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Model-Based Estimation of Blood Pressure Response to Epinephrine

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Abstract— **In this study, we present a model-based approach to estimation of blood pressure (BP) response to epinephrine. The proposed approach estimates systolic (SBP), mean (MAP) and diastolic (DBP) BP based on a 2-parameter windkessel (WK) model with dose-dependent total peripheral resistance (TPR), arterial compliance (AC) and stroke volume (SV) indices that is driven by the epinephrine dose, heart rate (HR). Using the epinephrine dose and hemodynamic response data collected for young/old normotensive and hypertensive subject groups, four group-specific models as well as a generalized model were developed and then were evaluated for BP estimation performance. The results indicated that the group-specific model is superior to its generalized counterpart; on average, the root-mean-squared SBP, MAP and DBP estimation errors associated with the group-specific model were only 34%, 52% and 69%, respectively, compared with the generalized model.**

I. Introduction

Hemodynamic variables of patients in critical care units must be carefully monitored and regulated using drug administrations to maintain hemodynamic stability and prevent potential physiologic complications. Among a variety of drugs administered to keep patient's hemodynamic stability is epinephrine, which is a catecholamine drug that is widely used to improve HR (chronotropic effect), cardiac contractility (inotropic effect) and arterial BP (vasoconstrictive effect). The ability to predict a patient's specific hemodynamic responses to drug administrations, including epinephrine, can contribute to better regulate the patient's hemodynamic variables and also to reduce the workload of personnel in the critical care units Consequently, developing methodologies and systems to estimate patient-specific hemodynamic response to drug administration can significantly benefit both the patient and the clinical personnel.

Despite its apparent importance, the amount of existing research on quantitative relationship between catecholamine drugs (especially epinephrine) and hemodynamic variables is seriously limited. Görges et al. [1] identified patient-specific sensitivity to administration of sodium-nitroprusside, dopamine and dobutamine using an adaptive filter approach and concluded that identifying each individual patient's sensitivity could improve BP prediction accuracy. Chase et al. [2] developed a method to predict hemodynamic responses to epinephrine administration based on a model of cardiovascular system and showed that BP and SV could be predicted with acceptable accuracy. However, the study did not consider the differences in response among different patient populations; instead, they used a model tuned using data obtained from a particular patient group and used it to predict hemodynamic response of general population. Gingrich and Roy [3] developed a descriptive incremental nonlinear single-input-multi-output model relating cardiac output (CO) and MAP to dopamine administration to demonstrate that the presence of heart failure largely affects the hemodynamic response to dopamine. Johnston et al. [4] compared pharmacokinetics and pharmacodynamics of dopamine and norepinephrine in critically ill head-injured patients and showed that dopamine pharmacodynamics had potential to predict CO and TPR but not useful to predict MAP, whereas norepinephrine did not show any meaningful correlation with CO, TPR and BP. MacGregor et al. [5] claimed that administration of dopamine based on body weight was not useful for pharmacodynamics predictions. They also found that plasma dopamine concentration can exhibit a large inter-individual variability. In essence, although there have been some attempts to relate catecholamine drug doses (including epinephrine) to several hemodynamic variables, systematic and model-based attempt to predict subject-specific hemodynamic responses to catecholamine drugs, such as epinephrine, in human subjects is very rare.

In this study, a model-based approach to estimation of BP response to epinephrine is presented. The proposed approach estimates SBP, MAP and DBP based on a 2-parameter WK model with dose-dependent TPR, AC and SV indices that is driven by the epinephrine dose and HR. Using the epinephrine dose and hemodynamic response data collected for young/old normotensive and hypertensive subject groups, four group-specific models as well as a generalized model were developed and then were evaluated for BP estimation performance.

