

# Computational modelling of cardiac control following myocardial infarction using an *in silico* patient cohort

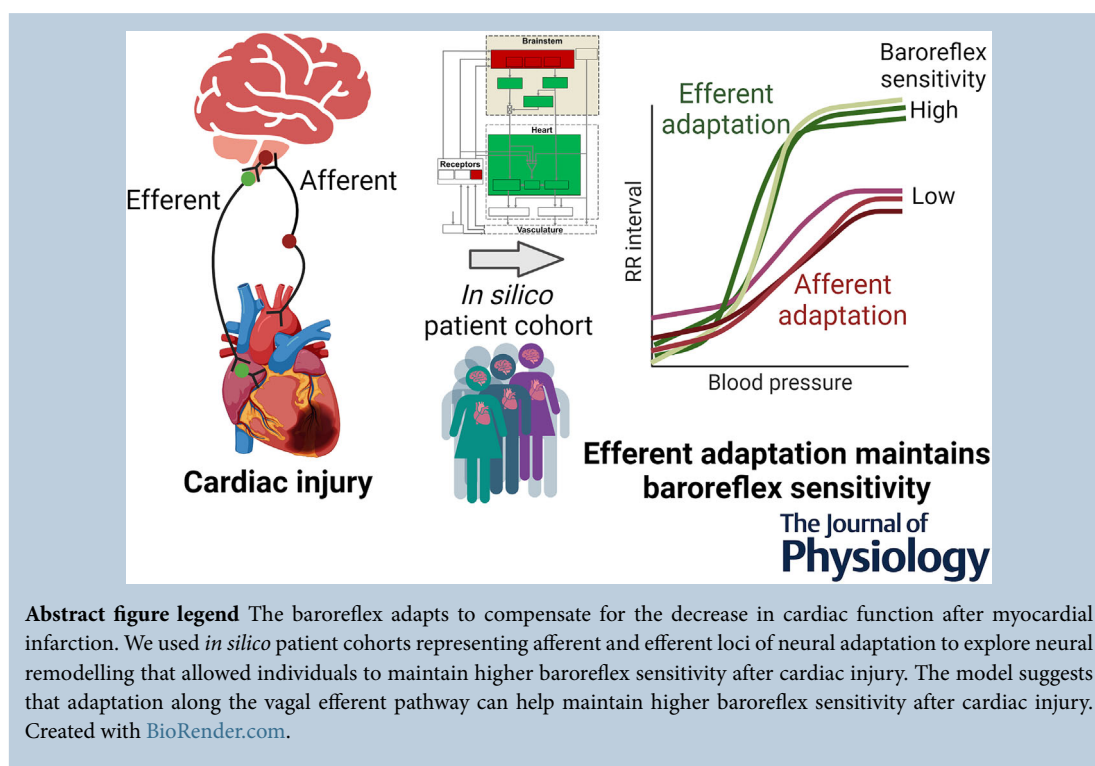
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Artificial intelligence generated content disclosure: ChatGPT-4 was used to generate plotting functions and improve commenting in code. All code generated was verified by reading the code and checking that the plotted output was reasonable.

**Abstract** Loss of cardiac physiological function following myocardial infarction (MI) is accompanied by neural adaptations in the baroreflex that are compensatory in the short term, but then become associated with long-term disease progression. One marker of these adaptations is decreased baroreflex sensitivity, a strong predictor of post-MI mortality. The relative contributions of cardiac remodelling and neural adaptation in the sensory, central brainstem and peripheral ganglionic loci to baroreflex sensitivity changes remain underexplored. We used a computational model-based approach that accounts for the short-term dynamics of closed-loop human cardiac control to integrate disparate experimental studies on neural adaptation following MI into a unified quantitative framework. We developed an ensemble of 59 distinct model parameterizations that account for the clinically observed heterogeneity of cardiac control in healthy individuals. We simulated an *in silico* cohort of 35,400 patients with MI, corresponding to six scenarios of one or more loci of neural adaptation coupled with cardiac remodelling. We evaluated the range of MI-induced shifts in arterial pressure, heart rate and baroreflex curve responses. Our results show that adaptation in any single neural locus coupled with cardiac remodelling is sufficient to account for the MI-induced haemodynamic and autonomic changes observed experimentally. Of the adaptation pathways, we found that individuals with central or peripheral vagal efferent adaptation and preserved baroreceptor gain could maintain high baroreflex sensitivity after ischaemic injury. These results suggest that there are a multitude of adaptive pathways for tuning the baroreflex circuit to shift cardiac control physiology, potentially explaining patient heterogeneity post-MI.

