ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2019; 24: 147-154
DOI: 10.12659/AOT.913869

Received: 2018.10.30
Accepted: 2018.12.18
Published: 2019.03.15

Prolonged Duration of Brain Death was Associated with Better Kidney Allograft Function and Survival: A Prospective Cohort Analysis

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Background: Brain death initiates hemodynamic, immunological, and hormonal changes that potentially compromise organ quality for transplantation. Therefore, it is generally believed that organs should be procured as soon as possible after the declaration of brain death. However, conflicting data exist regarding the impact of brain death duration on long-term graft function and survival.

Material/Methods: The effect of duration of brain death on graft survival and function of 1869 adult transplant recipients receiving kidneys from deceased donors after brain death was analyzed, using relevant donor and recipient characteristics and allograft related factors.

Results: Duration of brain death was a significant predictor for long-term graft survival, whilst there was no significant effect of duration of brain death on the incidence of delayed graft function or acute graft rejection after kidney transplantation. After dividing the study population into a "short durBD" (<10.6 hours) group and a "long durBD" (>10.6 hours) group, the 15-year graft survival estimates were significantly higher and the serum creatinine at 3 months after transplantation was significantly lower in the "long durBD" group.

Conclusions: Duration of brain death does not affect the incidence of delayed graft function or acute rejection after kidney transplantation. However, longer duration of brain death is associated with better kidney allograft function and survival.

MeSH Keywords: **Brain Death • Delayed Graft Function • Graft Rejection • Kidney Transplantation • Survival Analysis**

Abbreviations: **durBD** – duration of brain death; **HR** – hazard ratio; **OR** – odds ratio

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/913869

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Background

The immunological changes and hormonal dysregulation in brain-dead donors may contribute to the inferior outcomes of transplantation with a kidney from a brain-dead donor as compared to a kidney from a living donor [1–3]. This can be explained by the hemodynamic instability in the donor: when cerebral ischemia reaches the medulla oblongata, the sympathetic nerves are excited, causing the explosive release of endogenous catecholamines. This leading to an abrupt elevation of blood pressure and tachycardia, also called the "sympathetic or catecholamine storm". The release of catecholamines increases the heart load and oxygen consumption. High levels of catecholamines can also lead to overload of intracellular calcium, depletion of adenosine triphosphate, and therefore overproduction of oxygen free radicals and cell injury. Thereafter, a hypotensive phase commences, due to gradual depletion of catecholamines, causing further reduction of the oxygen supply to the internal organs [4,5]. Therefore, it is generally believed that organs should be procured as soon as possible once brain death is confirmed. This is supported by evidence from animal studies indicating that prolonged duration of brain death (durBD) is deleterious [6–8]. However, evidence from clinical cohort studies indicates that longer durBD is not detrimental, but beneficial by reducing the incidence of delayed graft function [9–12]. Conflicting evidence exists regarding the influence of brain death duration on long-term kidney graft function and survival [10,12].

We aimed to study the impact of brain death duration on long-term outcome in deceased donor kidney transplantation. Therefore, we analyzed data from the Netherlands Organ Transplant Registry (NOTR).

Material and Methods

Patients

Data was obtained from a prospectively maintained electronic database called the Netherlands Organ Transplant Registry (NOTR, Dutch Transplant Foundation, Leiden, the Netherlands). The dataset that we used included a consecutive series of donation after brain death kidney transplantations from May 1, 2002 to December 31, 2015 in the Netherlands. Inclusion criteria were: initial kidney transplantation in adult recipients aged ≥18 years with recorded data of durBD, immediate or delayed graft function, graft rejection within the first year after kidney transplantation, and graft survival.

The following characteristics were available and extracted from the database: donor age, gender, body mass index, hypotensive period(s) and lowest creatinine during the brain death period, history of systemic diseases (e.g., hypertension, diabetes mellitus), date and time of brain death declaration and start of cold perfusion; recipient gender, age, body mass index and duration of dialysis prior to kidney transplantation; anastomosis time, cold ischemia time and human leukocyte antigen mismatches. DurBD was calculated by subtracting the time of start of cold perfusion and the time of declaration of brain death.

