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Pulsatile Perfusion Reduces the Incidence of Delayed Graft Function in Expanded Criteria Donor Kidney Transplantation

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The use of expanded criteria donors (ECD) has been proposed to help combat the discrepancy between organ availability and need. ECD kidneys are associated with delayed graft function (DGF) and worse long-term survival. The aim of this study is to evaluate the impact of pulsatile perfusion (PP) on DGF and graft survival in transplanted ECD kidneys. From January 2000 to December 2003, 4618 ECD kidney-alone transplants were reported to the United Network for Organ Sharing. PP was performed on 912 renal allografts. The prognostic factors of DGF were analyzed using multivariate logistic regression analysis. Risk factors for reduced allograft viability were greater in donors and recipients of PP kidneys. Three-year graft survival of ECD kidneys preserved with PP was similar to cold storage (CS) kidneys. The incidence of DGF in PP kidneys was significantly lower than CS kidneys (26% vs. 36%, $p < 0.001$). Despite having a greater number of risk factors for reduced graft viability, the ECD-PP kidneys had similar graft survival compared to ECD-CS kidneys. The use of PP, by decreasing the incidence of DGF, may possibly lead to lower overall costs and increased utilization of donor kidneys.

Key words: Delayed graft function, expanded criteria donors, kidney transplantation outcomes, pulsatile perfusion

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Introduction

There is a critical shortage of organs available for transplantation, and this gap between available donor organs and patients on the wait list continues to widen. The organ transplantation wait list increased by 8.1% from 2000 to 2001, while the number of transplanted organs increased by only 4.7% (1). To combat this growing discrepancy between availability and need, the United Network for Organ Sharing (UNOS) introduced a policy in 2001 for the use of expanded criteria deceased organ donors (ECD) (2). ECD donors display comorbidities that have been associated with declining renal function and have an inherent reduced renal graft viability, which translates into a relative risk of graft failure exceeding 1.7 when compared to an ideal donor (3). Growing acceptance and use of ECD kidneys has been accompanied with concerns about increases in delayed graft function (DGF) and primary nonfunction (4,5). The desire to qualitatively assess these kidneys prior to implantation has led to the use of back-table biopsies and/or pulsatile perfusion (PP) of these kidneys prior to transplantation.

PP involves an *ex vivo*, hypothermic pulsatile perfusion of the donor kidney that supplies oxygen and nutrients to the kidney and removes waste products. Machine perfusate solutions often consist of dialyzed hydroxyethyl starch to prevent interstitial edema, thereby lowering resistance. Adenosine is added as an ATP stimulator, phosphate as an H+ ion buffer and ATP production stimulator, gluconate for cellular swelling suppression, glutathione as an antioxidant, as well as other agents. This mimics circulation, helping to decrease vasospasm and vascular resistance. PP has diagnostic and therapeutic potential, allowing for the measurement of pre-transplantation parameters and pharmacological manipulation. Decreased flow rates, increased resistance and an increase in the calcium concentration measured during PP have been associated with DGF (6,7). Increased resistance with corresponding decreased flow rates may be noted in kidneys because of intrinsic parenchymal disease or acute tubular necrosis.

There have been numerous studies comparing PP to cold storage (CS) in donor kidneys (6–17). Early studies claimed there was no advantage of PP, finding no significant differences in DGF or graft survival between PP and CS

(10,11,13). However, more recently Schold et al. found that PP led to higher utilization rates of ECD kidneys and lower rates of DGF, most notably in higher risk kidneys (16). Several other studies report similar results (6–8,12,14–17).

The aim of this study was to compare two ECD kidney cohorts—ECD-PP kidneys compared to ECD-CS kidneys. We used the UNOS database to achieve a large sample size. Using graft survival and DGF frequency as primary endpoints, we evaluate the potential utility of PP in the ECD kidney donor population.

Materials and Methods

Study design

From January 2000 to December 2003, 4618 kidney-alone transplants from ECD were reported to UNOS (based on data from the Organ Procurement and Transplantation Network/UNOS as of July 4, 2004). Among these transplants, PP was performed on 912 donor kidneys (ECD-PP). For comparison, 3706 ECD grafts maintained in CS during the same period were included in the study (ECD-CS). Follow-up information reported to UNOS by July 2004 was included. Multiple organ transplantations and double or en-bloc kidney transplantations were excluded from the study.