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### Key points

- Baroreflex sensitivity is a strong indicator of post-myocardial ischaemia survival and is variable among individuals.
- We fine-tuned a computational model ensemble based on physiological observations to develop an *in silico* patient cohort consistent with the range of baroreflex responses observed experimentally.
- Simulation and analysis of the *in silico* cohort show that individuals with a functional afferent pathway and the ability to adapt along the vagal efferent pathway can maintain baroreflex sensitivity post-cardiac ischaemia.

## Introduction

Myocardial ischaemia and the subsequent injury to the cardiac tissue trigger a multitude of changes to heart physiology, including ventricular stiffening and loss of contractility. Reperfusion leads to an inflammatory response that further exacerbates the injury around the infarct. These changes can result in a variety of haemodynamic states ranging from hypotension to hypertension in different individuals (Ma et al., 2015). In addition to alterations in cardiac physiology, adaptation of closed-loop neuronal regulation occurs simultaneously in an attempt to maintain cardiovascular homeostasis. Although the majority of the investigational focus and therapeutic attention has been on the cardiac remodelling

aspect, there is mounting evidence that neural adaptation may also play a role in the aberrant physiological response following myocardial infarction (MI) (Sabbah, 2012). Neuronal adaptations to compensate for decreased cardiac function after MI deliver short-term gains that are assumed to result in long-term cardiovascular disease progression (Floras, 2009; Herring et al., 2025). Several questions regarding neural adaptation following myocardial infarction have been posed in the recent white paper by Herring et al. (2025). We aim to address one such neural adaptation, the observed decrease in baroreflex sensitivity after cardiac injury, which is correlated with increased cardiac mortality in patients with recent myocardial infarction (La Rovere et al., 1998).

The baroreflex is a complex control system that regulates cardiac function on a beat-to-beat basis via several neural loci. Adaptation contributing to decreased baroreflex function could originate from the periphery via the baroreceptors, the intrinsic cardiac nervous system (ICN), dorsal root ganglia and the stellate ganglia, or centrally in multiple autonomic nuclei, including the nucleus tractus solitarius (NTS), nucleus ambiguus (NA), dorsal motor nucleus of the vagus (DMV), rostral ventral lateral medulla and caudal ventrolateral medulla. There is a variety of evidence to support neuronal adaptation in response to ischaemic injury in these neural groups, including neuropeptide and morphological changes in the stellate ganglia (Ajjola et al., 2015) and transcriptomic changes in the DMV (Gorky et al., 2021), as well as structural and functional remodelling in the ICN (Rajendran et al., 2016). It is reasonable to expect that different loci of neural adaptation could adapt, depending on the individual, contributing to the heterogeneity observed clinically. We propose that differential balance of nuclei across the baroreflex arc may be partially responsible for the diversity in baroreflex function observed clinically.

