Personalized Simulated HUT as an At-home Prediction Model for Heart Rate Changes in Syncope Patients and At-home, Orthostatic Self-training Efficacy

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Personalized Simulated HUT as an At-home Prediction Model for Heart Rate Changes in Syncope Patients and At-home, Orthostatic Self-training Efficacy

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ABSTRACT

Head-up tilt (HUT) testing supports the diagnosis of syncope by detecting abnormalities in heart rate and blood pressure changes. Home-based self-training can be of benefit to neurocardiogenic patients if during clinical HUT, heart rate decreases in the early stage of being in an upright position. However, HUT testing is not always possible in the hospital as it is inconvenient and sometimes even risky for patients with cardiac abnormalities as it may trigger a loss of consciousness and arrhythmia. To address this, the current paper introduces a personalized HUT simulation to determine the efficacy of at-home training. To develop the model, Holter ECG recordings were obtained from 28 syncope patients and the simulated output was compared to clinical findings. The model aims to predict heart rate changes associated with the simulated HUT that can indicate efficacy of an at-home program. Heart rate represents a variable of velocity in the model measured in liters per second against gravity. The results show that a decrease in heart rate in early simulated HUT as determined by the model shows a greater than 84% efficiency for syncope patients to benefit from at-home training and allows physicians to recommend home training during an online or telemedicine consultation.

Keywords— head-up tilt test, syncope, blood flow, heart rate prediction

Clinical Relevance— The cardiovascular model predicts the patient-specific efficacy of at home tilt-training for patients diagnosed with syncope.

Introduction

Patients suffering from recurrent syncope episodes are often assessed through a head-up tilt (HUT) test for abnormalities in heart rate variability (HRV) and blood pressure and to determine whether a prolonged standing posture at home is beneficial in reducing episodes of syncope[1]. The patient begins the test resting on a tilt-table in the supine position and then is gradually inclined to a maximum angle of 80° and at an average speed of 15° per second. The higher the degree of tilt, the more intense the effect of gravity is on causing blood to pool in the lower extremities. The reduced venous return causes a change in blood volume, which leads to a drop in blood pressure above the center of gravity (COG)[4]. Baroreceptors sense the decrease in blood pressure and activate a sympathetic response leading to an increase in heart rate. In healthy individuals the baroreceptors sense an increase in pressure which, in turn, then decreases heart rate and blood pressure. However, patients diagnosed with syncope experience a sustained increase in heart rate in the upright position[5]. Abe and his team proposed a prolonged standing posture as an at-home, orthostatic self-training exercise for patients with neurocardiogenic syncope. Results indicated recovery from syncope in 12 out of 28 patients within 24 ± 6 days, characterized by a decrease in heart rate in the early stage of the upright position[1]. HUT testing is the most common method to diagnose and investigate syncope and presyncope. However, tilt testing presents risks to patients with structural and arrhythmic cardiac abnormalities such as loss of consciousness and arrhythmia. Only a few studies have investigated any type of modelling associated with HUT[6,7]. However, these models require more and complex variables that are not readily available to physicians for quick and efficient diagnosis. Moreover, the sample sizes for these studies are small and participants were all healthy.

This paper introduces a novel personalized at-home simulated HUT (sHUT) heart rate prediction model with justification of the parameters and variables used in the generated model. The aim is to provide patients with a means of assessing the likelihood of an extended standing posture to be effective in decreasing syncopal episodes based on their 5-minute heart rate recording. The novelty of this study is given to the fewer parameters required to calculate a predicted HUT response.

Results

During HUT exercises, patients with higher starting heart rates tend to respond better to standing rehabilitation exercise[1]. The following results shown in Figure 1 indicate that syncope patients had overall higher average heart rates which implies that they would respond better to HUT rehabilitation respective to the control group.

