Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation

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Although cold ischemia time has been widely studied in renal transplantation area, there is no consensus on its precise relationship with the transplantation outcomes. To study this, we sampled data from 3839 adult recipients of a first heart-beating deceased donor kidney transplanted between 2000 and 2011 within the French observational multicentric prospective DIVAT cohort. A Cox model was used to assess the relationship between cold ischemia time and death-censored graft survival or patient survival by using piecewise log-linear function. There was a significant proportional increase in the risk of graft failure for each additional hour of cold ischemia time (hazard ratio, 1.013). As an example, a patient who received a kidney with a cold ischemia time of 30 h presented a risk of graft failure near 40% higher than a patient with a cold ischemia time of 6 h. Moreover, we found that the risk of death also proportionally increased for each additional hour of cold ischemia time (hazard ratio, 1.018). Thus, every additional hour of cold ischemia time must be taken into account in order to increase graft and patient survival. These findings are of practical clinical interest, as cold ischemia time is among one of the main modifiable pre-transplantation risk factors that can be minimized by improved management of the peri-transplantation period.

Kidney International advance online publication, 17 September 2014; doi:10.1038/ki.2014.304

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Received 11 April 2014; revised 1 July 2014; accepted 10 July 2014

KEYWORDS: cold ischemia time; graft survival; kidney transplantation; patient survival

During the past 10 years in renal transplantation, the widespread use of mycophenolic acid, tacrolimus, and novel induction therapies has played a major role in decreasing the incidence of acute rejection episodes.[1–3] However, mid-term kidney graft and patient survival have not improved as much as expected. This could be because of the increased age of both recipients and donors and is associated with the higher frequency of expanded criteria donors (ECDs).[4] Another endeavor should be achieved to reduce delayed graft function (DGF) risk.[5] DGF is well known to influence mid-term graft outcomes, and it increases hospitalization duration and the frequency of concomitant acute rejection.[6,7] The incidence and severity of DGF have remained stable but varies from 25 to 50% among deceased donor kidneys.[8,9] DGF is the consequence of well-described risk factors,[10,11] among which cold ischemia time (CIT) seems to be one of the main explicative variables.[12,13] CIT acts at least in part through pathophysiological pathways that induce ischemia reperfusion injuries.[10,14] To improve mid-term outcomes, it could be preferable to optimize the transplantation organization with the aim of shortening CIT as most as possible and preventing ischemia injury through other strategies such as machine perfusion, before treating lesions already established in the graft.

Even though CIT is a well-known risk factor among the renal transplantation community, its precise etiological role on mid-term graft outcomes is still under debate as illustrated by the wide heterogeneity of results observed in

the literature. On one hand, some authors have shown that CIT was not significantly associated with graft survival among transplanted patients.[15–18] On the other hand, numerous other studies established that CIT represents a major risk factor of graft survival.[12,14,19–24] Nevertheless, there is no consensus whether CIT should be considered as a continuous risk factor or whether threshold values can be considered to identify subgroups with a relevant excess in the risk of mid-term graft and patient outcomes.[12,16,18,20] For instance, Salahudeen *et al.*[20] demonstrated a significantly worse graft survival for patients with a CIT higher than 30 h, whereas Opelz *et al.*[12] described that increasing CIT up to 18 h was not associated with an increased risk of graft failure. In addition to the heterogeneity of cutoff values used to define high-risk patients, the definition of these values is often arbitrary. Besides, the majority of the previous studies analyzed graft and patient survival and death-censored graft survival; only Johnson *et al.*[17] studied the association of the CIT with patient survival, and they showed a nonsignificant association of continuous CIT on patient death. Therefore, taking the opportunity of a large prospective, multicentric, and validated cohort, the aim of this study was to revisit the potential relationship between the CIT and either the graft failure (death-censored) or the patient death using an etiological approach.

RESULTS

Characteristics at the time of transplantation

The mean CIT was 20.6 h (range from 6 to 58.6 h; s.d. = 7.8). The CIT duration was between 6 and 16 h for 1274 (33.2%) patients, 16 and 24 h for 1531 (39.9%), 24 and 36 h for 853 (22.2%), and longer than 36 h for 181 patients (4.7%). Figure 1 displays boxplots of CIT for each year of transplantation. Over the past decade, we observed a global decrease in CIT duration (median from 23.0 h in 2000 to 16.3 h in 2011). However, this progress was more important

