Does separating the resistive index into pre- and post-glomerular resistance and vascular compliance improve the diagnostic accuracy of renal transplant doppler ultrasound?

F Edward Boas, Terry Desser, and Aya Kamaya.

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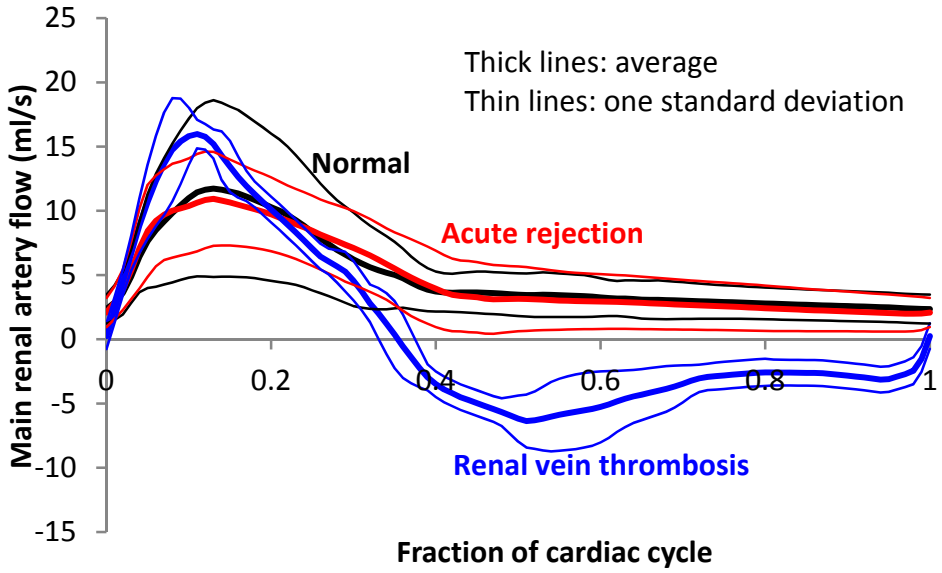
Purpose: Doppler ultrasound resistive index (RI) is a widely used parameter in the assessment of renal transplant function, but current work suggests that its sensitivity and specificity for acute rejection is low. Although RI (which is a measure of pulsatile flow) does increase with post-glomerular vascular resistance, it also increases with increased vascular compliance (decreased atherosclerosis), decreased pre-glomerular vascular resistance, increased pulse pressure, and increased heart rate. We postulated that separating out these potentially confounding factors and directly calculating vascular resistance and compliance, would allow for more accurate assessment of kidney transplants.

Materials and methods: 47 kidney transplant ultrasounds were analyzed. RI was measured at the segmental renal arteries. We modeled the transplanted kidney vasculature as a tube with a pre-glomerular and post-glomerular vascular resistance, and a vascular compliance (three-element Windkessel model). This model accurately describes *in vivo* blood flow in rat kidneys. The arterial blood pressure was modeled using a range of waveforms from the MGH/MF Waveform Database, adjusted to match the patient's measured heart rate, systolic blood pressure, and diastolic blood pressure. The parameters of the model were adjusted to fit the experimental mid renal artery velocity waveforms. The final diagnosis was determined from pathology (when available) and the nephrology clinic visit notes.

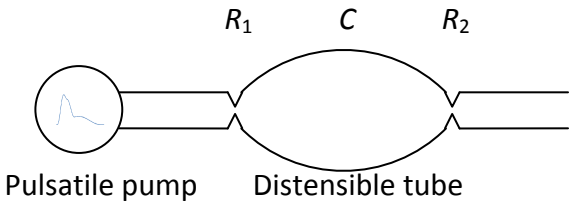
Results: Normal transplant kidneys have an average RI of 0.71 ± 0.11, and kidneys in acute rejection have an RI of 0.77 ± 0.11. Using a cutoff of 0.8 results in a sensitivity of 38% and specificity of 63% for acute rejection. A resistive index > 1 was only seen in renal vein thrombosis (2 cases). Waveforms for acute rejection, chronic rejection, hydronephrosis, and delayed graft function all had a large amount of overlap with normal waveforms (Figure A). Using the three-element Windkessel model, we showed that these 4 diagnoses are associated with vascular resistances and compliances within 1 standard deviation of normal, and none of the differences were statistically significant (Figure B). On the other hand, renal vein thrombosis is associated with a non-significant increase in post-glomerular resistance, and a significant decreases in pre-glomerular resistance (p=0.01) and vascular compliance (p=0.0003).

Conclusion: Doppler ultrasound of kidney transplants has limited value in diagnosing acute rejection. We examined resistive index, pre-glomerular resistance, post-glomerular resistance, vascular compliance, and the shape of the mid renal artery velocity waveform. None of these variables could reliably predict acute rejection, chronic rejection, hydronephrosis, or delayed graft function. However, resistive index > 1 was associated with renal vein thrombosis in 2 out of 2 cases.

