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THE NATURAL HISTORY OF KIDNEY GRAFT CORTICAL MICROCIRCULATION DETERMINED BY REAL-TIME CONTRAST-ENHANCED SONOGRAPHY (RT-CES)

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INTRODUCTION

Background: Decreasing kidney graft cortical microcirculation has been related to poor prognosis in kidney transplantation. Cortical capillary blood flow (CCBF) can be measured by real-time contrast-enhanced sonography (RT-CES)

Aim: to describe the natural history of CCBF over time under diverse conditions of kidney transplantation, to explore the influence of donor conditions and recipient events, and to determine the capacity of CCBF for predicting renal function in medium term.

Figure 1a

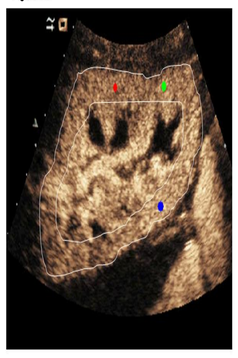


Figure 1b

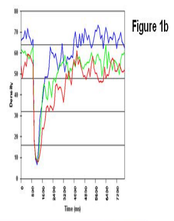
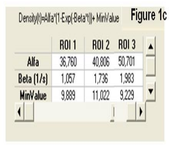


Figure 1c



This Figure shows renal graft perfusion by contrast media in a longitudinal view. Red, green and blue circles are regions of interest selected in the proximal and distal renal cortex. The white line identifies and isolates the renal cortex. Once uniform graft perfusion was achieved, microbubbles were destroyed with a high mechanic ultrasound pulse. The replenishment kinetics was recorded stored in order to perform time-intensity curves using a software tool (Figure 1b). Cortical capillary blood flow for each region of interest could be estimated (Figure 1c).

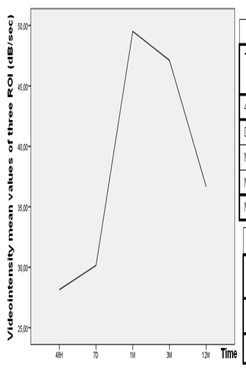
MATERIALS AND METHODS

We evaluated all patients who underwent kidney transplantation in our unit from 2009 to 2010 by RT-CES (n=79). All available patients at each moment were studied after 48 h, 5-7 days, and 1, 3 and 12 months after transplantation. Cortical capillary blood flow was measured. Clinical variables were analyzed

Statistical analysis: Mean ± SD and medians and quartiles are employed whenthere is a non-normal distribution. The influence of CCBF has been determined by univariate and multivariate analysis using mixed regression models based on sequential measurements for each patient over time.

We used a first-order autoregression model as the structure of the covariation between measures. The post-hoc comparisons were considered using the Bonferroni correction. Serum creatinine was selected as the prognosis marker for graft outcome following the recommendations of several authors. The CCBF values with the corresponding serum creatinine values measured simultaneously were compared in terms of prognosis.

RESULTS



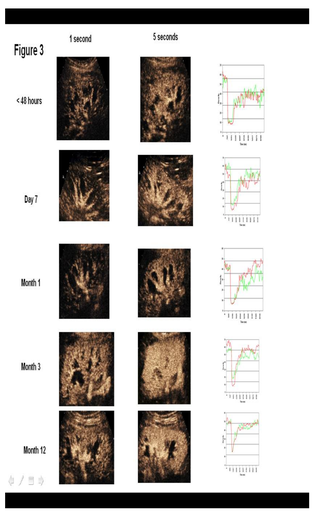
Estimates

Time	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
48 Hour	28,647	4,166	196,152	20,430	36,863
Day 7	30,700	4,515	202,604	21,797	39,603
Month 1	49,380	4,591	202,529	40,328	58,432
Month 3	49,641	4,553	201,633	40,663	58,618
Month 12	36,439	3,748	167,327	29,045	43,834

Type III Tests of Fixed Effects

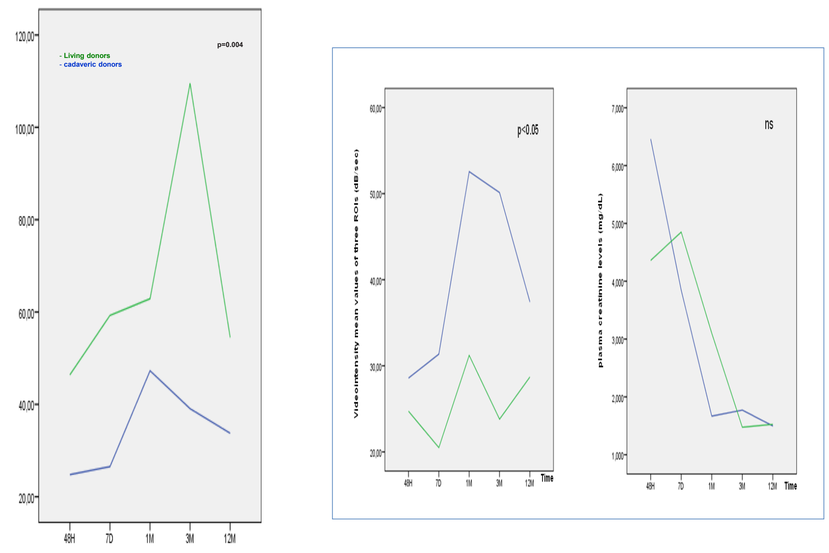
Source	Numerator df	Denominator df	F	Sig.
Intercept	1	92,712	279,834	,000
Time	5	173,163	4,586	,001

Estimated CCBF mean values of the 79 patients studied at various times after transplantation. It is notable that the CCBF starts at lower levels than those that will be reached at months 1 and 3 (this peak varies among patients). It is also remarkable that, after month 3, CCBF values follow a partial descent until month 12, remaining at an intermediate level between the initial and maximum values.



