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ARTICLE

A quantitative systems pharmacology approach to predict the safe-equivalent dose of doxorubicin in patients with cardiovascular comorbidity

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Abstract

Patients with cardiovascular comorbidity are less tolerant to cardiotoxic drugs and should be treated with reduced doses to prevent cardiotoxicity. However, the safe-equivalent dose of antitumor drugs in patients with cardiovascular disease/risk is difficult to predict because they are usually excluded from clinical trials as a result of ethical considerations. In this study, a translational quantitative system pharmacology-pharmacokinetic-pharmacodynamic (QSP-PK-PD) model was developed based on preclinical study to predict the safe-equivalence dose of doxorubicin in patients with or without cardiovascular disease. Virtual clinical trials were conducted to validate the translational QSP-PK-PD model. The model replicated several experimental and clinical observations: the left ventricular ejection fraction (LVEF) was reduced and the left ventricular end-diastolic volume (LVEDV) was elevated in systolic dysfunction rats, the LVEF was preserved and LVEDV reduced in diastolic dysfunction rats, and patients with preexisting cardiovascular disease were more vulnerable to doxorubicin-induced cardiac dysfunction than cardiovascular healthy patients. A parameter sensitivity analysis showed that doxorubicin-induced cardiovascular dysfunction was mainly determined by the sensitivity of cardiomyocytes to cardiotoxic drugs and the baseline value of LVEDV, reflected in LVEF change percentage from the baseline. Blood pressure was the least sensitive factor affecting doxorubicin-induced cardiotoxicity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Patients with cardiovascular comorbidity are less tolerant to cardiotoxic drugs and should be treated with reduced doses to prevent cardiotoxicity. However, the safe-equivalent dose of antitumor drugs in patients with cardiovascular disease/risk is not fully predictable because they are usually excluded from clinical trials as a result of ethical considerations.

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WHAT QUESTION DID THIS STUDY ADDRESS?

In this study, a translational quantitative system pharmacology-pharmacokinetic-pharmacodynamic (QSP-PK-PD) model was developed based on preclinical study to predict the safe-equivalence dose of doxorubicin in patients with or without cardiovascular disease.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Here, we propose a mechanism-based approach for quantification of the safe-equivalent dose in patients with preexisting cardiovascular diseases as demonstrated in Figure 3. Safe-equivalent doses for patients with preexisting cardiovascular disease were calculated by comparing incidence rates of cardiac events with that of cardiovascular healthy patients.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The developed QSP-PK-PD model integrally quantifies the effect of a drug and the cardiovascular disease/risk factor on the pathophysiological processes in the biological system, which provide an *in silico* tool to evaluate the patient-specific tolerance dose to cardiotoxic drugs.

INTRODUCTION

With significant advances in the field of oncology, the number of cancer survivors has steadily increased.[1] However, anticancer treatment-induced cardiovascular complications, such as left ventricular systolic dysfunction, are now recognized to limit oncological therapeutic opportunities or worsen the long-term prognosis of patients with cancer, especially in those with cardiovascular disease.[2–4] Ferdinandy et al.[5] defined this unexpected cardiotoxicity in patients with preexisting cardiovascular disease or risk as "hidden cardiotoxicity" and suggested that it arose from the altered tolerance of the heart to cardiotoxic agents in this subpopulation. Patients with cardiovascular comorbidity are less tolerant to cardiotoxic drugs and should be treated with reduced doses to prevent hidden cardiotoxicity. However, patients with cardiovascular disease/risk are always excluded from clinical trials, resulting in a knowledge gap about the safe-equivalent dose of antitumor drugs in this subpopulation.

Drug-induced cardiac dysfunction is characterized by insufficient blood supply by the heart. According to the Frank-Starling mechanism, blood supply by the heart is determined by the interaction between preload, afterload, and myocardial contraction. Cardiac preload and afterload are reflected by left ventricular end-diastolic volume (LVEDV) and peripheral resistance,[6] respectively. Myocardial contraction is determined by both systolic function and diastolic function of cardiomyocytes, which are represented by bioenergy production and myocardial compliance. Patients with cardiovascular disease always suffer changes in one or more of these physiological processes, which compromises the tolerance of the heart to cardiotoxic agents.

Pharmacokinetic (PK)–pharmacodynamic (PD) modeling is a promising approach for dose optimization by quantifying the general drug exposure–effect relationship.[7,8] However, the interpopulation translational ability is limited, as the influence of physiological change on drug effect is mostly ignored in the conventional PK-PD model. The newly emerged quantitative systems pharmacology (QSP) model has been proposed to integrally analyze the mechanism of disease progression and drug action by incorporating detailed biological processes in the PK-PD model.[9] With the QSP model, physiological changes and their influence on drug effects could be integrally characterized, providing a feasible approach to predict the influence of preexisting cardiovascular disease on drug-induced cardiotoxicity.

Doxorubicin is a highly effective chemotherapeutic agent with dose-dependent cardiotoxicity.[10,11] Preexisting cardiomyopathy and hypertension have been identified as increasing the cardiotoxic risk of doxorubicin,[12,13] suggesting an inconsistent safe dose of doxorubicin treatment in the presence or absence of cardiovascular comorbidities. In this study, a translational QSP-PK-PD model was developed based on a preclinical study to predict the safe-equivalence dose of doxorubicin in patients under different cardiovascular statuses using virtual clinical trials.

MATERIALS AND METHODS

Data collection

Literature research was conducted to collect the PK profile and heart distribution of doxorubicin after intravenous (i.v.) bolus or intraperitoneal (i.p.) administration and the cardiac effects of doxorubicin in rats. The inclusion and

exclusion criteria are that (1) the dosing approach should be i.v. or i.p. administration of doxorubicin solution, (2) no other drug was simultaneously given, and (3) at least three PK data points or two PD data points should be reported after drug administration. For each included article, plasma/heart doxorubicin concentration-time data, LVEDV, left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), and mean arterial pressure (MAP) results were collected for model development and validation. Collected data used for model development and validation are summarized in Table S1.