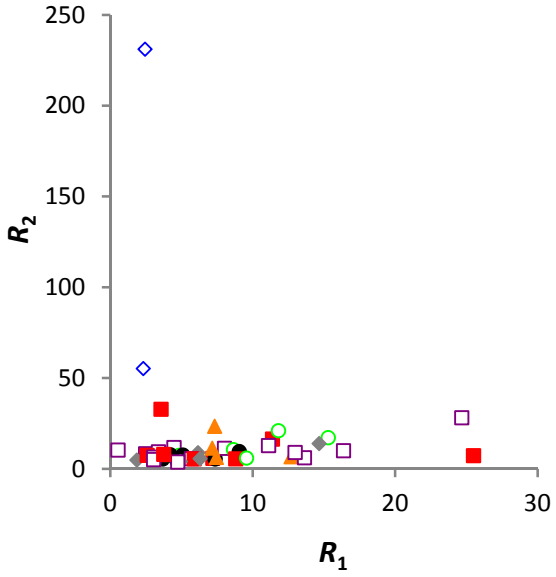
A

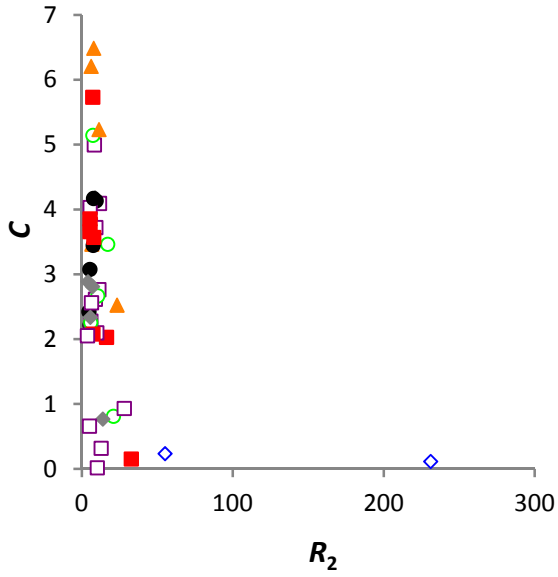


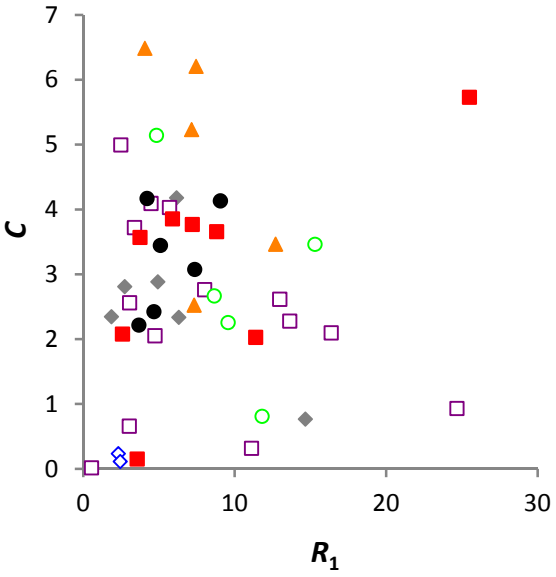
B **Three element Windkessel model**



- Normal
- Delayed graft function
- Acute rejection
- Chronic rejection
- Hydronephrosis
- Renal vein thrombosis
- Other







Supporting data

Patient selection

54 non-consecutive kidney transplant ultrasounds performed at Stanford Hospital between 2005 and 2009 were identified. Of these, 1 was excluded from calculations that required vital signs, because no vital signs were available within 1 month of the ultrasound. 6 were excluded because there were multiple renal transplant arteries. 1 was excluded because of a poor quality arterial waveform.

Data acquisition

Spectral doppler was recorded in the mid renal artery, and manually traced to obtain the velocity waveform. The renal artery radius was not recorded, so we assumed a main renal artery radius of 5 mm in order to calculate flow. The beginning of the cycle was defined as the earliest point before the peak velocity with increasing forward flow.

For each patient, a diagnosis was assigned based on radiology, pathology, and clinical data:

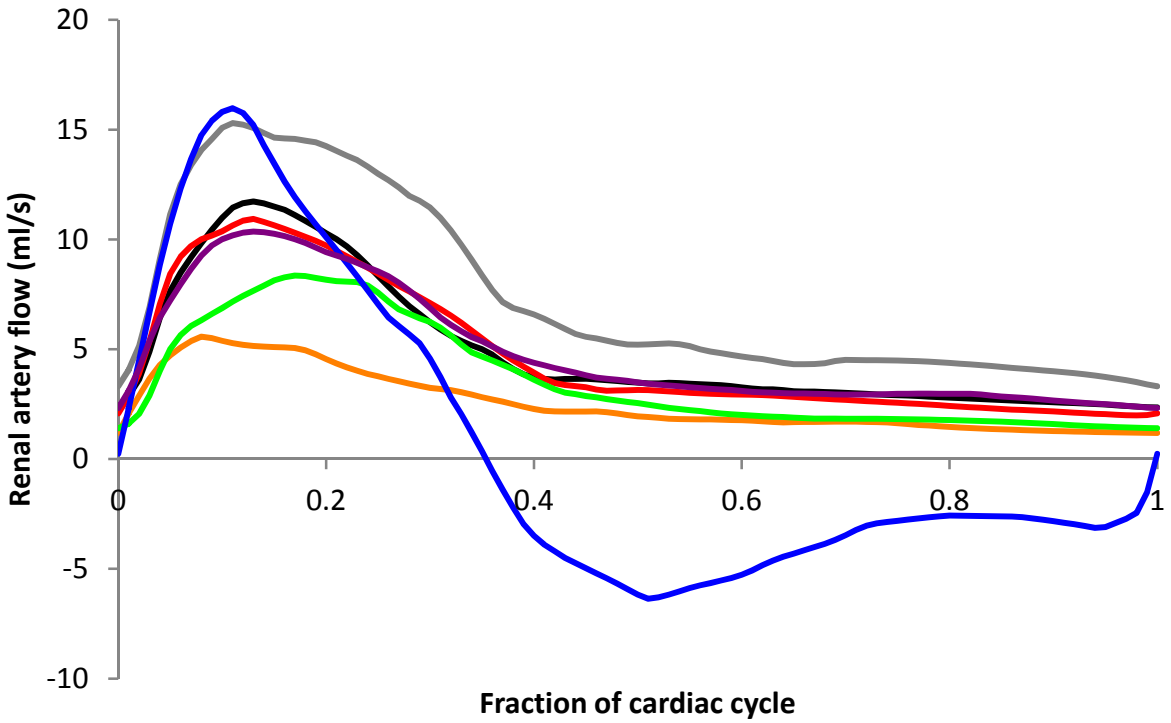
Symbol	Diagnosis	Number of patients
● —	1. Normal, with creatinine ≤ 1.5	7
◆ —	2. Delayed graft function post-operatively	6
■ —	3. Acute rejection	8
▲ —	4. Chronic rejection, transplant glomerulopathy, or drug toxicity, creatinine > 1.5	5
○ —	5. Hydronephrosis	5
◇ —	6. Renal vein thrombosis	2
□ —	7. Other	14

The symbols, colors, and numbers associated with each diagnosis shows in this table are used throughout this paper.