II. Methods

A. Data

We used data published in previous literature [6,7], which include hemodynamic responses of 14 normotensive young (NY; 30+/-2yr) and 18 normotensive old (NO; 60+/-2yr) subjects as well as 10 hypertensive young (HY; 36+/-1yr) and 17 hypertensive old (HO; 59+/-1yr) subjects. Normotensive and hypertensive BP were defined as <130mmHg SBP & 85mmHg DBP and >140mmHg SBP & 95mmHg DBP, respectively. Following a rest period of at least 60min, epinephrine was administered at 20ng/kg/min and then was increased to 40, 80, 120 and 160ng/kg/min. Each dose was administered for 8min. HR, BP (SBP, MAP and DBP) and SVI were measured at steady state before epinephrine administration and during

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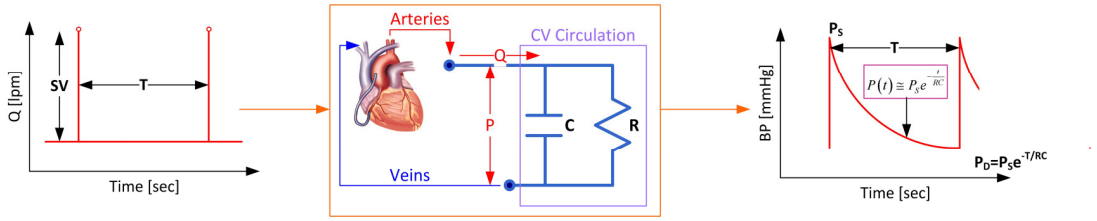

Fig. 1. 2-parameter WK model.

the last 2-3min at each dose. HR and SVI were measured using echocardiography, whereas BP was measured using an automatic arm BP cuff.

Group-averaged hemodynamic response data to epinephrine administration were extracted and used in our modeling study. In the absence of individual subject data, inter-individual variability in the hemodynamic responses reported in the original literature was ignored.

B. Model Development

In this study, we developed a low-order physiology-based model to estimate BP response to epinephrine administration. The model can estimate SBP, MAP and DBP responses by using HR and epinephrine dose as inputs. Specifically, we used the 2-parameter WK model [8,9] whose TPR, AC and SV parameters are dependent upon the epinephrine dose, so that epinephrine's inotropic and vaso-constrictive effects on cardiovascular system can be readily reproduced. In this preliminary study, the dependence of TPR, AC and SV parameters on epinephrine dose was modeled into low-order (2^{nd}-order) polynomials. Using the data described in Section II(A), model was developed for each individual group (NY, NO, HY, HO). Moreover, a generalized model (GM) was developed using the hemodynamic response data averaged over all groups.

Fig. 1 shows the 2-parameter WK model. Its mathematical expression is given by:

$$\frac{dP(t)}{dt} = -\frac{1}{RC}P(t) + \frac{1}{C}HR \cdot \delta V \tag{1}$$

where R, C and δV represent TPR, AC and SV, respectively. Since SVI [7] rather than SV is used in this study, (1) is re-written as follows:

$$\frac{dP(t)}{dt} = -\frac{1}{\bar{R}\bar{C}}P(t) + \frac{1}{\bar{C}}HR \cdot \delta \bar{V} \tag{2}$$

where $\delta \bar{V}$ is SVI, and $\bar{R}$ (in mmHg·min·m^2/l) and $\bar{C}$ (in ml/mmHg/m^2) are defined as TPR index (TPRI) and AC index (ACI), respectively. Solving (2) for BP yields

$$P(t) = P_d e^{-\frac{t}{\bar{R}\bar{C}}} + \frac{\delta \bar{V}}{\bar{C}} e^{-\frac{t}{\bar{R}\bar{C}}} \tag{3}$$

Noting that epinephrine has chronotropic, inotropic and vaso-constrictive effects on cardiovascular system, we modeled the parameters SVI, TPRI and ACI in (3) as functions of epinephrine dose. In this study, a simple polynomial dose-dependence was examined:

$$\theta = \sum_{i=0}^{N} \eta_i u^i \tag{4}$$

where $\theta \in \{\text{SVI, TPRI, ACI}\}$ is a polynomial function of the epinephrine dose (i.e. infusion rate) u, and N is the order of the polynomial. From (3)-(4), the following relationships between BP versus TPRI and ACI are obtained:

$$P_m = \bar{R} \cdot HR \cdot \delta \bar{V} \tag{5.1}$$

$$P_d = P_s e^{-\frac{T}{\bar{R}\bar{C}}} \tag{5.2}$$

$$(P_s - P_d)\bar{C} = \delta \bar{V} \tag{5.3}$$

where P_s, P_m and P_d are SBP, MAP and DBP, respectively, and $T = \frac{1}{HR}$ is the heart period.