QSP-PK-PD model

A QSP-PK-PD model was developed to integrally describe the influence of doxorubicin and physiological changes on cardiac function. The PK model to determine drug exposure in the heart was first developed. The estimated PK model was then incorporated into the QSP-PK-PD model to optimize the QSP and PD parameters using the collected data of doxorubicin-induced changes in cardiac function in healthy, hypertension, and LVEDV-enlarged rats. Details of the model equations, fitting, and simulation are summarized in Supplementary Document S1.

QSP model

As shown in Figure 1, a QSP model was developed to depict the interrelationship between preload, afterload, and myocardial contractility. In the current model, natural progressions of LVEDV enlargement and hypertension were ignored because of their slower progression compared with the onset of drug effects.[14] Turnover functions were applied to characterize the homeostatic features of physiological processes using the zero-order production rate constant (k_{in}) and the first-order dissipation rate constant (k_{out}) to describe their rates of production and dissipation. Inhibitory and stimulatory effects on the physiological processes were considered to influence production or dissipation, which are described in detail in the Supplementary Materials.

Preload

Cardiac preload was quantified by LVEDV, which is determined by myocardial compliance, MAP, and LVESV. Myocardial compliance and MAP were considered to influence the production of LVEDV, whereas LVESV was considered to influence the dissipation of LVEDV (Equation 1). LVESV, the remaining left ventricular volume after myocardial contractility, is numerically equal to the difference between LVEDV and stroke volume (SV) (Equation 2). LVEF is a gold standard for left ventricular systolic dysfunction diagnosis and is calculated by the ratio of SV and LVEDV (Equation 3).

$$\begin{aligned}\frac{\mathrm{dLVEDV}}{\mathrm{d}t} &= k_{\mathrm{in\_LVEDV}}\cdot(1+\mathrm{FB_{MAP}}\times\mathrm{MAP})\cdot E_{\mathrm{MC\_LVEDV}} - k_{\mathrm{out\_LVEDV}}\cdot(1-\mathrm{FB_{LVESV}}\cdot\mathrm{LVESV})\cdot\mathrm{LVEDV}\\ \mathrm{LVEDV}(0) &= \mathrm{LVEDV_{base}}\end{aligned} \tag{1}$$

$$\mathrm{LVESV} = \mathrm{LVEDV} - \mathrm{SV} \tag{2}$$

$$\mathrm{LVEF} = \frac{\mathrm{SV}}{\mathrm{LVEDV}} \tag{3}$$

The explanation of model parameters is summarized in Table S3.

Afterload

Perivascular pressure is usually considered as the afterload of blood supply in the heart, and it could be reflected by blood pressure.[15] Snelder et al.[16] developed a model to investigate the interrelationships between heart rate (HR), total peripheral resistance (TPR), SV, and MAP, which was adapted in this study. With turnover function to describe the change of HR, TPR, and SV (Equations 4–6), MAP was calculated by the product of HR, TPR, and SV and exerts negative feedback control on the production of these three factors (Equation 7). In this QSP model, we also considered the effect of bioenergy production ($E_{\mathrm{EP\_SV}}$) and myocardial compliance ($E_{\mathrm{MC\_SV}}$) on SV. According to Snelder et al., feedback effect ($\mathrm{FB_{MAP}}$) was decreased with baseline of MAP according to the relationship described in Equation (8). In the present study, a fixed exponent of −1.98 was used to incorporate the effect of $\mathrm{MAP_{base}}$ on $\mathrm{FB_{MAP}}$.[16]

$$\begin{aligned}\frac{\mathrm{dHR}}{\mathrm{d}t} &= k_{\mathrm{in\_HR}}\cdot(1-\mathrm{FB_{MAP}}\times\mathrm{MAP}) - k_{\mathrm{out\_HR}}\cdot\mathrm{HR}\\ \mathrm{HR}(0) &= \mathrm{HR_{base}}\end{aligned} \tag{4}$$

$$\begin{aligned}\frac{\mathrm{dTPR}}{\mathrm{d}t} &= k_{\mathrm{in\_TPR}}\cdot(1-\mathrm{FB_{MAP}}\times\mathrm{MAP}) - k_{\mathrm{out\_TPR}}\cdot\mathrm{TPR}\\ \mathrm{TPR}(0) &= \mathrm{TPR_{base}}\end{aligned} \tag{5}$$

$$\begin{aligned}\frac{\mathrm{dSV}}{\mathrm{d}t} &= k_{\mathrm{in\_SV}}\cdot(1-\mathrm{FB_{MAP}}\times\mathrm{MAP})\cdot E_{\mathrm{MC\_SV}}\cdot E_{\mathrm{BM\_SV}} - k_{\mathrm{out\_SV}}\cdot\mathrm{SV}\\ \mathrm{SV}(0) &= \mathrm{SV_{base}}\end{aligned} \tag{6}$$

