Cardioinhibitory Carotid Sinus Syndrome - A Mathematical Model

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***Abstract*— Carotid sinus massage (CSM) is a simple clinical test for stimulating the carotid sinus reflex. During CSM, firm longitudinal massage is applied at the point of maximal pulsation over the carotid bifurcation resulting in relative bradycardia. CSM is used to diagnose Cardioinhibitory Carotid Sinus Syndrome (CICSS). CICSS is an age-related disorder, characterized by profound symptomatic cardioinhibition (> 3 seconds pause) following CSM. CICSS prevalence increases with age and is responsible for 1 to 20% of all pacemaker implantations per year. Treatment options for CSS are limited and much debate still remains around its underlying etiology. In this paper we present a first computer simulation of carotid sinus massage (CSM) in older adults and demonstrate its ability to simulate normal heart rate responses to CSM. Importantly we demonstrate that our mathematical model requires inclusion of model elements to simulate autonomic control of perinodal T-cell activity in order to replicate the profound cardioinhibitory response observed in CICSS. Our model findings implicate CSS as a candidate biomarker of biological aging and frailty.**

I. Introduction

Carotid Sinus Massage (CSM) is a simple clinical test for stimulating the carotid sinus reflex [1][2]. During CSM, firm longitudinal massage is applied at the point of maximal pulsation over the carotid bifurcation at the level of the crichoid cartilage [2][3]. The 'classical' cardiovascular response to CSM is well accepted. Strain sensitive baroreceptors embedded in the adventitial layers of the internal carotid artery (ICA) are activated by massage induced deformation of the ICA wall. Action potentials generated by increased strain are transmitted to cardiovagal and vasomotor areas of the brainstem medulla via glossopharyngeal nerves. Vagal activation and sympathetic withdrawal ensues, resulting in cardioinhibition and vasodilatation, leading to bradycardia and systemic hypotension [4]. Importantly, this response is presumed hypersensitive and exaggerated in Carotid Sinus Hypersensitivity (CSH). When CSH is accompanied by symptoms Carotid Sinus Syndrome (CSS) is diagnosed. Cardioinhibitory CSS (CICSS) is an age-related disorder, characterized by exaggerated cardioinhibitory (> 3 seconds pause) responses to CSM [4]. CICSS is responsible for 1 to 20% of all pacemaker implantations per year [5]. CSS is a well-recognized finding in those with syncope and recurrent unexplained falls in the elderly [6][7]. A number of issues remain surrounding our understanding of CSS. Firstly treatment options are inadequate in a significant proportion of older adults [6][7]. Secondly, much debate still remains around the underlying pathophysiology of CSH and CSS with central [8], and peripheral [9] hypotheses being suggested. Finally only CSM consistently detects the "so-called" hypersensitive response in CSS, while other well-known tests of baroreflex and autonomic control often suggest the presence of blunted or unchanged neural control in the same pathology. This confusion may in part be due to the lack of clarity surrounding the effects of CSM at a systems level, and the influence of age and disease on the baroreflex. Further insight into the mechanisms of CSM and the effects of normal and pathological ageing on the baroreflex, should foster development of treatment options for CSS and next generation diagnostic approaches. As a step toward greater understanding of CSM and CICSS, we develop a mathematical model of the baroreflex, capable of simulating the primary cardioinhibitory responses to CSM. This model is used to develop insight into candidate mechanisms that underlie the etiology of CICSS.

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II. Aim

The following are the aims of this paper.

1. Develop a comprehensive cardiovascular model capable of simulating the normal heart rate response to CSM.
2. Simulate pathological 'hypersensitive' cardio-inhibitory responses to CSM.

III. Model Development

A. Vascular Model Architecture

Our cardiovascular model consists of a compartmental electrical equivalent model which predicts blood pressure and volumetric blood flow (Fig.1) after Heldt et al. [10]. Each compartment is represented by a vascular segment building block shown in Fig.1, where a compliance element, C_i, is separated by resistance to flow (inflow R_n and outflow R_{n+1}). The following governing equation for a generic compartment to represent the nth vascular segment is derived (Note - the extra vascular pressure, Pe, is set to zero) as follows

$$C\, dP_n/dt = (P_{n-1} - P_n + P_h)/R_n - (P_{n+1} - P_n)/R_{n+1}. \quad (1)$$

A. Cardiac Model

A pulsatile time-varying capacitance model was selected to model the pumping action of the heart [11].

