Population pharmacokinetic analysis of tacrolimus in Chinese cardiac transplant recipients

Yan Gong,1 Ming Yang,2 Yongfeng Sun,3 Jing Li,4 Yongning Lu,1 Xingang Li5,6

ABSTRACT
Objective Usage of tacrolimus is complicated by its narrow therapeutic index and wide between- and within-subject pharmacokinetic variability. We aimed to obtain more information regarding the influence of various covariates on the disposition of tacrolimus in the early phase after cardiac transplantation using a population pharmacokinetic method, and provide information for the individualisation of drug dosing in the clinical setting.

Methods Routine therapeutic drug monitoring concentrations (897 observations) were retrospectively collected from 146 hospitalised patients. One compartment model with first-order absorption (absorption rate constant K_a was fixed as 4.48/hour) was employed to establish the population pharmacokinetic model using a non-linear mixed-effects modelling approach. Various demographic parameters, postoperative day and concomitant medications influencing drug clearance and distribution volume were investigated in this study. Bootstrap and prediction-corrected visual predictive check were employed to validate the final model. With the goal of tacrolimus trough concentrations within the therapeutic window, simulation was performed.

Results Pharmacokinetic parameter population typical estimates for clearance (CL/F) and apparent distribution volume (V/F) were 14.23 L/hour and 760.80 L, respectively. Postoperative day and co-administration of Wuzhi capsules were identified as important factors affecting CL/F. Total body weight was significantly associated with the V/F. Results of model evaluation indicated a good stable and precise performance of the final model. Based on the simulation results, a simple-touse dosage regimen table to guide clinicians with drug dosing was created.

Conclusion The final population model could provide information for the individualised dosing of tacrolimus for cardiac transplant recipients.

INTRODUCTION
Organ transplantation is the treatment of choice for patients with end-stage organ failure. Kidney and liver transplants accounted for >90% of all large-organ transplants in China until 2011.1 In recent years, more and more heart transplants have been performed in China.3 Various pharmacokinetic (PK) studies of immunosuppressant agents, such as tacrolimus and ciclosporin, were mostly conducted among kidney or liver transplant patients. However, data involving heart transplant recipients was scarce.1 It has been reported that a 50% reduction in systematic clearance of drugs (such as milrinone, carperitide, molsidomine, theophylline, ciclosporin and hydralazine) was observed in decompensated congestive heart failure (New York Heart Association (NYHA) III and IV).2 Guidelines for the use of tacrolimus in cardiac transplant recipients recommend that the target level of tacrolimus be achieved as soon as possible (within the first few days post-transplant).4 The reduced blood flow to the gastrointestinal tract, the peripheral tissues, as well as the liver and kidneys, may lead to a different PK profile of tacrolimus in a heart transplant recipient compared with a kidney or liver transplant patient.

Tacrolimus is a potent immunosuppressant drug primarily used to prevent and treat graft rejection after solid organ transplantation, and it exhibits higher patient and organ survival rates than ciclosporin. Moreover, tacrolimus leads to lower rejection rates and longer freedom from rejection. At present, when prioritising efficacy, tacrolimus is the first choice immunosuppressive drug for heart transplant recipients.5 Usage of tacrolimus is complicated by its narrow therapeutic index and wide between- and within-subject PK variability.6 Adequate drug exposure is needed for the prevention of rejection, but overexposures may increase the risk of toxicities, which affect long-term allograft and patient survival. Multiple factors may affect the dosing of tacrolimus. Regular therapeutic drug monitoring (TDM) is therefore essential for tacrolimus in clinical practice. With oral dosing, a steady-state blood concentration of tacrolimus is usually achieved within approximately 48 to 72 hours. Trough whole-blood levels for a heart transplant patient should be maintained between 15 to 20 ng/mL during the early postoperative period (days 0–60), between 10 to 15 ng/mL during the intermediate period (2–6 months), and between 5 to 10 ng/mL after 6 to 9 months.4 Patient concentrations are often outside the target range.