$$\mathrm{MAP} = \mathrm{HR}\cdot\mathrm{TPR}\cdot\mathrm{SV} \tag{7}$$

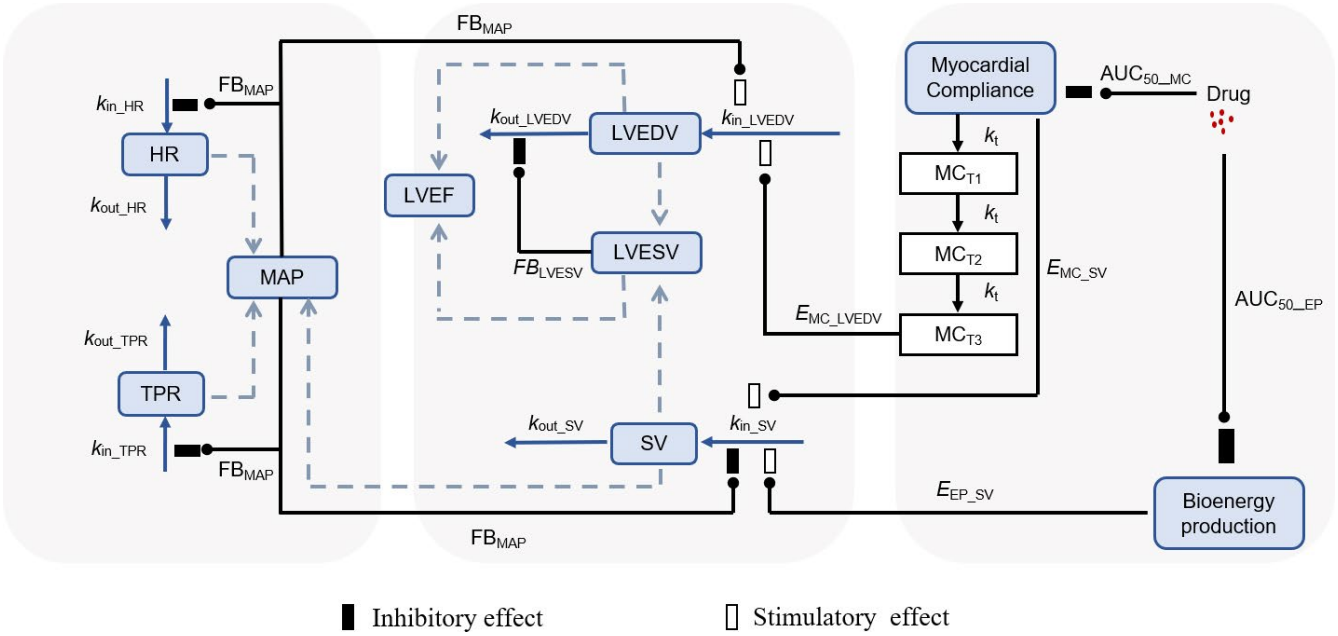

FIGURE 1 Schematic diagram of the quantitative system pharmacology–pharmacodynamic model. AUC_{50_EP}, area under curve of doxorubicin in heart tissue at half-maximal induction of energy production impairment; AUC_{50_MC}, area under curve of doxorubicin in heart tissue at half-maximal induction of myocardial compliance impairment; E_{EP_SV}, effect of energy production on production of SV; E_{MC_SV} and E_{MC_LVEDV}, effects of myocardial compliance on production of SV and LVEDV; FB_{LVESV}, feedback constant of LVESV on dissipation of LVEDV; FB_{MAP}, feedback constant of MAP on production of HR, TPR, LVEDV, and SV; HR, heart rate; k_{in_HR}, k_{in_TPR}, k_{in_LVEDV}, and k_{in_SV}, zero-order production rate constants of HR, TPR, LVEDV, and SV, respectively; k_{out_HR}, k_{out_TPR}, k_{out_LVEDV}, and k_{out_SV}, first-order dissipation rate constant of HR, TPR, LVEDV, and SV, respectively; k_t, transduction rate of myocardial compliance effects; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MAP, mean arterial pressure; MC_{T1}, MC_{T2}, and MC_{T3}, myocardial compliance effects in transit compartments 1, 2, and 3, respectively; SV, stroke volume; TPR, total peripheral resistance. Dashed lines indicate that arrow-pointed physiological parameters can be calculated by the parameters at the other end of lines. Lines ending in closed circles indicate an effect is being exerted. Open and solid boxes differentiate between stimulatory and inhibitory effects

$$FB_{MAP} = FB_{MAP\_0} \cdot \left(\frac{MAP_{base}}{MAP_0}\right)^{-1.98} \quad (8)$$

Myocardial contraction

Myocardial contraction is determined by both systolic function and diastolic function of cardiomyocytes, which are represented by bioenergy production and myocardial compliance. Bioenergy production determines the contractile ability of cardiomyocytes. Myocardial compliance denotes the passive stiffness of cardiomyocyte contraction and dilatation. Myocardial compliance influences SV for contraction damage as well as LVEDV for dilatation damage. Bioenergy production and myocardial compliance were set as one when the drug effect was absent.

PD model

Doxorubicin-induced cardiotoxicity has been reported to involve reduced energy production, cardiomyocyte death, and myocardial fibrosis,[17,18] which interferes with both systolic and diastolic function of myocytes. As the individual effect of doxorubicin on energy production and cardiomyocyte death was not estimated in this study, their cooperative effect on myocardial contractility was described with Equation (9). Doxorubicin-induced myocardial fibrosis could compromise myocardial compliance and lead to diastolic dysfunction. A transit compartment model was introduced to describe the toxic effect of doxorubicin on rats with reduced LVEDV. In rats with LVEDV enlargement, this transit model was ignored. Doxorubicin is reported to cause clinically cumulative dose-dependent cardiotoxicity.[19,20] Thus, the toxic effect of doxorubicin was evaluated by area under curve from time zero to dosing interval (AUC_{0-t}) of doxorubicin rather than concentration in the heart compartment.

$$E_{drug\_EP} = e^{-\frac{AUC_{0-t}^{h}}{\left(AUC_{0-t}^{h} + AUC_{50\_EP}^{h}\right)}} \quad (9)$$

$$\frac{dMC_{T1}}{dt} = \left(\frac{AUC_{0-t}}{AUC_{0-t} + AUC_{50\_MC}} - MC_{T1}\right) \cdot k_t \quad MC_{T1}(0) = 0 \quad (10)$$

$$\frac{dMC_{Ti}}{dt} = (MC_{T(i-1)} - MC_{Ti}) \cdot k_t \quad MC_{Ti}(0) = 0 \quad i = 2, 3 \tag{11}$$

$$E_{MC\_LVEDV} = 1 - MC_{T3} \tag{12}$$

$$E_{MC\_SV} = 1 - \frac{AUC_{0-t}}{AUC_{0-t} + AUC_{50\_MC}} \tag{13}$$

Clinical prediction of doxorubicin-induced cardiac dysfunction

Translation of model parameters from rat to human

The QSP-PBPK-PD model developed based on rats' data was then scaled up to humans to assess the translational ability and predictability of this model. The interspecies scaling of PK and the prediction of heart exposure to doxorubicin was conducted by our previously published physiologically based PK (PBPK) model.[21] In the QSP model, the physiological baseline, such as the initial values of LVEDV, HR, MAP, and SV, was directly replaced by human values[22] as shown in Table 1. Parameters describing the dissipation rate were estimated in rats and allometrically scaled to humans based on body weight (Equation 14):

$$\frac{k_{Rat}}{k_{Human}} = \left(\frac{Weight_{Rat}}{Weight_{Human}}\right)^r \tag{14}$$

where k_{Human} is the scaled human parameter, and k_{Rat} is the model-predicted parameter in rats. Standard body weights of 250 g and 70 kg were assumed for rats and humans, respectively. The standard allometric exponent for the rate constant was −0.25.[23–25] The feedback effects of MAP and LVESV were described by FB_{MAP} and FB_{LVESV}, respectively. FB_{MAP_0} was hypothesized to be constant across species because MAP baseline values were close in rats (106 mmHg) and humans (91 mmHg). FB_{LVESV} was scaled by LVESV baseline values (Table 1, Equation 15).