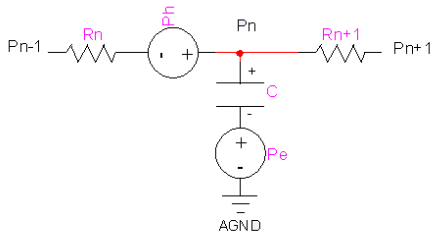

Figure 1: Electrical Equivalent circuit of a vascular segment compartment (Adapted from [10])

The pressure-volume relationship during systole, P_s, is given by

$$C\, dP_s = E_s(V - V_0) \quad (2)$$

where E_s is peak systolic elastance and V_0 is systolic unstressed volume, while during diastole the pressure volume curve follows a positive exponential function

$$P_d = P_0\, e^{(ke(V-Vs)-1)} \quad (3)$$

where P_0 and k_e are parameters describing this function and V_s is the diastolic unstressed volume. A time dependent expression for cardiac chamber pressure, P(t), results where

$$P(t) = (1-\sigma(t))P_d + \sigma(t)\, P_s. \quad (4)$$

Cardiac valves are modelled by pressure dependent resistances.

B. Autonomic Reflex Control

Autonomic reflexes responsible for short term regulation of arterial blood pressure and blood flow are included. Elements of note include a unilateral baroreflex and CSM stimulation model, autonomic control of perinodal T Cells.

1) Arterial Baroreflex Model

A modified model of the baroreflex based on a set-point non-linear negative feedback topology was adopted after Heldt et al. [10]. Mean arterial blood pressure, P_a, is sensed by arterial baroreceptors which regulate effector organs. Carotid sinus pressures are calculated according to

$$p_{cs} = \rho g h_{cs} \sin\alpha(t) + P_a - p_{car} \quad (5)$$

where h_{cs} is the vertical height of carotid sinus above the aorta, α is the standing angle, p_{car} is pressure dropped across the carotid artery and P_a is the mean aortic pressure. Sensed blood pressures are subtracted from the set-point pressure, p_{set}, to give an effective error signal, e, for the control system, which is then passed through a static soft limiter function [11]:

$$f = 18 \arctan(e/18) \quad (6)$$

2) SA Node Control

Cardiac pacemaker activity is simulated using an Integral Pulse Frequency Modulation (IPFM) scheme [12]. An input signal, $m_{SA}(t)$, is integrated until the result crosses a predetermined firing threshold, T_{SA}. The equation for the integrator input is given by

$$m_{SA}(t) = (k_0 - k_1(k_2 f_p(t) - k_3 f_s(t)) + sp \quad (7)$$

where k_0 is the baseline rate of rise of the SA node cell potential, k_1 controls the influence of autonomic activity on the SA node, $f_s(t)$ and $f_p(t)$ are time-dependent firing frequencies of sympathetic and parasympathetic systems, sp is the tonic activity of autonomic activity at the SA node, k_2 is the weight of parasympathetic activity and k_3 is the weight of sympathetic activity. A beat is initiated every time the function $m_{SA}(t)$ exceeds T_{SA}, allowing the current HR to be calculated as

$$HR = 1/(t_i - t_{i-1}) \quad (8)$$

where t_i and t_{i-1} are the times of occurrence of the current and previous beats respectively and the beat index is denoted by i.

3) Perinodal T Cell Control

Here a modified integrate and fire model described by Ward et al. [12] is used to simulate the tissue polarization potentials of perinodal T cells

$$m_{AV}(t) = (k_4 - k_5(k_6 f_{pav}(t) - k_7 f_{sav}(t)) + k_8 RP_{n-1}(t) + AT_{av} \quad (9)$$

where k_4 is the normal rate of rise of the perinodal T cell resting potential, k_5 adjusts overall autonomic effects on these cells, k_6 and k_7 are the weight of parasympathetic and sympathetic influence on the T cells, k_8 is the weight of the recovery effect, $f_{pav}(t)$ and $f_{sav}(t)$ are the time-varying sympathetic and parasympathetic effects on the perinodal T cells, RP_{n-1} represents the preceding R-to-P interval and AT_{av} is the tonic background T cell activity activity.