We approach this hypothesis using a computational modelling and simulation strategy to overcome the challenges in unpacking the experimental complexity to discern the contributions of each neural locus to baroreflex adaptation in health and disease. Experimental interventions will probably induce new adaptations in other parts of the closed-loop cardiovascular control system, making it difficult to tease apart the cause and effect relationships. Closed-loop computational models of the baroreflex are established predictive tools for describing the heart rate response to blood pressure changes (Ursino, 1998). These models have been used to predict changes under a variety of conditions and gain insights on physiological phenomena including exercise (Park et al., 2020), hypoxia (Ursino & Magosso, 2000) and respiratory sinus arrhythmia (Ben-Tal et al., 2012). To date, many models of the baroreflex have been proposed, but only a few have considered baroreflex changes following myocardial infarction (Kember et al., 2017), and only in ways that do not explicitly include cardiac damage. On the other hand, computational approaches that explicitly model the cardiac physiology are usually computationally expensive finite-element models or are focused on the immune response following MI, and do not include baroreflex regulation in the quantitative scheme (Berberoglu & Göktepe, 2015; Sáez & Kuhl, 2016). Furthermore, computational models that account for individual heterogeneity of cardiac physiology have been explored to a limited extent and are actively emerging in recent studies (Argus et al., 2022; Niederer et al., 2020; Yang et al., 2023). These computational models tend to address the cardiac, respiratory or drug response level,

but limited work has been done on variability of the baroreflex.

In the present study, we aim to address a question on adaptations in cardiac control with cardiovascular disease posed in the recent white paper on translational advancements and potential in neurocardiology (Herring et al., 2025). The white paper brings forward the question ‘How does localized pathology in specific regions of the neural hierarchy influence the behaviour of the system as a whole?’ We aim to address this question more specifically by exploring the question of how localized pathology in the heart influences the system as a whole and how specific regions of the neural hierarchy can compensate for that pathology. We hypothesize that adaptation in a subset of neural loci is sufficient for maintenance of baroreflex sensitivity after ischaemic insult. We generate and simulate an *in silico* patient cohort that accounts for inter-individual heterogeneity, and is consistent with the range of haemodynamic behaviour observed clinically, to capture closed-loop cardiac autonomic control aspects with high fidelity. Our overall strategy is to compare pre- vs. post-ischaemia/reperfusion models over the range of neural loci of adaptation and identify characteristics of virtual patients with higher baroreflex sensitivity after myocardial injury.

## Methods

The present model extends our previously published work on baroreflex control of the cardiovascular system (Gee et al., 2023). Briefly, the cardiovascular control model consists of two main parts: (1) the cardiovascular system, represented by ordinary differential equations derived from mass balances of blood flow through body compartments, and (2) the neural control system, represented by sigmoidal functions representing the saturating firing behaviour of neurons (Fig. 1). The cardiovascular system model includes representations of the pulmonary and systemic circulatory systems and a pulsatile model of the heart. The neural portion of the model includes representations of sensory neuronal groups as well as brainstem and ICN neuronal groups. This model is used to simulated pre-ischaemia/reperfusion (pre-I/R) and post-ischaemia/reperfusion (post-I/R) *in silico* patient cohorts to examine adaptation following cardiac injury and the role of inter-individual variability.

### Pre-ischaemia model ensemble

The plausible range of baroreflex curves in healthy individuals was quantified using data from five individuals and measured using neck chamber pressure (Seredyński et al., 2021). To quantify the characteristics of these

baroreflex curves, these individual data were fit to the sigmoidal function:

$$RR_{interval} = \frac{A1}{1 + \exp [A2 (ECSP - A3)]} + A4 \quad (1)$$

which was previously used by Fadel et al. (2003) and Seredyński et al. (2021). In this case, we have fit the RR interval response to estimated carotid sinus pressure (ECSP), which is the pre-stimulus mean arterial pressure minus the neck chamber pressure. The parameter *A1* represents the response range (maximum – minimum), *A2* represents the gain coefficient (i.e. the slope of the sigmoid), *A3* represents the centring point for the horizontal shift of the sigmoid and *A4* represents the minimum response. Equation (1) is used to quantitatively compare the model predictions of overall baroreflex function with experimentally measured baroreflex curves and filter out plausible models.