$$\frac{FB_{LVESV\_Rat}}{FB_{LVESV\_Human}} = \frac{LVESV_{0\_Human}}{LVESV_{0\_Rat}} \tag{15}$$

Cardiotoxicity prediction in both cardiovascular healthy patients and patients who have cardiovascular disease

In clinical practice, doxorubicin-induced cardiotoxicity was defined as a more than 10% decrease in LVEF from baseline, with the resting LVEF becoming abnormal (less than the institutional lower limit of normal, which is usually set at 50%).[20,26] As a reduction of ejection fraction is the critical criterion of doxorubicin-induced cardiac dysfunction in clinical practice, a PD model for doxorubicin-induced systolic dysfunction was used in a translational investigation. It is assumed that the sensitivity of myocytes to doxorubicin is identical in humans and rats according to cell viability results reported by Burridge et al. (median lethal dose [LD_{50}], 0.1643 μM) and Zhou et al. (LD_{50}, 0.1744 μM).[27,28] The PD parameter (AUC of doxorubicin in heart tissue at half-maximal induction of energy production impairment [AUC_{50_EP}]) estimated from rats was directly used in the human PD model.

Virtual clinical studies were conducted to predict the probability of cardiotoxicity incidence after doxorubicin therapy. Virtual patients were generated by Monte Carlo simulations of the physiological baseline values with 30% variations (Table 1).[21] To compare the differences in doxorubicin-induced cardiotoxicity, the enrolled virtual patients were classified into healthy and disease groups according to their cardiovascular status. Patients with LVEDV indexed to body surface area ≥81.5 ml m^{-2}[29] were considered to have enlarged LVEDV and MAP ≥115 mmHg (systolic pressure ≥140 mmHg, diastolic pressure ≥90 mmHg) as hypertension. Changes in LVEF during 1 year were simulated after infusion of varied doses of doxorubicin every 3 weeks. According to the criteria of doxorubicin-induced cardiotoxicity as mentioned previously, the percentage of patients with LVEF reduced 10% from baseline was considered as the probability of cardiotoxicity incidence under the treated dose. The simulated rate of cumulative dose–cardiac dysfunction incidence result was compared with the reported incidences of doxorubicin-induced cardiotoxicity to validate the developed QSP-PK-PD model.[25]

Sensitivity analysis

Sensitivity analysis was conducted to assess the impacts of cardiomyocyte sensitivity to doxorubicin and preexisting cardiovascular disease on drug-induced cardiotoxicity. A nine-folder range was simulated for AUC_{50_EP} as the sensitivity of cardiomyocytes to doxorubicin showed such a range in a previous study.[27]. The following three types of patients with cardiovascular disease were simulated based on a 50% variation of baseline values in LVEDV (113–180 ml) and MAP (91–150 mmHg): (1) hypertension combined with LVEDV enlargement, (2) isolated LVEDV enlargement, and (3) isolated hypertension.

TABLE 1 Parameters of the rat and human quantitative system pharmacology–pharmacodynamic models

Parameter	Unit	Description	Value in rat	Value in human	CV (%)	Source/Reference	Scaling
SV_0	ml	Typical value of baseline stroke volume value	0.3	65/115	30	[16,22]	Cardiovascular healthy/diseased human baseline value used
$LVEDV_0$	ml	Typical value of baseline left ventricular end-diastolic volume value	0.385	113/141	30	[16,22]	Cardiovascular healthy/diseased human baseline value used
HR_0	beats·h^{-1}	Typical value of baseline heart rate value	423	70	30	[16]	Actual human baseline value used
TPR_0	mmHg·h·ml^{-1}	Typical value of baseline total peripheral resistance value	0.84	0.02/0.025	30	[16]	Cardiovascular healthy/diseased human baseline value used
Weight	kg	Body weight of subjects	0.25	70	30	Assumed	Actual human baseline value used
Height	m	Height of subjects	–	1.65	30	Assumed	Actual human baseline value used
FB_{MAP_0}	mmHg^{-1}	Feedback of MAP on HR, TPR, and SV	2.9×10^{-3}	2.9×10^{-3}	–	[16]	Constant across species
FB_{LVESV}	ml^{-1}	Feedback of LVESV on LVEDV	1.43	2.532×10^{-3}	12.4	Estimated in rat/ scaled in human	Allometrically scaled
k_{out_SV}	h^{-1}	Dissipation rate constant of SV compartment	0.126	0.0308	–	[16]	Allometrically scaled
k_{out_LVESV}	h^{-1}	Dissipation rate constant of LVEDV compartment	0.126	0.0308	–	[16]	Allometrically scaled
k_{out_HR}	h^{-1}	Dissipation rate constant of HR compartment	11.6	2.83	–	[16]	Allometrically scaled
k_{out_TPR}	h^{-1}	Dissipation rate constant of TPR compartment	3.58	0.875	–	[16]	Allometrically scaled
AUC_{50_EP}	mg·h·ml^{-1}	AUC of doxorubicin in heart tissue at half-maximal induction of energy production impairment	1390	1390	7.06	Estimated in rat	Constant across species

Abbreviations: AUC, area under curve; CV, coefficient of variation; HR, heart rate; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; MAP, mean arterial pressure; SV, stroke volume; TPR, total peripheral resistance.

Data analysis and simulation

Model parameters were jointly optimized by population approach using the stochastic approximation expectation maximization algorithm in Monolix (Version 2018R1; http://lixoft.com/products/monolix/). All simulations were conducted by using Berkeley Madonna (Version 8.3.23; http://www.berkeleymadonna.com/). Details of the data analysis and simulation are summarized in the Supplementary Material.