Chronic rejection / transplant glomerulopathy was considered “normal,” if the creatinine was ≤ 1.5 and the patient was doing well clinically. “Other” includes pyelonephritis, ATN, and pre-renal ARF. There weren’t enough examples of any single diagnosis in “other” to analyze separately.

Waveforms

The average renal artery flow waveform for each diagnosis is shown below. Normal, acute rejection, and “other” are virtually indistinguishable. However, delayed graft function is distinguished by increased systolic and diastolic flow. (This may actually be due to the increased blood pressure in these patients.) Renal vein thrombosis is distinguished by reversed diatolic flow. Chronic rejection is distinguished by decreased systolic and disatolic flow.

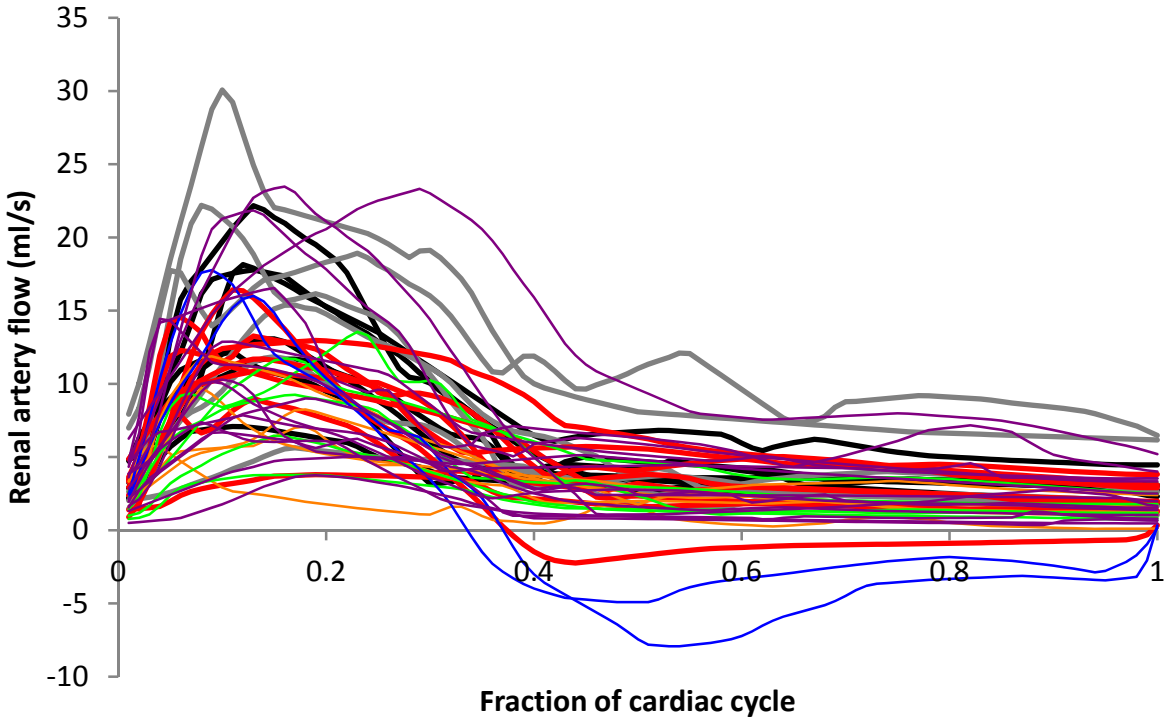


We can try to predict the diagnosis by comparing the renal artery flow waveform to the ones shown in the previous graph. Specifically, we calculate the root-mean-square difference (in standard deviations) between the unknown waveform and the average waveforms shown above. The result is shown below:

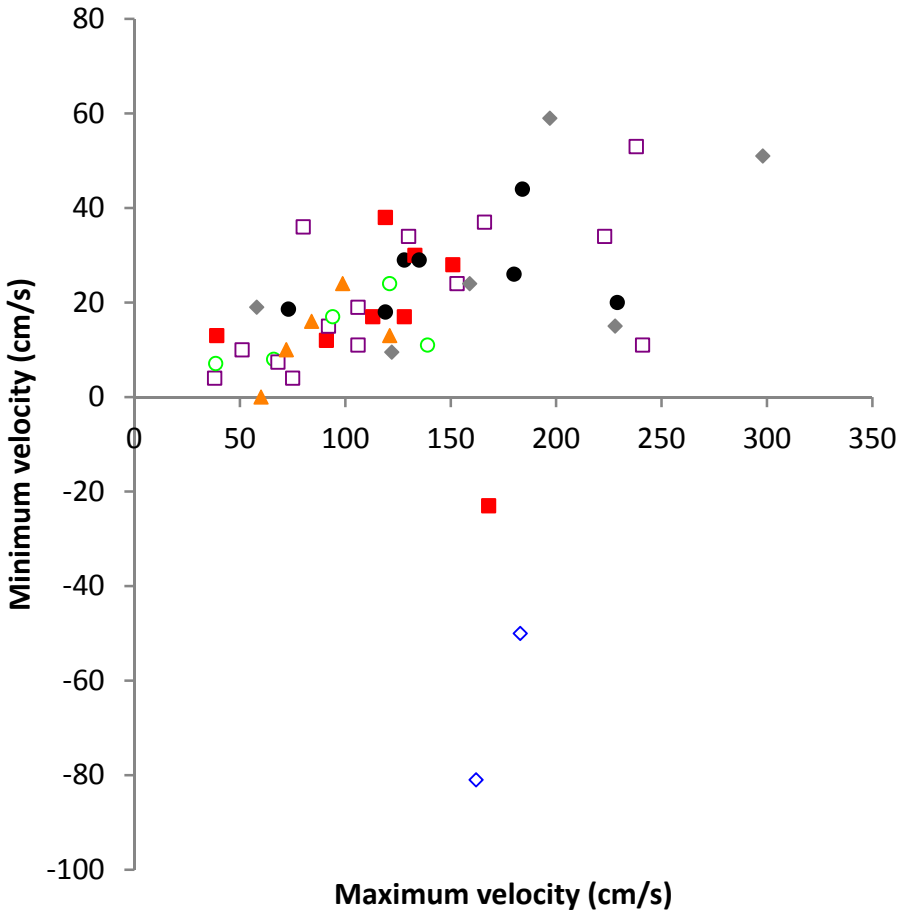
		Actual diagnosis						
		1	**2**	**3**	**4**	**5**	**6**	**7**
Predicted diagnosis	**1**	0%	0%	0%	0%	0%	0%	0%
	2	33%	67%	38%	0%	0%	0%	38%
	3	11%	17%	13%	13%	0%	0%	0%
	4	22%	0%	13%	63%	40%	0%	31%
	5	0%	0%	13%	13%	20%	0%	13%
	6	0%	0%	0%	0%	0%	100%	0%
	7	33%	17%	25%	13%	40%	0%	19%

