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Intraoperative central venous pressures related to early graft function in deceased donor kidney transplant recipients with low immunological risks

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This study aims to analyze data from patients who received kidney transplantation from deceased donors to investigate the anesthetic factors influencing early and late graft outcomes, including the incidence of slow graft function (SGF), delayed graft function (DGF), and 3-year graft outcomes. We retrospectively analyzed 202 recipients who underwent deceased donor kidney transplantation from March 2010 to December 2020. Anesthetic monitoring data during the intraoperative period was analyzed at 5-minute intervals, and basic clinical parameters were evaluated. The mean recipient age was 46.6 ± 10.3 years, and the mean donor age was 41.7 ± 12.7 years. Anesthetic time averaged 285.8 ± 70.2 min, and operation time averaged 223.1 ± 44.0 min. The incidence of SGF was 11.8%, and the incidence of DGF was 3.9%. Mean central venous pressures (CVPs) were higher in recipients with SGF or DGF (11.7 mmHg) compared to those with immediate graft function (9.7 mmHg). Higher CVP was identified as an independent risk factor for SGF or DGF (odds ratio 1.219, $p = 0.006$). This study suggests that intraoperative monitoring of CVP is crucial for predicting short-term graft function in deceased donor kidney transplantation and should be managed to prevent excessive fluid intake.

Kidney transplantation (KT) has been known as the treatment of choice for patients with end-stage renal disease. Especially for patients on waiting list who have to receive a deceased donor KT, delayed graft function (DGF) is one of the most common complications, defined as the need for the dialysis within the first week after transplantation[1]. The incidence of DGF varies among studies and is definition dependent, and DGF occurs more frequently in deceased donor KT than living donor KT[2,3]. For kidney transplant recipients, DGF had a 41% increased risk of graft loss and was associated with a 38% relative increase in the risk of acute rejection[1,4–6]. Furthermore, cases where some level of graft dysfunction is observed even without progression to DGF are called slow graft function (SGF). SGF refers to a state in which serum creatinine decreases slowly but does not require dialysis and has many different definitions for each study[7–9]. Importantly, SGF is also related to acute rejection and poor long-term graft survival[7,10].

Mainly, it has been shown that the occurrence of SGF or DGF is closely related to donor factors, but perioperative hemodynamic management is also known to be related to the occurrence and prevention of SGF or DGF[11,12]. Proper management of fluid levels is crucial in order to minimize perioperative complications, as hypovolemia can contribute to additional kidney damage while excessive fluid therapy may lead to pulmonary edema related to right ventricular dysfunction[13]. Therefore, intraoperative anesthetic management of kidney transplant patients is a critical aspect that significantly influences both patient and graft outcomes. As indicators for appropriate fluid management, central venous pressure (CVP) has been used as one of traditional anesthesiologic monitoring elements for effective fluid management during transplant surgery[14–16]. The prior way of fluid management during KT was to evaluate the volume status based on CVP and increase CVP by providing a sufficient amount of fluids. However, according to a recently published guideline, there is insufficient evidence to target high CVP with large volume fluid management[17]. On behalf of targeting high CVP, individualized goal-directed fluid therapy is suggested to be the preferred method for optimizing the fluid management[18]. However,

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it is also true that there is a possibility of hypoperfusion occurring when individualization is attempted, so there are questions about whether a target should be set when performing fluid management[19].

In this study, we analyzed the CVP value during KT surgery, analyzed the correlation between CVP and SGF or DGF occurrence under conventional fluid management.

