A Model-Based Meta-Analysis Evaluating Gender Differences on Blood Flow Responses to Brachial Artery Infusions of Acetylcholine, Albuterol, ATP, Bradykinin, Estradiol, Glyceryl Trinitrate, L-NMMA, Nevibolol, Norepinephrine, Sodium Nitroprusside, Substance P, and Verapamil

Andy R. Eugene
1. Department of Molecular Pharmacology and Experimental Therapeutics, Gonda 19, Mayo Clinic

#Corresponding author: Andy R. Eugene, MD, PhD. Division of Clinical Pharmacology, Department of Molecular Pharmacology and Experimental Therapeutics, Gonda 19, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Telephone: +1-507-284-2790; Fax: +1-507-284-4455. E-mail: eugene.andy@mayo.edu

ABSTRACT

Introduction: Numerous studies have emerged over the course of several decades describing the properties of drugs eliciting vasodilatory or vasoconstrictor responses in the human vasculature. During drug development, decisions to move forward with testing with a new chemical entity are very costly. To fund or not to fund development, go or no-go, decisions are often limited by efficacy comparisons with the current products on the market. The primary aim of this paper is to use dose-response modeling and simulations to quantify differences in blood flow to Acetylcholine, Albuterol, ATP, Bradykinin, 17β-Estradiol, Glyceryl Trinitrate, L-NMMA, Nevibolol, Norepinephrine, Sodium Nitroprusside, Substance P, and Verapamil.

RUNNING TITLE
A Model-Based Meta-Analysis Evaluating Gender Differences on Blood Flow Responses to Brachial Artery Infusions of vasodilators or vasoconstrictors

KEYWORDS
blood flow responses, brachial artery, Acetylcholine, Albuterol, ATP, Bradykinin, Estradiol, Glyceryl Trinitrate, L-NMMA, Nevibolol, Norepinephrine, Sodium Nitroprusside, Substance P, and Verapamil

WORD COUNT
4 571

CONFLICT OF INTERESTS
no conflicts of interest

ABBREVIATIONS
ED50: dose achieving 50% of maximum effect
FBF0: effect at baseline rest
FBFmax: dose resulting in maximum effect
FBF: forearm blood flow
MBMA: model-based meta-analysis
Methods: Five studies were identified in the literature that included a total of 12 compounds. Infusion doses were normalized to nmol/min and forearm blood flow values were normalized and scaled to the percent increase or decrease in forearm blood flow from baseline resting values. The original published studies were mathematically modeled using the Emax model or Sigmoid Emax model equation parameters. Lastly, dose-response simulations of higher doses using a virtual population were produced to account for population variability.

Results: The gender difference between the Emax estimates, interpreted as the %Change from Baseline resting forearm blood flow, were found to be: Albuterol 253%, Acetylcholine 231%, Substance P 159%, Verapamil 145%, Bradykinin 42%, Sodium Nitroprusside 41%, and Glyceryl Trinitrate 26%. Contrastingly, Norepinephrine and L-NMMA Emax gender difference resulted in a 6% and 7% difference, respectively.

Conclusion: These results provide insight into the differences in men and women seen in anti-hypertensive patient management. Further, the modeling estimates provide pharmacometricians evaluating new compounds with mathematical parameters for comparative efficacy studies through the various phases of drug development.

INTRODUCTION

Venous occlusion plethysmography (VOP) is a methodology that was originally reported in the literature by A.W. Hewlett and J.G. Van Zwaluwenburg in 1909 [1]. The technique describes an approach to measure blood flow based from factors affecting the forearm vasculature. Since the methodology has been formally presented in the published literature, countless of articles have documented the clinical utility of VOP and is currently the key method for evaluating the physiological responses to various doses of drugs modulating the cardiovascular system. Throughout this time, physicians and scientists evaluating the mechanisms of vasodilation and vasoconstriction have used various compounds to test arterial response based on endothelial dependence (e.g. Acetylcholine or Bradykinin), endothelial independence (e.g. Sodium Nitroprusside or Glyceryl Trinitrate), or other mechanisms like the calcium channel blocking effects of drugs (e.g. Verapamil).