Delayed graft function can be predicted with a sensitivity of 67% and a specificity of 75%.
Chronic rejection can be predicted with a sensitivity of 63% and a specificity of 78%.
Renal vein thrombosis can be predicted with a sensitivity and specificity of 100%.
None of the other diagnoses can be made with any degree of accuracy.

The full set of waveforms for each ultrasound scan, color coded by diagnosis, is shown below.



Maximum and minimum flow velocity for each diagnosis is shown below:



Resistive index and other simple models

The mid main renal artery resistive index for each diagnosis is shown below:

Diagnosis	RI (average)	(stdev)	*t* test for comparison to normal
1	0.81	0.06	
2	0.82	0.11	0.91
3	0.83	0.15	0.72
4	0.86	0.09	0.31
5	0.85	0.05	0.30
6	1.39	0.16	0.11
7	0.83	0.10	0.67

The diagnosis for each range of resistive indices is shown below.

RI range	Fraction	Diagnosis						
		1	2	3	4	5	6	7
<0.7	9%	0%	25%	50%	0%	0%	0%	25%
0.70 – 0.79	21%	40%	10%	10%	10%	0%	0%	30%
0.80 – 0.89	49%	9%	9%	17%	13%	17%	0%	35%
0.90 – 0.99	13%	17%	33%	0%	0%	17%	0%	33%
≥1	9%	0%	0%	25%	25%	0%	50%	0%

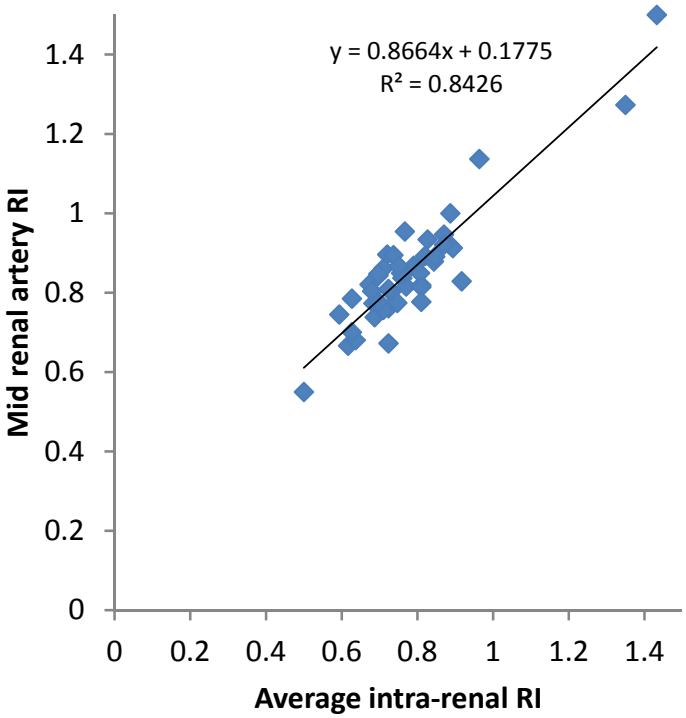
No diagnosis can be confidently made based on the resistive index. For example, here is the sensitivity and specificity for detecting acute rejection based on the resistive index:

		Sensitivity	Specificity
Cutoff	0.8	63%	28%
	0.9	13%	77%
	1	13%	92%

A resistive index ≥ 0.9 was found in every diagnostic category considered: normal, acute rejection, chronic rejection / transplant glomerulopathy, hydronephrosis, delayed graft function, and renal vein thrombosis.

A resistive index >1, with reversed diastolic flow, was only seen in acute rejection and renal vein thrombosis.

We can also look at average intra-renal resistive indexes. These are highly correlated with mid main renal artery RIs:



Average intrarenal RI > 0.9 is associated with delayed graft function, acute rejection, and renal vein thrombosis. Average intrarenal RI > 1.0 is associated with only renal vein thrombosis:

RI range	Fraction	Diagnosis						
		1	2	3	4	5	6	7
<0.7	28%	23%	8%	15%	0%	0%	0%	54%
0.70 – 0.79	35%	13%	13%	19%	19%	13%	0%	25%
0.80 – 0.89	28%	8%	15%	15%	15%	23%	0%	23%
0.90 – 0.99	4%	0%	50%	50%	0%	0%	0%	0%
≥1	4%	0%	0%	0%	0%	0%	100%	0%

Using average intra-renal RI, there is low sensitivity and specificity for acute rejection:

Cutoff	Sensitivity	Specificity
0.7	75%	29%
0.75	63%	50%
0.8	38%	63%
0.9	13%	92%
1	0%	95%

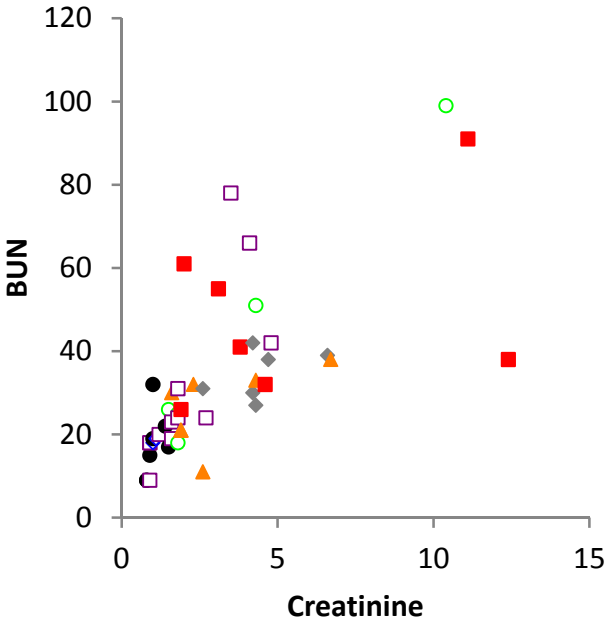
Diagnosis	RI (average)	(stdev)
1	0.71	0.11
2	0.79	0.11
3	0.77	0.11
4	0.77	0.08
5	0.80	0.06
6	1.39	0.06
7	0.72	0.09

Instead of using the resistive index, we can calculate resistance as (mean arterial pressure) / (average flow).

