The Effects of Pharmacological Drugs on the Aortic Pressure Waveform: Understanding Mechanisms through Modelling

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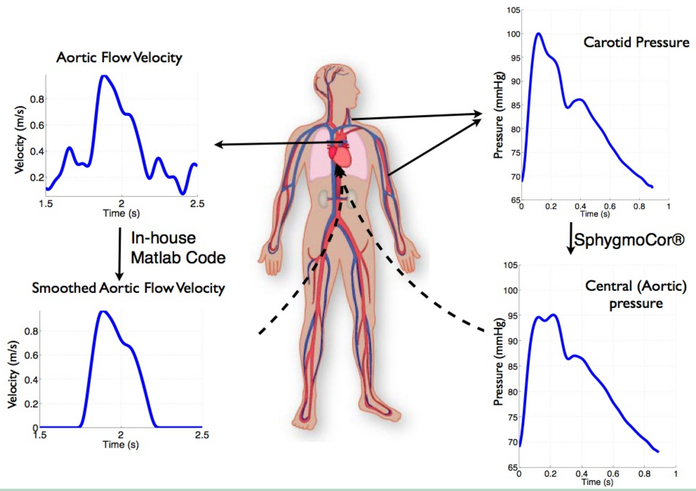
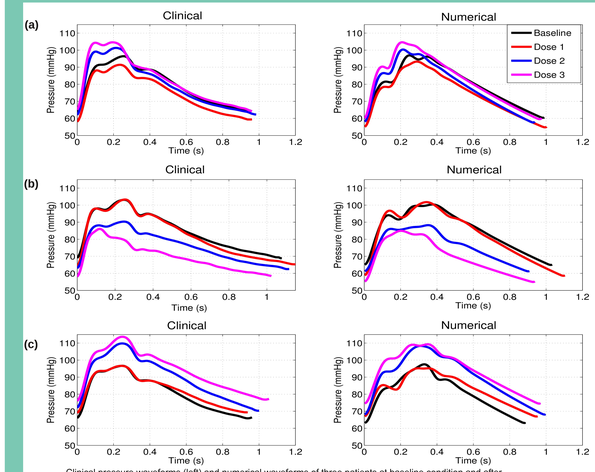


Clinical Measurements

Healthy volunteers aged 35 to 63 years received cumulative doses of;

- Dobutamine (DB, n=10) ;
- Nitroglycerin (NTG, n=8);
- Nor-epinephrine (NE, n=9).

Central pressure waveforms were measured by carotid tonometry using the SpygmoCor system. Aortic diameter and blood flow rate velocity were measured by echocardiography.



Clinical pressure waveforms (left) and numerical waveforms of three patients at baseline condition and after the administration of 3 cumulative doses of DB (a), NTG (b) and NE (c).

Model Predictive Capabilities

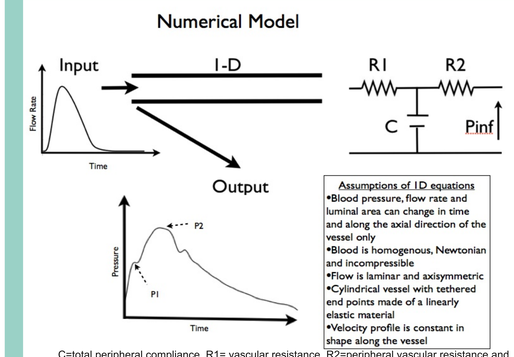
The numerical pressure waveforms relative to the clinical data were reproduced with an average normalised root-mean-square-error < 7.6%, 7.1% and 6.1% for DB, NTG and NE respectively when unique models were simulated for each measured patient data.

Drug type	Average systolic pressure error (%)	Average diastolic pressure error (%)	Average mean pressure error (%)
DB	-7.4	8.2	-0.1
NTG	-8.3	5.9	-0.2
NE	-2.4	8.0	-0.2

The Challenge

Pharmacological drugs that change the physical properties of the cardiovascular system are commonly used in the clinic; however the physical mechanism of action of these drugs upon central (aortic) blood pressure can be complex, and as yet not fully understood.

We investigate the ability of a numerical model of pulse wave propagation to predict the main features of the central pressure waveform at baseline and during infusion of drugs with differential actions on the myocardium and arterial tree.



C=total peripheral compliance, R1= vascular resistance, R2=peripheral vascular resistance and Pinf=asymptotic pressure.