Definitions

ECD was defined as all deceased donors >60 years of age or donors who were 50–59 years of age and had two of the following: donor hypertension, donor history of cerebrovascular accident or terminal serum creatinine value greater than 1.5 mg/dL. DGF was defined as the need for dialysis during the first week following transplantation.

Statistical analysis

Graft survival rates were estimated using the Kaplan-Meier product limit method. The log-rank test was used for comparison of the survival curves. The nonparametric Kruskal-Wallis equality of populations rank test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. p-Values less than 0.05 were considered statistically significant. All reported p-values were 2-tailed. For graft survival, all patient deaths were considered as graft failures regardless of whether the graft was functioning or not at the time of patient death. Patient death with functioning graft was censored to determine death-censored graft survival.

Potential predictors for DGF were analyzed using univariate and multivariate logistic regression analysis. Donor age, terminal serum creatinine, cold ischemic time (CIT) and peak recipient panel-reactive antibodies (PRA) were categorized in order to adjust their nonlinearity effect on logistic regression and Cox's proportional hazard models. In multivariate analysis, missing values were inputted using the mean value for continuous variables or modal value for categorical variables. Less than 5% of variables analyzed in the multivariate model were missing.

Results

The use of ECD kidneys for transplantation has slightly increased from 1157 ECD donors in 2000 (15.3% of kidney transplants) to 1363 ECD donors in 2003 (17.2%). Over the same time period, a more substantial increase was noted in the use of PP for these ECD kidneys, increasing from 139 in 2000 (12.7% of ECD kidneys) to 357 in 2003 (28.4%).

Table 1: Pre-transplantation recipient, donor and graft variables: ECD-CS vs. ECD-PP

	Cold storage	Pulsatile perfusion	p-Value
Recipient			
Age (year)	54.5 ± 12.3	56.0 ± 11.4	0.003
Peak PRA (%)	12.1 ± 22.2	11.2 ± 23.4	0.60
African American (%)	30.0	33.6	0.04
Regraft (%)	7.0	5.8	0.21
Pretransplantation dialysis (%)			
None	5.2	4.7	0.52
Peritoneal dialysis	12.0	15.5	0.005
Hemodialysis	82.7	79.8	0.04
Donor			
Age (year)	59.8 ± 6.1	61.1 ± 6.3	<0.001
Serum creatinine (mg/dL)	1.1 ± 1.0	1.2 ± 1.1	0.03
African American (%)	9.7	9.5	0.86
CVA (%)	85.2	83.6	0.23
Hypertension (%)	65.2	63.3	0.27
Diabetes (%)	9.4	12.7	0.003
Donation after cardiac death (%)	0.9	6.5	<0.001
History of smoking (%)	48.6	46.3	0.27
ECD graft			
Cold ischemia time (h)	20.1 ± 8.9	18.9 ± 8.1	0.03
No. of HLA-A, B, DR Ag mismatches	3.7 ± 1.8	4.1 ± 1.5	<0.001

Demographics

The characteristics of recipients, donors and grafts that are known to affect graft survival are shown in Table 1 according to storage type. Recipients in the ECD-PP group were statistically older (56.0 vs. 54.5 years, $p = 0.003$) and a higher fraction was African American compared to ECD-CS recipients (33.6 vs. 30.0%, $p = 0.04$). More ECD-PP recipients were on peritoneal dialysis (15.5 vs. 12.0%, $p = 0.005$), while more ECD-CS recipients were on hemodialysis (82.7 vs. 79.8%, $p = 0.04$). ECD-PP came from older donors (61.1 vs. 59.8 years, $p < 0.001$) with statistically higher serum creatinine (1.2 vs. 1.1 mg/dL, $p = 0.03$). ECD-PP also demonstrated a significantly higher frequency of diabetes (12.7 vs. 9.4%, $p = 0.003$) and cardiac death (6.5 vs. 0.9%, $p < 0.001$). ECD-CS had longer CIT (20.1 vs. 18.9 h, $p = 0.03$), although the mean CIT in both groups was well under 24 h. ECD-PP also tended to have a greater number of HLA-A, B, and DR mismatched antigens with the recipient than ECD-CS kidneys (4.1 vs. 3.7, $p < 0.001$).