C. Carotid Sinus Massage

To model CSM at time, T_1, we transiently decouple the carotid sinus feedback loop under stimulation, increase its input pressure, P_{cs}, to 300mmHg (equivalent to increasing its strain) for the duration of the stimulus, while simultaneously increasing carotid artery resistance, R_{cs} by increasing the external pressures surrounding the carotid. With cessation of CSM, at time T_2, carotid resistance is returned to its nominal value and baroreceptor input is recoupled to the prevailing carotid sinus pressures. It is important to note that system pressures and flows are governed by the resistance change in the carotid only. The duration of CSM was chosen to last 5 seconds as recommended in the International Syncope Guidelines [4].

D. Parameter Selection

The model parameterisation was based on values in literature for a 170cm, 70kg male with a total blood volume of 5100ml and cardiac output of 4800 ml/min. For brevity model parameters are not detailed further here.

E. Experimental Protocol

Clinical data was obtained from patients (N=92, 46 male, 67+/-7.5 years) who were recruited prospectively from a clinical Falls and Blackout facility. Patients underwent routine clinical and cardiovascular assessment. Continuous BP responses were then recorded (200Hz; 12 bit AD) using a calibrated volume clamp method (Finometer®, Finapres Medical Systems, Arnhem, The Netherlands) in a quiet, comfortably lit room maintained at an ambient temperature of 21-23°C. A 12-lead, 500Hz, electrocardiogram (Mortara

Eli 350, Mortara Instruments Inc., 7865N, 86TH Street Milwaukee, WI53224, USA) was also performed according to international guidelines during CSM to monitor rate and rhythm changes following CSM. Participants rested in the supine position for 10 minutes. CSM was then performed. Firm longitudinal massage was applied for 5 seconds at the point of maximal pulsation over the carotid sinus on the right and then left sides allowing at least 60-seconds interval between each stimulus [4]. Systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) values were monitored throughout the supine, CSM stimulation and recovery periods. The study had ethical approval from the local ethics committee.

IV. Results

A. Simulation of the Normal Response to Carotid Sinus Massage in Older Adults

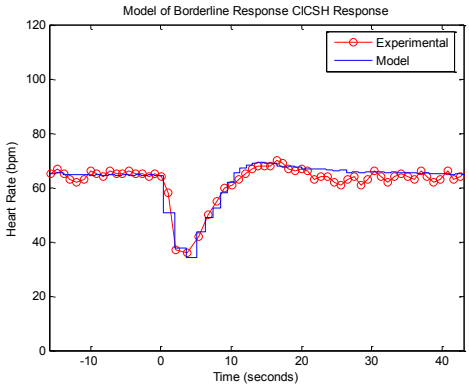

Figure 2: Typical heart rate response to carotid sinus massage (CSM). Comparison of model (blue) and clinical data (red). N = 1.

1) Heart Rate Response to CSM

Fig. 2 shows the comparison of a patient record of HR to model predicted values. Model based transient responses to left sided CSM are similar to experimentally recorded data, although some differences exist. Minor tuning was performed to improve matching of data. In particular, matching of resting heart rate and blood pressure set points, increased range of baroreflex sigmoid range and decreased gain of the vascular baroreflex loops were required. All other parameters remained fixed.

B. Simulation of Cardioinhibitory Carotid Sinus Syndrome

1) SA Node Model of CICSS

Initial matching of the pathological heart rate response (Figure 3) was attempted using a pure SA node model coupled with increasing baroreflex gain and range. However adequate slowing was difficult to achieve under this structure. Physioloigically unrealistic values for baroreflex gain (>60msec/mmHg), baroreflex range (>800mmHg), and CSM stimulus (800mmHg) equivalent pressure were required to obtain significant slowing.

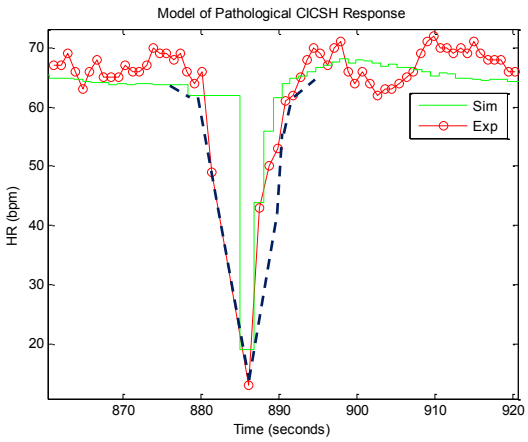

Figure 3: Cardioinhibitory CSS. N =1.