Endpoints

The long-term outcome measure was graft survival. Graft failure was defined as the return to dialysis or re-transplantation and was censored upon death with a functioning graft. The short-term outcome measures were delayed graft function, defined as the need for dialysis after transplantation; acute rejection, defined as the need for treatment for graft rejection within the first year after kidney transplantation; serum creatinine 3 and 12 months after kidney transplantation.

Risk of bias

To address potential sources of bias, baseline donor and recipient characteristics and allograft related factors of exposed and unexposed participants were compared, and follow-up outcome data on immediate or delayed graft function, graft rejection within the first year after kidney transplantation, and graft survival were considered for selection bias; multivariable analysis with relevant donor and recipient demographics and allograft related were performed for confounding factors [13–18].

Statistical analysis

To evaluate the effect of durBD on graft survival after kidney transplantation, uni- and multivariable Cox proportional hazards models were performed with relevant donor and recipient characteristics and allograft related factors. Binary logistic regression, with relevant donor and recipient characteristics and allograft related factors, was used to identify whether durBD was associated with the incidence of delayed graft function or acute rejection. After measuring the effect of durBD as a continuous variable, we divided our study population equally by the median in the "short durBD" (<10.6 hours) group and the "long durBD" (>10.6 hours) group [10]. The effect of "short durBD" versus "long durBD" on graft survival was expressed graphically using the Kaplan-Meier method for illustrational purposes; the statistical difference between groups was assessed by the log-rank test. The effect on serum creatinine 3 and 12 months post-operatively was evaluated using the Mann-Whitney U test. All statistical analyses were performed using SPSS software, version 25 (SPSS Inx., Chicago, IL, USA). *P*-values <0.05 were considered statistically significant.

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Table 1. Baseline donor and recipient demographics and allograft related factors (n=2460).

Baseline characteristics	Included pairs (n=1,869)		n	Excluded pairs (n=591)		n	*P*-value
Duration of brain death period (hours)	10.6	(8.9–12.5)	1,869	N/A		591	N/A
Donor gender (Male)	833	(44.6%)	1,869	313	(53.0%)	591	**.000**
Donor age (years)	54	(45–63)	1,869	51	(42–58)	591	**.000**
Donor body mass index (kg/m^2)	24.5	(22.5–26.9)	1,869	25.1	(23.3–27.8)	591	**.000**
Expanded criteria donor	696	(37.2%)	1,869	157	(26.6%)	591	**.000**
Donor history of hypertension	505	(28.0%)	1,806	179	(42.3%)	423	**.000**
Donor hypotensive period(s)	658	(37.3%)	1,762	122	(34.2%)	357	.252
Donor history of diabetes mellitus	24	(1.3%)	1,859	0	(0.0%)	19	.618
Donor history of cardiac arrest	449	(24.4%)	1,843	76	(20.1%)	378	.064
Donor use of inotropic medication	1,616	(86.5%)	1,869	22	(95.7%)	23	**.049**
Donor cause of death: stroke	587	(31.4%)	1,869	163	(27.6%)	591	.073
Donor cause of death: trauma	290	(15.5%)	1,869	89	(15.1%)	591	.789
Donor lowest creatinine (µmol/L)	64	(50–100)	1,868	69	(53–104)	591	.707
Recipient gender (Male)	1,151	(61.6%)	1,869	300	(50.8%)	591	**.000**
Recipient age (years)	57	(45–65)	1,869	54	(44–61)	591	**.000**
Recipient body mass index (kg/m^2)	25.4	(22.8–28.4)	1,725	24.8	(22.2–28.1)	564	.181
Recipient dialysis duration (years)	3.67	(2.42–4.99)	1,702	2.98	(1.90–4.58)	542	**.017**
Cold ischemia time (hours)	14.6	(11.5–19.0)	1,665	18.0	(14.5–22.7)	551	**.000**
Anastomosis time (minutes)	33	(26–40)	1,662	32	(25–40)	534	.376
Number of HLA mismatches	3	(2–4)	1,859	2	(0–3)	589	**.000**
Delayed graft function	277	(17.5%)	1,583	82	(16.0%)	513	.429
Acute graft rejection within 1 year	110	(5.9%)	1,869	38	(6.4%)	591	.628
Graft failure	293	(15.7%)	1,869	100	(16.9%)	591	.472

Values are expressed as the median (25th–75th percentile), unless stated otherwise. HLA – human leukocyte antigen.