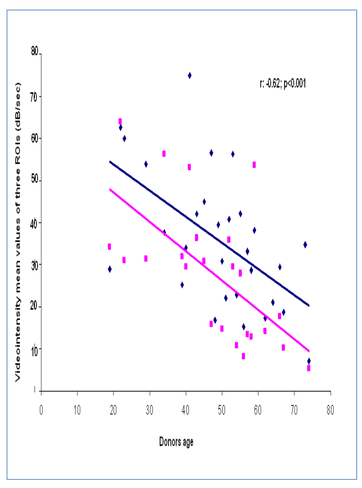
Actual example of the studies performed in a cadaver donor recipient over time.

RT-CES images obtained at 1 (a) and 5 (b) seconds from refilling after bubble destruction at various times 1 year after transplantation. On the corresponding right side, time-intensity curves obtained at 2 regions of interest (red and green) are shown (c). Initial image (1a and 1b) demonstrates obvious renal flow in the large vessels (a and b) and renal cortex (b). At days 7 and 30, these images are very similar, reflecting the same structures at each moment. However, images at month 3 show early cortical flow (4a) not present in prior examinations (1-3a), demonstrating faster cortical refilling. Very similar features are found at month 12 (5). Images 1-5c show time-intensity curves that reflect the number of cortical capillaries in the refilling phase. There is a notable correspondence between the 2 measurements along all studies (red and green) and the differences in the area under the curve (AUC) between 1c and 2-5c.

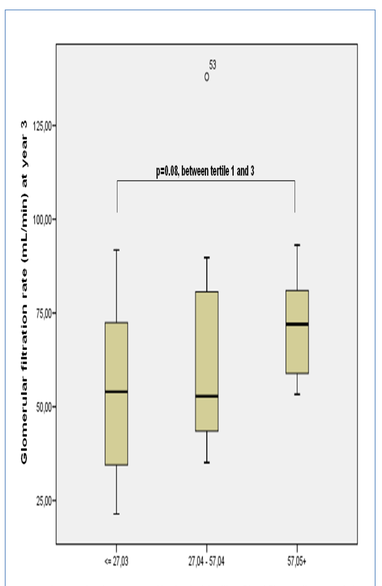


By mixed model analysis the CCBF value follow-up was statiscally significant higher among grafts from living donors relative to encephalic death cadaver donors.

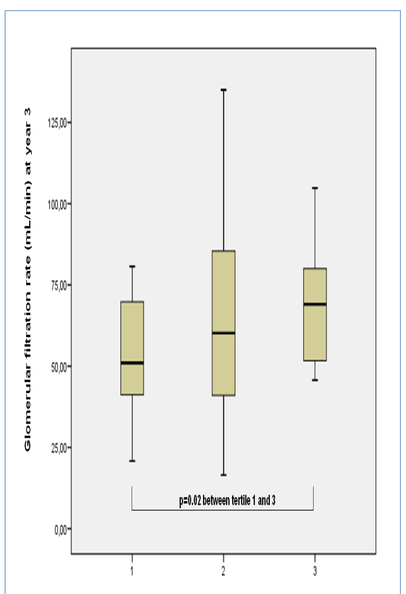
On the left panel the CCBF values of patients with (green) and with no (blue) acute rejection demonstrate significant differences by mixed model analysis over time. In contrast, plasma creatinine levels (right panel) behaved with no differences for the same patients.



Significant relationship between donor's age and CCBF at 48 hours (pink points), and the average CCBF value over the whole follow-up (blue points, r: -0.62, p<0.001).



Box diagrams representing GFR values reached at year 3 by different groups of patients, grouped by CCBF tertile at month 1



Patients with CCBF on the highest tertile compared to those in the lowest tertile at year 1, with similar plasma creatinine levels. The first group reached a significant higher GFR at year 3 (mean value GFR 70 vs. 48 ml/min)

Type III Tests of Fixed Effects

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	91,360	53,216	,000
Donor[&]	1	106,143	17,559	,000
DGF[‡]	1	109,914	,370	,544
Donor´s hypertension	1	107,019	,327	,569
Acute rejection	1	84,902	3,193	,078
Donor´s age	1	109,365	12,384	,001
Creatinine[*]	1	184,845	4,904	,028

[&]: living vs cadaveric donors. [‡]:Dalayed graft function
[*]Serum creatinine at the same time than ultrasonography

Multivariant analysis. There was an independent significant relationship between CCBF and type of donor (living vs. cadaver), donor´s age and serum creatinine level.

The existence of acute rejection was almost significant

CONCLUSIONS

In conclusion RT-CES is a tool that can be able to accurately quantify and iteratively measure the cortical graft microcirculation in kidney recipients. We have described the natural history of cortical capillary blood flow under the regular clinical conditions and it could become a reference for any clinician that use contrast enhanced sonography in this field. CCBF data are consistent with the clinical variables evaluated, and therefore it is congruent with actual knowledge. They are necessary more studies with homogeneous design for confirming these results.

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