RESULTS

Cardiotoxicity of doxorubicin on rats with/without cardiovascular disease

As shown in Table S2, blood supply by heart was reduced in rats with cardiovascular disease. Compared with the control group, reduced LVEF (4% and 7%) and enlarged LVEDV (23.1 μl and 31.1 μl) were observed in myocardial hypertrophy and spontaneously hypertensive rats before doxorubicin treatment. After doxorubicin treatment, cardiac function reached the nadir on the eighth day when 3.5%, 12.1%, and 10.4% of LVEF were reduced in healthy, myocardial hypertrophy, and spontaneously hypertensive rat groups, respectively. Fifteen days later, LVEF was completely or partially recovered in all three doxorubicin-treated groups accompanied by an enlarged LVEDV. These results suggested that diastolic dysfunction was induced by doxorubicin administration.

Rat QSP-PK-PD model development and validation

After estimating the PK model to describe doxorubicin exposure in the heart (detailed information is provided in the Supplementary Material), parameters in the QSP and PD models were concurrently estimated based on data from three reported studies and three in-house studies. The developed QSP-PK-PD model extensively incorporated prior knowledge of doxorubicin-induced cardiotoxicity to determine the interaction between drug effect and systemic response. The optimized PK parameters are listed in Table S4, whereas the QSP and PD model parameters are listed in Table S5. As shown in Figures 2 and S3, the developed QSP-PK-PD model adequately captured the changes in LVEF, LVEDV, LVESV, and MAP under different doxorubicin dosing regimens.

In the developed QSP model, four turnover equations were used to describe the changes of LVEDV, SV, HR, and TRP, and their interactions to maintain the homeostasis of the cardiovascular system. The experimentally determined values of LVEDV, SV, HR, and TRP before doxorubicin treatment were used as the initial values of these parameters. The dissipation rate constants of TPR, LVEDV, and HR as well as the feedback effects of MAP on HR, TPR, and SV were adapted from a previous study by Snelder et al.[16] Finally, three systemic parameters were optimized (Table S4). FB_{LVESV} describes the feedback of LVESV on LVEDV and was estimated as 1.43. The effect of reduced myocardial compliance on LVEDV change was described by a transit model with the transit rate constant k_t equaled 0.021 h^{-1} because of the delayed progression of myocardial hypertrophy.

In the PD model, doxorubicin was considered to affect both myocardial contraction and compliance. The Hill model was used to describe the effect of doxorubicin on the generation of energy production and myocardial compliance. In both models, the maximal effect was set as one. The Hill coefficient was manually tuned to describe the exposure–effect relationship of doxorubicin on bioenergy production ($h = 3$) and myocardial compliance ($h = 1$). AUC_{50_EP} and AUC_{50_MC} are the drug exposure at 50% of maximal drug impairment on bioenergy production and myocardial compliance. These two parameters were estimated as 1390 and 1704 $mg{\cdot}h{\cdot}ml^{-1}$ with good precision (relative standard errors were estimated as 7.06% and 14.5%), respectively. The lower value of AUC_{50_EP} compared with AUC_{50_MC} suggested that bioenergy production is the more prevalent mechanism of doxorubicin-induced cardiotoxicity.

Incidence of cardiac event simulations in humans

With interspecies scaling of the QSP and PD model parameters and incorporation of the reported PBPK model, a translational QSP-PK-PD model was established to predict doxorubicin-induced cardiotoxicity in humans. Overall, 13,994 virtual patients were simulated with the Monte Carlo approach, including 5395 patients with and 8599 patients without cardiovascular comorbidity. Using their own baselines of cardiovascular state, the variation of LVEF in humans was simulated following doxorubicin treatment with a cumulative dose range from 120 to 900 mg m^{-2}, which is generally within the clinically applied dosage of doxorubicin.[19,20,22,26] Figure S4 shows the simulated LVEF changes from the baseline of virtual patients for different doses. Rates of doxorubicin-induced cardiac events versus cumulative doxorubicin dose in virtual patients with or without preexisting cardiovascular disease are depicted in Figure 3. As expected with anthracycline, the incidence of doxorubicin-induced cardiac dysfunction increased with