To develop an averaged cardiovascular control model capturing this pre-I/R RR interval response to carotid sinus pressure changes, we re-estimated a minimal set

Table 1. Updated parameter values for nominal model that differ from Gee et al. (2023)

| Parameter     | Value | Units |
|---------------|-------|-------|
| $PN_{NA,min}$ | 1.69  | Hz    |
| $PN_{NA,max}$ | 7.33  | Hz    |

of parameters from our previously published model (Gee et al., 2023). The two parameters representing the minimum and maximum firing rate of the population of ICN neurons that regulate heart rate were re-fit to match the average baroreflex curve response of the data from Seredyński et al. (2021). All other parameter values were the same as in the previous model and the new parameter values are provided in Table 1.

The sensory neuronal groups include baroreceptors that convert arterial pressure changes into electrical signals. Based on prior models (Gee et al., 2023; Park et al., 2020; Ursino, 1998), the baroreceptors are represented by a linear derivative first-order dynamic function and

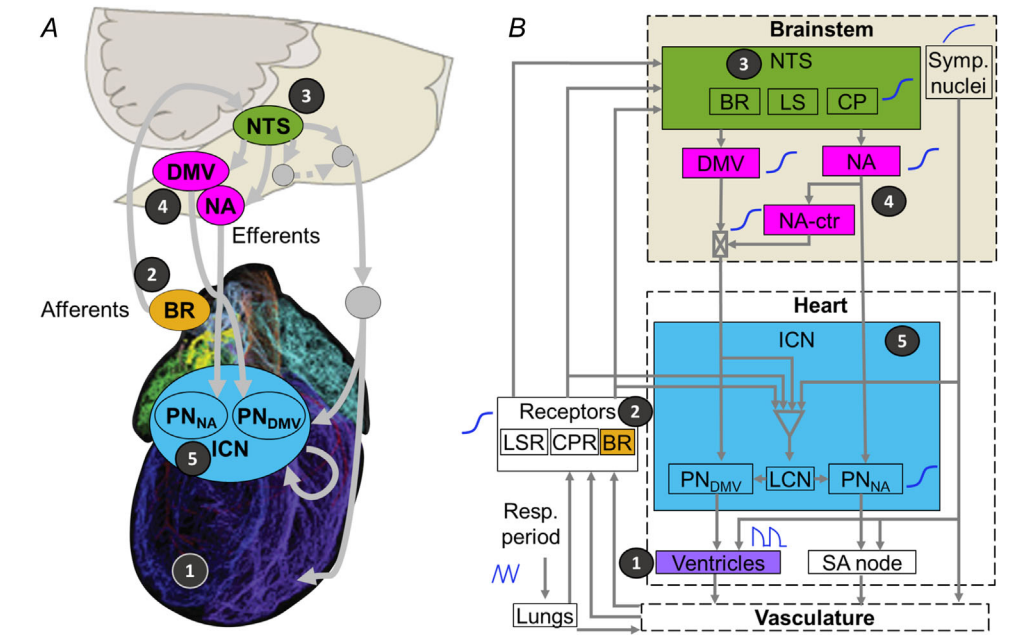


Figure 1. Baroreflex anatomy and physiology mapped onto alternative computational models representing adaptation in different loci of neural regulation

A) anatomical representation of neuronal controllers involved in closed-loop regulation of cardiovascular function. B) schematic of closed-loop baroreflex model. Parameters representing cardiac muscle property changes that occur after myocardial ischaemia and reperfusion are adapted in alternative model 1. Alternative models 2–5 represent cardiac parameter adaptation to represent myocardial injury along with neural adaptation in: (2) the baroreceptors, (3) the nucleus tractus solitarius (NTS), (4) the nucleus ambiguus (NA) and the dorsal motor nucleus of the vagus (DMV), and (5) the intrinsic cardiac nervous system (ICN). The lines in blue represent the forms of the functions (e.g. sigmoidal for the neuronal groups). Image of the heart reproduced with permission from Achanta et al. (2020). NA-ctr, nucleus ambiguus contribution to cardiac contractility; LS, lung stretch receptor subtype; CP, cardiopulmonary receptor neuronal subtype; LSR, lung stretch receptor; BR, baroreceptor; CPR, cardiopulmonary receptor; PN<sub>DMV</sub>, principal neuron with inputs from the DMV; PN<sub>NA</sub>, principal neuron with inputs from the NA; LCN, local circuit neuron; SA, sinoatrial; resp., respiration; symp., sympathetic. Created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