Population PK is the study of sources and correlates of variability in drug exposure and response, and it describes the typical relationships between physiology and PK, the interindividual variability in these relationships, and their residual intraindividual variability. Knowledge of population kinetics can help to choose the initial drug dosage, and modify dosage appropriately in response to observed drug levels. Therefore, it is important to conduct a tacrolimus population PK study in cardiac transplant recipients. Knowledge of factors that affect PK can be derived from population PK studies. The non-linear mixed-effects modelling approach can offer the possibility to

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 simultaneaously characterise the PK parameters, and evaluate the variability of highly variable drugs with good precision and accuracy. Sparse data, such as routine TDM data, can be employed for this purpose.

In this study, TDM data of tacrolimus were collected from hospitalised heart transplant patients, using a population PK modelling method to evaluate the potential factors and to provide information for the individualisation of tacrolimus dosing.

## METHODS

### Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. The study was conducted at Wuhan Union Hospital and the protocol was approved by the Research Ethics Committee of Wuhan Union Hospital (Ethical code: [2016]S249).

### Patient selection and data collection

Routine TDM data (1–96 days post-operation) were retrospectively collected from 146 patients in Wuhan Union hospital from 1 January 2014 to 31 December 2015. The main information provided by the patient data is illustrated in table 1. All patients were cardiac transplant recipients and were given tacrolimus capsules (0.5 mg/capsule or 1.0 mg/capsule, Prograf, Astellas-Pharma China, Inc) twice a day. The initial doses were calculated on a 0.10–0.15 mg/kg/day basis in two divided doses. Subsequent doses were adjusted based on clinical evidence of efficacy and toxicity, as well as tacrolimus TDM results (15 to 20 ng/mL). We included adult heart transplant patients (≥17 years) who were administered tacrolimus, corticosteroids and mycophenolate as the immunosuppressant therapy post-operation. Corticosteroids were started with intravenous administration (2.0–2.5 mg/kg every 8 hours) in the first 3 days and then switching to oral dosing; doses of the drug were gradually decreased over the days from transplantation. Mycophenolate was orally administered 24–48 hours after transplantation; the daily dose was 0.75–1 mg every 12 hours in the first 2 weeks, and then reduced to 0.5 mg every 12 hours.

Recipients who received combined lung–heart transplantation or were taking tacrolimus manufactured by other pharmaceutical companies were excluded. In addition, patients with incomplete medical record data were also excluded. In total, 10 patients were excluded from the study. All patients were hospitalised and treated under the supervision of medical and nursing staff.

The data were collected from medical records, including dose regimen of tacrolimus, date and time of blood sampling, drug concentrations, age (AGE), total body weight (BW), height (HT), serum creatinine (Scr), postoperative day (POD), sex (SEX), haemoglobin (HB), haematocrit (HCT), albumin (ALB), total bilirubin (TBIL), unconjugated bilirubin (IBIL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT) and concomitant medications of Wuzhi (WZ) capsules (multiple dosages of WZ capsules have been prescribed for the patients, and dosing for the heart transplant recipients ranged from 66 to 264 mg per day, in two divided doses).

WZ capsules are a preparation of the ethanol herbal extract of Schisandra sphenanthera. The preparation was approved for clinical use in China for the protection of liver function after transplantation. Fundamental experiments have proven that the drug can affect the activity of the CYP3A enzyme, so it was included as a covariate screening in the study. As azoles were not regularly prescribed for the cardiac transplant recipients in Wuhan Union hospital, the co-administration effect of azoles (CYP3A inhibitors) were not investigated in this study. We reconfirmed the information before model development.

### Tacrolimus determination

Tacrolimus concentration measurement was determined by Viva-E Drug Testing System (Seimens Healthcare, Erlangen, Germany) with enzyme multiplied immunoassay technique. The lower limit of quantitation of the assay was 2 ng/mL, ranging from 2 to 30 ng/mL.

### Population PK model

Population PK analysis was carried out using the Phoenix NLME 8.0 programme (Certara, St Louis, Missouri, USA). A one-compartment with first-order absorption model was employed. The First-order Conditional Estimation with Extended Least Squares (FOCE-ELS: this method is essentially equivalent to the NONMEM FOCE methodology with interaction) method was used throughout the process of model building. In order to avoid the effect of fluctuation on the stability of the model, the value of \( K_s \) (absorption constant) was fixed as 4.48/hour at the stage of stacking the covariates.