2) Perinodal T cell Model of CSH/CSS

The abrupt pause in the heart rate response in Figure 3 suggests a threshold crossing in the dynamics of heart rate control. One possible mechanism of this is sinoatrial exit block or AV nodal block. Here we included a model of autonomic perinodal T cell control to capture this behaviour. Simulations using physiologically appropriate values of baroreflex sensitivity (5msec/mmHg), baroreflex range (40mmHg) and CSM stimulus amplitude (80mmHg equivalent pressure) were performed to capture this response. Furthermore to induce sinoatrial exit block the gain of autonomic limb serving perinodal T cells was higher than the SA node by a factor of 3.5. A pause of over 3 seconds was achieved using this model configuration (See Figure 3).

V. Discussion and Conclusion

In this paper we describe a mathematical simulation of the cardiovascular response to CSM in normal individuals and pathological responses in those with CICSS. Novel aspects of the model include a model of the CSM stimulus, bilateral baroreceptors, and components to capture baroreflex modulation of perinodal T cell activity. The model reproduces the normal cardioinhibitory response to CSM quite convincingly. This would suggest that a simple SA node model coupled with a non-linear soft limiting baroreflex feedback function accounts adequately for the normal variations in CSM responses seen in healthy adults. However as the degree of cardioinhibition approaches 3 seconds the model performance diverges from experimental responses i.e. significant overshoot and underdamped oscillations occur in BP and HR responses. These are presumably caused by an abnormally high baroreflex gain and range.

Experimental evidence on the other hand supports an age-related blunting and slowing of responses in autonomic disorders, although the presence of overshooting BP responses should also be acknowledged [13]. The prevalence of CSS is also known to increase in the presence of other autonomic disorders associated with blunted autonomic responses e.g. orthostatic hypotension [14]. The hypersensitivity hypothesis proposed by O'Mahony et al.

[15] suggests that upregulation of central alpha2 adrenoceptors underlies the exaggerated responses seen in CSH. This however has yet to be supported experimentally [16][17]. Furthermore measurements of baroreflex sensitivity in CSS have been conflicting with both increased [18] and decreased baroreflex gain [17] reported.

Given the increased susceptibility of individuals to sino-atrial exit block with age [19], we included a model of perinodal T cell control. This addition allows significant cardioinhibition to be simulated. The relative gain between T cell's and the SA node was increased and important in determining the degree of sino-atrial exit block. If this model is correct this would suggest that differences in cardiac cell sensitivity to vagal stimulation may predispose certain individuals to profound cardioinhibition as they age. Future experimental work at a cellular and tissue levels is required to confirm this hypothesis.

Other important factors in determining the CSM response include an increased strain stimulus magnitude imparted during CSM, a small decrease (or no change in baroreflex sensitivity) and an increased baroreflex range. It is possible that CSM represents a larger strain stimulus compared to other baroreflex stimuli, and therefore recruits supranormal levels of baroreceptors during massage. Age-related changes in the baroreceptors e.g. changes in resetting stimulation threshold and saturation effects may play a role here [20]. Given the close proximity of carotid body to the baroreceptors, and the established link between respiratory modulation of arterial pressure [23] and heart rate it is likely that cardiorespiratory integration may modulate the CSM response.

The direction and magnitude of factors involved in modelling CICSS responses suggest that blunting and saturation of regulatory autonomic responses in the face of large CSM disturbance stimuli may occur more easily with increasing age. In CICSS this may increase the magnitude and duration of the initial response to the CSM stimulus, increasing sensitivity to sino-atrial exit block and reducing the rate of recovery thereby prolonging asystole and may be an alternative to the "hypersensitivity theory" previously suggested [15]. Furthermore the pathological responses seen in CSH/CSS are suggestive of age-related dysregulation, a hallmark of frailty [21]. We therefore suggest that CICSS is a possible biomarker of biological ageing and frailty and therefore associated with age-related clinical outcomes such as falls [22]. It is our hope that that this work will shed further light on the underlying mechanisms of CICSS and inform future clinical management strategies for CSS.

VI. Acknowledgment

The authors would like to acknowledge the support of the patients and staff of the Falls and Blackout Unit, St James's Hospital, Dublin, and the Department of Medical Physics and Bioengineering, St. James's Hospital, Dublin.

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