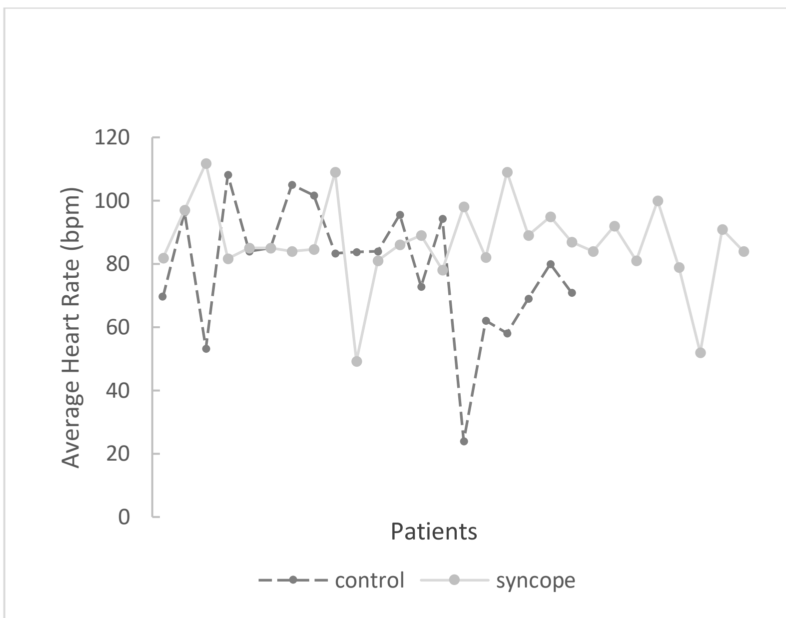

Figure. 1. Average starting heart rates corresponding to the control group and syncope group.

Figure 2 pertains to the calculated personalized predicted efficacy of the orthostatic self-training rehabilitation exercise proposed in Abe etal. [1] for syncope patients. This efficiency was calculated by calculating the heart rate decreases between the 10-minute intervals from the 24-hr Holter readings. The heart rate decreases in bpm found for the syncope, presyncope, and palpitation groups were 30.3±1, 12.9±3, and 21.3±5 respectively. The results suggest that 26 of the 28 patients would benefit from the at-home program with percentage likelihood above 85%. One other patient result of 84.6% may also indicate a good candidate, whereas the patient with the next best likelihood of 72.4% of successful outcome with the orthostatic self-training exercise may derive less benefit.

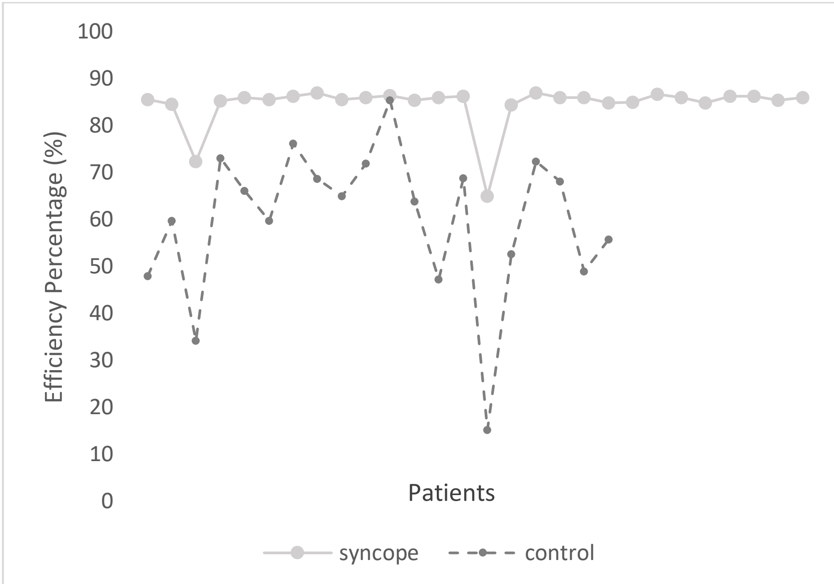

Figure 2. Efficacy Percentage for control group and syncope group.

A decrease in blood flow of -254.31 ml/min was calculated using Eqn. (5) for the early stage of the sHUT test indicating that blood flow decrease may be an imperative factor in predicting stand up training and rehabilitation outcomes for syncope patients. The average heart rate decrease found over the 10 minute intervals over the 24-hour Holter data was also calculated for the 28 syncope and 20 palpitations patients. The heart rate decrease was then used to observe patient specific rehabilitation efficacies with a higher decrease in heart rate indicating a higher rehabilitation efficacy rate.