Results

Demographics

Between May 1, 2002 and December 31, 2015 there were 2460 initial transplantations performed with kidneys donated after brain death, in adults in the Netherlands, including 1869 transplants with recorded data of durBD. Data on time of start of cold perfusion or time of declaration of brain death was not recorded for 591 transplants (24.0%), and these transplants where therefore excluded. Data on graft function and/or graft survival was not recorded for 286 transplant recipients (15.3%) who were lost to follow-up. Therefore, 1583 donor-recipient pairs were included in this analysis. Demographics of donors and recipients, and allograft-related factors are shown in Table 1. The median durBD was 10.6 hours; the distribution of durBD is shown in Figure 1. For 99.0% of all donors the durBD was shorter than 24 hours.

Duration of brain death and graft function

Data on direct or delayed graft function after kidney transplantation were available for 1583 recipients (84.7%). Donors of these recipients who had immediate graft function (n=1306) had a median durBD of 10.7 hours (range, 9.0 to 12.5 hours), while donors of recipients who suffered from delayed graft function (n=277) had a median durBD of 10.5 hours (range, 8.9 to 12.8 hours). In recipients who needed treatment for rejection

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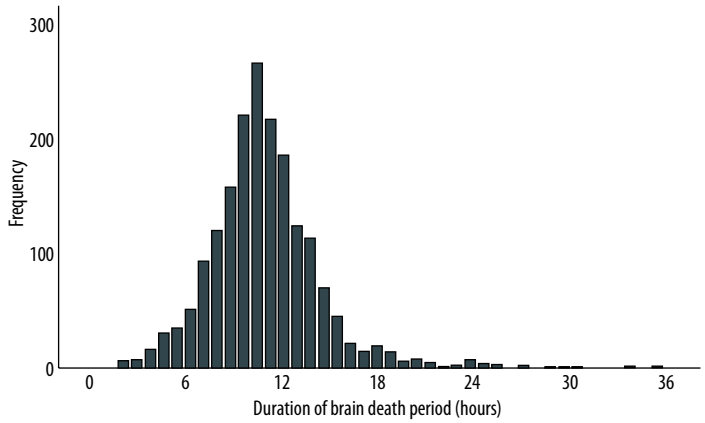

Figure 1. Distribution of duration of brain death period in hours.

Table 2. Multivariable binary logistic regression analysis for delayed graft function and acute graft rejection.

Graft function	Delayed graft function			Acute graft rejection		
	Odds ratio (95% CI)		*P*-value	Odds ratio (95% CI)		*P*-value
Duration of brain death period (hours)	1.042	(0.999–1.087)	.058	1.054	(0.999–1.112)	.055
Donor gender (Female/Male)	1.569	(1.128–2.183)	**.008**	0.942	(0.588–1.508)	.804
Donor age (years)	1.036	(1.015–1.057)	**.001**	1.034	(1.003–1.067)	**.033**
Donor body mass index (kg/m^2)	1.044	(1.004–1.086)	**.031**	1.006	(0.952–1.062)	.841
Expanded criteria donor	0.955	(0.564–1.617)	.863	0.975	(0.459–2.069)	.948
Donor history of hypertension	1.365	(0.946–1.970)	.096	0.663	(0.380–1.158)	.149
Donor hypotensive period(s)	0.774	(0.547–1.095)	.148	1.027	(0.633–1.667)	.915
Donor history of diabetes mellitus	0.671	(0.078–5.791)	.717	1.595	(0.195–13.039)	.663
Donor history of cardiac arrest	1.461	(0.992–2.152)	.055	0.895	(0.501–1.598)	.707
Donor use of inotropic medication	1.238	(0.744–2.061)	.411	1.240	(0.595–2.582)	.566
Donor cause of death: stroke	0.709	(0.482–1.043)	.081	0.832	(0.492–1.407)	.493
Donor cause of death: trauma	1.069	(0.662–1.727)	.784	0.502	(0.223–1.131)	.096
Donor lowest creatinine (µmol/L)	1.001	(1.000–1.001)	.079	1.001	(1.000–1.001)	**.029**
Recipient gender (Female/Male)	1.307	(0.930–1.839)	.123	1.496	(0.910–2.461)	.112
Recipient age (years)	0.996	(0.982–1.010)	.595	0.992	(0.973–1.012)	.433
Recipient body mass index (kg/m^2)	1.083	(1.043–1.124)	**.000**	1.038	(0.984–1.095)	.175
Recipient dialysis duration (years)	1.196	(1.100–1.300)	**.000**	0.970	(0.857–1.098)	.633
Cold ischemia time (hours)	1.050	(1.022–1.078)	**.000**	1.023	(0.984–1.095)	.245
Anastomosis time (minutes)	1.002	(0.989–1.015)	.761	0.987	(0.968–1.007)	.195
Number of HLA mismatches	1.038	(0.915–1.177)	.562	0.988	(0.829–1.176)	.888

