Transpl Int (1996) 9: 57–61

ORIGINAL ARTICLE

Anders Lundell
Nils H. Persson
Ragnar Källen
Henrik Ekberg

Impaired renal artery blood flow at transplantation is correlated to delayed onset of graft function

Received: 1 March 1995
Received after revision: 6 June 1995
Accepted: 13 June 1995

A. Lundell (✉) · N.H. Persson · R. Källen · H. Ekberg
Transplant Unit,
Department of Surgery,
Malmö University Hospital,
S-21 401 Malmö, Sweden
Fax: + 46 40 336 211

Abstract The aim of this prospective study was to evaluate a transit time flowmeter (Transonic, USA) in renal transplantation with respect to feasibility and estimation of graft circulation. Subsequently, the measurements were evaluated for their ability to predict delayed onset of function, occurrence of acute rejection or graft loss within 3 months after transplantation. Renal artery blood flow was measured and resistance calculated in 100 transplants – 62 cadaveric donor (CD) and 38 living donor (LD) – immediately after restoration of graft circulation and before wound closure. Low blood flow (< 250 ml/min) and high resistance (> 392 mPRU) correlated positively with a long cold ischemia time and delayed onset of graft function, including the need for post-transplant dialysis. No correlation with rejection or graft loss was found. Blood flow measurements with the transit time flowmeter were easy to perform and immediate estimation of transplant circulation was achieved. Transplants at risk for delayed onset of function were identified.

Key words Transit time flowmeter, kidney transplantation · Kidney transplantation, flow measurement, transit time flowmeter · Flow measurement, kidney transplantation

Introduction

A method that is suitable for perioperative measurement of volume blood flow in renal transplants has to be accurate, reproducible, and easy to use. The measurement procedure should not endanger the transplant and the interpretation of the results should be simple. A low blood flow could indicate a technical problem, making an intraoperative correction necessary. Ideally, the results of the measurements could be used to predict delayed onset of graft function, rejection, or early graft loss.

An invasive method that is suitable for intraoperative use is the transit time flowmeter, which was introduced in 1983 [1, 4]. It is based on ultrasound but not Doppler (frequency shift). The transit time principle is the traveling time of an ultrasonic burst between two transducers placed at a constant distance. The transducers serve intermittently as emitter and receiver. In the direction of the blood flow, upstream, the traveling time is decreased and, conversely, it is increased against the direction of the blood flow, downstream, when compared with a master, zero, signal. The time difference between the traveling time of the up- and downstream ultrasonic burst is the transit time of the flow. The flowmeter automatically integrates all transit time differences over the entire cross sectional area of the vessel and the result is digitally displayed in ml/min.

The aim of the present investigation was, in a prospective manner, to evaluate the use of the transit time flowmeter in renal transplantation with respect to feasibility and estimation of graft circulation, and to study whether or not the results could be used to predict delayed onset of function, occurrence of acute rejection, or graft loss within 3 months after transplantation.

Methods

Cadaveric donor (CD) kidneys were perfused with University of Wisconsin preservation solution and living donor (LD) kidneys with Perfadex (Medisan, Sweden) solution. Standard surgical procedures were followed.

The arterial anastomosis was made to the internal iliac artery in primary transplantations. In retransplantations, or when the internal iliac artery was atherosclerotic, the external iliac artery was used. The venous anastomosis was made to the external iliac vein. Postoperatively, the patients were treated according to a uniform protocol. Immunosuppresssion included cyclosporin (Sandoz, Switzerland), azathioprine (Wellcome, England), and prednisolone (KABI, Sweden).

A transit time flowmeter, Transonic TC 101 D and, starting in 1993, Transonic HT 107 (Transonic, USA), was used for the measurements. The flow probes were HS4 or HS6 probes, with an ultrasonic beam of 4- or 6-mm width, respectively. The probes were sterilized in 60° gaseous formaldehyde. The space between the probe and the artery was filled with sterile physiological saline. Care was taken to place the probe parallel to the longitudinal axis and to avoid kinking of the vessel. The signal was monitored for 20–30 s and when stable the value was registered. The position of the probe was changed if the signal was unstable. The probes were automatically calibrated by the flowmeter.