Discussion

In this study, average, instead of exact, values of lower body height and total peripheral resistance were used to develop the model as these variables were not available in our clinical data for each participant[1]. Direct afferents such as blood volume and pressure were not modelled. Heart rate was predicted based on gravitational force impact and blood flow decrease for syncope patients as part of the simulated HUT. Our model can then be applied to predicting efficacy of the at-home orthostatic training outcome as suggested by Abe and colleagues.[1]

Blood flow and heart rate correlation

The differences in the decrease in blood flow calculated for the early stage of the simulated HUT test between the syncope and palpitation groups indicated that the model provided results as expected from a clinical HUT. As the model depends on blood flow as its main factors, it suggests that a blood flow decrease is an important factor in predicting rehabilitation outcome of syncope patients. Assuming a recovery by syncope patients after a decreased blood flow is observed in the early stage of the upright position during the sHUT test may be justified by the slower pooling of blood in the legs. If blood flow decreases early on during the sHUT test, blood would not flow as fast as it normally would to the legs with the onset of gravity and lead to slowing the effects gravity during the sHUT test for some syncope patients. The proposed sHUT model has the advantage that patients with different etiologies can determine their HUT results from the model at home on a daily basis from a 5 minute heart rate recording. Clinically ECGs have not been useful as even during Holter monitoring of 24 hours, syncope events may not occur[2]. Prolonged standing or HUT testing in hospital can also be avoided by using the sHUT model and thus reducing risk of vasodepressor type neurally mediated syncope (VT-NMS)[3].

Analysis of efficacy percentage and heart rate changes

The results obtained from the model show the patient-specific heart rate decrease needed for his or her blood flow to decrease parallel to that of patients from experiments discussed in [1]. The personalized predicted efficacy found through comparing patient heart rate results from the sHUT with the heart rate decrease of successfully recovered syncope patients from [1], we found that the syncope group demonstrated much higher efficacies averaging approximately 85%, whereas the control group averaged approximately 65% indicating that our model is specific for characteristics of heart rate changes associated with syncope patients. This could prove that at-home orthostatic self-training exercises can be beneficial for some syncope patients compared to patients with palpitations that were used as the control group. The higher overall efficacy seen in the syncope group can be understood as the possible success of the model. Moreover, a similar trend is seen when observing the decrease in heart rate results across the two groups. The model indicated a relatively higher decrease in heart rate (~30 bpm) averaged over the first, third, and fifth minute during the sHUT exercise in the syncope group , further confirming the possible efficacy of the proposed home training based on our model in line with the criteria outlined in [1]. The palpitation group (control) showed a lesser decrease (~23 bpm) compared to the syncope group. This indicates that the HUT exercises are more likely to be of benefit for the syncope patients.

The Syncope group presented a similar decrease in their average heart rate over 5-minute intervals of a 24-hour Holter recording with an average reading of 30.5 bpm. However, some patients did not fit the model. Patient 2M5h5-1 stood as a minor outlier with a heart rate decrease of 4 bpm from the upper bound. The control groups also had a relatively lesser decrease in the average HR at 23 bpm. Patient 7K8d5-3 was the only outlier present in the control group with a decrease of 4 bpm deviation from the lower bound. The one outlier in the syncope group could point to the possibility that patient 2M5h5 may have a presyncope or possibly present with palpitations as the control group was defined by presence of palpitations. It could also mean that there are other underlying conditions that this patient is experiencing which may directly affect their results. The patient's diagnosis is being reviewed to ensure whether a HUT test is safe and efficient for this patient. Finally, patient 7K8d503 presented as an outlier in the control group and could possibly be classified as presyncope. Considering the extremely small heart rate decrease retrieved by this model, it is possible that the patient may be experiencing episodes of presyncope, leading to results at the opposite end of the spectrum relative to that seen for the average syncope patients in this study. The at home orthostatic self-training exercise duration of 30 minutes twice daily for 30 days can be adjusted in order to provide a more personalized and efficient program for distinctive syncope patients. This model may also potentially help to understand whether a syncope has different underlying pathophysiology that affects HUT test outcomes and lead to better potential treatment outcomes.

Having heart rate as the only input for this model is recognized as this study's limitation since the output is reduced to sympathetic regulation efficiency. Future work leaves room for more extensive analysis on the effects and manipulations this model introduces to the patients' ECG signals and respective HRV analysis. Moreover, this study can extend its variables to observation of time-specific measurements (e.g. early morning measurements) to observe the effect rehabilitation could have on syncope at different times of the day. It would also be worthwhile to extend this model to include blood pressure as a parameter in order to measure the capabilities of the current model and judge whether blood pressure is a more effective parameter for this simulation. Additionally, future studies may observe the applied efficacy of HUT exercises on the current patients included in the study to further confirm this model's accuracy. To enhance the model's specificity, future alterations can also be made to add more sensitive input variables including resistance pressure from arteries and veins in both the upper and lower compartments of systemic circulation in the body. This could also potentially extend the model's use to classification and diagnosis of syncope which would reduce the burdens presented by HUT.