In the first step, an exploratory analysis of the mean, SD and coefficient of variation of all candidate variables was performed. Graphical and linear regressions were used to test the relationship of PK variables versus covariates. Additionally, the interaction between variables was also analysed in order to eliminate components from the candidate predictor relationships. In the process of model development, continuous covariates (POD, AGE, BW, HT, SCR, HB, HCT, ALB, TBIL, IBIL, ALP, ALT, ASAT, GGT) were evaluated using the following equations:

<table>
<thead>
<tr>
<th>Table 1 Summary of patient data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Number of patients (male/female)</td>
</tr>
<tr>
<td>Number of observations</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Total body weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
</tr>
<tr>
<td>Postoperative day</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
</tr>
<tr>
<td>Unconjugated bilirubin (μmol/L)</td>
</tr>
<tr>
<td>Alkaline phosphatase (UL)</td>
</tr>
<tr>
<td>Alanine aminotransferase (UL)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (UL)</td>
</tr>
<tr>
<td>γ-Glutamyl transpeptidase (UL)</td>
</tr>
<tr>
<td>Wuzhi capsule (+)</td>
</tr>
<tr>
<td>Prednisone (+)</td>
</tr>
<tr>
<td>Tacrolimus dose (mg/day)</td>
</tr>
<tr>
<td>Drug concentrations (μg/mL)</td>
</tr>
<tr>
<td>Main comorbidities</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Graft failure</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Acute rejection</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
</tr>
</tbody>
</table>
\[ P_i = tvP \times \left( \frac{Cov}{Cov_{median}} \right)^\theta \]  

(1)

where \( P_i \) represents the individual parameter estimate of the \( i \)th subject, \( tvP \) represents the typical value of this parameter, \( Cov \) and \( Cov_{median} \) are the covariate and the median of covariate, respectively, and \( \theta \) is the corresponding coefficient. Preliminary PK analysis indicated that the proportional model was suitable for the description of residual error.

\[ C_i = C \times (1 + \varepsilon) \]  

(2)

where \( C x \) and \( C \) are individual observations and predictions, respectively, \( \varepsilon \) accounts for the proportional error of predictions, which is normally distributed with mean zero and variances of \( \sigma^2 \). Categorical covariates (SEX: male=1 and female=2; WZ capsules: co-administration=1 and none=0) were incorporated using indicator variables.

Initially, a structure model was formed without any covariates. The candidate covariates were then added to the structure model to identify its significance in turn. If objective function value (OFV) of the model reduced more than 3.84 (\( p<0.05, df=1 \)), the covariate was considered to be retained in the model. After the stage of forward selection, covariates need to be re-evaluated by improving the test level (\( p<0.001, df=1 \)) in the stage of backward elimination. Each covariate was independently removed from the model one at a time to identify its relevance. An increase in the \( \Delta OFV \) of over 10.83 was required for confirmation. When two or more covariates were found to significantly improve the model, the covariate causing the largest reduction was left in the final model.

**Model evaluation**

A visual evaluation method was carried out by inspection of the scatter plots of drug concentrations versus population prediction (PRED) and individual predicted (IPRED) concentrations. The relative prediction errors were graphically described by conditional weighted residuals (CWRES) plotted against PRED and time. Additionally, the Normal Quantile-Quantile (QQ) plot was also used to evaluate how well the distribution of CWRES matched a standard normal distribution.