a sigmoidal static function in series as indicated by experimental results (Chapleau & Abboud, 1987):

$$\tau_p \frac{d\dot{P}}{dt} = P_{br} + \tau_z \frac{dP_{br}}{dt} - \dot{P} \quad (2)$$

$$f_{br} = \frac{f_{min} + f_{max} * \exp\left(\frac{\dot{P} - P_n}{k_a}\right)}{1 + \exp\left(\frac{\dot{P} - P_n}{k_a}\right)} \quad (3)$$

Equation (2) converts the measured arterial pressure  $P_{br}$  to the output variable of the dynamic function  $\dot{P}$  (with dimensions of pressure). The time constants  $\tau_p$  and  $\tau_z$  are for the real pole and real zero in the linear dynamic block.  $\dot{P}$  is converted to the baroreceptor firing rate ( $f_{br}$ ) in eqn (3), with the minimal and maximal output firing rate given by  $f_{min}$  and  $f_{max}$ , respectively.  $P_n$  is the intrasinus pressure at the central point of the sigmoidal

inputs with information on arterial pressure, cardio-pulmonary receptor inputs with information on pressure in the heart chambers, and lung stretch receptor with information on lung inflation). NTS neurons project to the NA and DMV, which transmit signals through the vagus nerve to the ICN. Neuronal tracing studies have shown that the NA and DMV project to separate populations of principal neurons (PN) in the ICN, and so we have included representations of those neuronal groups in the model (PN<sub>NA</sub> and PN<sub>DMV</sub>). These separate populations interact via local circuit neurons (LCN) that also incorporate sensory information, forming an inner feedback loop (Cheng et al. 2004).

Effector functions based on mathematical relationships derived from experimental measurements then translate firing rates from the ICN into changes in heart rate (HR) and ventricular elastance (Ursino, 1998). Experiments on the effects of sympathetic activity and the time delays observed were used to inform a logarithmic relationship between elastance and sympathetic firing rate:

$$\sigma_{E,s}(t) = \begin{cases} G_{s,E_{max},lv} * \ln[f_{es,h}(t - D_{E,s}) - f_{es,min} + 1] & \text{if } f_{es,h} \geq f_{es,min} \\ 0 & \text{if } f_{es,h} < f_{es,min} \end{cases} \quad (5)$$

curve and  $k_a$  is the gain constant describing the magnitude of the response of the firing rate to pressure changes. Larger values of  $k_a$  mean the baroreceptors are less sensitive to pressure changes.

Sensory signals from the baroreceptors are sent to the brainstem where neuronal groups are represented by sigmoidal functions of the form:

$$f_{out,j} = \frac{f_{min,j} - f_{max,j}}{1 + \left(\frac{f_{input,j}}{f_{midpt,j}}\right)^k} + f_{max,j} \quad (4)$$

Equation (4) describes the input–output behaviour of the  $j^{th}$  neuronal group, where  $f_{min,j}$  and  $f_{max,j}$  are the minimal and the maximal output firing rates. Changes in the value of the parameter  $f_{midpt,j}$  shift the range of input firing rates to which the neuronal group is sensitive and the sigmoidal gain,  $k_j$ , represents the magnitude of the output firing rate change in response to a change in input firing rate.