Biopsy results

The majority of ECD kidneys were biopsied at donor procurement centers and/or transplant centers. Among biopsied renal allografts at transplant centers, significantly higher fractions of glomerulosclerosis >10% (27.3 vs. 18.1%, $p = 0.002$) and interstitial fibrosis (48.5 vs. 40.5%,

Table 2: Post-transplantation graft function and rejection episodes: ECD-CS vs. ECD-PP

	Cold storage	Pulsatile perfusion	p-Value
Delayed graft function (%)	37.1	25.8	<0.001
Primary nonfunction (%)	3.2	2.6	0.37
Rejection (%)			
Initial hospital stay	7.5	6.8	0.46
At 6 months	16.4	16.0	0.80
At 1 year	18.9	19.0	0.96

$p = 0.03$) were noted in ECD-PP kidneys compared to ECD-CS kidneys.

Graft function and rejection

There was a 10% higher rate of DGF in ECD-CS kidneys compared to ECD-PP kidneys (37% vs. 26%, $p < 0.001$; Table 2), but no difference in the incidence of primary nonfunction. Interestingly, although DGF is a risk factor for rejection, we did not observe a lower rejection frequency in the ECD-PP cohort at discharge, 6 months, or 1 year after transplantation in spite of the decrease in DGF. Additionally, we examined the rates of DGF in donation after cardiac death (DCD) donors and donation after brain death (DBD) donors. DGF occurred in 34.5% of DBD donors compared to 54.3% of DCD donors ($p < 0.001$).

Unadjusted and adjusted odds ratios of developing DGF are given in Table 3 using univariate and multivariate logistic regression analyses, respectively. After adjusting for all other factors, the use of PP resulted in 49% less risk of developing DGF compared with CS (OR = 0.51, $p < 0.001$). Other predictive factors in the donor for the development of DGF include, as expected, DCD donors, serum creatinine, history of hypertension, increased CIT and suboptimal graft biopsy results (glomerulosclerosis >10%, interstitial fibrosis, arteriosclerosis). In the recipient, prognostic factors for DGF include increased PRA, HLA-DR mismatches, African American race and a history of diabetes and pretransplantation hemodialysis.

Graft survival

As shown in Figure 1, among ECD kidney transplants, grafts experiencing DGF yielded statistically significant lower graft survival rates (70.1% and 53.0% at 1 and 3 year) compared with those of grafts without DGF (87.8 and 74.4% at 1 and 3 year, logrank $p < 0.001$). When separating the donor kidneys by storage method, there was no difference in graft survival between kidneys with immediate graft function by storage method (Figure 2). However, it was noted that ECD-PP kidneys with DGF had a poorer graft survival than ECD-CS kidneys with DGF, although this difference was not statistically significant ($p = 0.12$).

Overall, ECD-PP kidneys yielded similar graft survival rates compared with ECD-CS kidneys up to 3 years post-transplantation ($p = 0.49$; Figure 3). Although ECD-PP