To evaluate the stable and predictive performance of the final model, a non-parametric bootstrap method and a visual prediction-corrected predictive check (pcVPC) was carried out after the model building. The bootstrap method involves repeated random re-sampling with replacement from the original dataset for 1000 times. More than 800 successful re-samplings were required for the stability evaluation of the final model. Additionally, the values of estimated parameters, such as the median and 95%CI, from the bootstrap procedure were compared with those estimated from the original dataset. No significant difference was observed, indicating a reliable final model. The pcVPC used 1000 times Monte Carlo simulation to generate concentration–time profiles. In a pcVPC, the variability coming from binning across independent variables is removed by normalising the observed and simulated dependent variables based on the typical population prediction for the median independent variable in the bin. The pcVPC has an enhanced ability to diagnose model misspecification, especially with respect to random effects models in a range of situations. The observed concentration–time data were graphically superimposed on the median values, and the 5th and 95th percentiles of the simulated concentration–time profiles. The model was deemed precise if the observed concentration data were approximately distributed within the 5th and 95th prediction interval.

**Simulation**

This study aimed to provide dosing guidance for the use of tacrolimus in cardiac transplant recipients. Trough whole-blood levels for a heart transplant patient should be maintained between 15 to 20 ng/mL during the early postoperative period (0–2 months), and between 10 to 15 ng/mL during the intermediate period (2–6 months). After the final model was developed, tacrolimus concentrations at different times were calculated based on the relationship between PK parameters and the covariates. Patients were divided into different subgroups according to covariates significantly associated with PK. Simulations were conducted using the Phoenix NLME software to find the optimal individualised dosing regimen for different subgroups of patients. Simulation was performed to ensure that >90% of the trough concentrations were within target concentration during the therapy. A simple to use dosage regimen table was derived based on the results of simulations.

**RESULTS**

**Model development**

A one-compartment with first-order absorption model best fitted the observed concentrations. The parameter estimates of CL and V/F were 14.01 L/hour and 869.61 L, respectively. When adding the candidate covariates separately to the structure model, CL was markedly affected by POD and the co-administration of WZ; V/F was significantly influenced by BW. After forward selection and backward elimination of all the covariates, the final model presented as follows:

\[ \text{CL,F} (\text{L/h}) = 14.23 \times (\text{POD}/12)^{-0.12} \times \exp (0.39 \times (\text{WZ} = 1)) \times \exp (\text{wCL}) \]  

(3)

\[ \text{V/F} (\text{L}) = 846.91 \times (\text{BW}/66)^{-0.06} \times \exp (\text{nV}) \]  

(4)

where in equation 3, POD was calculated by days; when patients were co-administered WZ, the value of item ‘\( \exp(0.39 \times (\text{WZ} = 1)) \)’ is ‘\( \exp(0.39) \)’, otherwise the values 1. 12 and 66 stand for the median value of POD and BW, respectively. Parameter estimates for the final model are summarised in table 2. A good estimation of all the model parameters was obtained (relative standard error (RSE) < 30%).

**Goodness-of-fit**

Goodness-of-fit plots were used to assess the reliability of both the structural model and the final pharmacokinetic model. These plots included scatter plots: observations against PRED, observations against IPRED, CWRES versus time, CWRES versus PRED, and Normal QQ plots (figure 1). Goodness-of-fit plots did not show systematic bias for both structural and final pharmacokinetic model predictions. A significant improvement in the predictive performance of the final model (figure 1A–E) was achieved as compared with the basic one (figure 1A–E).

**Model evaluation**

The validation of the final model by bootstrapping and pcVPC also indicated satisfactory results. A total of 966 re-samplings of the original dataset were successfully performed in the process of bootstrap evaluation, indicating a qualified stability for the final model. Table 2 also summarises the parameter estimates for the final model and bootstrap replicates; the comparable data values indicate a good prediction of the final model. The distribution of the 1000 simulated concentration–time curves and the comparison with the observations in the original dataset are shown in figure 2. Most determined concentrations were within the 90% prediction interval of model-predicted concentrations,
suggesting the precise performance of the final model. However, pcVPC plots showed that the median of the observed and predicted concentration was not in agreement in the large POD. In this study, most of the data were in the POD <40 days, and we only obtained limited pharmacokinetic data in the large POD. We tried our best to optimise the final model and this was the best one we could get. This deviation may come from a random error.