The first measurement was made immediately after restoration of renal circulation, and the second after completion of the ureterocystostomy, approximately 30 min later. Mean systemic arterial pressure was measured as brachial pressure and calculated as mean arterial pressure = systolic pressure – 2/3 (systolic pressure – diastolic pressure). Resistance was calculated as 1000 (mean arterial pressure/flow) and presented as milli peripheral resistance units (mPRU). The variation in blood flow and resistance between the first and second measurements was calculated. The median flow and resistance for all transplants at the first measurement were used as cut-off points for correlation to delayed onset of graft function. Delayed onset was defined as absence of a spontaneous decrease in serum creatinine within 24 h after transplantation compared to the preoperative serum creatinine value. The results were also correlated to the incidence of acute rejection, verified by needle biopsy, and to loss of graft function, defined as a permanent need for dialysis up to 3 months after transplantation.

Statistics

The Mann-Whitney U-test, chi-square test, or Fischer's exact test (two-tailed) was used when appropriate to compare groups. Values given are median and quartile ranges, if not otherwise stated.

Ethics

The investigation was approved by the Ethics Committee for Human Investigations, University of Lund, Sweden M125/91. The patients gave their informed consent before transplantation.

Results

One hundred recipients of a first or second cadaveric donor (CD, $n = 62$) or living donor (LD, $n = 38$) renal graft, who underwent transplantation between November 1990 and July 1994, were included in the study.

Table 1 Renal artery blood flow and resistance in 100 renal transplants

	First measurement	Second measurement	
Flow (ml/min)	250 (166–360)	405 (265–562)	$P < 0.001$
Resistance (mPRU)	392 (253–568)	226 (189–338)	$P < 0.001$

Values are median and quartile ranges

Table 2 Renal artery blood flow in transplants with or without an intra-arterial injection of papaverin or verapamil

	First measurement	Second measurement	
Intra-arterial papaverein or verapamil injection ($n = 16$)	120 ml/min (68–238)	375 ml/min (124–450)	$P < 0.05$
No injection of papaverin or verapamil ($n = 84$)	264 ml/min (178–366)	411 ml/min (296–522)	$P < 0.05$

Values are median and quartile ranges

Blood flow measurements were made whenever the flowmeter and flow probes were available and, therefore, for practical reasons, another 116 recipients were not measured. There were 63 men and 37 women. Their median age was 44 (range 34–54) years. The measurements were easy to perform and the whole procedure was completed in 2–3 min. The flow probes were, however, sensitive to misalignment, and residual air between the probe and the vessel led to an unstable flow signal, if any. It was, nevertheless, always possible to obtain a stable flow signal. The median time between measurements was 35 (range 30–45) min.

At 3 months, patient survival was 100 % and graft survival 96 %. Four patients lost their grafts due to: vascular rejection ($n = 2$), vasculitis ($n = 1$), and progression of the underlying renal disease, Fabry's syndrome ($n = 1$). Acute rejection (vascular or cellullar) was diagnosed by graft biopsy in 41 patients, 14 (38 %) in the LD and 27 (43 %) in the CD group.

In general, graft circulation improved during the interval between the first and second measurements. The graft renal artery blood flow and calculated resistance both differed significantly when the two measurements were compared (Table 1). The cut-off values for flow and resistance were 250 ml/min and 392 mPRU, respectively. Due to a low flow in 16 (3 LD and 13 CD) transplants at the first measurement, 40 mg of papaverin (NM Pharma, Sweden) or 2,5 mg verapamil (Meda, Sweden) were injected into the renal artery. The injections enhanced blood flow significantly (Table 2).