Using the VOP technique, drug companies are able to evaluate potential new chemical entities or fixed-dose combination drug products, which hope to provide clinicians with more treatment options for patients. Often times, these initiatives with testing a new potential drug in the pipeline are often limited by the efficacy of the drug to a placebo or the current standard of care for that condition. Model-based meta-analyses provide key decision-makers with efficacy comparisons of the time to treatment response or with doses achieving comparative efficacy for dose selection via dose-response modeling and simulations as will be done in this article.

Using this background, the primary aim of this paper is to use methods in quantitative pharmacology and pharmacometrics to define doses for twelve compounds. The secondary aim of this paper is to conduct a clinical trial simulation (CTS) based on the model parameters identified for two nitrovasodilators, Glyceryl Trinitrate and Sodium Nitroprusside, to then identify gender-stratified doses and population doses resulting in an equivalent physiological response as would be measured using VOP. To accomplish this, I will utilize data from already published vascular studies and model the data points to establish the base model Emax parameters. From there, I will then simulate the blood flow responses of higher infusion doses that were not included in the original studies. I hypothesize that all of the selected vasodilators will achieve at least a 200% increase of forearm blood flow from baseline resting values for the vasodilators. Further, for Norepinephrine and the nitric oxide synthase inhibitor NG-Monomethyl L-Arginine (L-NMMA), I hypothesize that both compounds will result in a decrease in the forearm blood flow by at least 20%, from baseline resting values.

MATERIAL AND METHOD

Data Source

Dose-response data are based from five publications evaluating the effects of ten vasodilators and two compounds decreasing blood flow. The vasoconstrictor Norepinephrine and NOS inhibitor L-NMMA are referenced from the Chan and colleagues 2003 article [2]. Likewise, the vasodilators Acetylcholine, Bradykinin, and Nitroglycerin are referenced from the same Chan et al publication [2]. Original dose-response data for Albuterol, Substance P, Nitroprusside, and Verapamil are referenced from the Kneale et al 200 article [3]. Adenosine Triphosphate (ATP) data is referenced from the Shiramoto and colleagues 1997 publication [4]. Estradiol data is from the Gilligan and colleagues 1995 article [5]. Lastly, the Nevibolol dose-response data are from the Cockcroft and colleagues 1995 manuscript [6]. All drug infusion doses were normalized to nmol/min while the forearm blood flow responses were scaled from resting forearm blood flow levels in mL/100mL/min to %Change calculated as ((FBFnew – FBBaseline) / FBBaseline)*100. Thus, resting values will equate to zero percent and either increase or decrease for vasodilation or vasoconstriction, respectively. In all studies, the compounds were introduced via a brachial artery infusion and responses recorded via the venous occlusion plethysmography (VOP) technique as originally reported by A.W. Hewlett and J.G. Van...
Zwaluwenburg in 1909 [1].

**Dose-Response Modeling and Simulations**

Dose-response modeling and simulations of a virtual patient population were conducted in the R programming language (version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria) [7, 8]. R programming language scripts were written to for both the DoseFinding and Multiple Comparisons Procedure-Modeling (MCP-Mod) R packages [9, 10]. The MCP-Mod modeling package has been approved by both the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use and the United States Food and Drug Administration which designated the package fit-for-purpose (FFP) [11, 12]. Based on the EMA qualification report, the committee determined the R package an efficient statistical tool for Phase II dose finding studies [11]. The Multiple Comparisons Procedure allows for population dose-response testing and estimation of model uncertainties by enabling researchers to design candidate models in clinical trial design [9, 13]. The FDA’s evaluation was conducted by the Office of Biostatistics and the Office of Clinical Pharmacology in the Office of Translational Sciences, Center for Drug Evaluation and Research [12]. Overall, the package has been shown to efficient for hypothesis -testing, modeling, and simulation to analyze phase 2 dose-ranging studies to identify suitable doses for confirmatory phase 3 clinical trials [9, 11–13].

\[
\text{Response} = \frac{FBF_{\text{max}} * \text{Infusion Dose}}{ED50 + \text{Infusion Dose}}
\]

Equation 1: Pharmacodynamic modeling equation describing the forearm blood flow response based on infusion doses. FBF0= resting blood flow, FBFmax= maximum blood flow, ED50= infusion dose resulting in 50% of maximal response.