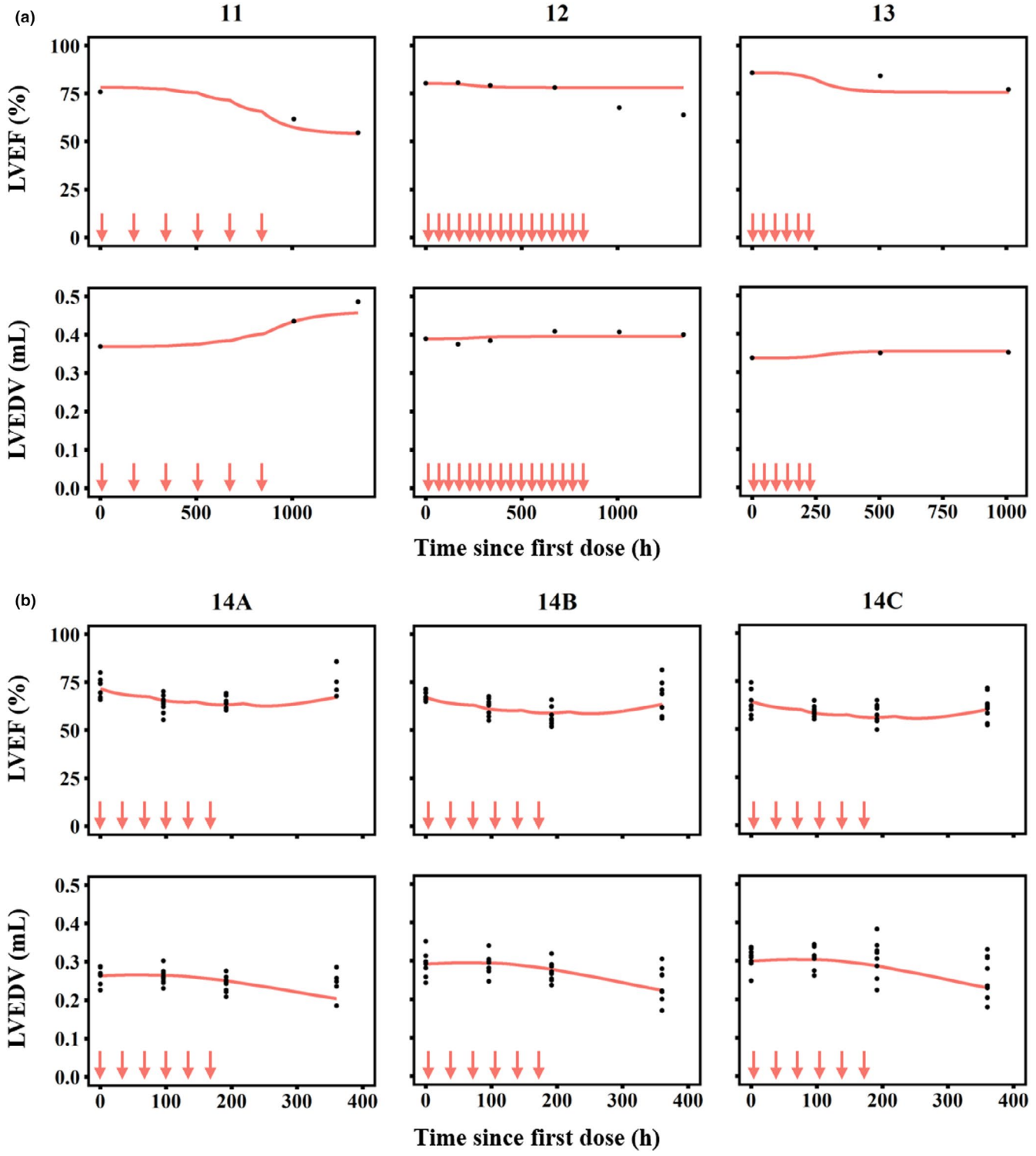

FIGURE 2 Model fittings for LVEF and LVEDV in rat. (a) Plots of model predictions in systolic dysfunction rats. (b) Plots of model predictions in diastolic dysfunction rats. Red lines indicate predictions of LVEF and LVEDV, black points indicate observations, and red arrows indicate the dosing time points. LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction

the cumulative dose of drug administration. The probability of developing drug-induced cardiac dysfunction versus the total dose of doxorubicin was higher in patients with previous myocardial hypertrophy or hypertension compared with cardiovascular healthy patients. The model performance is verified against the reported incidence of doxorubicin-induced cardiac dysfunction.[26] The simulated probability of developing drug-induced cardiac dysfunction was slightly lower than the reported incidence in both patients with and without preexisting cardiovascular

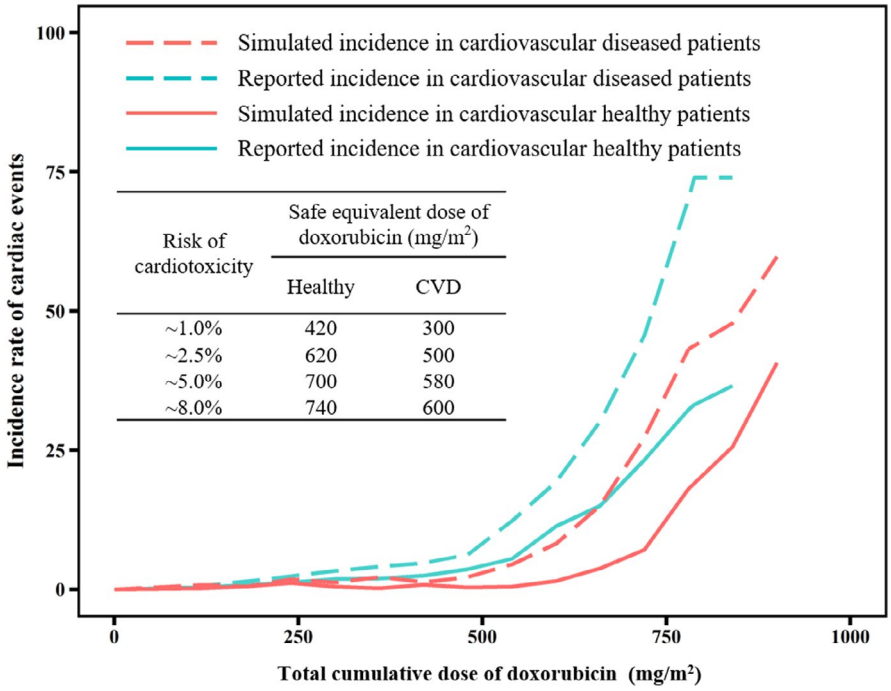

FIGURE 3 Simulated and reported cumulative probability of developing doxorubicin-induced cardiac dysfunction versus total cumulative dose of doxorubicin for cardiovascular healthy patients or patients who have cardiovascular disease. Healthy indicates cardiovascular healthy patients, and CVD indicates patients with preexisting cardiovascular diseases. CVD, cardiovascular disease