C. Model Parameter Estimation

Using the hemodynamic response data for different epinephrine doses, the dose-dependent WK model was developed for each subject group (group-specific model) as well as for all subject groups (generalized model). In the parameter estimation process, we used hemodynamic response data for 0ng/kg/min (baseline), 80ng/kg/min and 160ng/kg/min doses.

For each subject group, BP (including SBP, MAP and DBP; these are the desired outputs of the model) as well as HR and SVI data were used to determine the values of TPRI and ACI that can best estimate SBP, MAP and DBP values for a given epinephrine dose (i.e. 0ng/kg/min, 80ng/kg/min or 160ng/kg/min). For this purpose, the following multi-objective parameter optimization problem was formulated using the relationship between BP versus TPRI and ACI (5) to minimize worst-case errors:

$$\{\bar{R}^*, \bar{C}^*\} = \arg\min J(\bar{R}, \bar{C}) = \arg\min\{\|w_1 F_1 \quad w_2 F_2 \quad w_3 F_3\|_\infty\} \tag{6}$$

where $\bar{R}^*$ and $\bar{C}^*$ are optimal TPRI and ACI for a given epinephrine dose, and $F_i = F_i(\bar{R}, \bar{C})$, $i = 1,2,3$ are specified as follows:

$$F_1(\bar{R}, \bar{C}) = \delta \bar{V} - \bar{C} \cdot P_s \left(1 - e^{-\frac{T}{\bar{R}\bar{C}}}\right) \tag{7.1}$$

$$F_2(\bar{R}, \bar{C}) = \delta \bar{V} - \bar{C} \cdot P_d \left(e^{\frac{T}{\bar{R}\bar{C}}} - 1\right) \tag{7.2}$$

$$F_3(\bar{R}, \bar{C}) = HR \cdot \delta \bar{V} \cdot \bar{R} - P_m \tag{7.3}$$

In this study, we used the differential evolution (DE) algorithm [10] to solve the optimization problem (6), which is a derivative-free optimization method that is

suited for problems with real-valued, multi-modal and continuous-valued cost functions. During the optimization, the weights w_i, $i = 1,2,3$ were adjusted for each subject group so that estimation errors for SBP, MAP and DBP were balanced, i.e. close in magnitude. Once the optimal values of TPRI and ACI for the three epinephrine doses considered were estimated by solving (6), they were curve-fitted using (4) to yield dose-dependent TPRI and ACI as 2nd-order polynomial functions of epinephrine dose. In addition, SVI was also modeled as a 2nd-order polynomial of epinephrine dose so that the resultant dose-dependent 2-parameter WK model can estimate BP solely based on HR and epinephrine dose measurements.

In order to develop a generalized model that incorporates hemodynamic response data of all subject groups, the hemodynamic response data (i.e. HR, SVI, SBP, MAP and DBP) were averaged over all groups, and the resultant response data thus obtained were used to determine SVI, TPRI and ACI (which are representative of all the groups) as 2nd-order polynomial functions of epinephrine dose by solving the optimization problem (6) as described above.

D. Model-Based Blood Pressure Estimation

In order to assess the model's efficacy to estimate BP, we used the hemodynamic response data to all available epinephrine doses (0, 20, 40, 80, 120 and 160ng/kg/min). The fidelity of both group-specific and generalized models was evaluated.