Results

A total of 202 recipients with low immunological risks received deceased donor KT. The mean age was 46.6 years, and male recipients were 119 (58.9%). According to criteria mentioned before, the incidence of SGF was 22 (10.9%) and the incidence of DGF was 8 (3.8%). 172 recipients recovered their graft function immediately (85.1%). The basic characteristics between IGF and SGF + DGF group were expressed in Table 1. The mean age of patients were not different and more male patients were in SGF + DGF group (70.0%). The mean body mass index (BMI) was significantly higher in SGF + DGF group than IGF group (21.9 ± 2.9 vs. 23.9 ± 3.5, $p = 0.001$). The mean duration of anesthesia time was 283.3 ± 46.9 min in IGF group and 300.3 ± 145.0 min in SGF + DGF group and the mean operation time were 223.2 ± 46.5 min in IFG group and 222.6 ± 56.1 min in SGF + DGF group. Mean total ischemic time of two groups were 286.4 ± 92.9 min in IGF group and 317.9 ± 90.8 min in SGF + DGF group. In terms of ischemic time, warm ischemic time of SGF + DGF group was significantly longer than IGF group (54.1 ± 23.5 vs. 43.4 ± 13.1 min, $p = 0.021$). More total fluid was administered in the SGF + DGF group than IFG group during operation (4133.8 ± 1136.5 vs. 3645.5 ± 954.5, $p = 0.013$). In addition, total bleeding and transfusion amounts were greater in SGF + DGF group. The mean donor creatinine levels were 0.83 mg/dL in IGF group and 1.1 mg/dL in SGF + DGF group ($p < 0.001$). There was no difference in 1- and 3-year graft survival rates depending on whether SGF or DGF occurred or not (98.8% vs. 100.0% at 1-year and 97.1% vs. 96.7% at 3-year, respectively).

	IGF group ($n = 172$)	SGF + DGF group ($n = 30$)	*P* value
Recipient variables			
Age (yr)	46.4 ± 10.5	47.7 ± 8.8	0.515
Male sex	98 (56.9%)	21 (70.0%)	0.228
Body mass index (kg/m^2)	21.9 ± 2.9	23.9 ± 3.5	0.001
Dialysis modality			1.000
Hemodialysis	152 (87.9%)	26 (86.7%)	
Peritoneal dialysis	21 (12.1%)	4 (13.3%)	
Dialysis duration (month)	101.04 ± 262.3	45.7 ± 51.6	0.277
PRA positivity at transplantation			
Class I	30 (17.4%)	8 (26.7%)	0.368
Class II	30 (17.4%)	9 (30.0%)	0.367
HLA mismatches	3.5 ± 2.0	3.3 ± 1.7	0.552
Operation time (minutes)	223.2 ± 46.5	222.6 ± 56.1	0.951
Anesthesia time (minutes)	283.3 ± 46.9	300.3 ± 145.0	0.528
Total ischemic time (minutes)	286.4 ± 92.9	317.9 ± 90.8	0.087
Warm ischemic time (minutes)	43.4 ± 13.1	54.1 ± 23.5	0.021
Cold ischemic time (minutes)	242.9 ± 90.9	263.8 ± 91.1	0.248
Total fluid intake during operation (mL)	3645.5 ± 954.5	4133.8 ± 1136.5	0.013
Total fluid intake during operation per body weight (mL/kg)	62.2 ± 17.5	61.9 ± 17.1	0.955
Total bleeding (mL)	379.5 ± 340.8	654.3 ± 990.1	0.014
Transfusion during operation (mL)	423.0 ± 285.7	697.2 ± 853.9	0.369
Graft weight (gram)	207.7 ± 40.1	202.7 ± 62.7	0.677
Donor variables			
Age (yr)	41.7 ± 13.2	41.3 ± 10.8	0.886
Male sex	113 (65.3%)	19 (63.3%)	0.833
Donor creatinine level (mg/dL)	0.83 ± 0.31	1.1 ± 0.27	0.001
Donor's eGFR (ml/min)	103.96 ± 29.76	85.84 ± 26.25	0.004
Cause of death (CVA)	64 (37.2%)	13 (43.3%)	0.546

Table 1. Basic characteristics between two groups. The continuous variables were expressed by mean ± Standard deviation and number of cases with percentages were for the categorical variables. *CVA* Cerebrovascular accident, *eGFR* Estimated glomerular filtration rate ,*HLA* Human leukocyte antigen, *PRA* Panel reactive antibody.

