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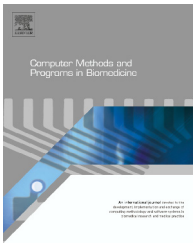

Piecewise nonlinear mixed-effects models for modeling cardiac function and assessing treatment effects

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ABSTRACT

Mixed-effects model is an efficient tool for analyzing longitudinal data. The random effects in a mixed-effects model can be used to capture the correlations among repeated measurements within a subject. Mixed effects model can be used to describe individual response profile as well as population response profile. In this manuscript, we apply mixed-effects models to the repeated measurements of cardiac function variables including heart rate, coronary flow, and left ventricle developed pressure (LVDP) in the isolated, Langendorff-perfused hearts of glutathione s-transferase P1/P2 (*GSTP*) gene knockout and wild-type mice. Cardiac function was measured before and during ischemia/reperfusion injury in these hearts. To describe the dynamics of each cardiac function variable during the entire experiment, we developed piecewise nonlinear mixed-effects models and a change point nonlinear mixed effect model. These models can be used to examine how cardiac function variables were altered by ischemia/reperfusion-induced injury and to compare the cardiac function variable between genetically engineered (null or transgenic) mice and wild-type mice. Hypothesis tests were constructed to evaluate the impact of deletion of GSTP gene for different cardiac function variables. These findings provide a new application for mixed-effects models in physiological and pharmacological studies of the isolated Langendorff-perfused heart.

1. Motivation

Myocardial ischemia/reperfusion (I/R) injury has resulted in significant morbidity and numerous studies have been carried out to discover endogenous mechanisms to protect the heart against I/R injury. Glutathione s-transferase P (GSTP) has been identified as an antioxidant cardiac enzyme that protects against I/R injury by catalyzing the removal of toxic lipid peroxidation products [1]. In an isolated heart, cardiac function is monitored over time and function is characterized by heart rate (i.e., the number of beats per minute (bpm)), coronary blood flow (mL/min), and left ventricle developed pressure (LVDP) (i.e., the difference of left ventricle systolic pressure and left ventricle diastolic pressure; mmHg). To examine whether GSTP gene protects against I/R injury, the isolated, Langendorff-perfused hearts from GSTP-null mice (KO) and wild type mice (WT) were exposed to 30 min of ischemia followed by 45 min of reperfusion [1]. The cardiac function variables (heart rate, coronary blood flow, and LVDP) were measured continuously including 5 min pre-ischemia, 30 min of ischemia, and 45 min of reperfusion. The data were summarized in 1 min intervals. Heart rate, coronary blood flow, and LVDP are shown, respectively, in Fig. 1 Panels A1–A3 for