**Clinical Trial Simulation**

Using the gender-stratified model parameters estimated from the MCP-Mod statistical procedure, a Clinical Trial Simulation (CTS) was conducted using R [7, 8]. Monte-Carlo simulations of 70-virtual males and 70-virtual females were created for each nitrovasodilator at each of the following fifteen doses: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, and 70 nmol/min. The population pharmacodynamic (PopPD) modeling of Glyceryl Trinitrate and Sodium Nitroprusside were computed using nonlinear mixed effects modeling (NLME) Stochastic Approximation Expectation Maximization (SAEM) algorithm implemented in R [14].

**RESULTS**

**Retrospective Studies Included for Dose Response Modeling**

The original Chan and colleagues articles included thirty four males and thirty five females to account for the gender differences for Acetylcholine, Bradykinin, Glyceryl Trinitrate, Norepinephrine, and L-NMMA [2]. The second major forearm blood flow study which investigated the effect of gender on the systemic vasculature response was by Kneale and colleagues and included twenty one males and seventeen females [3]. The vasodilator drugs used in the Kneale study included Albuterol, Substance P, Sodium Nitroprusside, and Verapamil.

The remaining three studies included in this modeling and simulation analysis study included mainly one gender. Nevibolol was studied by Cockcroft and colleagues and included eight males [6]. For the 17β-Estradiol infusion data, thirty three post-menopausal women were studied by Gilligan and colleagues and included in this analysis [5]. Lastly, an infusion of ATP into the forearm via a brachial artery infusion was evaluated in thirty one males and 2 females in a publication by Shiramoto and colleagues in 1997 [4]. Table 1 includes a table of the demographic information and an overview of the study data modeled in this paper.

**Dose Response Modeling**

Following completion of the dose response simulations, a total of 13,861 data points were created to account for population variability at each respective dose. Eleven of the twelve drugs were modeled using the Hill Emax equation while the ATP dose-response data were modeled using the Sigmoidal Emax equation which accounts for the sigmoidal behavior of the curve that is modeled as an exponential gamma term in the model equation. The dose-response modeling results each of the twelve drugs identifying the infusion doses normalized to nmol/min with the corresponding percent change in FBF from baseline rest are reported throughout the paper.

**Simulation Findings for Norepinephrine and L-NMMA**

In comparing the vasoconstrictor effects of norepinephrine and nitric oxide synthase inhibition effects of L-NMMA resulting in a decrease of forearm blood flow, L-NMMA was found to result in a greater decrease in blood flow than norepinephrine. There were minimal gender differences between Norepinephrine and L-NMMA, 6% and 7% respectively. The estimated model parameters for Norepinephrine were estimated to be for men: E0Male= -33, ED50Male=35 and for women: E0Female= -27, ED50Female=30. Further, for L-NMMA, the model estimates were found to be for men: E0Male=100, ED50Male=0.56 and for women: E0Female=100, ED50Female= -41, ED50Female=1.74. Figure 1 illustrates the dose response simulation findings.

**Simulation Findings for Nevibolol, ATP, and 17β-Estradiol**

The estimated model parameters for Nevibolol were estimated to be: Emax=80 and ED50=1310. For ATP, the estimates were: Emax=170, ED50=3.87,
and \( h=2.07 \) (Hill exponential constant). Further, for 17\( \beta \)- Estradiol, the model estimates were found to be Emax = 1592 and ED50 = 165. The model-based dose response simulation findings for Nevibolol, ATP, and 17\( \beta \)- Estradiol are graphically depicted in Figure 2.