There was a significantly lower blood flow and higher resistance in CD grafts than in LD grafts, both at the

Table 3 Renal artery blood flow and resistance in 62 cadaveric donor (CD) and 38 living donor (LD) renal transplants at the first and second measurements

	First measurement	Second measurement
Flow		
CD	200 ml/min (150–307)	349 ml/min (220–540)
LD	340 ml/min (215–400)	480 ml/min (402–628)
	$P < 0.001$	$P < 0.01$
Resistance		
CD	435 mPRU (295–686)	257 mPRU (202–429)
LD	300 mPRU (246–415)	212 mPRU (177–258)
	$P < 0.01$	$P < 0.01$

Values are median and quartile ranges

Table 4 Renal artery blood flow and resistance in 100 transplants correlated to cold ischemia time

Cold ischemia	First measurement	Second measurement
Flow		
≤ 11 h	330 ml/min (226–400)	464 ml/min (402–622)
> 11 h	190 ml/min (150–274)	327 ml/min (190–430)
	$P < 0.01$	$P < 0.01$
Resistance		
≤ 11 h	300 mPRU (244–436)	211 mPRU (165–258)
> 11 h	438 mPRU (256–657)	280 mPRU (197–456)
	$P < 0.05$	$P < 0.05$

Values are median and quartile ranges

Table 5 Renal artery blood flow in transplants with delayed or immediate onset of function and transplants with or without post-transplant dialysis

	First measurement	Second measurement
Delayed onset ($n = 21$)	163 ml/min (125–330)	250 ml/min (124–423)
Immediate onset ($n = 79$)	260 ml/min (184–365) $0.1 > P > 0.05$	423 ml/min (320–595) $P < 0.05$
Post-transplant dialysis ($n = 7$)	130 ml/min (94–170)	110 ml/min (72–330)
No dialysis ($n = 93$)	190 ml/min (150–350) $P < 0.05$	372 ml/min (235–450) $P < 0.05$

Values are median and quartile ranges

first and second measurements (Table 3). In both groups the circulation improved significantly between measurements.

The median cold ischemia time for all transplants was 11 (range 1–17) h, with an upper limit of 38 h. For CD transplants it was 15 h 30 min (13–20 h) and approximately 1 h in LD transplants. Kidneys with a cold ischemia time exceeding the median (11 h) had a significantly lower blood flow and higher resistance, both at the first and second measurements, than kidneys with a cold ischemia time of shorter duration (Table 4).

Table 6 Resistance in transplants with delayed or immediate onset of function and transplants with or without post-transplant dialysis

	First measurement	Second measurement
Delayed onset ($n = 21$)	564 mPRU (249–750)	309 mPRU (209–870)
Immediate onset ($n = 79$)	363 mPRU (253–500) $P < 0.05$	222 mPRU (179–301) $P < 0.05$
Post-transplant dialysis ($n = 7$)	743 mPRU (480–833)	720 mPRU (217–1416)
No dialysis ($n = 93$)	379 mPRU (243–647) $P < 0.05$	256 mPRU (191–381) $P < 0.05$

Values are median and quartile ranges

Delayed onset of function occurred in 21 transplants – 1 LD and 20 CD grafts – and 7 of them had at least one post-transplant dialysis. Nineteen of the transplants with delayed onset of function had a cold ischemia time exceeding 11 h. Transplants with a delayed onset had a significantly lower blood flow (Table 5) and higher resistance (Table 6) than those with an immediate onset of function. The degree of restitution of graft circulation, as evidenced by the difference between the two measurements, was also correlated with onset of graft function. In 17 transplants, a decreased or unchanged graft blood flow was registered at the second measurement, and in 6 (35 %) of them the onset of function was subsequently delayed. Fifteen out of 83 (18 %) transplants with improved circulation, i.e., increased blood flow at the second measurement, had a delayed onset of function (P = NS). Similar results were found with regard to the calculated resistance. Low blood flow and high resistance were particularly evident in the seven patients in need of post-transplant dialysis. The median flow in this group had decreased by the second measurement.

At a flow lower than the cut off value of 250 ml/min or a resistance higher than the cut-off value of 392 mPRU, the proportion of transplants with a delayed onset of function was significantly larger than the proportion of transplants with an immediate onset of function (Table 7). The highest predictive values of flow and resistance for delayed onset of function were found at the second measurement (Table 8).

Finally, the proportion of rejection episodes or graft loss in transplants with a blood flow lower or higher than 250 ml/min or a resistance higher or lower than 392 mPRU did not differ significantly.