Simulated Head-Up-Tilt Model

HUT testing has been an essential part of a clinical review for vasovagal or cardiogenic syncope. HUT has been necessary in the diagnosis of vasovagal syndrome because there has been no found difference found between the heart rates and stroke volumes of healthy patients and syncope patients[11]. However, this predictive mathematical approach picks up heart rate trends to simulate the predicted HUT response for patients with an ultimately proven accuracy of syncopal behaviors. As compared to the previous mathematical HUT models[7,8], this study uses less parameters for sHUT calculation. Previous models require left and right ventricular interaction and blood volume, and blood pressure. These parameters are not always readily available for quick diagnosis. With less parameters, physicians would find more efficiency in predicting syncope in patients in order to begin earlier treatment methods. Moreover, unlike the previous studies, this study has used data from three distinct groups: syncope, presyncope, and palpitations (control). Former mentioned studies have only studied models on healthy patients of smaller sample sizes. This allows the proposed model a more accurate analysis of results and precision.

The objective of this model was to construct a simple model that are limited to essential elements. This allows for a clearer and focused observation on the specific system dynamics that are studied. This model may potentially be manipulated to diagnose patients with syncope using Holter data as an alternative to HUT tests for diagnosis in future work. This could possibly eliminate the unwanted side-effects that pertain to the HUT test experienced by patients. It may also be further studied to be used as an indicator of underlying conditions in syncope and palpitation conditions.

Methods

Patient data

Data were collected at the Wangaratta Cardiology and Respiratory Centre in Australia from a group of 28 syncope patients and 20 palpitation patients, which were taken as a control group. All data were de-identified and an ethics approval was obtained from the Charles Sturt Human ethics Committee under approval number H18161. All methods were also performed in accordance with the relevant guidelines and regulations. All participants underwent an information session and informed written consent was obtained from all participants. The study included 29 females (17 syncope patients) and 19 males (11 syncope patients) with 43% of the cohort above 60 years of age, the oldest patient being 92 (syncope patient) and the youngest 20 years old (control group).

Modelling

The model uses the heart as the main compartment with heart rate as the velocity (quantified by Bernoulli's principle) and the total peripheral resistance as an inversely related component to blood flow to allow for lack of direct measures of blood volume and blood pressure. Moreover, the average lower body height was considered. The tilt angle used in this study is the upright position in order to be parallel with the angle used in[1]. The sHUT test simulation and heart rate change is predicted from ECG data retrieved from 5-minute intervals taken every 10 minutes from 24-hour Holter recordings.

The current sHUT model further predicts efficacy of an at-home program for reducing syncope based on the heart rate results determined from the simulated HUT test with sparse input data. The data for the model included heart rate change of healthy individuals following sHUT, which is then retrofitted into the model to determine the resulting blood flow and initial heart rate to predict the patient-specific heart rate decrease based on [1]. The output of the model is then compared to results presented in [1]. The remaining input variables are constants and include gravitational acceleration, blood density, and peripheral resistance.

ECG data and HRV analysis

The raw ECG data was preprocessed using the Librow MATLAB code [10] for ECG filtering via fast Fourier transform (FFT) to remove lower frequencies with a threshold for frequencies under 4 Hz.

Mathematical Model

This section explains the proposed cardiovascular model to find the approximate blood flow of each patient during the at-home sHUT. This model is based on the rehabilitation data from the paper by Abe et al.[1], which showed the desired heart rate decrease in the upright position (80°) required for the optimum at-home rehabilitation program outcome. In our model the heart rate was derived from the approximate blood flow:

- Derivation of Darcy's law for volumetric flow

Darcy's law describes the relationship between flow Q in ml/s, pressure difference over a tube ($p_1 - p_2$) and total peripheral resistance r[7] given as:

$$Q = ka\frac{h_1 - h_2}{l} \; or \; q = \frac{Q}{a} = -k\frac{dh}{dl}, \tag{1}$$

where*:*

k(ml/m^{2}s) is the hydraulic permeability*,* h(m) is the height of elevation or hydraulic head with $h = p/(\rho g) + z$*,* z(m) is the elevation at the bottom a(m^2) is the area, and l(m) is length.