**Simulation Findings for Acetylcholine, Sodium Nitroprusside, and Glycerol Trinitrate**

In accomplishing the secondary aim of this paper, simulated Glycerol Trinitrate and Sodium Nitroprusside doses resulting in equivalent forearm blood flow responses, reported as the %change from rest, are shown in Table 2. The results show that for Glycerol Trinitrate, women require lower doses when compared to men in order to reach equivalent vasodilator capacity. Further, in order to reach a 200% increase in FBF, women (16.5nmol/min) would require half of the Glycerol Trinitrate dose as compared to men (33nmol/min). Contrastingly, from Sodium Nitroprusside, men require lower doses when compared to women to evoke equivalent increases in FBF. In comparing the two nitrovasodilators, the model results suggest that Sodium Nitroprusside would result in greater arterial vasodilation when compared to Glycerol Trinitrate.

Further, when comparing the Emax results for the Acetylcholine to Sodium Nitroprusside and Glycerol Trinitrate, the modeling and simulation results show that Acetylcholine has greater ability to increase blood flow, from rest, when compared to Sodium Nitroprusside and Glycerol Trinitrate. Further, when evaluating the gender differences in vasodilation, the difference between the maximum blood flow for between men and women 23.1%. Whereas, the gender differences of the dilator potential Sodium Nitroprusside and Glycerol Trinitrate were 41% and 26%, respectively. The estimated model parameters for Acetylcholine were estimated to be for men: EmaxMale=284 and ED50Male=61 and for women: EmaxFemale=514, ED50Female=53. For Sodium Nitroprusside, the model estimates were found to be for men: EmaxMale=337 and ED50Male=12 and for women: EmaxFemale=297 and ED50Female=18. Further, for Glycerol Trinitrate, the model estimates were found to be for men: EmaxMale=249 and ED50Male=7.67 and for women: EmaxFemale=276 and ED50Female=6.37. Figure 3 illustrates the graphical illustration for the dose response simulations.

**Simulation Findings for Albuterol, Bradykinin, Substance P, and Verapamil**

The estimated model parameters for Albuterol were estimated to be for men: EmaxMale=390 and ED50Male=13.8 and for women: EmaxFemale=643, ED50Female=5. For Bradykinin, the model estimates were found to be for men: EmaxMale=251 and ED50Male=34655 and for women: EmaxFemale=209 and ED50Female=27442. Further, for Substance P, the model estimates were found to be for men: EmaxMale=467 and ED50Male=6.71 and for women: EmaxFemale=626 and ED50Female=15. Lastly, for Verapamil, the model estimates were found to be for men: EmaxMale=447 and ED50Male=97 and for women: EmaxFemale=591 and ED50Female=240. Figure 4 illustrates the results for the dose response simulations. Based on the modeling findings for these four compounds, gender difference in the estimated %change in forearm blood flow from resting values were found to be: Albuterol=253%, Bradykinin=42%, Substance P=159%, and Verapamil=145%. Figure 4 illustrates the model-based dose response simulations for Albuterol and Verapamil while Figure 5 illustrates the results for Substance P and Bradykinin.

**Clinical Trial Simulation to Identify Equivalent Dosing of Nitrovasodilators**

The results of the Clinical Trial Simulation that was aimed to provide model estimates for a general population, without accounting for gender, was composed of 70-virtual males and 70-virtual females totaling 4200 doses and the corresponding blood flows for both Glycerol Trinitrate and Sodium Nitroprusside. To account for population variability of potential study participants with the following demographics: young, elderly, athletic, and with suffering from chronic conditions, the following values were used for the coefficients of variation: EO=20%, Emax=40%, ED50=40% for the Monte-Carlo Simulations.