Table 3: Prognostic factors for developing DGF in ECD kidneys

Factors	Unadjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Donor				
DCD vs. DBD	2.26 (1.50–3.40)	<0.001	3.17 (2.05–4.91)	<0.001
Terminal serum Cr >1.5 vs. ≤ 1.5 mg/dL	1.29 (1.09–1.51)	0.002	1.25 (1.05–1.49)	0.01
History of hypertension yes vs. no	1.21 (1.06–1.38)	0.003	1.09 (1.02–1.16)	0.01
Female vs. male	0.83 (0.73–0.93)	0.002	0.85 (0.75–0.97)	0.01
Suboptimal graft* vs. all others	1.46 (1.21–1.75)	<0.001	1.40 (1.16–1.70)	0.001
Cold ischemia time				
13–24 vs. 0–12 h	1.33 (1.15–1.53)	<0.001	1.33 (1.14–1.70)	<0.001
25–30 vs. 0–12 h	1.51 (1.23–1.85)	<0.001	1.48 (1.19–1.82)	<0.001
>30 vs. 0–12 h	2.45 (1.97–3.05)	<0.001	2.15 (1.70–2.74)	<0.001
Recipient				
Peak PRA >50 vs. 0–50%	1.42 (1.16–1.74)	0.001	1.74 (1.40–2.15)	<0.001
Female vs. male	0.78 (0.69–0.89)	<0.001	0.77 (0.67–0.87)	<0.001
African American vs. other races	1.39 (1.22–1.58)	<0.001	1.28 (1.12–1.47)	<0.001
Diabetes vs. others	1.25 (1.09–1.44)	0.001	1.26 (1.10–1.45)	0.001
Dialysis type				
Peritoneal vs. none	1.47 (1.15–1.87)	0.002	1.43 (1.12–1.84)	0.004
Hemodialysis vs. none	2.01 (1.67–2.41)	<0.001	1.90 (1.57–2.30)	<0.001
HLA-A mismatches (range 0–2)	1.10 (1.01–1.20)	0.02	1.02 (0.93–1.13)	0.65
HLA-B mismatches (range 0–2)	1.19 (1.09–1.29)	<0.001	1.08 (0.97–1.20)	0.14
HLA-DR mismatches (range 0–2)	1.18 (1.09–1.28)	<0.001	1.15 (1.04–1.26)	0.005
Transplant location shared vs. local	1.20 (1.05–1.36)	0.007	1.01 (0.87–1.18)	0.85
Storage type PP vs. cold storage	0.59 (0.50–0.69)	<0.001	0.51 (0.43–0.61)	<0.001

DCD = donation after cardiac death; DBD = donation after brain death.

*Graft with at least one of the following biopsy results performed at transplant center: (1) glomerulosclerosis >10%; (2) fibrosis; and (3) arteriosclerosis.

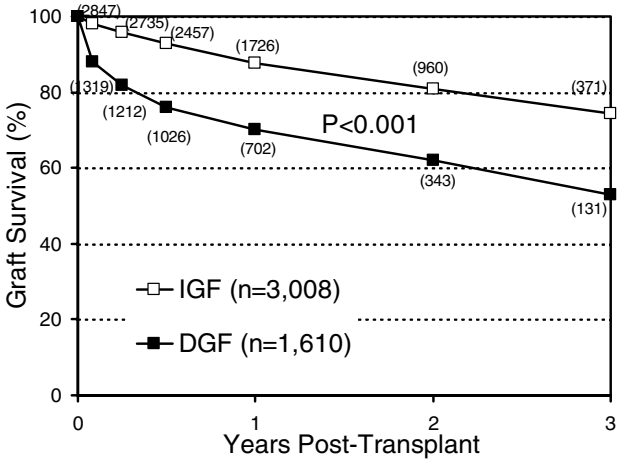

Figure 1: The impact of delayed graft function (DGF) on expanded criteria donors (ECD) kidney transplantation. Numbers in parenthesis indicate the number of patients at risk at post-transplantation follow-up time (1, 3 and 6 months and 1, 2 and 3 years).

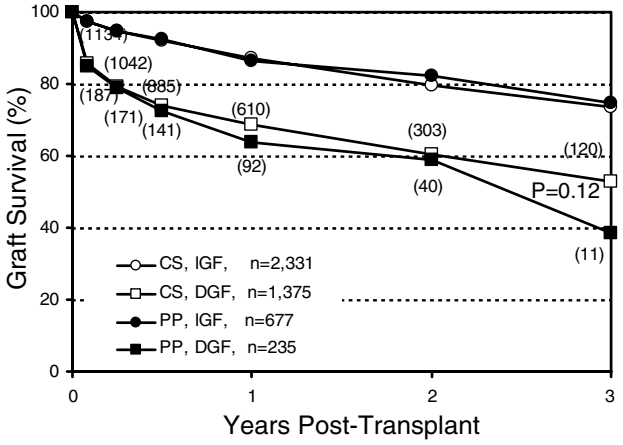

Figure 2: The impact of DGF on graft survival according to storage method (cold storage [CS] vs. pulsatite perfusion [PP]).

kidneys had a lower incidence of DGF, those kidneys that did develop DGF had a tendency toward poorer graft survival than ECD-CS kidneys with DGF. This effect led to similar overall graft survival curves. Death-censored graft survival yielded similar results, although there was a slightly lower graft survival rate among ECD-CS kidneys compared with ECD-PP kidneys (logrank $p = 0.21$).