Using a linear relationship analogous to Ohm's law, the volumetric flow q (ml/m^{2}s) between compartments in cardiovascular regulation can be computed as in Eqn. (2):

$$q = \frac{p_{out} - p_{in}}{r} \tag{2}$$

- Heart rate quantified by Bernoulli's Principle

In fluid dynamics, Bernoulli's principle relates velocity, pressure, fluid elevation, and fluid density (accounting for internal friction) shown in Eqn. (3)[9]:

$$\frac{1}{2}\rho v_1^2 + \rho g h_1 + p_1 = \frac{1}{2}\rho v_2^2 + \rho g h_2 + p_2 \tag{3}$$

Eqn. (3) explains that the mechanical energy of a flowing fluid that exerts kinetic energy, gravitational potential energy and fluid pressure remains constant. By rearranging Eqn. (3) (Appendix A.), the final velocity can be calculated as:

$$v_1 = \sqrt{v_2^2 + 2g(h_2 - h_1) + \frac{2}{\rho}(p_2 - p_1)} \qquad (4)$$

where:

v_1 is the velocity at elevation 1, p_1 is the pressure at elevation 1 based on Bernoulli's Equation, h_1 is the height of elevation 1, p^2 is the pressure at elevation 2, v_2 is the velocity at elevation 2, h_2 is the height of elevation 2**,** ρ is the density of the fluid, and g is the acceleration due to gravity.

When considering the heart as a dynamic system, the velocity pertains to the heart rate. Therefore, in this model, pressure (blood pressure) will be substituted with velocity (heart rate), allowing for heart rate to be the main input for the model, which matches the data from[1].

- Modelling HUT

HUT response has previously been modeled by taking the hydrostatic pressure (blood pressure) into account[6]. However, the current model aims to replace pressure with heart rate as velocity (as derived previously) to simulate the HUT response as pressure is not available. Tilt angle setting is variable in the model and set at 80 degrees complying with HUT standards.

The relationship between physics and physiology is that the gravitational impact of HUT on the patient causes blood to pool in the lower extremities. The pressure thus increases below the center of gravity and increases above it. Therefore, gravity is considered and added to the flow equation. This fits naturally into the gravitational potential energy factor at specific elevations in Bernoulli's equation. This flow equation is presented in a SIMULINK model in Figure 3. The calculated gravitational effects and the modified flow equations are shown as Eqn. (5) and Eqn. (6):

$$q = \frac{\rho g h sin\theta(t) + \frac{1}{2}\rho(v_2^2 - v_1^2)}{r} \qquad (5)$$

The inverse solution equation is then given by:

$$v_2 = \sqrt{\frac{2rq}{\rho} - 2ghsin\theta(t) + v_1^2} \qquad (6)$$

where:

q is the blood flow, ρ (kg/m^3) is the blood density, $\theta(t)$ is the tilt angle (in radians), v_1 (l/s)is the heart rate before training in, v_2 is the heart rate after training, g (m/s^2) is the constant of gravitational acceleration, h (m) is the absolute patient height, $\rho gh\ sin\theta(t)$ represents the hydrostatic pressure between the lower and upper body parts.

References

1. H. Abe et al., “Effects of Orthostatic Self-Training on Head-Up Tilt Testing and Autonomic Balance in Patients with Neurocardiogenic Syncope. J. Cardiovasc. Pharm. 2003;41:S73-S76
2. Kapoor WN. Evaluation and management of the patient with syncope. JAMA. 1992 Nov 11;268(18):2553-60. PMID: 1404823
3. Hasegawa M, Komiyama T, Ayabe K, Sakama S, Sakai T, Lee KH, Morise M, Yagishita A, Amino M, Sasaki A, Nagata E, Kobayashi H, Yoshioka K, Ikari Y. Diagnosis and prevention of the vasodepressor type of neurally mediated syncope in Japanese patients. PLoS One. 2021 Jun 25;16(6):e0251450. doi: 10.1371/journal.pone.0251450. PMID: 34170907; PMCID: PMC8232444.
4. L.A. Runser, R.L. Gauer, A. Houser. Syncope: Evaluation and differential diagnosis. Am. Fam. Phys. 2017;95(5):303-12
5. P.J. Lacolley, B.M. Pannier, M.A. Slama, J.L. Cuche, A.P. Hoeks, S. Laurent, et al. Carotid arterial haemodynamics after mild degrees of lower-body negative pressure in man. Clin. Sci. 1992;83(5):535-40.
6. K.J. Chun, H.R. Yim, J. Park, S.J. Park, K.M. Park, Y.K. On, et al. Role of baroreflex sensitivity in predicting tilt training response in patients with neurally mediated syncope. Yonsei Med. J. 2016;57(2):313-20.
7. N.D. Williams, O. Wind-Willassen, A.A Wright; REU Program, Mehlsen J, Ottesen JT, Olufsen MS. Patient-specific modelling of head-up tilt. Math Med Biol. 2014;31(4):365-92.
8. E. Lim, G.S. Chan, S. Dokos, S.C Ng, L.A. Latif, S. Vandenberghe, M. Karunanithi, N.H. Lovell. A cardiovascular mathematical model of graded head-up tilt. PLoS One. 2013;8(10):e77357.
9. J.C. Manning, Applied Principles of Hydrology. Prentice Hall, Third edition, 276p, 1997.
10. B. R. Munson, D.F Young, T.H. Okiishi, Fundamentals of Fluid Mechanics. Fifth edition. New York, NY: John Wiley & Sons, Inc., 2006.
11. S. Chernenko, “ECG processing - R-peaks detection,” *R*. [Online]. Available: http://www.librow.com/articles/article-13. [Accessed: 06-May-2020].
12. K. Buszko, S. Kujawski, J.L. Newton, P. Zalewski, Hemodynamic Response to the Head-Up Tilt Test in Patients With Syncope as a Predictor of the Test Outcome: A Meta-Analysis Approach. Front Physiol. 2019 Mar 7;10:184.
13. L. K. Hill et al., Resistance reconstructed estimation of total peripheral resistance from computationally derived cardiac output – biomed. Bio. Sci. Instrum. 2013;49:216-223