HLA – human leukocyte antigen.

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Table 3. Multivariable Cox proportional hazards analysis for graft survival.

Graft survival	Hazard ratio (95% CI)	P-value
Duration of brain death period (hours)	0.933 (0.882–0.987)	**.015**
Donor gender (Female/Male)	1.247 (0.870–1.789)	.230
Donor age (years)	1.035 (1.012–1.058)	**.003**
Donor body mass index (kg/m^2)	0.965 (0.923–1.009)	.120
Expanded criteria donor	1.203 (0.699–2.073)	.505
Donor history of hypertension	1.164 (0.781–1.733)	.456
Donor hypotensive period(s)	0.921 (0.640–1.325)	.657
Donor history of diabetes mellitus	5.415 (1.608–18.237)	**.006**
Donor history of cardiac arrest	1.213 (0.802–1.835)	.360
Donor use of inotropic medication	1.886 (0.994–3.578)	.088
Donor cause of death: stroke	0.611 (0.398–0.937)	**.024**
Donor cause of death: trauma	0.812 (0.481–1.370)	.435
Donor lowest creatinine (µmol/L)	1.001 (1.000–1.001)	**.013**
Recipient gender (Female/Male)	1.088 (0.755–1.567)	.651
Recipient age (years)	0.973 (0.959–0.987)	**.000**
Recipient body mass index (kg/m^2)	1.008 (0.966–1.051)	.726
Recipient dialysis duration (years)	0.996 (0.903–1.099)	.939
Cold ischemia time (hours)	1.015 (0.987–1.045)	.286
Anastomosis time (minutes)	0.994 (0.980–1.007)	.336
Number of HLA mismatches	0.927 (0.808–1.064)	.283
Delayed graft function	2.279 (1.541–3.369)	**.000**
Acute graft rejection within 1 year	4.122 (2.541–6.686)	**.000**

HLA – human leukocyte antigen.

within 1 year after transplantation (n=110), the donors had a median durBD of 10.2 hours (range, 9.0 to 12.5 hours), while durBD was 10.7 hours (range, 8.9 to 12.5 hours) in donors of rejection-free recipients (n=1759).

To evaluate the effect of durBD on the incidence of delayed graft function and acute rejection, binary logistic analyses with relevant donor and recipient characteristics and allograft related factors were performed. In a univariable logistic regression analysis, the effect of durBD was not significant for the incidence of delayed graft function with an odds ratio (OR) of 1.012 (P=0.503) or the incidence of graft rejection in the first year after transplantation with an OR of 1.012 (P=0.641). In a multivariable logistic regression analysis, the effect of durBD remained nonsignificant for the incidence of delayed graft function with an OR of 1.042 (P=0.058) or acute rejection with an OR of 1.054 (P=0.055). Table 2 shows the variables used in the multivariable analysis.

To identify factors influencing durBD, we entered each variable separately into the regression model. Donor age was the only factor that significantly influenced durBD. Subsequently, we tested the correlation between durBD and donor age. These variables were correlated with a Pearson's coefficient of –0.144 (P=0.000), indicating donors with a prolonged durBD were younger of age.