Table 7 Proportion of delayed onset of graft function in 100 renal transplants correlated with graft renal artery blood flow and resistance

	Proportion (%) at first measurement	Proportion (%) at second measurement
Flow		
≤ 250 ml/min	15/51 (29)	10/22 (45)
> 250 ml/min	6/49 (12)	11/78 (14)
	$P < 0.05$	$P < 0.05$
Resistance		
> 392 mPRU	11/32 (34)	6/10 (60)
≤ 392 mPRU	10/68 (15)	15/90 (16)
	$P < 0.05$	$P < 0.05$

Values are median and quartile ranges

Table 8 Predictive values of flow and resistance for delayed onset of function with cut-off points 250 ml/min and 392 mPRU, respectively

	First measurement	Second measurement
Flow ≤ 250 ml/min:		
Positive predictive value	29 %	45 %
Negative predictive value	88 %	86 %
Specificity	54 %	85 %
Sensitivity	71 %	48 %
Resistance > 392 mPRU:		
Positive predictive value	34 %	60 %
Negative predictive value	85 %	83 %
Specificity	73 %	95 %
Sensitivity	52 %	29 %

Discussion

A simple and reliable method for intraoperative volume flow measurement in renal transplantation should present immediate information about renal graft circulation. A low or decreasing flow could indicate a technical error which, left uncorrected, would endanger the transplant. Ideally, the results could furthermore be used to predict delayed onset of graft function, occurrence of acute rejection, or graft loss. There is, however, a scarcity of simple and reliable methods for intraoperative volume flow measurements.

The transit time technique has not previously been reported for use in renal transplantation. In an experimental in vitro and in vivo validation study of the transit time flowmeter, we found a low error of measurement and a high reproducibility [10]. In the present investigation, we found that the transit time flowmeter was easy to use and that an immediate estimation of the arterial circulation in the transplant was achieved. The measurements did not unduly prolong operating time. A low blood flow and high resistance correlated significantly with a long cold ischemia time and with occurrence of delayed onset of graft function. The flow measured in transplants after a long period of cold ischemia were significantly lower, both at the first and second measurements, than the flow in transplants with a short cold ischemia time. The lowest flow and highest resistance were found in transplants with a delayed onset of function and in need of post transplant dialysis. Generally, flow and resistance improved between measurements, but in patients with delayed onset of function resulting in post-transplant dialysis, median flow decreased at the second measurement. No correlation between incidence of acute rejection or graft loss and flow or resistance was found.

These last findings were in contrast to those of other authors [2] who used inert gas clearance. The reason for this discrepancy may involve differences in the measuring technique, but it may also be partly based on clinical differences. Several transplant centers have reported that the outcome in cases of delayed onset of graft function is impaired [3, 7]. For a number of years, we have used a wider definition of delayed onset, based on lack of a decrease in serum creatinine and not only on the need for dialysis. A modified immunosuppressive protocol is used in these cases, including anti-T-lymphocyte globulin prophylaxis and low dose oral cyclosporin. With this regimen, there is no significant difference in outcome between patients with or without delayed onset of graft function [5]. This might partly explain why low blood flow measurements, in our hands, correlate with delayed onset of function but not with graft loss. From the above, it could be argued that the predictive value of the blood flow measurements would be limited. However, our evaluation of graft function is based on postoperative serum creatinine values at 24 h. Immediate information on blood flow data would, therefore, be valuable in critical cases when initiation of antibody prophylaxis is considered on the day of operation, especially in patients with uncertain graft urine production.

Cadaveric donor transplants were found to have a lower graft blood flow than living donor transplants. However, this is probably not due to the difference in donor type, but merely a reflection of the difference in the cold ischemia time in the two kinds of procedures. Prolonged cold ischemia time may lead to acute tubular necrosis increased peripheral resistance and, thereby, a low renal artery flow, as well as a subsequent risk for impaired graft function [11].

The second measurement showed higher predictive values overall than the first, especially as a negative test. The second measurement seemed to be the more important of the two. High resistance was not a superior predictor of delayed onset of function compared to a low volume flow. One plausible explanation may be that we used the auscultatory measured brachial pressure for calculation of resistance. A puncture of the renal artery for direct measurement of blood pressure

could possibly have given more correct data [13]. However, we believe that the increased risk of damaging the artery and jeopardizing the transplant does not justify this procedure.