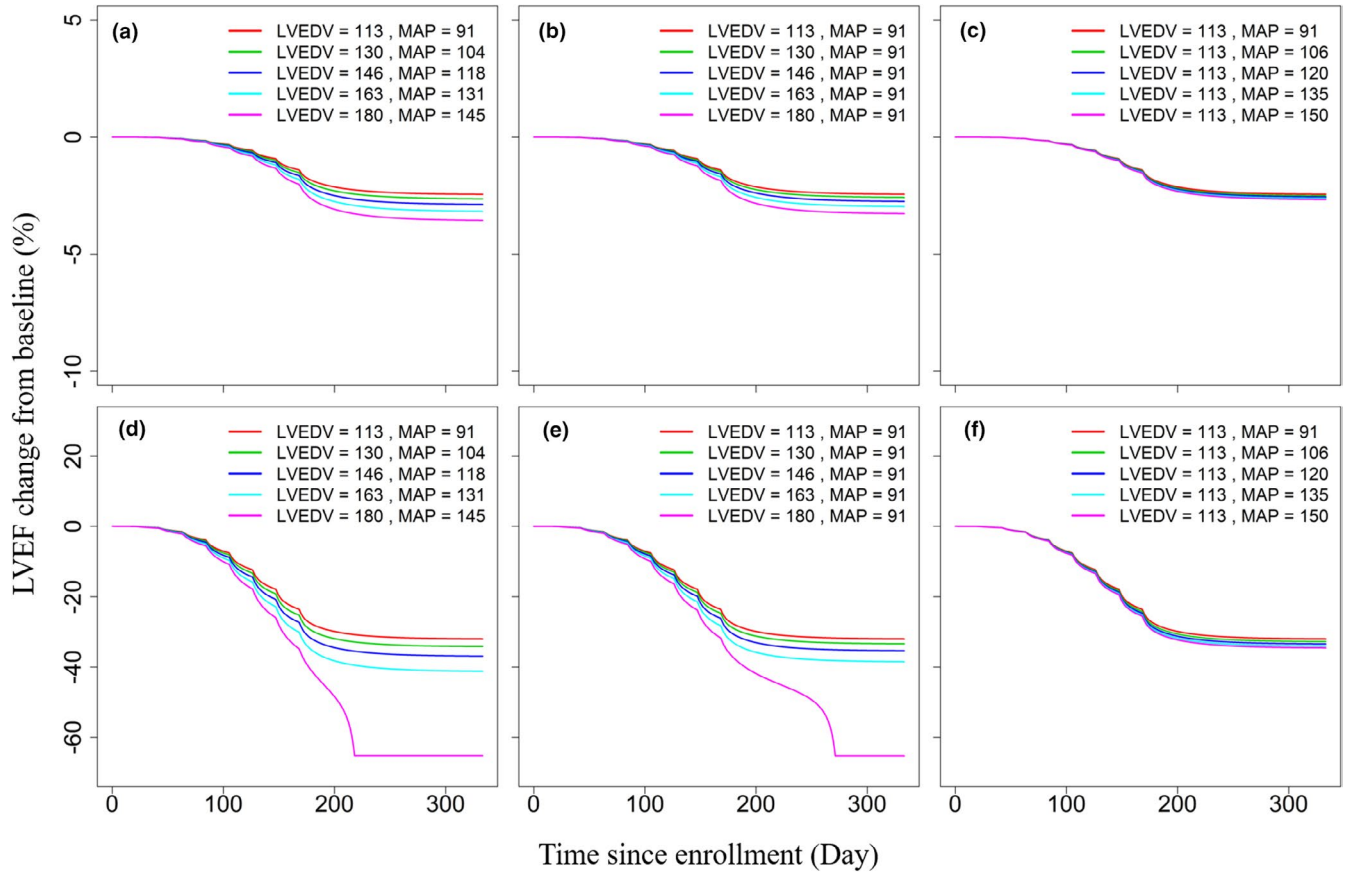

FIGURE 4 Sensitivity analysis of baseline values of MAP and LVEDV on LVEF decrease percentage. (a–c) Sensitivity of LVEDV and MAP baseline values in patients insensitive to doxorubicin-induced cardiotoxicity. (d–f) Sensitivity of LVEDV and MAP baseline values in patients sensitive to doxorubicin-induced cardiotoxicity. LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; MAP, mean arterial pressure

disease. The predicted difference of doxorubicin-induced cardiotoxic risk between these two populations is consistent with clinical observation.

Here, we propose a mechanism-based approach for quantification of the safe-equivalent dose in patients with preexisting cardiovascular diseases as demonstrated in Figure 3. Safe-equivalent doses for patients with preexisting cardiovascular disease were calculated by comparing incidence rates of cardiac events with that of cardiovascular healthy patients. For instance, the incidence of cardiac events was estimated as 2.5% for cardiovascular healthy patients when 620 mg m^{-2} of doxorubicin was applied. Under the same incidence of cardiac events (2.5%), a safe-equivalent dose of 500 mg m^{-2} was calculated for patients with preexisting cardiovascular diseases according to the established QSP-PK-PD model.

Sensitivity analysis

As shown in Figure S5, doxorubicin-induced cardiotoxicity is highly related to AUC_{50_EP}, a parameter reflecting the sensitivity of cardiomyocytes to doxorubicin. LVEF reduction increased from 5% to 32% of baseline when AUC_{50_EP} decreased from 1390 to 463.3 mg·h·ml^{-1}. Figure 4 suggests that patients with cardiovascular comorbidities could suffer more reduction of LVEF after doxorubicin treatment, and this change is cardiovascular disease dependent. Patients with both enlarged LVEDV and hypertension (Figure 4a,d) suffered more serious cardiotoxicity compared with those with enlarged LVEDV (Figure 4b,e). Blood pressure was the least sensitive factor affecting doxorubicin-induced cardiotoxicity (Figure 4c,f). Moreover, the sensitivity analysis also suggested that the influence of cardiovascular comorbidities is greater in patients who are more sensitive to doxorubicin.

DISCUSSION

Currently, iatrogenic cardiovascular disease has emerged as a hindrance to expanding the lifetime of cancer survivors by interrupting anticancer treatment.[3] In addition to conventional cytotoxic agents, unexpected cardiotoxicity is also reported in the clinical application of novel cancer therapeutics, such as tyrosine kinase inhibitors, immunotherapies, and proteasome inhibitors.[30,31] To reduce the risk of cardiovascular complications in cancer therapy, cardio-oncology services have emerged to optimize the treatment approach with safe and effective anticancer therapy. With cardio-oncology services, patients with cancer will be stratified into different subgroups before receiving cardiotoxic agents and then treated with a modified treatment approach.[32] Despite the risk stratification, a safe dose range for patients with cardiotoxic risk is also required to minimize cardiotoxicity in cancer therapy. However, patients with prior cardiovascular disease are usually excluded from clinical trials. The safe dose range for this subpopulation is usually unknown, resulting in empirical dosing modifications in patients with cardiotoxic risk.