Based on the pharmacometrics analysis the gender-specific Emax model parameters for Glycerol Trinitrate were estimated (value ± S.E.): to be for men: E0Male=3.2±0.204, EmaxMale=8.02±0.819, and ED50Male=7.65±1.939 and for women: E0Female=2.31±0.0186, EmaxFemale=6.41±0.0649, ED50Female=6.46±0.172 with a residual standard error (R.S.E) for men and women 0.205 and 0.0187, respectively. Likewise, the Sodium Nitroprusside estimates were calculated to be for men: E0Male=2.58±0.263, EmaxMale=8.91±1.009, and ED50Male=12.14±3.507 and for women: E0Female=2.03±0.150, EmaxFemale=5.78±0.934, and ED50Female=17.95±6.339 with a R.S.E for men and women of 0.273 and 0.159, respectively. Further, the graphical depictions for the model goodness-of-fit are shown in Figure 6 while the Prediction Corrected Visual Predictive Check (VPC) is shown in Figure 7.

The CTS results for Glycerol Trinitrate showed that the resting forearm blood flow was estimated to be 2.53mL/100mL/min and the maximum blood flow was 6.643mL/100mL/min within the dose range window of 0-70nmol/min. Further, the Glycerol Trinitrate infusion dose yielding 50% of the maximal blood flow effect was 11.15nmol/min. The results are provided in Table 3.

Similarly, the CTS results for Sodium Nitroprusside resulted in a resting forearm blood flow estimate of 2.31mL/100mL/min while the maximal blood flow is estimated to be 7.103mL/100mL/min within the dose range window of 0-70nmol/min. Finally, the Sodium
Nitroprusside ED50 parameter was calculated to be 14.18nmol/min. The final Sodium Nitroprusside results are provided in greater detail in Table 4. Lastly, the dose-response curve comparisons of vasodilators from the model-based meta-analysis parameters are shown in Figure 8.

**DISCUSSION**

In human cardiovascular research, the forearm vascular model is an integral method for understanding drug mechanisms of a potentially new compound or understanding the effects of a disease process on the human vasculature. The modeling and simulation results suggest that model estimates suggest that 17β-Estradiol results in the greatest percent increase in blood flow from resting values when compared to Acetylcholine, Albuterol, Bradykinin, Substance P, Verapamil, Glyceryl Trinitrate, and Sodium Nitroprusside. Further, when evaluating gender differences in this study, Albuterol (253%) exhibited the greatest difference in blood flow responses to intra-brachial vasodilator infusions, followed by Acetylcholine (231%). The gender difference between the Emax estimates, interpreted as the %Change from Baseline resting blood flow, were found to be: Albuterol 253%, Acetylcholine 231%, Substance P 159%, Verapamil 145%, Bradykinin 42%, Sodium Nitroprusside 41%, and Glyceryl Trinitrate 26%. Contrastingly, Norepinephrine and L-NMMA Emax gender difference resulted in a 6% and 7% difference, respectively.

These model parameters may be used for comparative efficacy studies during the drug discovery process when an institution is looking to evaluate their compound to known existing vasodilators analyzed in this paper. The simulated population pharmacodynamic findings aimed at identifying the equivalent doses for Glyceryl Trinitrate and Sodium Nitroprusside provide biomedical researchers latitude when conducting experiments when a nitrovasodilator is required. While Glyceryl Trinitrate is comparable to Sodium Nitroprusside in forearm blood flow studies, therapeutically, there are advantages to using nitroprusside due to clinical documentation and clinical experience with clinicians. However, for these vascular studies, where exogenous pharmacological compounds are infused via the brachial artery while forearm vascular responses are recorded using the venous occlusion plethysmography technique and interpreted to represent the systemic vasculature, Sodium Nitroprusside is often used as a control that provides endothelial independent vasodilation. In these forearm studies, nitroprusside doses are low enough so not to produce whole body systemic effects, such as tachycardia and/or hypotension to the study participant [15]. In this case, Glyceryl Trinitrate may be a suitable option to researchers and this article has provided equivalent dosing for those testing conditions. However, therapeutically nitroprusside has been shown to be very effective to decrease the systemic vascular resistance (SVR) while other compounds such as dopamine or a low-dose epinephrine may be also be used to decrease SVR [16].