Intraoperative CVP changes

Among intraoperative variables, CVP, systolic blood pressure (SBP), mean arterial pressure (MAP) were measured and analyzed for evaluating risk factors. The change in mean CVP during operation in the IGF group and SGF + DGF group is shown graphically in Fig. 1. Mean CVPs at baseline were 9.7 mmHg in recipients with IGF group and 11.7 mmHg in recipients with SGF or DGF group. The mean CVP values of SGF + DGF group were significantly high up to 30 min before reperfusion, including the baseline value. After reperfusion, there was no significant difference between the two groups, but SGF or DGF group still had a higher mean CVP value. Overall, an overall increase in CVP was seen in both groups throughout operation. When the cut off value of baseline CVP was set according to normal range of CVP in all patients and divided into groups above 12mmHg and below, SGF or DGF occurrence occurred significantly more when baseline CVP was above 12mmHg ($p = 0.025$).

Risk factors for occurrence of SGF or DGF

In a logistic regression test conducted including all relevant factors to identify risk factors, baseline CVP, recipient's BMI, donor serum creatinine, warm ischemic time and total fluid intake during operation were associated with SGF or DGF development (Table 2). Among these variables, only baseline CVP and fluid intake related to anesthesiologic factors during operation were selected and a logistic regression test was performed, and it was found that baseline CVP was a significantly involved risk factor in the development of SGF or DGF. (Odds ratio 1.186, $p = 0.006$).

The relationship between baseline CVP and right ventricular systolic pressure (RVSP)

To determine the relationship between CVP and pulmonary HTN, we retrospectively examined the echocardiogram results from preoperative period. Among them, the RVSP value, which is related to pulmonary hypertension, was analyzed. The RVSP value was significantly higher in the patient group with a CVP of 12 mmHg or more ($p = 0.049$). As a result of dividing the RVSP into 35, 40, and 45 mmHg standards, the overall probability of RVSP being high was higher in the group with higher CVP, but the result was not significant (Table 3).