We divided our study population equally by the median in a "short durBD" (<10.6 hours) group and "long durBD" (>10.6 hours) group. At 3 months after transplantation, serum creatinine was significantly lower in the "long durBD" group: "short durBD" group 138 µmol/L (range, 110 to 175 µmol/L) versus "long durBD" group 132 µmol/L (range, 106 to 162 µmol/L), P=0.003. At twelve months after transplantation, there was no significant difference: "short durBD" 133 µmol/L (range 107 to 168 µmol/L) versus "long durBD" 129 µmol/L (range, 107 to 159 µmol/L), P=0.085.

Duration of brain death and graft survival

Recipients with functioning grafts after transplantation (84.2%) had kidneys from donors with a median durBD of 10.7 hours

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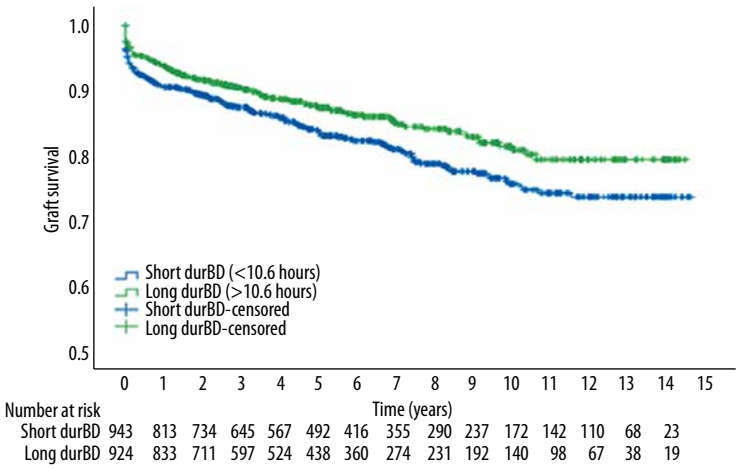

Figure 2. Kaplan-Meier survival curve and number at risk table for 15-years graft survival.

(range, 9.0 to 12.6 hours), while recipients with graft failure had donors with a median durBD of 10.1 hours (range, 8.2 to 12.0 hours).

Using the Cox proportional hazards model, the effect of durBD on the graft survival after kidney transplantation was analyzed with relevant donor and recipient characteristics and allograft related factors. In a univariable Cox analysis, durBD influenced the graft survival significantly with a hazard ratio (HR) of 0.941 (P=0.001). In a multivariable Cox analysis, durBD remained a significant independent predictor for graft survival after kidney transplantation with a HR of 0.933 (P=0.015). Table 3 shows the variables used in the multivariable analysis.

After dividing our study population equally by the median in a "short durBD" (<10.6 hours) group and a "long durBD" (>10.6 hours) group, Kaplan-Meier analysis showed that the 15-year graft survival (Figure 2) was significantly higher for recipients whom received a kidney from a donor with "long durBD" compared to a kidney received from a donor with a "short durBD" with a log rank of 6.094 (P=0.014). The estimated 15-year death-censored graft survival was 73.8%, for kidneys from donors with "short durBD" and 79.5% for kidneys from donors with "long durBD".

Discussion

We show that prolonged durBD was a significant independent predictor for better graft survival after kidney transplantation. Since brain death has well known deleterious hemodynamic effects, it seems logical to remove donor organs as soon as possible after brain death has been established. However, our data suggest that longer duration of brain death in the donor was not detrimental, but was correlated with better graft survival after kidney transplantation. At 3 months after transplantation, "long durBD" was associated with lower creatinine indicating better graft function. There was no association between duration of brain death and incidence of delayed graft function or acute rejection.