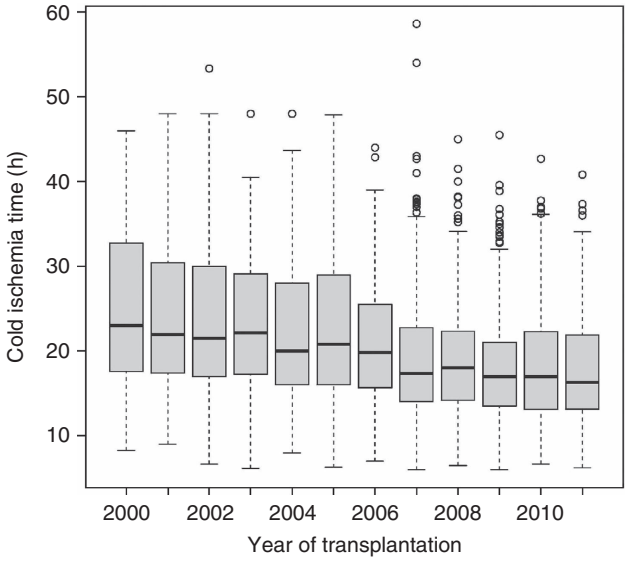

Figure 1 | Boxplots representing the minimum, the maximum, the first, second, and third quartiles of cold ischemia time duration for each year of transplantation.

Table 1 | Description of recipient, donor, and transplantation characteristics of the global study population and according to CIT-based groups (6–16, 16–24, 24–36, and > 36 h)

	Missing data	Global (*N* = 3839)	CIT from 6 to 16 h (*N* = 1274)	CIT from 16 to 24 h (*N* = 1531)	CIT from 24 to 36 h (*N* = 853)	CIT above 36 h (*N* = 181)	*P*-value
Quantitative characteristics: mean ± s.d.							
Recipient age (years)	0	51.6 ± 13.2	51.0 ± 13.4	52.3 ± 13.3	51.3 ± 12.7	51.4 ± 13.4	0.051
Recipient BMI (kg/m^2)	38	24.4 ± 4.3	24.3 ± 4.3	24.4 ± 4.2	24.5 ± 4.5	24.3 ± 4.4	0.894
Donor age (years)	0	50.5 ± 16.2	48.9 ± 16.4	52.1 ± 16.1	50.0 ± 15.5	50.3 ± 16.6	< 0.001
Donor serum creatinine (mg/ml)	0	93.9 ± 56.1	90.7 ± 47.9	96.0 ± 65.4	95.6 ± 51.3	91.6 ± 43.7	0.061
HLA incompatibilities ABDR	87	3.3 ± 1.3	3.4 ± 1.2	3.2 ± 1.3	3.3 ± 1.4	3.3 ± 1.3	< 0.001
Categorical characteristics: N (%)							
Recipient men	0	2365 (61.6)	794 (62.3)	958 (62.6)	504 (59.1)	109 (60.2)	0.345
Dialysis technique							0.047
Pre-emptive transplantation	0	304 (7.9)	120 (9.4)	123 (8.0)	54 (6.3)	7 (3.9)	
Hemodialysis	0	3251 (84.7)	1053 (82.7)	1300 (84.9)	735 (86.2)	163 (90.0)	
Peritoneal dialysis	0	284 (7.4)	101 (7.9)	108 (7.1)	64 (7.5)	11 (6.1)	
Detectable anticlass I PRA	0	750 (19.5)	228 (17.9)	313 (20.4)	165 (19.3)	44 (24.3)	0.131
Detectable anticlass II PRA	0	608 (15.8)	172 (13.5)	243 (15.9)	155 (18.2)	38 (21.0)	0.006
History of cardiovascular diseases	0	1394 (36.3)	427 (33.5)	557 (36.4)	335 (39.3)	75 (41.4)	0.022
History of hypertension	0	3036 (79.1)	981 (77.0)	1197 (78.2)	700 (82.1)	158 (87.3)	0.001
History of dyslipidemia	0	1138 (29.6)	380 (29.8)	450 (29.4)	250 (29.3)	58 (32.0)	0.894
History of diabetes	0	466 (12.1)	144 (11.3)	202 (13.2)	97 (11.4)	23 (12.7)	0.398
Donor men	0	2277 (59.3)	772 (60.6)	894 (58.4)	502 (58.9)	109 (60.2)	0.672
Expanded criteria donor	0	1295 (33.7)	379 (29.8)	589 (38.5)	264 (31.0)	63 (34.8)	< 0.001
Cerebrovascular donor death	0	2169 (56.5)	686 (53.9)	904 (59.1)	470 (55.1)	109 (60.2)	0.025
Depleting induction	17	1521 (39.6)	500 (39.3)	567 (37.0)	366 (42.9)	88 (48.6)	0.003
Delayed graft function	110	1204 (31.4)	280 (22.0)	474 (31.0)	342 (40.1)	108 (59.7)	< 0.001
Machine perfusion	0	48 (1.3)	24 (1.9)	14 (0.9)	10 (1.2)	0 (0)	0.0579

Abbreviations: BMI, body mass index; CIT, cold ischemia time; HLA, human leukocyte antigen; PRA, panel reactive antibody.
Quantitative characteristics expressed as the mean and s.d.; categorical characteristics expressed as number (%).