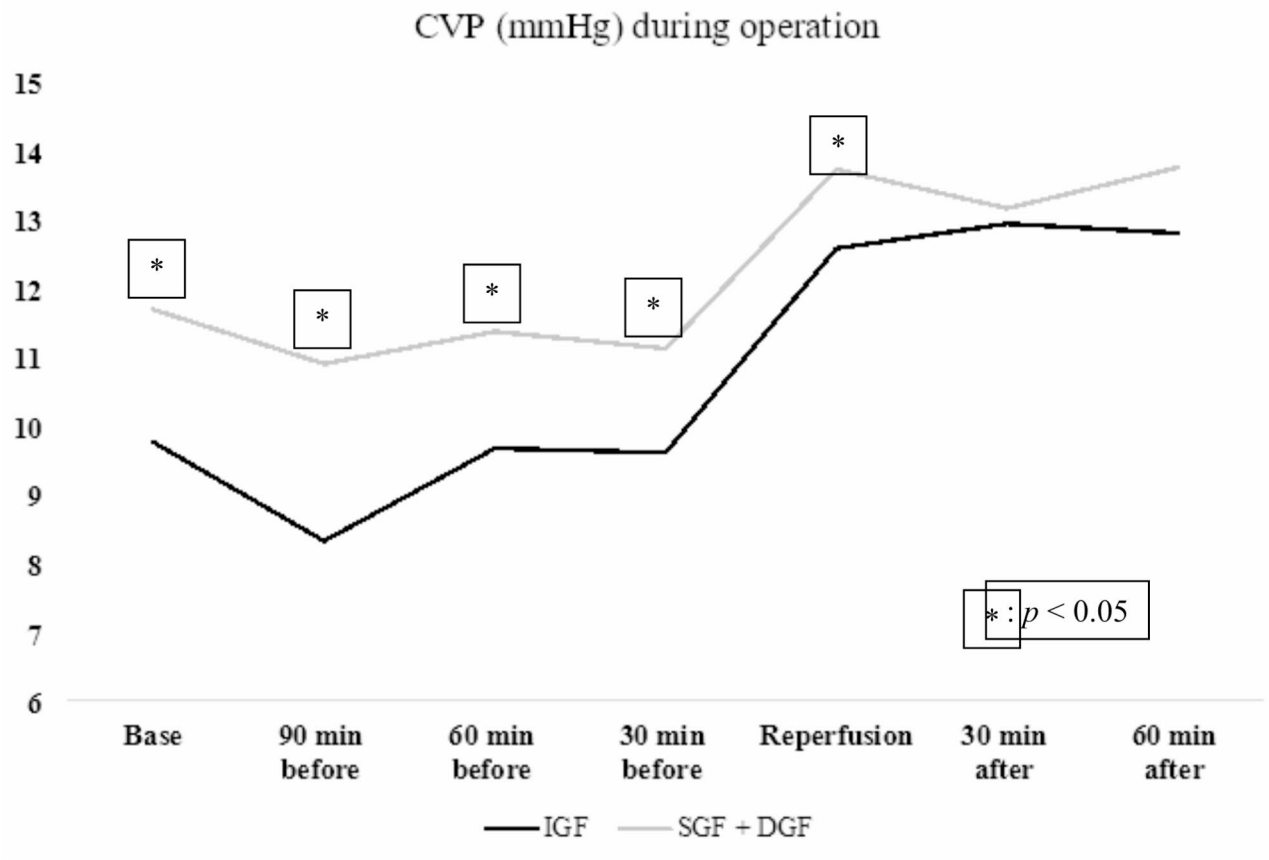

Fig. 1. Comparison of CVP during operation between two groups. *IGF* Immediate graft function, *SGF* Slow graft function, *DGF* Delyed graft function.

Variables	Unadjusted OR	*P* value	Adjusted OR	*P* value
Age (per 1 year)	1.013	0.513		
Baseline CVP (mmHg)	1.172	0.008	1.186	0.042
Recipient's BMI (per 1 kg/m^2)	1.223	0.001	1.157	0.078
Donor Cr (per 1 mg/dL)	12.229	0.001	24.067	0.001
Donor age (per 1 year)	0.998	0.904		
Donor cause of death (CVA)	1.290	0.525		
Warm ischemic time (per min)	1.038	0.002	1.026	0.130
Total fluid intake (per liter)	1.522	0.018	1.270	0.304
Total bleeding (mL)	1.001	0.065		

Table 2. Logistic regression analysis of anesthesiologic risk factors developing SGF or DGF. *BMI* Body mass index, *Cr* Creatinine, *CVA* Cerebrovascular accident, *CVP* Central venous pressure.

	CVP < 12 mmHg (*n* = 121*)	CVP > 12mmHg (*n* = 35*)	*P* value
Mean right ventricular systolic pressure	31.1 ± 7.6	34.1 ± 8.9	0.049
RVSP below or above 35mmHg	90/31	21/14	0.137
RVSP below or above 40mmHg	106/15	26/9	0.065
RVSP below or above 45mmHg	117/4	32/3	0.188

Table 3. Association between baseline central venous pressure and right ventricular systolic pressure. * Of the total 202 patients, fifty-six patients without RVSP data were excluded. *CVP* Central venous pressure, *RVSP* Right ventricular systolic pressure.

Discussion

In this retrospective study, we investigated CVP values during KT surgery and analyzed the correlation between CVP and SGF or DGF occurrence under conventional fluid management. The relationship between CVP and early renal graft function has been reported for a long time[20]. Hypovolemia along with prolonged ischemic time and previous acute tubular necrosis can lead to further graft injury during operation. To optimize volume status of kidney transplant recipients during operation, CVP was used as indicator for fluid management. Many studies suggested that maintaining proper CVP during operation especially at reperfusion period should be achieved by administrating fluid excessively[21]. However, according to recent studies, fluid management targeting CVP is not effective in preventing SGF or DGF and conventional treatment that supplies large fluid is not necessary is gaining persuasiveness[17]. Like these suggestions, the results of this study showed that when conventional fluid management was performed, SGF or DGF occurred more frequently in kidney transplant recipients with higher CVP. Therefore, this study can support the recommendation that larger volume fluid management targeting higher CVP is no longer beneficial.

In the perioperative setting, the primary objective is to prevent tissue hypoxia, which is a significant factor leading to organ dysfunction. Conventional indicators such as CVP may appear normal even in cases of tissue hypoxia, making them unreliable for predicting a potential mismatch between oxygen supply and demand. This is especially true if these indicators are not evaluated alongside perfusion markers like cardiac output, lactates, and central venous saturation[22–24]. Therefore, it is true natural that tissue perfusion cannot be measured by targeting CVP alone. However, the reason CVP or other variables have been used so far is because it is easy to measure the responsiveness to fluid administration during operation.