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Author contributions statement

R.K. and D.W. provided the ECG data for the modelling, D.H. conceived and conducted the experiment; D.W. assisted in the sampling of the experimental data; H.A. revised the findings; H.F.J. was involved in data collection, sampling and modelling. All authors contributed to the writing of the manuscript and reviewed the manuscript prior to submission. All authors have also read and agreed to the submission of this paper to Scientific Reports.

Additional information

There are no competing interests between authors.

Figures

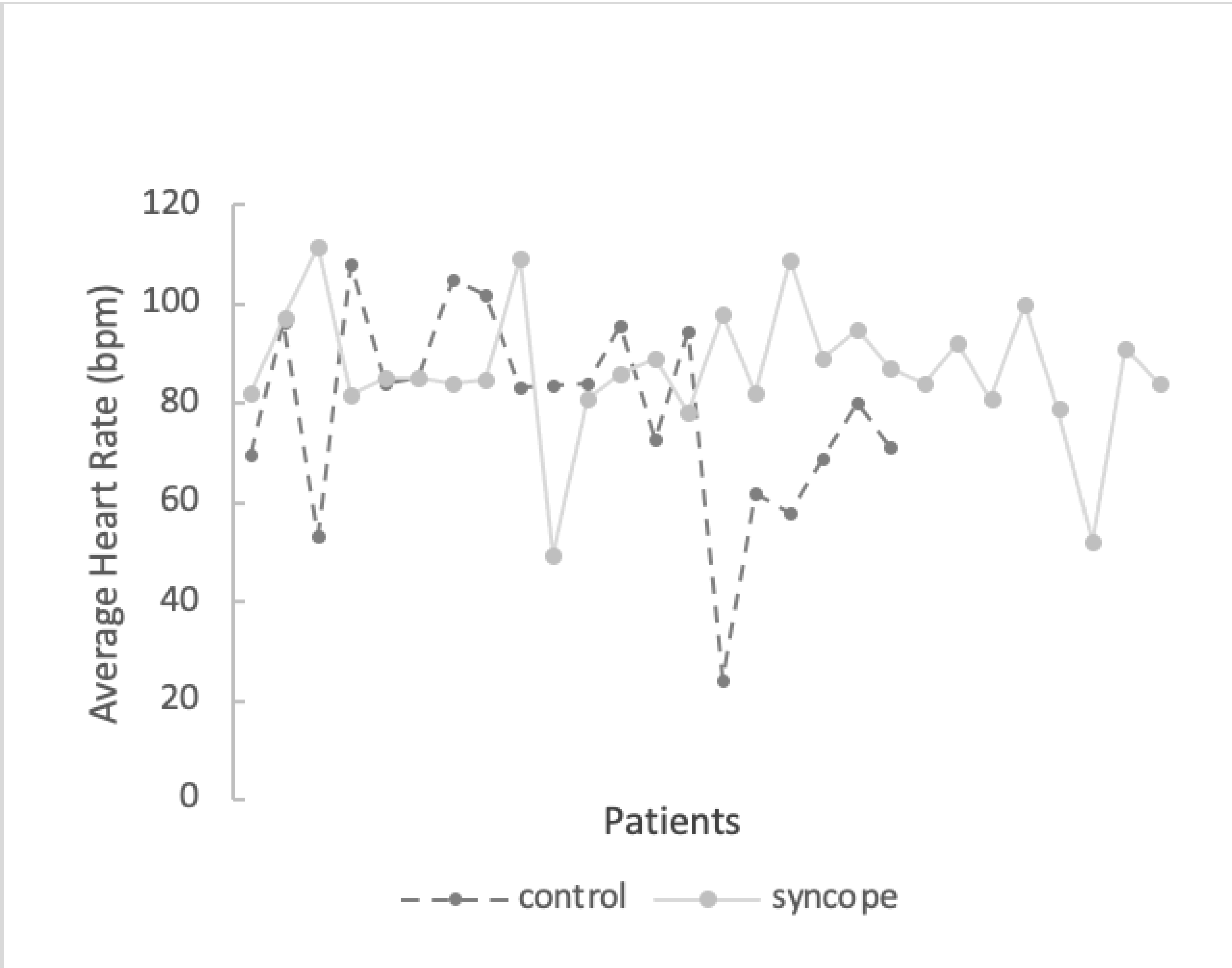

Figure 1

Average starting heart rates corresponding to the control group and syncope group.