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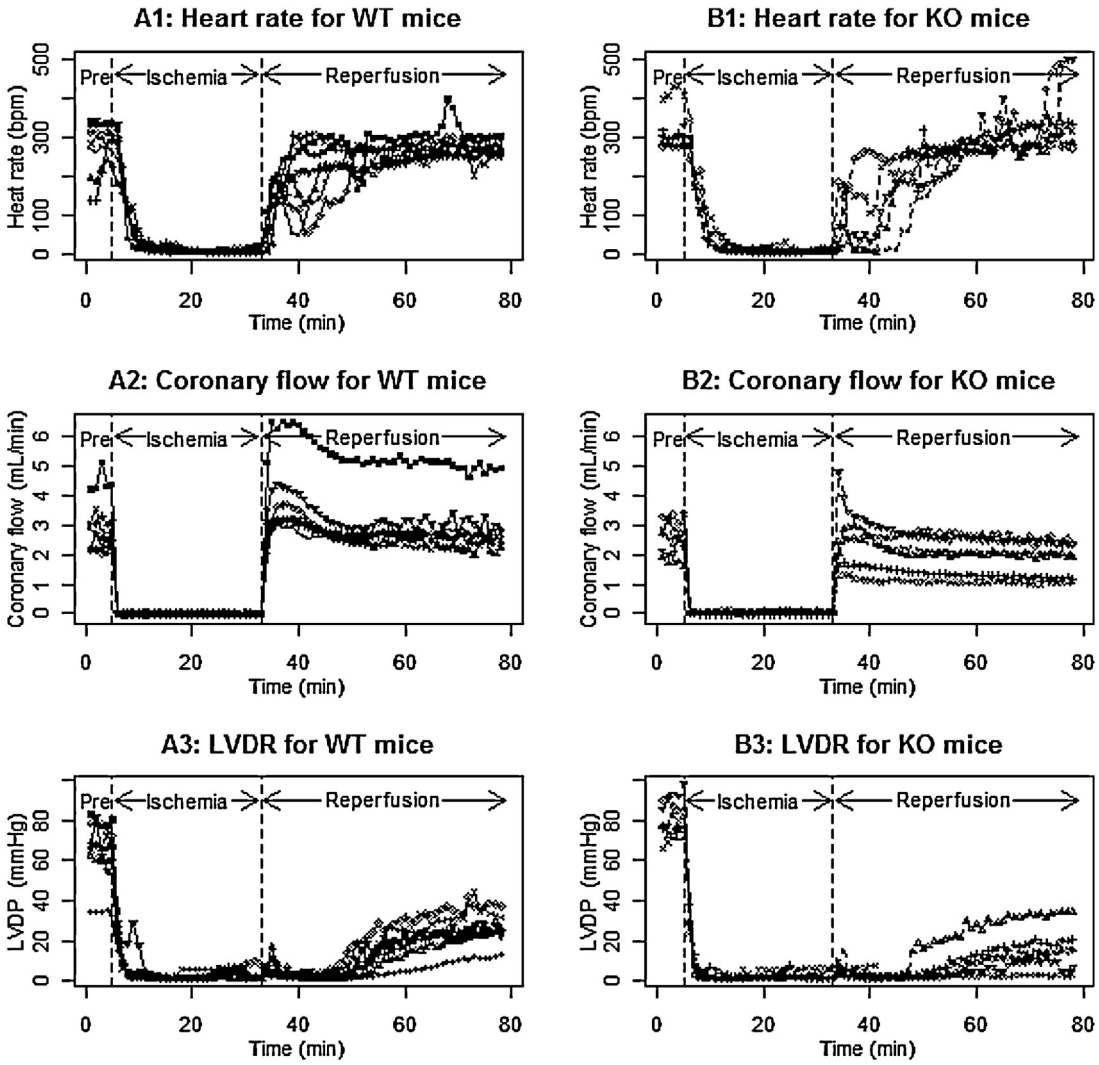

Fig. 1 – Individual profiles for heart rate (Panels A1 and B1), coronary flow (Panels A2 and B2), and left ventricle developed pressure (LVDP) (Panels A3 and B3) in WT mice and KO mice.

wild-type mice ($n=7$) and in Fig. 1 Panels B1–B3 for GSTP-null mice ($n=6$). Typically, the Student's t-test is used to test whether two groups are the same at each time point [2] or a repeated measures analysis of variance (rANOVA) is applied to test whether there are group difference, time effect, and group by time interaction [3]. The number of repeated observations for each subject is 80, and thus, the t-test without multiplicity adjustment seems inappropriate. The rANOVA requires that all individuals have a complete balanced data and a fixed time schedule, and the rANOVA treat time points as different levels of a factor variable. Because each cardiac function variable was recorded in 80 min interval, and each cardiac function variable changes dramatically over the three treatment periods (i.e., pre-ischemia, ischemia, and reperfusion), the application of rANOVA was limited. Thus, a more flexible model, mixed-effects model, seems to be more appropriate. In the mixed-effects model time points are not necessary fixed, time is treated as a continuous variable, and all available data can be used in mixed-effects model provided that data are missing at random [4]. In a mixed-effects model, the correlation between repeated measurements is captured by random effects [3]. Moreover, mixed-effects models provide a more flexible covariance structure for non-constant within-subject correlation [5]. Several studies have suggested that a mixed-effects model is very useful in biomedical research and especially in analyzing complex data with multi-source variance [6]. In many longitudinal analyses, change is assumed to be linear but in numerous situations, the change is not uniform but rather faster during some periods and slower in others [7]. In these cases, nonlinear mixed-effects (NLME) models or piecewise polynomials are more appropriate than linear mixed-effects (LME) models to describe these nonlinear changes. However, nonlinear models incorporate characteristics of the data, such as asymptotes and monotonicity; the parameters in nonlinear models are often interpretable; and nonlinear models often provide more reliable predictions for the response variable outside the observed range of the data than, say, polynomial models would [8]. Thus, in this paper, we applied NLME models to investigate the dynamics of the cardiac function variables.