There are other methods available for renal flow measurements, both qualitative and quantitiative, selective and nonselective. Duplex is a well-established method, giving both morphology and flow velocity. It has the advantage of being noninvasive but has limited means for measurement of volume flow. The reliability of a duplex examination also depends on the skill of the operator [6]. Inert radioactive gas clearance has been tried, but radiation hazards and a cumbersome measurement procedure have prevented widespread use [8]. The electromagnetic flowmeter is potentially accurate but difficult to calibrate [12].

The transit time flowmeters, Transonic TC 101 D and, later, Transonic HT 107 (Transonic, USA), were easy to handle and the flow probes needed no calibration. The measured renal artery blood flow values correlated well with renal flow measurements made by others [9]. There were, however, potential errors of measurement. The flow probes had to be placed along the longitudinal axis of the vessel. Air between the flow probe and the vessel gave an unstable, inaccurate signal, if any. In spite of this, it turned out to be a useful tool for our perioperative surveillance of blood flow in renal transplants.

In conclusion, measuring blood flow with a transit time flowmeter is easy and gives an immediate estimation of the arterial circulation in the transplant. Our measurements correlated significantly with the occurrence of delayed onset of graft function as well as with the need for post-transplant dialysis. This immediate information would be clinically valuable when the postoperative graft status is evaluated and variation in immunosuppressive regimen is considered. There were no significant correlations between blood flow measurements and rejection or graft loss during the first 3 postoperative months.

Acknowledgements This study was supported by The Swedish Medical Research Council, The Hulda Almroth Foundation, and The Royal Physiographic Society, Sweden.

References

1. Barnes RJ, Comline RS, Dobson RS, Drost CJ (1983) An implantable transit-time ultrasonic blood flow meter. J Physiol (London) 35: 2–3
2. Bergentz S-E, Brunius U, Gelin L-E, Lewis DH (1971) Operative blood flow measurement in transplanted human kidneys and subsequent rejection. Ann Surg 174: 44–47
3. Dawidson IJ, Sandor ZF, Coorpender L, Palmer B, Peters P, Lu C, Sagalowsky A, Risser R, Willms C (1992) Intraoperative albumin administration affects the outcome of cadaver renal transplantation. Transplantation 53: 774–782
4. Drost CJ (1983)Vessel internal diameter independent volume flow measurements with ultrasound. San Diego Biomed Symp 19: 299–302
5. Ekberg H, Persson NH, Källén R, Omnell-Persson M (1994) Prolonged donor intensive care exerts a negative impact on renal graft survival. Transplant Proc 26: 1756–1757
6. Grigg M, Wolfe JHN, Tovar A, Nicoloaides AN (1988) The reliability of Duplex haemodynamic measurements in the assessment of femorodistal grafts. Eur J Vasc Surg 2: 171–174
7. Halloran PF, Aprile MA, Farewell V, Ludwin D, Kinsey Smith E, Tsai SY, Bear RA, Cole EH, Fenton SS, Cattran DC (1988) Early function as the principal correlate of graft survival. Transplantation 46: 223–228
8. Lewis DH, Bergentz SE (1966) Renal blood flow measurements with Xenon-133 at the time of operation for renal artery stenosis. Surgery 59: 1043–1047
9. Lewis DH, Bergentz SE, Brunius U, Ekman H, Gelin LE, Hood B (1968) Blood flow in kidney transplants. A clinical evaluation of the 133Xenon method. Scand J Urol Nephrol 2: 36–39
10. Lundell A, Bergqvist D, Mattsson E, Nilsson B (1993) Volume blood flow measurements with a transit time flowmeter: an in vivo and in vitro variability and validation study. Clin Physiol 13: 547–557
11. Myers BD, Moran SM (1986) Hemodynamically mediated acute renal failure. N Engl J Med 314: 97–105
12. Shercliffe JA (1962) The theory of electromagnetic flow measurement. Cambridge University Press, Cambridge
13. Sonesson B, Länne T, Vernersson E, Hansen F (1994) Sex difference in the mechanical properties of the abdominal aorta in human beings. J Vasc Surg 20: 959–969