Discussion

The segregation of kidney allografts into standard criteria and expanded criteria donors is a relatively recent response to increased need by the recipient community. In an attempt to increase the availability of organs, a UNOS pol-

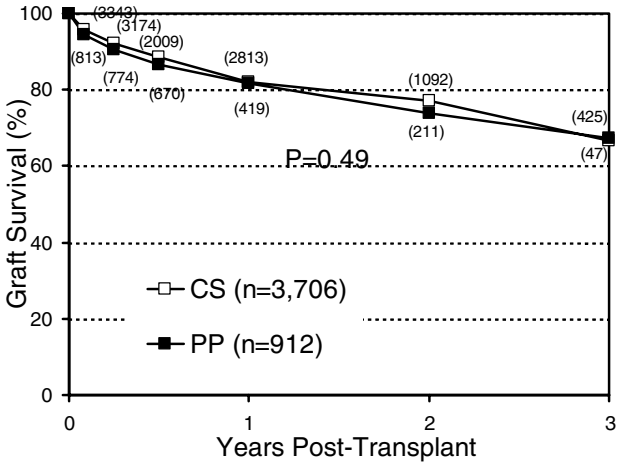

Figure 3: Overall graft survival of ECD kidney transplants according to storage method (ECD-CS vs. ECD-PP).

icy for ECD was established, incorporating older donors with comorbidities (2). The initial intent was that these kidneys would be implanted into an older patient population that could not tolerate the long waiting time to transplantation. Not surprisingly, the selection of higher risk donors for higher risk recipients has led to inferior outcomes when compared to the standard criteria donor-recipient cohort. Although the use of ECD kidneys has increased, concerns exist about DGF, the corresponding diminution in function with these kidneys (4,5) and its association with decreased long-term allograft survival (3,18–23).

To evaluate kidney function following storage with PP or CS, Grundmann et al. autotransplanted 72 canine kidneys following either PP or CS for 24–72 h. Using *p*-aminohippuric acid and inulin clearances as measures of immediate function, the authors found that immediate function of kidneys after 72 h of PP was significantly better than 24 h of CS (24). Other studies on autotransplanted canine kidneys that underwent PP or CS for 24 to up to 96 h showed similar benefits of PP with regards to immediate graft function (25–27). A more recent study using autotransplanted porcine kidneys also found that PP porcine kidneys had significantly lower peak serum creatinine and blood urea in the 2 weeks following transplantation (28).

Additional canine studies were performed with varying amounts of warm ischemia. Denham et al. autotransplanted canine kidneys after 15 min of warm ischemia followed by 24 h of PP or CS. Canine kidneys that underwent PP had significantly higher creatinine clearances after 2 h (29). Halasz et al. performed a similar experiment after subjecting canine kidneys to 20 min of warm ischemia and 48 h of storage by either PP or CS. All canines in the PP group survived with normalized serum creatinine, while none of the canines in the CS groups survived (30). The animal studies overall show a benefit in terms of early graft

function in kidneys that underwent PP. Canine kidneys subjected to various amounts of warm ischemia also showed a benefit, which may be important in the context of DCD kidneys.

Early randomized, controlled studies were conducted to compare the effects of PP and CS. Halloran et al. compared donor kidney pairs randomly assigned to CS or PP. There were 90 kidney pairs in the CS group and 91 kidney pairs in the PP group. The study found an increased risk of delayed function with CS but no difference in graft or patient survival after 1 year. The authors concluded that the increased cost of PP was not justified on the basis of equivalent graft and patient survival between the two storage methods (11). To better control donor factors, a few studies looked at kidneys from the same donor, randomly allocating one kidney to CS and the other to PP. One of these studies, based on 29 kidney pairs, found a significant decrease in post-transplantation dialysis in kidneys undergoing PP (17% vs. 63%, $p < 0.01$) (9). Two larger studies conducted in the same manner, however, found similar post-transplantation dialysis needs between storage methods. Mozes et al. reported no difference in rates of dialysis in the first week following transplantation for 96 kidney pairs undergoing PP vs. CS (10). Similarly, Merion et al. compared 51 kidney pairs, each allocated to either PP or CS, and found similar post-transplantation dialysis requirements (13). The trend following these earlier randomized trials thus favored the use of CS.