Previously, investigations into the relationship between CVP and DGF have predominantly centered on single-point CVP measurements. These measurements were typically taken at specific junctures, such as baseline, reperfusion, or post-anesthesia, to establish this connection. In our study, however, CVP was monitored continuously throughout the surgical procedure, allowing us to track CVP fluctuations in both the SGF + DGF group and the IGF group. This methodology distinguishes our study from others in the field. As a result of measuring and comparing CVP at various time points, including baseline CVP, it was found that when conventional fluid management was implemented, CVP continued to rise, peaked around the time of reperfusion, and was maintained. This is interpreted because most conventional fluid management is performed by targeting blood pressure or CVP at reperfusion period. Considering these changes in CVP, the value of CVP itself is more important than the CVP value at a specific point in time. Since there is no difference in the amount of fluid intake between the SGF + DGF and IGF groups, the value of baseline CVP can be considered to increase proportionally according to fluid intake. Therefore, if CVP is within the normal range based on baseline CVP, it could be concluded that increasing fluid intake to increase CVP does not help early graft function recovery.

High CVP values have a negative effect on graft function due to complications that may occur when fluid overload occurs when CVP is high[25]. Additionally, since most KT candidate patients have a high risk of developing cardiac complications, fluid overload may make them more vulnerable to heart-related complications. Therefore, in the pre-anesthesia evaluation performed before kidney transplant surgery, it would be important to examine

indicators that can predict problems caused by volume overload more accurately than the CVP value, such as RVSP. RVSP represents pulmonary hypertension, which is related to right ventricular function[26,27]. According to guidelines, more than 35 mmHg of RVSP indicates pulmonary hypertension[26]. As RVSP value increases, the severity of pulmonary hypertension is also increased. In this study, we investigated the RVSP values obtained from preoperative echocardiography results and compared them with the patients' CVP results. As a result, it was found that the average RVSP value was significantly higher in patients with CVP of 12 mmHg or higher. Therefore, if the baseline CVP value is high enough to be outside the normal range, it is expected that the RVSP value will also be high, and it is important to perform passive fluid intake during the operation to prevent cardiopulmonary complications that may occur. However, it should be considered that the volume status of dialysis patients may change depending on whether dialysis is performed or not. Therefore, it should be recognized that the RVSP results in echocardiography cannot accurately reflect the patient's volume status at the time of surgery.

Several limitations of our study existed. First, this study was conducted at a single center in Korea and was conducted in an area with a relatively low incidence of SGF or DGF. Therefore, in this study where the incidence of DGF is important, it can be said that the low incidence of DGF is a disadvantage in studying DGF risk factors. Second, although all echocardiograms measuring RVSP were performed before surgery, the date of surgery and the date of examination were different for each patient, which may slightly reduce the reliability of the research results. Finally, our study population was relatively small, compared with similar studies on evaluating CVP and graft function.

In this retrospective study, higher CVP was significant intraoperative risk factors for SGF or DGF during deceased donor kidney transplantation. Other factors, such as high body mass index, prolonged ischemic time, and higher donor creatinine level were also revealed as risk factors. Considering anesthesiologic factors that can be monitored during operation, CVP are important factors affecting short-term function after kidney transplantation and should be monitored to prevent excessive fluid intake. According to 3-year graft outcome, intraoperative CVP values are not thought to be a significant factor influencing long term graft function. As is well known, high immunologic risk factors that were excluded in this study are thought to be more important for long-term outcome.

Methods

Study population

We retrospectively analyzed the recipients who underwent deceased donor kidney transplantation from March 2010 to December 2020. Before evaluation, we excluded recipients with extended criteria donor, donor creatinine level above 1.5 mg/dL and acute rejection within 2 weeks after transplantation to consider the impact of the donor's condition on the early graft function. After exclusion, a total of 202 recipients were consisted of the eligible population for evaluation. Immunosuppressive regimen consisted of basiliximab as induction therapy, tacrolimus, mycophenolate mofetil and corticosteroids. Basiliximab was administered just prior to transplantation and 4 days after transplantation. Tacrolimus was initiated at 2 days before KT with an initial dose of 0.05–0.1 mg/kg. Steroids were administrated intravenously at 500 mg on the day of transplantation, 250 mg on the next day after transplantation, and were gradually tapered to a maintenance dose of more than 5 mg a day until 6-months post-transplant.