**Simulation**

A total of three covariates (POD, WZ and BW) were incorporated into the final model, and 12 subgroups were obtained according to the incorporated covariates. The range of POD during simulation was restricted to the ranges observed in the modelling data (1–96 days) to prevent distortion of results. The values of CL/F and V/F were calculated using equations 3 and 4, respectively (Ka were fixed as 4.48/hour). With the goal of having tacrolimus trough concentrations maintained within 15–20 ng/mL (POD=0–2 months) and 10–15 ng/mL (POD=2–6 months), the optimal dosage regimens for different subgroups and percentage of trough concentrations within target concentrations are listed in table 3. The results of this simulation were only used for patients whose POD were within 1–96 days. Simulation results showed that as POD increased, oral doses needed to be decreased as well to maintain optimal exposures. However, splitting the tacrolimus capsules is not convenient for patients. Based on the simulation results, we found that adjusting the calculated dosage according to the drug specification was acceptable (eg, 3.5 mg instead of 3.6 mg, 2.0 mg instead of 1.8 mg or 2.2 mg, 2.5 mg instead of 2.3 mg).

**DISCUSSION**

In this study, routine clinical PK data were retrospectively collected from 146 cardiac transplant patients in Wuhan Union Hospital to investigate potential covariates which may affect the PK parameters. A population PK model conducted on Chinese heart transplant patients has been built through the Phoenix NLME programme. Typical value of CL/F was 14.23 L/hour ($tvCL/F/BW_{median}$=0.22 L/hour/kg), which is relatively consistent with the estimated range (0.19–0.23 L/hour/kg) published in the literature. Since Ka was fixed, sensitivity analysis was performed to assess its impact on the CL/F and V/F. Because most of sampling points were in the elimination phase (trough concentration), Ka did not influence the CL/F and V/F significantly. In contrast to the published population PK investigations in China, tacrolimus PK in cardiac transplant recipients (0.22 L/hour/kg; POD: 12.0±11.9 days) showed a decreased clearance compared with healthy volunteers (CL: 0.52 L/hour/kg; POD: 6.24±1.19 days). When we set the value of POD to 6–7, the

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Final model</th>
<th>Bootstrap (1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (RSE %)</td>
<td>IIV (CV%)</td>
</tr>
<tr>
<td>Clear ance:</td>
<td>$CL/(L/h) = tvCL \times (POD/POD_{median})^{\theta_1} \times \exp (\theta_2 \times (WZ = 1)) \times \exp (\theta_3)$</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution:</td>
<td>$V/F (L) = tvV \times (BW/BW_{median})^{\theta_1} \times \exp (\theta_2)$</td>
<td></td>
</tr>
<tr>
<td>$tvCL/F (L/h)$</td>
<td>14.23 (5.39)</td>
<td>38.89</td>
</tr>
<tr>
<td>$tvV/F (L)$</td>
<td>846.91 (9.09)</td>
<td>85.95</td>
</tr>
<tr>
<td>$\theta_1$</td>
<td>−0.12 (20.02)</td>
<td>–</td>
</tr>
<tr>
<td>$e$</td>
<td>0.39 (19.00)</td>
<td>–</td>
</tr>
<tr>
<td>$\theta_3$</td>
<td>2.06 (22.33)</td>
<td>–</td>
</tr>
<tr>
<td>Residual error model (proportional error, CV%)</td>
<td>Proportional</td>
<td>0.30 (3.02)</td>
</tr>
</tbody>
</table>

CV, coefficient of variation; IIV, inter-individual variability; RSE, relative standard error.
The combined effects lead to an increase in CL/F as 95% confidence band, indicating the areas between the 5th and 95th percentiles representing the 90% prediction interval. Similarly, the red dotted line means the observed 50th percentile and the red dashed lines are the 5th and 95th percentiles of observations.

value of tacrolimus clearance calculated by our model was about 0.23 L/hour/kg, which decreased by about 56% compared with the healthy volunteers. This value is similar to clearance in liver transplant patients (CL: 0.26 L/hour/kg; POD: 7.72±4.19 days; age: 58.4±11.6 years). In the unstable clinical phase, whole blood clearance of tacrolimus and its metabolites is influenced by several adverse factors, among which reduced blood flow to various organs, severe cholestasis, anaemia and hypoalbuminaemia may all substantially alter the clearance. Low blood perfusion in liver and cholestasis (reflecting hepatic dysfunction) decrease the metabolism and transport of tacrolimus into the bile, resulting in a reduced clearance of tacrolimus. Rower et al constructed a population PK model that describes tacrolimus concentrations in paediatric patients receiving a heart transplant. Due to the differences between adults and children, PK parameters, CL/F (9.5 L/hour/kg) and V/F (233 L) were significantly lower than those in this model.