The present study developed a translational QSP-PK-PD model to identify the safe-equivalence dose of doxorubicin among patients under different cardiovascular statuses, which provides a paradigm to predict the safe dose range for patients with cardiovascular comorbidity. Cardiotoxicities stemming from cancer therapy are usually expressed as myocardial injury, cardiac dysfunction, and heart failure.[33] Reduced blood supply by the heart is usually observed in cancer therapy–induced cardiotoxicity. Preload, afterload, and myocardial contraction are three determinants of blood supply by the heart. They interact with each other to maintain the homeostasis of the cardiovascular system and sufficient blood supply under the control of nervous and endocrine systems. Changes of any determinants in patients can disrupt the homeostasis of the cardiovascular system and make the heart more sensitive to cardiotoxic drugs. System pharmacology is proposed to depict the dynamic response of an entire system to a particular stimulus because the system is governed by the collective responses of all components rather than an isolated identity.[34] The detailed physiologic processes of blood supply and pathologic processes of left ventricular systolic or diastolic dysfunction are described by integrally quantifying the interactions between preload, afterload, and myocardial contraction in a QSP model. To capture the homeostasis of cardiovascular system under complex feedback mechanisms, indirect response models were used to describe the physiological turnover processes of SV, LVESV, HR, and TPR. As these functions are biologic substance and structure based, their production or dissipation rates are determined by the turnover rates of biologic substances and/or structures. In interspecies scaling, an allometric exponent of −0.25 has been successfully applied to translate the dissipation rates of biological substances or elimination rate of xenobiotics from rats to human.[23–25] Therefore, the current study applied this translational approach to scale up the dissipation rates of SV, LVESV, HR, and TPR. The well predicted doxorubicin-induced cardiotoxicity verified that this approach was acceptable for clinical translation of the developed QSP model. QSP model parameters are systemic-specific parameters that could be ideally used to predict the drug efficacy of other cardiotoxic compounds. However, only doxorubicin was applied as tool drug to develop the QSP-PK-PD model in current study. It is a major limitation that the estimated QSP model parameters have not been

validated by other cardiotoxic compounds. Hence, the QSP model parameters are required to be validated by multiple compounds when the model is used to predict cardiotoxicity in new drug development. Moreover, the current QSP-PK-PD model is mainly developed to investigate the cardiotoxicity of cytotoxic drugs. Novel mechanisms and related parameters should be incorporated into the QSP model to predict the efficacy for compounds with cardiotoxic mechanisms differ from cytotoxin.

Compared with a conventional PK-PD model, a major advantage of QSP model integration is the distinguish of drug effect from disease progression, which is the cornerstone to estimate the safe-equivalent dose in patients with preexisting cardiovascular diseases. In sensitive analysis, cardiotoxicity was positively related to the enlarged LVEDV and/or elevated blood pressure, suggesting the developed QSP-PK-PD model was applicable to distinguish the disease progression from drug-induced cardiac injury and could be used to predict the safe-equivalent dose for patients with cardiovascular comorbidities. According to the developed QSP-PK-PD model, a reduction dose of 120 mg m^{-2} doxorubicin would be applicable in clinical practice to ensure equivalent safety for patients with preexisting cardiovascular diseases compared with cardiovascular healthy patients. Such a dose-reduction strategy is similar to that recommended by Alexander et al.[35] Their study indicated that for patients receiving doxorubicin therapy, left ventricular performance should be monitored at 500 mg m^{-2} in patients without underlying heart disease or at 400 mg m^{-2} in patients with known heart disease.

A major limitation of current QSP-PK-PD model in cardiotoxicity prediction is the underestimation of doxorubicin-induced cardiotoxicity for patients with preexisting cardiovascular diseases in dose ranges of more than 780 mg m^{-2}, which is much higher than the recommended safe dose of 550 mg m^{-2} in clinical practice.[19,20,22,26] One of the reasons for this underestimation may be the overestimation of baseline cardiac function in this population. To simplify the model, the baseline of myocardial contraction, a critical but inconveniently determined factor, were considered normal in all simulated patients, although it might only be applied to cardiovascular healthy patients. Another potential reason may be the high uncertainty in reported incidence of cardiac event as the sample size was extremely small. The reported incidence was calculated from six patients at 781 mg m^{-2}, five patients at 879 mg m^{-2}, and even less at higher doses.[26] To improve the predictive ability of our QSP model, the determination of biomarker levels would be helpful. For instance, cardiac troponin I and T are the gold standard biomarkers of cardiac injury, brain natriuretic peptide and N-terminal pro-B type natriuretic peptides are usually used to indicate increased transmural tension, and galectin-3 could be used to evaluate cardiac fibrosis.[33] Variations of these biomarkers are more sensitive to drug-induced cardiac injury than LVEF. Yet further studies are required to reveal the quantitative relationships between these biomarkers and myocardial contraction.

Apart from the prediction of a safe dose range of cardiotoxic agents in cancer therapy, the current QSP-PK-PD model also has potential for cardiotoxicity prediction in drug development. Although the cardiotoxicity of drug candidates has been tested in drug development, cardiac toxicity remains one of the major reasons for drug withdrawal.[36] One explanation for this is that cardiotoxicity is hidden in current animal models for toxicity tests and in patients without preexisting cardiovascular disease.[5] In the current study, rats with and without cardiovascular disease were used as the preclinical models to evaluate doxorubicin-induced cardiotoxicity using LVEF and LVEDV as biomarkers. Our results showed more LVEF reduction and LVEDV enlargement in rats with hypertension and myocardial hypertrophy, demonstrating that the cardiotoxicity of doxorubicin is hidden in a healthy rat model. With the translational QSP-PK-PD model, the hidden cardiotoxicity of doxorubicin was predicted in patients with cardiovascular comorbidities based on preclinical studies and validated using clinical results. Thus, the current study also provided a novel cardiac safety testing platform to evaluate hidden cardiotoxicity, at least in patients with hypertension and myocardial hypertrophy.

In conclusion, the present study developed a mechanism-based QSP-PK-PD model to capture the progression of drug-induced cardiac dysfunction. According to our analysis, preexisting cardiovascular disease could increase the risk of drug-induced cardiotoxicity. The developed QSP model integrally quantifies the effect of a drug and the cardiovascular disease/risk factor on the pathophysiological processes in the biological system, which provide an *in silico* tool to evaluate the patient-specific tolerance dose to cardiotoxic drugs.

CONFLICT OF INTEREST

The authors declared no competing interests for this work. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

AUTHOR CONTRIBUTIONS

L.S., Y.Y., and H.H. wrote the manuscript. L.S., K.H., and H.H. designed the research. L.S. and Y.Y. performed the research. Y.Z., Z.Z., and M.J. analyzed the data. Y.Z., X.L., K.H., and H.H. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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