There have been several more recent studies documenting the utility of PP, especially in ECD (6–8,12,14–17). Schold et al. examined the Scientific Registry of Transplant Recipients (SRTR) database from 1994 to 2003, focusing on the usage of PP (16). The study found that with ECD-PP compared to ECD-CS there was a higher utilization of ECD kidneys (70% vs. 59%, $p < 0.001$). Rates of DGF were 20% in PP kidneys and 28% in CS kidneys, with more significant reductions in DGF seen in kidneys with longer CIT. The study also examined paired transplanted kidneys from the same donor, with one kidney undergoing PP and the other CS. The kidneys that underwent PP had a significant decrease in DGF rate, despite similar CIT (19% vs. 26%, $p < 0.001$). Our study results show a similar decrease in the rate of DGF associated with PP, with ECD-PP kidneys showing a 10% lower rate of DGF than ECD-CS kidneys (Table 2).

We defined DGF as the need for dialysis within 1 week following transplantation. This is the definition of DGF used by many papers comparing PP and CS (6–10,14–16). However, this definition overestimates the true incidence of DGF, because it includes patients who underwent dialysis following transplantation for reasons such as electrolyte imbalances, vascular thrombosis, ureteral obstruction, etc. The flaw in this commonly used definition is that it incorporates a clinical decision and therefore increases the variability of reported incidences of DGF. Further studies comparing storage methods in terms of DGF should utilize a more objective measurement of delayed function.

Polyak et al. found that graft survival at 1 year was greater in ECD kidneys that were machine perfused (88% vs. 79%, $p = 0.02$) (14). In a literature review and meta-analysis of studies comparing PP and CS, Wight et al. created a quantified model based on available study information and calculated a predicted graft survival benefit of 2–3% in 10 years (17).

However, our study and others (15) show no difference in 3-year graft survival in kidneys undergoing PP vs. CS, despite a reduction in DGF. ECD-PP kidneys, however, were from statistically older donors with higher serum creatinine, and with more diabetes and cardiac death than kidneys that underwent CS. The recipients of ECD-PP kidneys were also statistically older than ECD-CS kidney recipients. Kidneys that had undergone biopsy at transplant centers and were maintained using PP had statistically more findings of glomerulosclerosis >10% and interstitial fibrosis. Despite the presence of more risk factors for graft failure, the use of PP led to similar graft survival compared to CS.

From our study it appears that coincident with the rise in the use of ECD kidneys there has been the utilization of renal PP by the kidney transplant community. It may be that the increase in utilization of PP since 2001 on the part of transplant programs can be explained by the desire for a diagnostic tool of functionality. Measurements during PP may give added information to the pre-transplantation analysis determining the suitability of the organ for transplant. Perhaps the decreased incidence of DGF is partly secondary to decisions made to abandon kidneys for transplantation based on pre-transplantation parameters. Sonnenday et al., however, warn against the refusal of donor kidneys based on perfusion parameters alone (31). They describe the successful transplantation of 11 donor kidneys that were initially refused by multiple other centers, often based upon poor perfusion parameters.

Burdick et al., examining UNOS data from 1988 to 1995, suggested that the use of PP in older kidneys might be cost-effective (8). The authors speculated that the cost savings associated with lower rates of DGF would offset the expense of PP. A meta-analysis performed by Wight et al. also suggests that PP may be less expensive than CS in the long run (17). With the 10% reduction in DGF found in our study, the cost savings associated with decreased dialysis and hospital days may lend further support to the use of PP. Specific cost-analysis studies need to be performed to quantify the potential cost savings associated with decreased DGF.

In summary, recent UNOS data show that the use of PP in ECD decreases the rate of DGF. This improvement may lead to lower overall costs and increased utilization of donor kidneys. Besides improving early graft function, PP also

has the ability to provide pre-transplantation parameters that have been associated in some studies with DGF. Our study did not find a benefit of PP in terms of graft survival, but long-term studies are needed to better clarify the effect of reduced DGF on long-term graft function in ECD kidneys preserved by PP. Further studies are also needed utilizing a more objective definition of DGF to more accurately determine the differences in DGF rates between storage methods.

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