Anesthetic protocol and fluid management

In the operating room, all patients were monitored with electrocardiogram (ECG), non-invasive blood pressure, pulse oximetry, and bispectral index (BIS). General anesthesia was achieved by administering 2 mg/kg propofol and 2–3 mcg/kg fentanyl intravenously, followed by the administration of 0.6 mg/kg rocuronium. After the loss of consciousness, sevoflurane was started with 3–5 vol% until endotracheal intubation. After intubation, the anesthetic gas was changed to desflurane, and desflurane was adjusted to maintain BIS between 40 and 60 at 5–7 vol%. A tidal volume of 8 mL/kg of the patients' ideal body weight was set, with a respiratory rate of 12–14 bpm to maintain normocapnia conditions. Furthermore, a radial artery catheter was placed, and a central venous catheter was positioned to allow hemodynamic and CVP monitoring. All anesthesiologic variables including heart rate, arterial blood pressure, O_2 saturation, CVP and respiratory rate were monitored and recorded every 5 min in the electronic medical record chart. The fluid management strategy involved administering 10–20 mL/kg/h of a combination of 0.9% normal saline, 0.45% half saline, and 5% human albumin throughout the entire surgical procedure. When severe hypotensive episodes (systolic blood pressure < 100 mmHg or mean arterial pressure < 65 mmHg) occurred, ephedrine and phenylephrine were considered the preferred vasopressor for management of hypotension during operation. All patients received 20 mg of furosemide 5 min before vascular declamping and 500 mg of methylprednisone at reperfusion intravenously. Finally, the amount of total fluid intake during operation was recorded and collected.

Study outcomes and data collection

The primary outcome of this study was incidence of DGF and SGF. The definition of DGF was the need for dialysis within 7 days after transplantation, and the definition of SGF was serum creatinine level greater than 3.0 mg/dL on post-operative day 5[7]. To investigate the incidence of SGF, serum creatinine levels and urine volume were collected until discharge. Patients whose renal function recovered immediately after transplantation were classified into immediate graft function (IGF) group, and patients who developed SGF or DGF were classified into one group and the values between the two groups were compared. In addition, we evaluated 1- and 3-year graft, patient survival rates in this study.

Intraoperative hemodynamic factors were recorded in the electronic medical record every 5 min, but the time from the start of surgery to reperfusion was different for each patient. Therefore, we unified these data based on the reperfusion time and collected records from 1 h to 30 min before reperfusion to 1 h after reperfusion.

Additionally, results of echocardiogram performed within 1 year before transplant surgery were collected in all patients for identifying patients who may be more susceptible to elevated CVP.

Statistical analysis

For categorical variables, data were expressed as a number of patients and a percentage of derived groups, analyzed by Pearson's χ^2 test and Fisher's exact test. Continuous variables were expressed as a mean ± standard deviation and analyzed by using the student's *t*-test and Mann-whitney test. Logistic regression analysis was used to confirm independent risk factors for the development of SGF or DGF. The *P*-value less than 0.05 was considered significant. Data analysis was conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Ethics

This study was approved by the Ajou University Hospital Institutional Review Board (AJOUIRB-MDB-2020-387). Patients authorized the use of their health records for research and had waived informed consent because this study was a retrospective study. For the deceased donor kidney transplants, informed consent was obtained either from the donor previously or from a relative or kin at the time of transplantation. This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. Also, this study was conducted in accordance with the Declaration of Istanbul on organ trafficking and transplant tourism. This study did not involve organs or tissues procured from prisoners.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Jun Bae Bang and Hyo Eun Ahn contributed to the conceptualization, methodology, formal analysis, and investigation of the study. Hyo Eun Ahn was responsible for writing the original draft of the manuscript. Jun Bae Bang reviewed and edited the manuscript, supervised the project, and acquired the necessary funding and resources. Both authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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