The Model

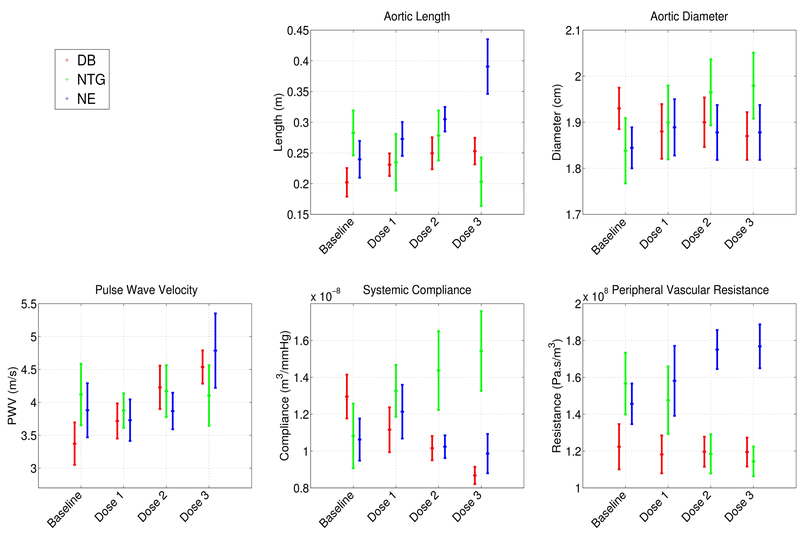
The parameters extracted from the clinical data were used to create patient specific input conditions for a single-vessel, nonlinear 1-D model of pulse wave propagation in the human aorta.

The oulet of the vessel was coupled to a three-element Windkessel model of the downstream vasculature.

Conclusions

-Our results support the use of 1-D modelling to investigate the characteristics of the cardiovascular system that determine pulse wave morphology when modulated by pharmacological agents with differential actions on the myocardium and arterial tree.

-Comparison of clinical data and numerical predictions enabled us to quantify which actions of the pharmacological drugs can be captured by our model, thus allowing us to differentiate to what extent physiological changes contributes to changes in the pressure waveform.



The arms of the bar indicate standard error of the mean, with the central notch indicating the mean value.

Model Parameters from Clinical Data

-Aortic length calculated as the product of pulse wave velocity and half the time taken between the first shoulder and the peak of the pressure waveform

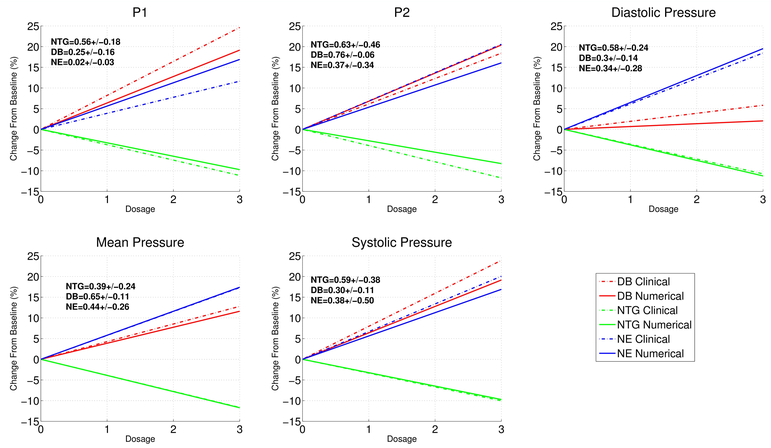
-Pulse wave velocity calculated using simultaneous pressure and flow measurements [1]

-Systemic compliance computed by dividing the value of the time constant of the decline in pressure during diastole as derived using Fourier harmonics [2] by our measurement of net resistance

-Peripheral vasculare resistance is calculated as the mean pressure over the mean flow rate.

Numerical Pressure Predictions

The model best captures changes from baseline conditions for cumulative doses of NE. Statistically signifigant similarity of results between the clinical and numerical data for NE are seen for P1 at dose 2 and 3, systolic and diastolic pressure at dose 2 when the Student's T-test is applied with a signifigance threshold of 5%.



Change from baseline conditions for the measured paramters of P1,P2, diastolic pressure, mean pressure and systolic pressure with the administration of cumulative doses of NTG, DB and NE. The values shown in the top left hand side of each figure is the drugs mean p value when the Student's T-test is applied with alpha equal to 0.05. Next to the mean p value is the standard deviation of the p value across the drug class.

Acknowledgements

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References

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2. Stergiopulos, N., et al, 1994, Ann Biomed Eng, 22(4), 392-397
3. Parker, K., 2009, Med Biol Eng Comput, 47, 175-188