In 2001, Muruve et al. performed the first study comparing the effect of durBD on graft survival [9]. The authors retrospectively analyzed the effect of durBD on graft survival of 627 donor-recipient pairs with "short durBD (<24.7 hours), "medium durBD" (24.7 to 59.2 hours), and "long durBD" (>59.2 hours). Using the univariate analyses, durBD had no significant effect on graft survival 1 year and 10 years after kidney transplantation. In the same year, Kunzendorf et al. performed a similar study and concluded that kidney allografts procured from donors with "long durBD" (>7.8 hours) in comparison to "short durBD" (<7.8 hours), exhibited a significantly better graft survival 10 year after kidney transplantation and lower incidence of delayed graft function [10]. In our view, it is important to note that Kunzendorf et al. only performed a Kaplan-Meier survival analysis. Therefore, their data did not show that "long durBD" was an independent predictor of long-term graft survival. In 2007, Guner et al. performed a retrospective analysis of 24 donor-recipient pairs with "short durBD" (<12 hours) and "long durBD" (>12 hours), according to their observation that 12 hours was the period usually required to stabilize the condition of the brain-dead organ donor [11]. Serum creatinine at 3 months after kidney transplantation was significantly lower in the "long durBD" group. There was no difference in serum creatinine at 12 months post kidney transplantation. In 2010, a retrospective analysis of the Organ Procurement and Transplant Network was performed by Nijboer et al. for 20 773 donor-recipient pairs [12]. A multivariate Cox regression hazards model and multivariate binary logistics regression indicated that the effect of durBD was not significant for

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graft survival at 1 year and 3 years after kidney transplantation or for the incidence of delayed graft function, respectively.

A beneficial effect of long durBD is contra-intuitive, since brain death causes hemodynamic changes, hormone dysregulation, a pro-inflammatory environment, and apoptosis of liver and kidney cells [2,18–20]. There are several possible explanations for this paradox. First, longer durBD implies longer stay at the intensive care unit and therefore more opportunity to counterbalance the effects of a hypotensive period. However, in our series, we did not find that hypotensive period(s) during brain death modulated the effects of durBD on graft function and long-term graft survival.

Second, a longer durBD could provide opportunity for the donor organs to recover from the catecholamine storm. A study in rats showed that there is a continuous deterioration of liver and kidney function from 1 to 6 hours after brain death, but, provided that the donor is hemodynamically stable, no further deterioration occurs in the subsequent 5 hours [21].

Moreover, there is increasing evidence that the application of brief, non-lethal periods of ischemia and reperfusion, activates an innate immune response that confers protection against later prolonged periods of ischemia. These effects are also present in remote areas, called "remote ischemic preconditioning" [22]. Kunzendorf et al. suggested that the sublethal ischemia of organs due to brain death can lead to ischemic preconditioning, and therefore have protective effects on the kidney allograft [10].

Strengths and limitations

An important strength of this study was the use of a large cohort and the fact that the data were collected in a prospective manner. However, data were obtained from multiple centers, which implies multiple protocols with respect to the transplantation procedure. This could have introduced some heterogeneity. Also, durBD was defined as the interval between declaration of donor brain death and start of cold perfusion. This could have caused some underestimation of the durBD since brain death can already be present before it is formally established. It should also be noted that the durBD in the United States, as shown by Muruve et al. (median durBD 24.7 to 59.2 hours) and Nijboer et al. (median durBD 23.8 hours), are generally longer when compared to Europe, as shown by Kunzendorf et al. (median durBD 7.8 hours). This is probably due to the fact that in the United States more time is spent to obtain informed consent for donation and because multi-organ procurement is usually planned during office hours. Whereas in Europe the surgery of the donor is commonly performed as soon as possible, often during the night [12]. Since the 2 largest studies comparing the impact of durBD on graft survival were performed with data from the United States, it is difficult to compare these outcomes with our data [9,12].

Conclusions

In conclusion, we showed that prolonged duration of brain death is a significant independent predictor for better long-term kidney graft survival. There was no significant effect of duration of brain death period on the incidence of delayed graft function or acute rejection within 1 year after kidney transplantation, but kidney function at 3 months after transplantation was better in the "long durBD" group. Therefore, our recommendation is to optimize donor management, in contrast to procuring the organs as fast as possible. Further research is necessary to unravel the mechanism of this effects and to define the optimal duration of the brain death period.

Acknowledgements

The authors are indebted to all colleagues in the various Dutch transplant centers for submitting their data to the Netherlands Organ Transplant Registry and to Cynthia Konijn of the Dutch Transplant Foundation for assistance with the data management.

Conflicts of interest

None.

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