For each of the five models developed (four group-specific plus generalized models), BP was estimated using HR and epinephrine dose as the only inputs to the model, considering that they are easy measurements that can be readily accessed in real clinical practice. Based on the errors between measured versus estimated BP responses obtained for all six epinephrine doses, the root-mean-squared errors (RMSE) and the maximum absolute errors (MXAE) between measured versus estimated BP values were calculated to quantify the predictive capability of the developed models.

One of our particular interests was to examine the potential benefit of using group-specific model over generalized model. It is expected that group-specific model will outperform its generalized counterpart, but to the best of our knowledge, the degree of improvement has never been investigated in existing studies. For this purpose, we compared each of the group-specific models against the generalized model in estimating BP response of the underlying group (e.g. we compared the NY-group-specific model and the generalized model in estimating SBP, MAP and DBP responses of NY group).

III. Results and Discussion

A. Generalized and Group-Specific Models

The polynomial-approximated SVI, TPRI and ACI parameters are compared for group-specific and generalized models in Fig. 2, which clearly indicates that the generalized model is expected to exhibit limited efficacy in estimating SVI, TPRI and ACI of all the subject groups (in particular, NY and NO groups for SVI, and NY and HO groups for TPRI and ACI).

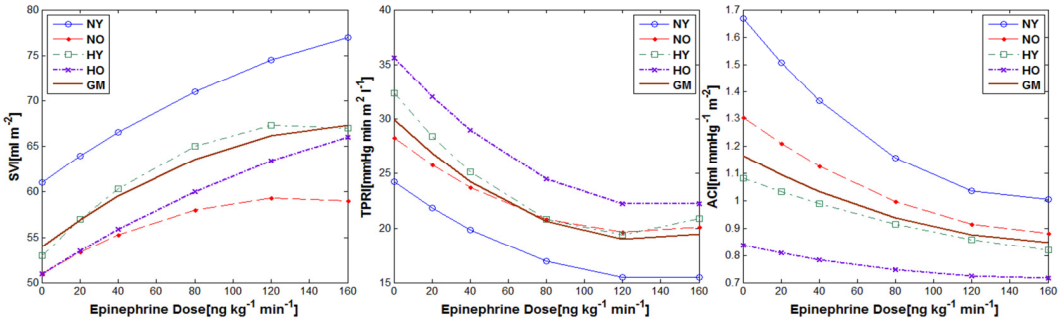

Fig. 2. Dose-dependence of physiologic parameters (SVI, TPRI and ACI) in the WK model in individual subject groups modeled as 2nd-order polynomial.

TABLE I. BP Estimation Errors Of Group-Specific And Generalized Models Using HR And Epinephrine Dose Measurements. Group: Subject Group Whose BP Response Was Estimated; Model: Group-Specific (NY, NO, HY, HO) Or Generalized (GM) Model Used To Estimate BP Response; RMSE: Root-Mean-Squared Error; MXAE: Maximum Absolute Error; The Values In The Parentheses Represent Improvement (Positive) Or Deterioration (Negative) Of Errors In Comparison To The Group-Specific Model Of The Underlying Subject Group.

Group	Model	MAP [mmHg]		SBP [mmHg]		DBP [mmHg]	
		RMSE	MXAE	RMSE	MXAE	RMSE	MXAE
NY	NY	4.5	7.8	4.6	7.9	4.6	9.0
	GM	12.0 (-167%)	16.0 (-105%)	10.2 (-122%)	15.6 (-98%)	3.7 (20%)	6.0 (33%)
NO	NO	3.8	6.1	3.9	6.1	3.8	6.9
	GM	12.7 (-234%)	16.3 (-167%)	11.8 (-203%)	15.6 (-156%)	4.3 (-13%)	6.5 (5.8%)
HY	HY	4.6	7.4	4.8	8.4	4.8	7.8
	GM	2.8 (39%)	4.4 (41%)	11.0 (-129%)	13.8 (-64%)	8.3 (-73%)	11.2 (-44%)
HO	HO	6.1	10.5	6.1	12.6	6.0	11.0
	GM	8.9 (-46%)	14.6 (-39%)	23.7 (-289%)	30.8 (-144%)	11.7 (-95%)	17.4 (-58%)