Considering the differences in the gender-stratified responses to the same pharmacological compounds analyzed in this model-based meta-analysis, recent meta-analyses evaluating patient management using pharmacotherapy provided evidence that women experience greater numbers of adverse drug reactions (ADRs) as compared to men [17–19]. These results suggest that tailoring doses, based on gender, may be required to account for the biochemical and physiological differences between men and women in patient population and also during biomedical research experiments [20]. Attempting to account for all of the potential biochemical mechanisms resulting in the varied physiological responses between men and women seen in this article are out of scope for this study. What appears to be rather clear is the myriad of findings to suggest that in both biomedical research and in clinical patient management, the need for precision dosing is clearly warranted and may improve overall treatment of those who are in search of healing.

**CONCLUSIONS**

The results of this quantitative pharmacological study provides insight that gender clearly influences the pharmacodynamics of Acetylcholine, Albuterol, Bradykinin, Glyceryl Trinitrate, L-NMMA, Norepinephrine, Sodium Nitroprusside, Substance P, and Verapamil. Further, extending the infusion doses of the aforementioned compounds and also ATP, Nevibolol, and 17β-Estradiol further increases understanding as to how these drugs respond at higher doses and allows one to scale the infusion doses (x-axis) to the blood flow (y-axis) response when needing to identify equivalent dosing between compounds. Overall, the study results provide pharmacometricians with mathematical model parameters for comparative efficacy studies throughout the various phases of drug development, as well as, provide insight to researchers and clinicians to the differences in response that men and women experience during anti-hypertensive patient management.

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Figure 2:
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Figure 6:
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Figure 8:
Dose Response curve comparisons of vasodilators from the model-based meta-analysis parameters computed in this analysis.
### TAB. 1. FOREARM BLOOD FLOW STUDIES INCLUDED IN THE ANALYSIS

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug(s)</th>
<th>Males</th>
<th>Female(s)</th>
<th>Age (yrs)</th>
<th>Drug Administration</th>
<th>Blood Flow Recording Method</th>
</tr>
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<tbody>
<tr>
<td>Chan et al 2003</td>
<td>ACH, BK, GTN, NE, L-NMMA</td>
<td>n=34</td>
<td>n=35</td>
<td>30-53</td>
<td>Brachial Artery</td>
<td>VOP</td>
</tr>
<tr>
<td>Cockcroft et al 1995</td>
<td>Nevibolol</td>
<td>n=8</td>
<td>-</td>
<td>20-34</td>
<td>Brachial Artery</td>
<td>VOP</td>
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<td>Gilligan et al 1995</td>
<td>Estradiol</td>
<td>-</td>
<td>n=33</td>
<td>59±7</td>
<td>Brachial Artery</td>
<td>VOP</td>
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<tr>
<td>Kneale et al 2000</td>
<td>Albuterol, Substance P, SNP, Verapamil</td>
<td>n=21</td>
<td>n=17</td>
<td>males: 28±7, females: 2 8±5</td>
<td>Brachial Artery</td>
<td>VOP</td>
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<tr>
<td>Shiramoto et al 1997</td>
<td>ATP</td>
<td>n=31</td>
<td>n=2</td>
<td>26±3</td>
<td>Brachial Artery</td>
<td>VOP</td>
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### TAB. 2. EQUIVALENT INFUSION DOSES FOR GLYCERYL TRINITRATE AND SODIUM NITROPRUSSIDE

<table>
<thead>
<tr>
<th>Effect</th>
<th>GTN Dose: Male (nmol/min)</th>
<th>GTN Dose: Female (nmol/min)</th>
<th>SNP Dose: Male (nmol/min)</th>
<th>SNP Dose: Female (nmol/min)</th>
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<tbody>
<tr>
<td>100%</td>
<td>7</td>
<td>5</td>
<td>5</td>
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<td>150%</td>
<td>12.50</td>
<td>9</td>
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<td>175%</td>
<td>15</td>
<td>12</td>
<td>18.5</td>
<td>31</td>
</tr>
<tr>
<td>200%</td>
<td>33</td>
<td>16.5</td>
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### TAB. 3. FINAL POPULATION PHARMACODYNAMIC