These sigmoidal functions are used to describe brainstem neuronal subtypes in the NTS, NA and DMV as well as peripheral neuronal subtypes in the ICN. The NTS includes separate representations for neuronal subtypes based on previous single-neuron transcriptomic analysis, which indicated that neuronal subtypes in the NTS are distinct based on the inputs they receive (Park et al., 2014). Therefore, the model incorporates NTS neuronal subtypes that receive different types of sensory input (baroreceptor

where  $\sigma_{E,s}$ , is the effect of sympathetic activity on elastance,  $G_{s,E_{max},lv}$  is a gain value,  $D_{E,s}$  is a time delay, and  $f_{es,min}$  is a sympathetic activity constant, based on experiments on the effects of sympathetic activity and the time delays observed (Ursino, 1998). A first-order filter with time constant  $\tau_{T,s}$

$$\frac{d\Delta \frac{1}{E_{max,lv_s}}(t)}{dt} = \frac{1}{\tau_{E,s}} \left[ -\Delta \frac{1}{E_{max,lv_s}}(t) + \sigma_{E,s}(t) \right] \quad (6)$$

further blunts the effects on elastance. The parasympathetic contribution to ventricular elastance has a linear relationship between the vagal firing rate  $f_{ev,h}$  multiplied by gain  $G_{E,v}$  with time delay  $D_{E,v}$ ,

$$\sigma_{E,v} = G_{E,v} * f_{ev,h}(t - D_{E,v}) \quad (7)$$

also blunted by a first-order filter.

$$\frac{d\Delta \frac{1}{E_{max,lv_v}}(t)}{dt} = \frac{1}{\tau_{E,v}} \left[ -\Delta \frac{1}{E_{max,lv_v}}(t) + \sigma_{E,v}(t) \right] \quad (8)$$

The change in elastance as a result of sympathetic activity ( $\Delta \frac{1}{E_{max,lv_s}}$ ) and the change as a result of parasympathetic activity ( $\Delta \frac{1}{E_{max,lv_v}}$ ) are summed to

produce the effect of neural activity on left ventricular elastance:

$$\frac{1}{E'_{max,lv}} = \Delta \frac{1}{E_{max,lv_s}} + \Delta \frac{1}{E_{max,lv_v}} \quad (9)$$

The effect of neural activity is added to the baseline elastance, obtained from a denervated heart (Park et al., 2020; Ursino, 1998; Ursino & Magosso, 2000) with the baseline elastance ( $E_{max,lv,0}$ ) to calculate the ventricular elastance:

$$E_{max,lv} = E'_{max,lv} + E_{max,lv,0} \quad (10)$$

Equations representing the effects of sympathetic activity on arterial resistances and venous unstressed volumes have the same form as eqns (5) and (6). Parameters were similarly adapted from previous models, which were measured or deduced from empirical observations of relationships between physiological variables (Park et al., 2020; Ursino, 1998; Ursino & Magosso, 2000).

### Summary of experimental data used to filter accepted models

Data from three studies were used to filter the accepted models. The data used to constrain the pre-I/R baroreflex curves were from Sereďński et al. (2021). These baroreflex curve data were collected in healthy subjects using a neck chamber pressure device to control carotid sinus pressure, whereas RR interval was measured. Because paired pre- and post-I/R data were not available in humans, experimental data from rats were used (Mastitskaya et al., 2012). HR and mean arterial pressure (MAP) were measured prior to myocardial ischaemia caused by a left anterior descending artery ligation. After 30 min of cardiac ischaemia, the heart was reperfused and HR and MAP were measured again 120 min later. There were other HR and MAP measurement timepoints included in the study, but the 120 min post-ischaemia timepoint was selected because it was the closest in time to what could be measured clinically post-I/R. In addition, this study included other experimental groups with selective silencing and activation of the dorsal motor nucleus of the vagus. However, because of the limited data points, large number of parameters estimated in this model, and low likelihood of finding appropriate baroreflex curve data to help constrain the model, the other experimental group data points were not used. The available post-I/R baroreflex curve data were from MI patients 30–72 h after the first occurrence of chest pain. The patients had no evidence of a previous MI, no history of hypertension, diabetes, or other major cardiovascular diseases. Baroreflex curve data were measured using neck chamber pressure.