Resistance	Fraction	Diagnosis						
		1	2	3	4	5	6	7
< 10	7%	0%	33%	0%	0%	0%	0%	67%
10 – 19	43%	25%	15%	25%	0%	10%	0%	25%
20 – 29	24%	9%	9%	9%	27%	9%	0%	36%
30 – 39	11%	0%	20%	20%	20%	20%	0%	20%
≥ 40	15%	0%	0%	14%	14%	14%	29%	29%

This is also very non-specific.

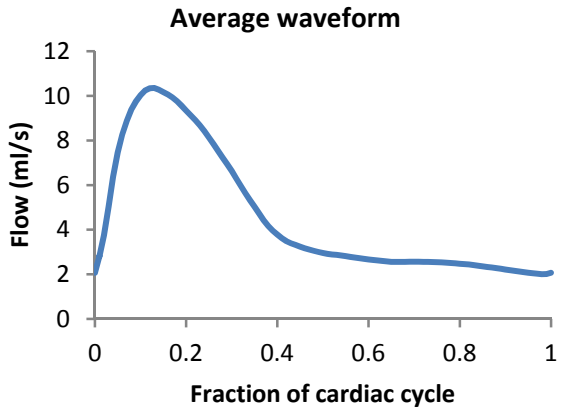
The highest levels of creatinine are associated with acute rejection and hydronephrosis:

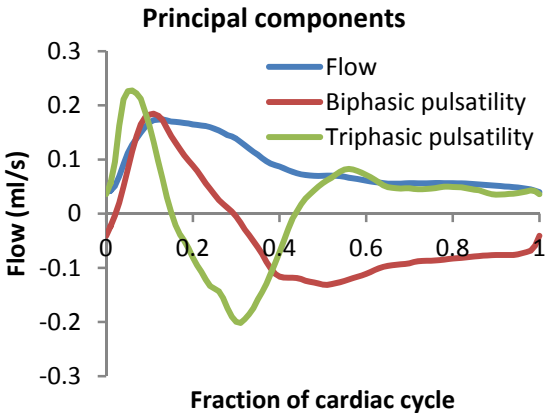


Principal component analysis

The flow waveforms were analyzed using principal component analysis, which analyzes the variability in the waveforms, and automatically breaks them down into a small number of “principal components” which are added together to explain most of the variation among the waveforms. This type of analysis has been used for facial recognition (it can take a photograph and describe it with a handful of numbers).

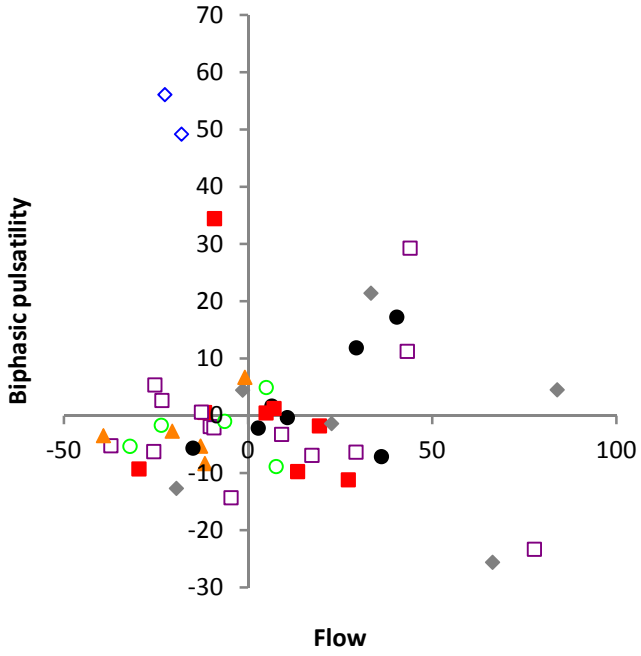
In our case, the first three principal components explain 97% of the variance in the data set:

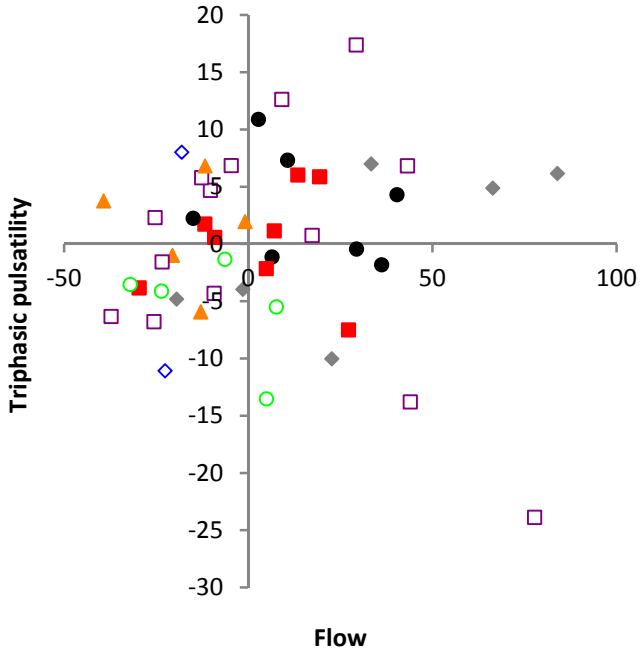


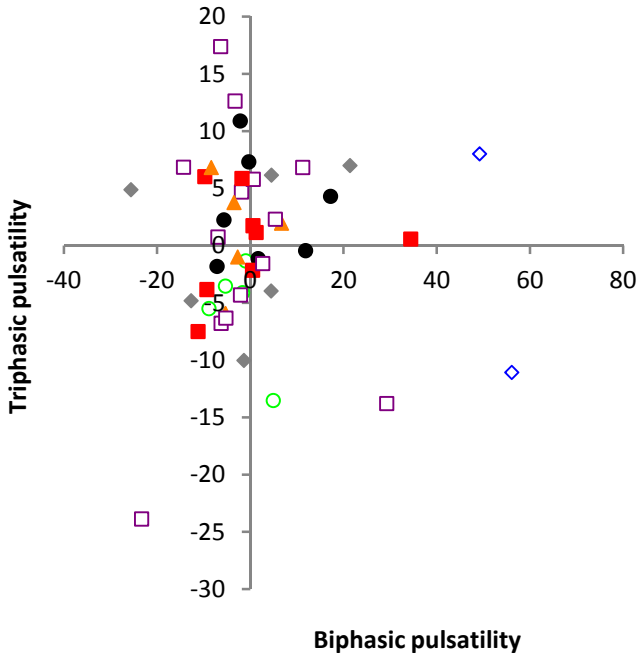


By inspection, we can see that the first principal component corresponds to flow, the second principal component increases systolic and decreases diastolic flow (biphasic pulsatility), and the third principal component decreases or reverses flow in early diastole (triphasic pulsatility).

We can now plot the diagnosis as a function of these principal components:







There is still a lot of overlap between normal and the other diagnoses.

Two-element Windkessel model

The kidney is modeled as a resistor and a capacitor in parallel (the two-element Windkessel model). The arterial blood pressure is modeled as a sine wave going between the measured systolic and diastolic blood pressures. The resistance and capacitance can then be solved as a function of the maximum and minimum flow.

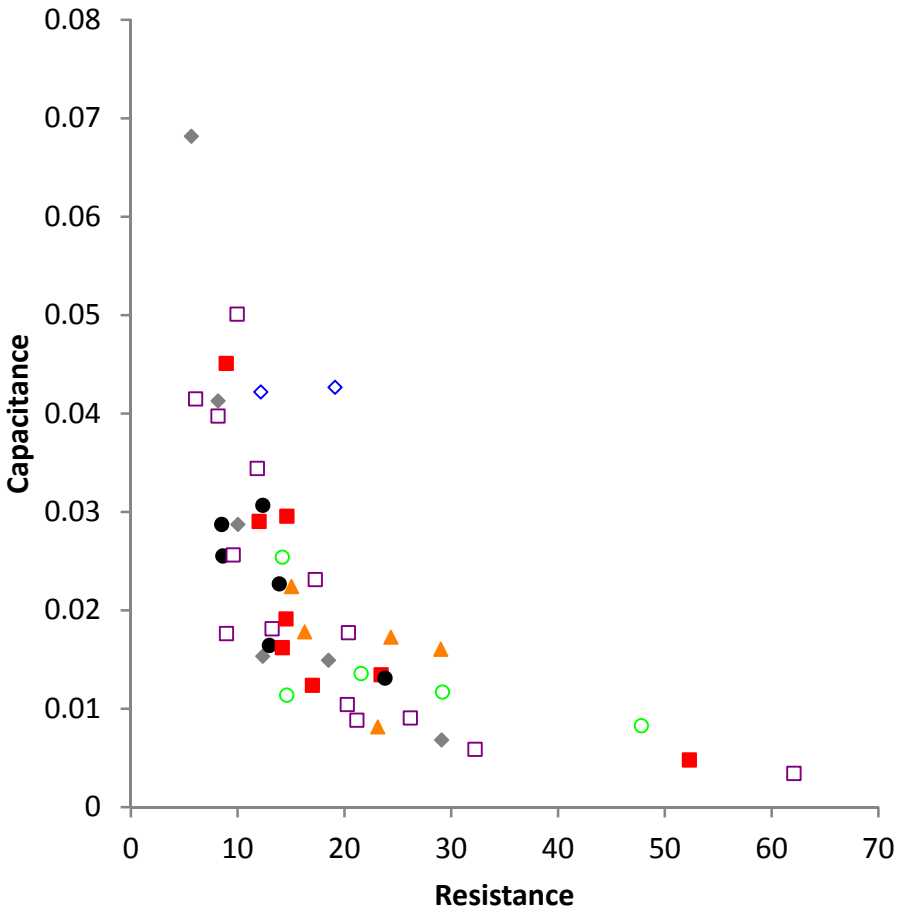
$$C = \frac{2\sqrt{(I_S D - I_D S)(I_S S - I_D D)}}{2\pi f (S^2 - D^2)}$$

$$R = \frac{D+S}{I_D + I_S}$$

where:

C = capacitance (ml / mm Hg)
R = resistance (mm Hg / (ml/s))
I_S = maximum flow (ml/s)
I_D = minimum flow (ml/s)
S = systolic blood pressure (mm Hg)
D = diastolic blood pressure (mm Hg)
f = heart rate (beats per second)

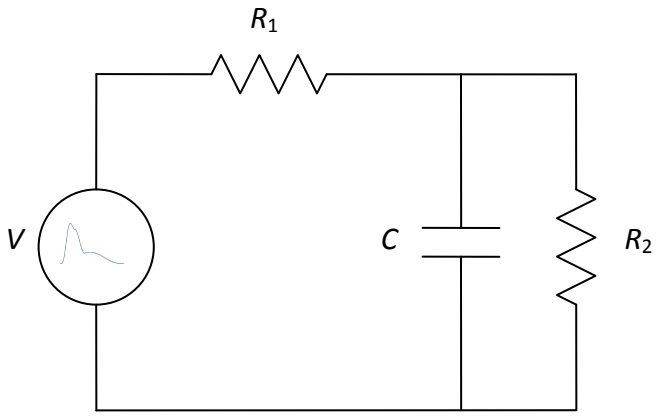
We can then plot the diagnosis as a function of the resistance and capacitance of the kidney:



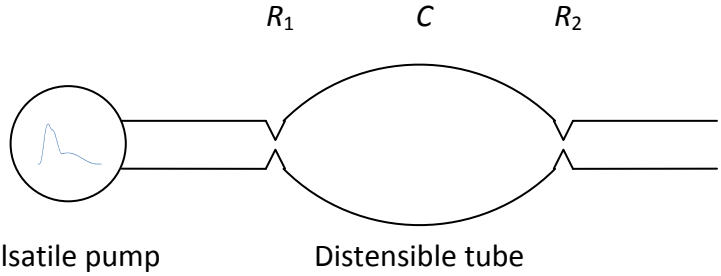
Again, there is a large amount of overlap among diagnoses.