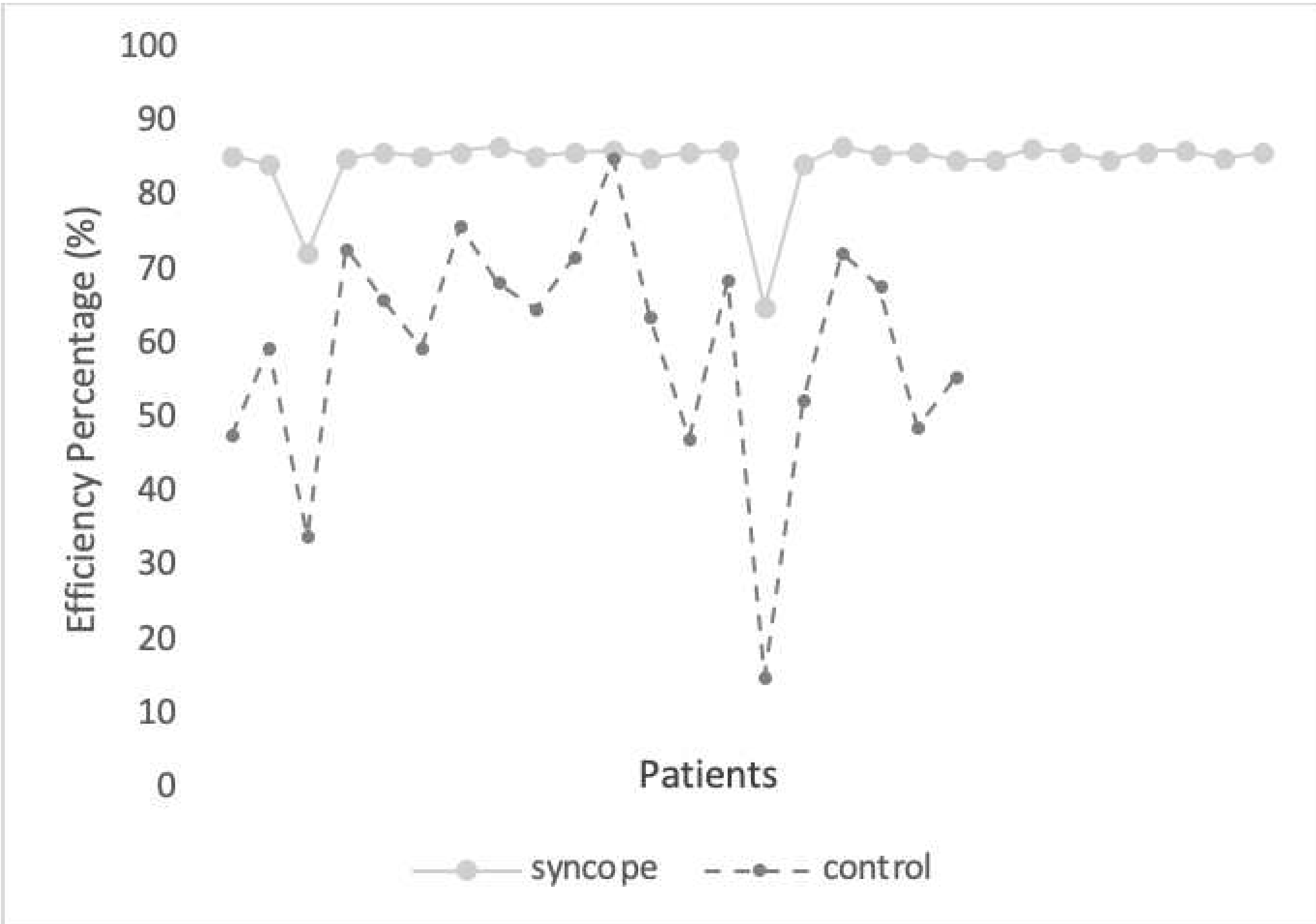

Figure 2

Efficacy Percentage for control group and syncope group

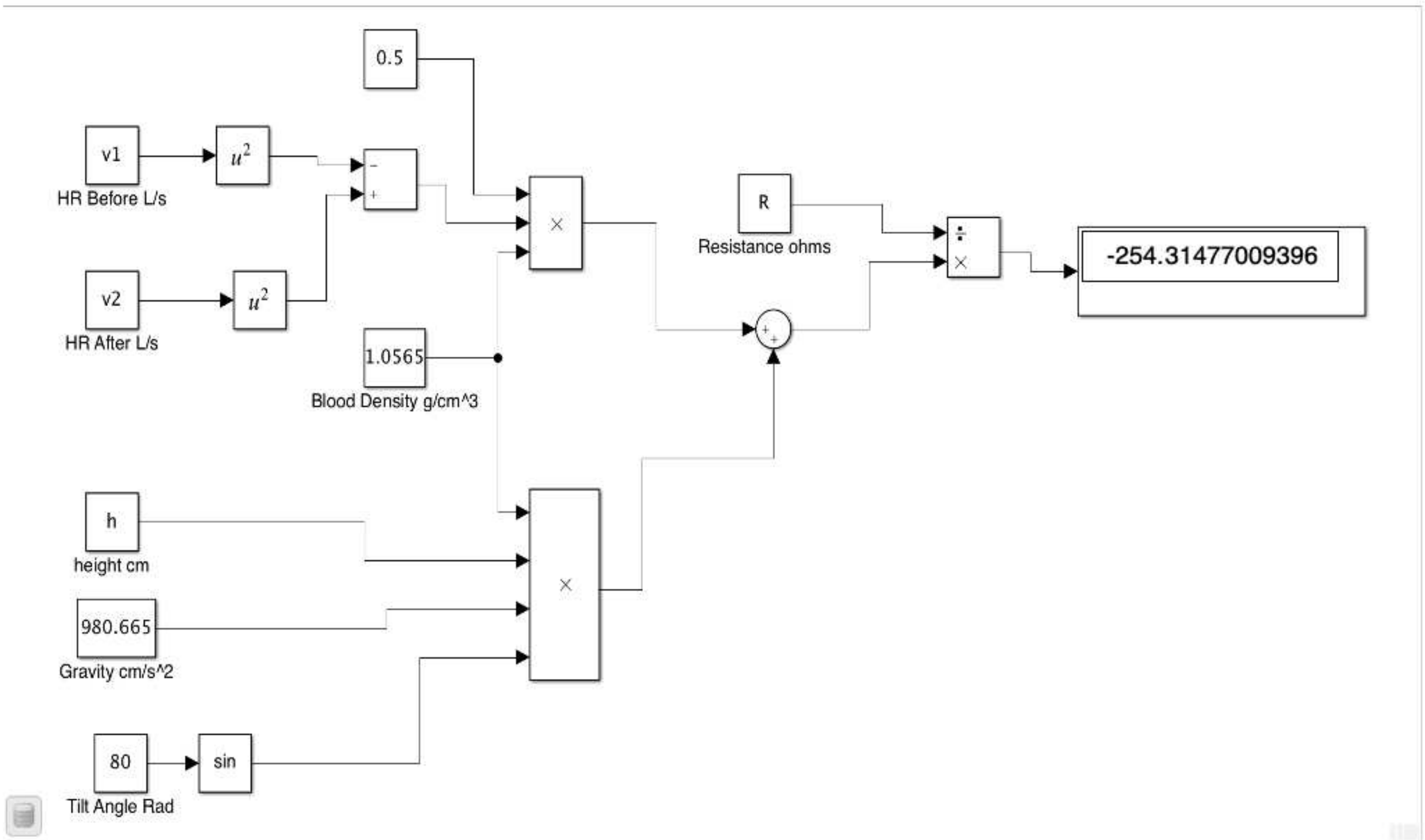

Figure 3

Simulink model for Eq 6

Supplementary Files

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- AppendixA.png