold would have the condition. Although this analysis is based on modeling with untested assumptions regarding the sensitivity of the 2 SD threshold, it suggests substantially better results than those based on using the 250 cm/s threshold.

Of consideration, using a higher Doppler threshold would likely decrease the sensitivity in identifying patients with TRAS as it is unlikely that every patient with true TRAS would have renal transplant artery PSV exceeding 2 SD above the mean. It would be far better to tailor the use of Doppler threshold values based on clinical suspicion, coexisting risk factors, and/or coexisting Doppler findings. Gottleib et al. showed that analysis of the arterial waveform within the kidney with attention to the acceleration time (AT) had far better performance in detecting significant proximal arterial stenosis in transplant kidneys compared to using peak systolic velocity. Limited by few patients in their study, they showed that AT exceeding 0.1 s had 95% accuracy in the diagnosis of TRAS [22]. DeMorais et al. found 100% sensitivity for detecting TRAS using acceleration time exceeding 0.1 s in their cohort of 22 patients with TRAS [16]. Patel et al. have already suggested that higher PSV thresholds should be utilized for surveillance patients without clinical suspicion or risk factors [4], although the 300 cm/s is still too low based on results from the current investigation. Suggesting the possibility of TRAS on Doppler leads to further testing and/or intervention, thus using either a much higher renal transplant artery PSV threshold (such as 340–400 cm/s, reflecting 2 SD above the mean) or *no threshold* when the patient has normal arterial waveforms, no risk factors, and no clinical suspicion for TRAS should be considered. Similar comments can be made regarding the use of the RAA-to-EIA ratio. Using Doppler data for "surveillance" for TRAS only in the context of patients who are either at risk for developing or with clinical suspicion of TRAS should substantially reduce the number of false-positive assessments that result when Doppler thresholds are applied indiscriminately to all patients.

The ability to adequately visualize the renal artery anastomosis and obtain an exact angle correction for spectral Doppler evaluation can be challenging. Although all studies were performed by sonographers with RDMS credentials who routinely perform visceral Doppler evaluation in our IAC- and ACR-accredited laboratory, technical error in measuring the PSV could contribute to false elevation. One limitation of our study is that we could not retrospectively analyze studies to determine the accuracy of PSV determination, and we did not prospectively assess intraobserver and interobserver variability in measuring the PSV. However, this is an inherent limitation of renal transplant Doppler evaluation in any clinical practice, in which technical limitations and variability undoubtedly exist. Further investigations regarding the intraobserver and interobserver variability in transplant renal artery PSV determination might further suggest that using any threshold

for suspecting renal artery stenosis has limitations if there is substantial inherent variability in determining PSV. Another limitation of our data is the recognition that although our patient population was selected to identify only "normal" grafts, those transplants with relatively higher renal artery anastomosis PSV may in fact have had unspecified degrees of anatomic stenosis. To the extent that physicians managing transplant patients are unlikely to request interventions on an anatomic stenosis in the absence of any clinical manifestations, these "clinically silent" TRAS cases may be not be important to detect anyway.

In conclusion, our study shows that there is a wide range of renal transplant artery PSV values and RAA-to-EIA ratios in patients who prove to not have any issues with TRAS. The traditional value of transplant renal artery velocity exceeding 250 cm/s is surpassed by 19%–28% of patients, depending on the time of evaluation, making it a poor threshold for accurately identifying which patients need further testing or intervention. Still, worse results are found using the RAA-to-EIA ratio of 1.8. Our study results highlight the need for placing the Doppler findings in the context of clinical suspicion and underlying risk for developing TRAS. In the surveillance population, the use of any threshold is problematic because the incidence of TRAS is so low, and perhaps other Doppler features such as acceleration time and waveform pattern could prove more useful.

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of Interest Drs. Kristin Robinson, J. Scott Kriegshauser, Nirvikar Dahiya, Scott Young, Chris Czaplicki, and Maitray Patel declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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