Three-element Windkessel model

Electrical diagram for the three-element Windkessel model:



Hydraulic analogue:



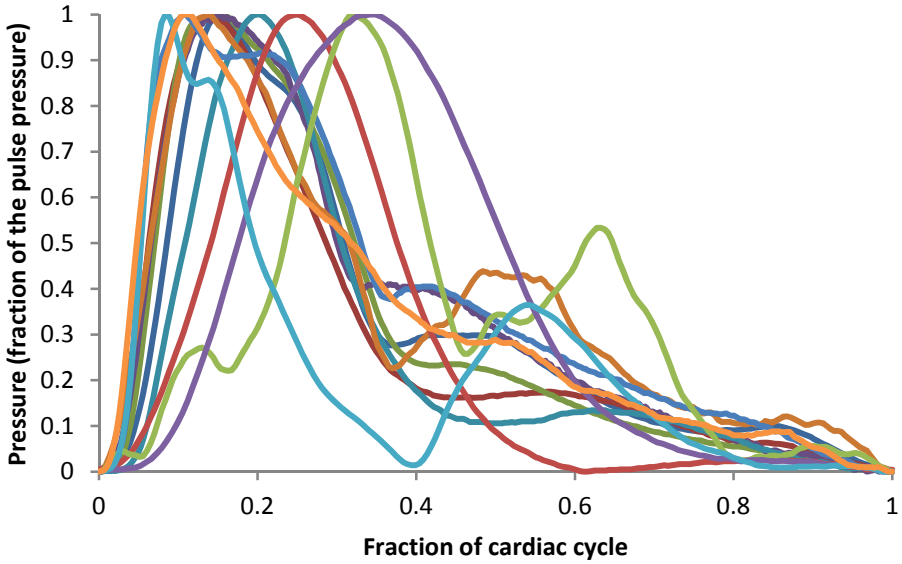
The differential equation for this model is: $\left(1+\frac{R_1}{R_2}\right)I(t)+CR_1I'(t)=\frac{V(t)}{R_2}+CV'(t)$

R_1 is the pre-glomerular resistance, including the anastomosis. R_2 is the post-glomerular resistance, and C is the vascular compliance. The resistive index is increased by decreasing R_1, increasing C, or increasing R_2.

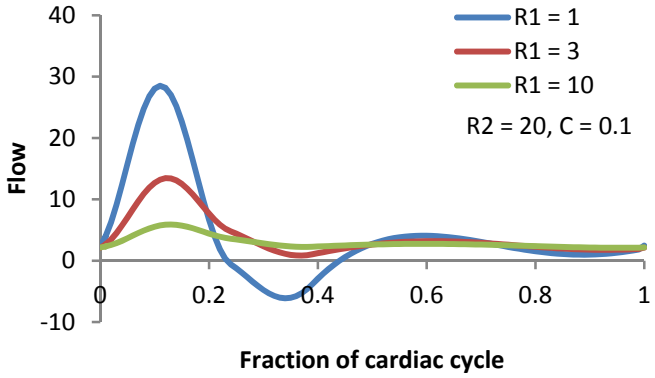
The three-element Windkessel model was solved using the fourth-order Runge-Kutta method. However, when R_1 or R_2 are small, the $I'(t)$ term in the differential equation is small, and Runge-Kutta doesn't converge. In this case, the $I'(t)$ term is dropped, and $I(t)$ is calculated directly from $V(t)$ and $V'(t)$. The parameters for the model (R_1, R_2, C, arterial pressure waveform, and phase shift between peak pressure and peak flow) were optimized using Powell's method to fit the experimental flow waveform. Multiple values for R_1, R_2, and C were approximately equally consistent with the experimental data. We picked the solution within 1% of the minimum RMS error which minimized R_1^2+R_2^2+C^2.

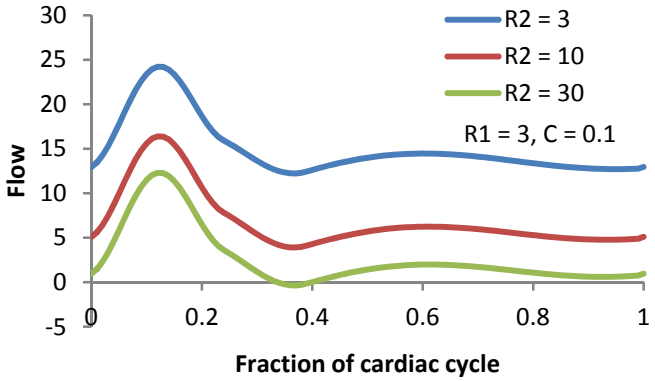
The arterial pressure varied between the measured systolic and diastolic blood pressure. However, the actual arterial pressure waveform was not available, so we modeled it, based on waveforms from the MGH/MF Waveform Database (http://www.physionet.org/pn3/mghdb/), which were fit to a parametric model with up to three pressure peaks per cardiac cycle.