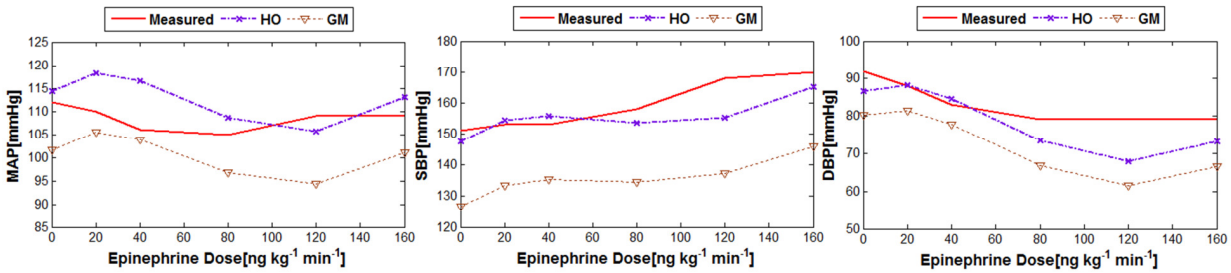

Fig. 3. Estimation of BP response of HO subject group with group-specific generalized models using HR and epinephrine dose measurements. Measured: measured (actual) HO data; HO: BP of HO subject group estimated with HO group-specific model; GM: BP of HO subject group estimated with generalized model. Errors are summarized in Table I.

B. Model-Based Blood Pressure Estimation

The BP estimation efficacy of group-specific and generalized WK models based on HR and epinephrine dose measurements is compared in Table I. In general, group-specific models were superior to the generalized model; though there are incidences where generalized model slightly outperformed its group-specific counterpart (e.g. RMSE and MXAE of DBP in NY group, MXAE of DBP in NO group, and RMSE and MXAE of MAP in HY group), they did not stand out due to the large overall improvement in BP estimation efficacy provided by the group-specific models over the generalized model. Compared with the generalized model, on average, RMSE and MXAE associated with the group-specific model were only 75% and 82% for MAP, 37% and 48% for SBP and 80% and 97% for DBP, respectively. Fig. 3 shows the measured versus estimated (by both group-specific and generalized models) MAP, SBP and DBP of HO subject group with respect to the epinephrine dose, which clearly indicate the advantage of using group-specific model instead of generalized model.

C. Limitation of Study

This study has a number of limitations. First, only steady-state hemodynamic responses were examined in this study. Together with the limited number of epinephrine dose-hemodynamic response data, low-order polynomial models well approximated the dose dependence of SVI, TPRI and ACI parameters. It is anticipated, however, that improvements on these polynomial models may be needed if transient as well as steady-state hemodynamic responses are to be reproduced by the proposed dose-dependent WK model. In particular, the polynomial-based SVI, TPRI and ACI models may be replaced by dynamic models representing the pharmacokinetics and pharmacodynamics of epinephrine.

Second, due to the absence of individual hemodynamic response data, it was not possible to assess the impact of inter-individual variability in epinephrine response on BP estimation. It is expected that both group-specific and generalized models will exhibit variability (i.e. distribution) in BP estimation errors once individual response is considered in the analysis. In this study, we demonstrated that group-specific WK model outperforms its generalized counterpart using the mean-value data, i.e. the average hemodynamic responses pertaining to each subject group. To further support the utility of the group-specific model over the generalized model, the degree of variability and degradation in BP estimation performance of both group-specific and generalized models due to inter-individual hemodynamic variability must be compared.

IV. Conclusion

In this study, a model-based approach was presented for estimating BP responses to epinephrine administration. The proposed low-order, dose-dependent WK model developed for each subject group was able to estimate BP responses of the underlying subject group accurately, and it also outperformed generalized model to a large extent.

Future work will be to better understand the limitation of the proposed approach, validate its efficacy in estimating hemodynamic response at the level of individual subjects, and evolve it into clinically applicable methods.

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