### Parametric sensitivity analysis

To decrease the number of cardiac parameters to estimate to represent the pre- and post-I/R models, we performed a global sensitivity analysis to determine which parameters significantly affected HR and MAP. A density-based sensitivity analysis known as PAWN (Pianosi & Wagener, 2018) was selected because the underlying distribution of the outputs was unknown and because this method has been used successfully in other cardiovascular system models (Gee et al., 2023; Park et al., 2020). To determine the underlying distribution, PAWN uses cumulative density functions (CDF) to characterize the model output of interest ( $y$ ) and determine the output sensitivity to the parameter of interest ( $\theta$ ). Two sets of simulations were performed. The first set varied all parameters simultaneously to produce unconditional CDFs ( $F_y(y)$ ). The second set varied all inputs except the parameter of interest to produce conditional CDFs ( $F_{y|\theta_i}(y|\theta_i)$ ). To determine the sensitivity of the output to changes in the parameter of interest, the distance between the unconditional and conditional CDFs was quantified using the Kolmogorov–Smirnov (KS) statistic. The sensitivity index for the  $i^{th}$  input factor is:

$$S_i = \text{statmax}_{\theta_i, y} |F_y(y) - F_{y|\theta_i}(y|\theta_i)| \quad (11)$$

where stat is a statistic chosen by the user (e.g. median). If the conditional and unconditional CDFs are close together, the output is sensitive to that parameter because varying other parameters did not cause a significant change in the output. If they are far apart, the output is not sensitive to the input parameter of interest. Because the KS statistic depends upon the value of the constant parameter, the PAWN method determines the KS statistic across many values. To combine these KS statistics, we use a summary statistic (e.g. median) to characterize the distribution of the KS statistic. This summary statistic varies from 0 to 1, with a value closer to 1 indicating a greater parametric influence on the output. To determine a threshold value for significant summary statistics, the PAWN method introduces a dummy parameter, which is known to have no effect on the output. If the summary statistic of a parameter is greater than the summary statistic of the dummy parameter, the output is sensitive to that parameter. In this analysis, we performed 40 000 simulations with six conditioning intervals and checked for convergence by performing additional simulations and confirming that the results remained the same. The PAWN method also includes bootstrapping to determine 95% confidence intervals for each sensitivity index.

### Peripheral vs. central contributions to heart rate regulation

The peripheral vs. central contributions to heart rate regulation were quantified using the Shapley value, which is a metric from game theory used to estimate the contributions of each player in a coalition game (Loh et al., 2022). To obtain the Shapley values, accepted parameter sets were used as the inputs to a support vector machine regression model with a polynomial kernel function that predicts heart rate. The regression model was validated using the mean square error between the predicted and actual heart rates. Because the relationship between each parameter and heart rate could be non-linear, the Shapley value was calculated for each parameter set. The average over each of these sampled points was calculated for each individual model for central (NTS, NA, DMV) and peripheral (ICN, baroreceptors) parameters. The ratio of peripheral to central contributions was then taken for each parameter set.

### Clustering analysis

Post-I/R models were clustered based on average afferent vagal activity, average efferent vagal activity, and baroreceptor responsivity. The analysis was performed using the tsne function in MATLAB R2023b (MathWorks Inc., Natick, MA, USA) with the Barneshut algorithm (van der Maaten, 2013), which was selected for its computational efficiency. The 'cityblock' distance metric was used because the input metrics are in different units. Twenty was used for the perplexity value, which quantifies the weighting of the local vs. global aspects of the data in running the analysis.