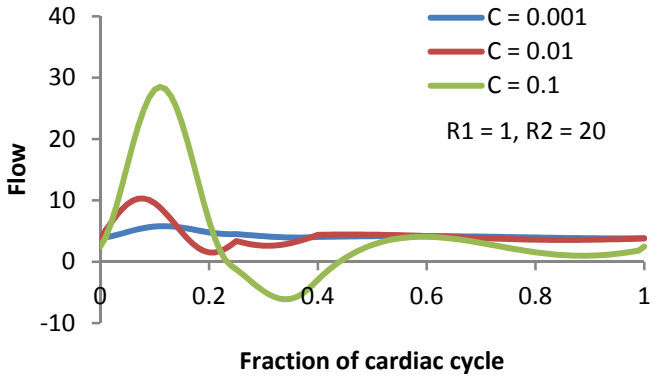
Arterial pressure waveforms from the MGH/MF Waveform Database:



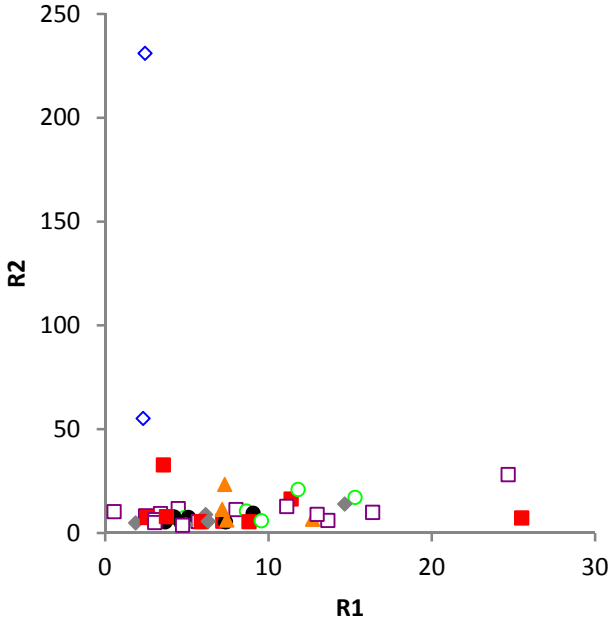
The three-element Windkessel model produces reasonable results:

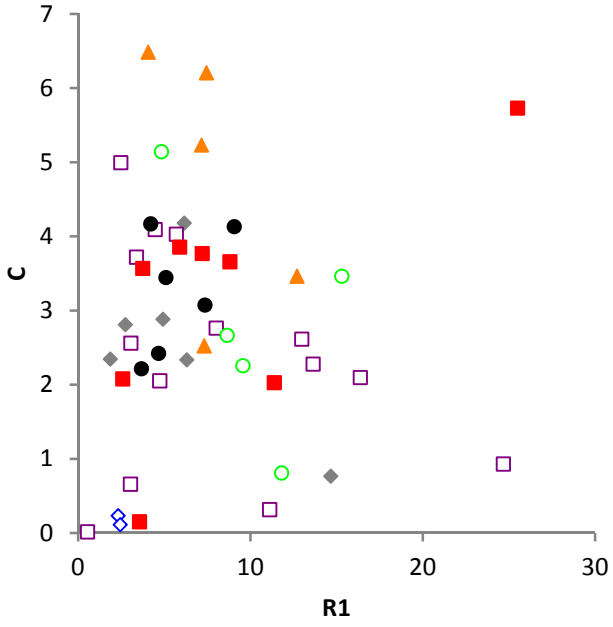


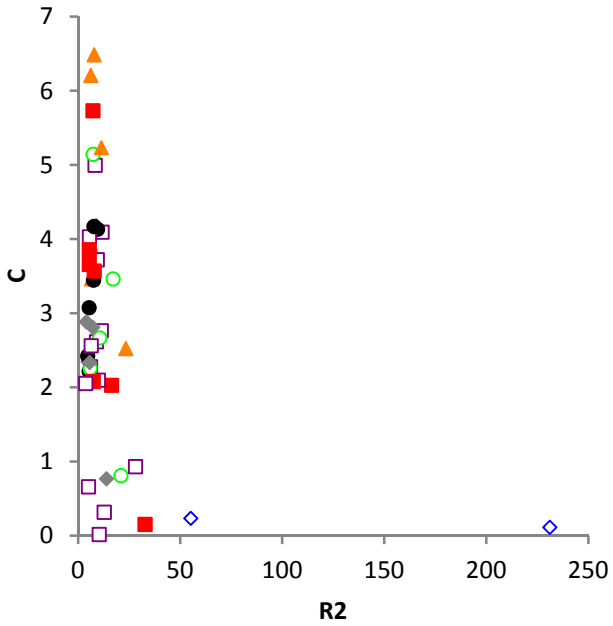




Increasing R_1 turns a triphasic waveform into a biphasic or monophasic tardus-parvus waveform. Increasing R_2 decreases flow and increases RI. Increasing C increases RI without affecting average flow.







In our data set, for normal transplant kidneys, the average calculated pressure after R_1 is 55 mm Hg. In primate glomeruli, the pressure is 45 mm Hg (Source: *Clinical physiology of acid-base and electrolyte disorders* by Rose and Post, page 36). This supports the idea that R_1 is the pre-glomerular resistance, and R_2 is the post-glomerular resistance. The three element Windkessel model also accurately describes *in vivo* blood flow in rat kidneys (Abu-Naser M et al, "Vascular resistance estimation in renal hemodynamics using a time-varying Windkessel model." ICASSP 2005).

There is still a large amount of overlap among diagnoses.

Diagnosis	Count	R1 average	R1 stdev	R2 average	R2 stdev	C average	C stdev	RMS difference from normal (in standard deviations)
1	6	5.68	2.09	6.71	1.85	3.24	0.83	0.00
2	6	6.11	4.56	7.41	3.63	2.55	1.10	0.31
3	8	8.59	7.44	11.05	9.48	3.10	1.66	0.34
4	5	7.74	3.11	11.08	7.17	4.78	1.73	0.66
5	5	10.03	3.88	12.40	6.46	2.87	1.60	0.76
6	2	**2.38**	0.09	143.12	124.38	**0.17**	0.09	2.40
7	14	8.16	6.79	9.83	5.93	2.37	1.51	0.46

In the above table, values of R_1, R_2, or C that are significantly different from normal are bolded.

We can attempt to make the diagnosis from R_1, R_2, and C, using an ellipsoid to determine which values belong to a given diagnosis. The result of this is shown below:

		Sensitivity	Specificity
Diagnosis	3	75%	68%
	4	60%	100%
	5	100%	68%
	6	100%	100%