In this study, tacrolimus clearance was found to vary with POD and the co-administration of WZ capsules; distribution volume was significantly influenced by BW. POD is a significant covariate with high recognition among various studies.

Tacrolimus is a fat-soluble drug, which binds strongly to erythrocytes and plasma proteins. Recovery of gastrointestinal function and increased intake of food can alter tacrolimus bioavailability. The combined effects lead to an increase in CL/F as POD increases. Recovery of the gastrointestinal function may play a leading role in the absorption of tacrolimus, which leads to an increase in the clearance of tacrolimus.

Table 3 Dosing regimens (twice a day, μg) for cardiac transplant recipients based on the POD, BW and drug combination

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>POD=0–60 days (trough concentration within 15–20 ng/mL)</th>
<th>POD=61–96 days (trough concentration within 10–15 ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BW &lt;60 kg</td>
<td>BW=60–80 kg</td>
</tr>
<tr>
<td>Without WZ</td>
<td>2500 (93.3)*</td>
<td>2500 (92.2)*</td>
</tr>
<tr>
<td>With WZ</td>
<td>3500 (96.8)*</td>
<td>3500 (94.1)*</td>
</tr>
</tbody>
</table>

*Percentage of trough concentrations within target concentrations during therapy. BW, body weight; POD, postoperative day; WZ, Wuzhi.
patients, but the effect was largely driven by CYP3A5*3.29 Genetic polymorphisms of metabolising enzymes and transport proteins should be investigated for the individualisation of tacrolimus dosing for cardiac transplant patients in further prospective studies.

In summary, the well-known covariates POD, WZ capsules and BW were successfully identified as the important factors affecting tacrolimus CL/F and V/F in heart transplant patients. This model was stable and precise, and simulation was performed based on the final PK model. The final model could provide information for the individualised dosing of tacrolimus.

Limitations
Several limitations should be addressed. (1) Cardiotoxicity is found among people who take tacrolimus, (taking the drug for <1 month). The tacrolimus pre-dose concentration is associated with increased left ventricular wall thickness in paediatric liver transplant recipients. Systolic and diastolic hypertension is associated with tacrolimus left ventricular wall thickness in paediatric liver transplant recipients. Several limitations should be addressed. (1) Cardiotoxicity is found among people who take tacrolimus, (taking the drug for <1 month). The tacrolimus pre-dose concentration is associated with increased left ventricular wall thickness in paediatric liver transplant recipients. Systolic and diastolic hypertension is associated with tacrolimus left ventricular wall thickness in paediatric liver transplant recipients. Two months after transplantation, the final PK was stable and precise, and simulation was performed based on the final PK model. The final model could provide information for the individualised dosing of tacrolimus.

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Contributors
YL and XL conceived and designed this study. YG, MY and XL performed the analysis. YG and XL wrote the manuscript. YL, YS, and JL supervised the quality of the study. All authors read and approved the final manuscript.

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Competing interests
None declared.

Patient consent
Next of kin consent obtained.

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What this paper adds
What is already known on this subject
► Due to a narrow therapeutic index and wide between- and within-subject pharmacokinetic variability of tacrolimus, routine therapeutic drug monitoring is necessary for patients.
► The postoperative day is a well-known covariate affecting tacrolimus clearance.

What this study adds
► Tacrolimus pharmacokinetics in Chinese cardiac transplant recipients showed a decreased clearance compared with healthy volunteers.
► The covariates postoperative day, Wuzhi capsules and body weight were identified as the important factors affecting tacrolimus clearance and distribution volume in heart transplant patients.