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<th>Estimate</th>
<th>S.E. (lin)</th>
<th>R.S.E. (%)</th>
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<tbody>
<tr>
<td>E0 (mL/100mL/min): baseline blood flow</td>
<td>2.53</td>
<td>0.0516</td>
<td>2.04</td>
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<tr>
<td>Emax (mL/100mL/min): maximal blood flow effect within dose range of less than 70nmol/min</td>
<td>6.643</td>
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<tr>
<td>ED50 (nmol/min): infusion dose resulting in 50% of maximal effect</td>
<td>11.15</td>
<td>0.415</td>
<td>3.73</td>
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</table>

**Interindividual Variability**

- $\omega_{E0}$, variance for E0: 0.0582, 0.00696, 12
- $\omega_{Emax}$, variance for Emax: 0.0512, 0.00612, 12
- $\omega_{ED50}$, variance for ED50: 0.1950, 0.02331, 12

**Residual (intra-individual) error**

- CV (%), interindividual deviation of each parameter; RSE (%), percentage of relative standard error (100%×SE/EST); $\sigma$, variance of intraindividual deviation of fitted forearm blood flow response.
### TAB. 4. FINAL POPULATION PHARMACODYNAMIC PARAMETER ESTIMATES FOR SODIUM NITROPRUSSIDE

<table>
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<th>R.S.E. (%)</th>
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<td>E0 (mL/100mL/min): baseline blood flow</td>
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<td>0.0291</td>
<td>1.26</td>
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### Interindividual Variability

<table>
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<th>R.S.E. (%)</th>
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<tr>
<td>(\omega_{E_{\text{max}}}), variance for Emax</td>
<td>0.0658</td>
<td>0.00786</td>
<td>12</td>
</tr>
<tr>
<td>(\omega_{E_{\text{D50}}}), variance for ED50</td>
<td>0.0511</td>
<td>0.00611</td>
<td>12</td>
</tr>
</tbody>
</table>

### Residual (intra-individual) error

<table>
<thead>
<tr>
<th>Error</th>
<th>Estimate</th>
<th>S.E.</th>
<th>R.S.E. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.00454</td>
<td>7.82E-05</td>
<td>1.73</td>
</tr>
</tbody>
</table>

### FIG. 1. DOSE-RESPONSE SIMULATION RESULTS COMPARING GENDER DIFFERENCES OF NOREPINEPHRINE AND L-NMMA...
FIG. 2. DOSE-RESPONSE SIMULATION RESULTS COMPARING NEVIBOLOL, ADENOSINE TRIPHOSPHATE, AND 17ß-ESTRADIOL.

FIG. 3. DOSE-RESPONSE SIMULATION RESULTS COMPARING ACETYLCHOLINE, SODIUM NITROPRUSSIDE, AND GLYCERYL TRINITRATE.
FIG. 4. DOSE-RESPONSE SIMULATION RESULTS COMPARING ALBUTEROL AND VERAPAMIL...

![Graphs comparing dose-response simulation results for Albuterol and Verapamil for males and females.]

FIG. 5. DOSE-RESPONSE SIMULATION RESULTS COMPARING SUBSTANCE P AND BRADYKININ...

![Graphs comparing dose-response simulation results for Substance P and Bradykinin for males and females.]

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FIG. 6 GOODNESS-OF-FIT RESULTS ILLUSTRATING THE OBSERVED VERSUS PREDICTED BLOOD FLOW RESPONSES...

![Graphs showing goodness-of-fit results for Glyceryl Trinitrate and Sodium Nitroprusside.](image)

FIG. 7. THE PREDICTION CORRECTED VISUAL PREDICTIVE CHECK FOR (TOP) GTN: GLYCERYL TRINITRATE AND (BOTTOM) SNP...
BIBLIOGRAPHY


7. [R Core Team]. R: A Language and Environment for Sta-tistical Computing 2015.