### Model equations

All model equations are adapted from Gee et al. (2023); Park et al. (2020); Ursino (1998); Ursino and Magosso (2000). The full set of nominal model parameters can be found at [https://github.com/Daniel-Baugh-Institute/CardiovascularControl/tree/main/Virtual\\_patient\\_cohorts](https://github.com/Daniel-Baugh-Institute/CardiovascularControl/tree/main/Virtual_patient_cohorts).

The vascular system is composed of mass and force balances. These equations from first-order principles are derived for the pulmonary and systemic circulatory system. The body compartments included in the model are the systemic, splanchnic, extrasplanchnic, skeletal muscle, thoracic and pulmonary arteries, and veins. In the pulmonary arteries, we have the mass balance for flow out of the right ventricle and into the pulmonary arteries:

$$\frac{dP_{pa}}{dt} = \frac{1}{C_{pa}} (F_{o,r} - F_{pa}) \quad (12)$$

The corresponding force balance at the pulmonary arteries is:

$$\frac{dF_{pa}}{dt} = \frac{1}{L_{pa}} (P_{pa} - P_{pp} - R_{pa} * F_{pa}) \quad (13)$$

The conservation of mass at pulmonary peripheral circulation (pp) is modelled as:

$$\frac{dP_{pp}}{dt} = \frac{1}{C_{pa}} \left( F_{pa} - \frac{P_{pp} - P_{pv}}{R_{pp}} \right) \quad (14)$$

The conservation of mass at pulmonary veins (pv) is modelled as:

$$\frac{dP_{pv}}{dt} = \frac{1}{C_{pv}} \left( \frac{P_{pp} - P_{pv}}{R_{pp}} - \frac{P_{pv} - P_{la}}{R_{pv}} \right) \quad (15)$$

The mass balance at systemic arteries (sa) is:

$$\frac{dP_{sa}}{dt} = \frac{1}{C_{sa}} (F_{o,l} - F_{sa}) \quad (16)$$

The force balance at systemic arteries is:

$$\frac{dF_{sa}}{dt} = \frac{1}{L_{sa}} (P_{sa} - P_{sp} - R_{sa} * F_{sa}) \quad (17)$$

Conservation of mass at peripheral systemic circulation – splanchnic, extrasplanchnic, and lower body compartments (sp, ep, mp) is:

$$\frac{dP_{sp}}{dt} = \frac{1}{C_{sp} + C_{ep} + C_{mp}} * \left( F_{sa} - \frac{P_{sp} - P_{sv}}{R_{sp}} - \frac{P_{sp} - P_{ev}}{R_{ep}} - \frac{P_{sp} - P_{mv}}{R_{lb}} \right) \quad (18)$$

where

$$R_{lb} = \frac{1}{R_{mp}} + \frac{1}{R_d} \quad (19)$$

To incorporate the effects of varying abdominal pressure  $P_{abd}$  as a result of respiration, transmural pressure is calculated by subtracting  $P_{abd}$  from  $P_{sp}$ . Equations for  $P_{abd}$  are provided in later equations:

$$P_{sp-trans} = P_{sp} - P_{abd} \quad (20)$$

This transmural pressure is subsequently used to determine downstream pressures.

The conservation of mass at the extrasplanchnic venous circulation (ev) is:

$$\frac{dP_{ev}}{dt} = \frac{1}{C_{ev}} \left( \frac{P_{sp} - P_{ev}}{R_{ep}} - \frac{P_{ev} - P_{tv}}{R_{ev}} - \frac{dV_{u,ev}}{dt} \right) \quad (21)$$

The mass balance at the skeletal muscle, part of the lower body (mv) is:

$$\frac{dP_{mv}}{dt} = \frac{1}{C_{mv}} \left( \frac{P_{sp} - P_{mv}}{R_{lb}} - \frac{P_{mv} - P_{tv}}{R_{mv}} - \frac{dV_{u,mv}}{dt} \right) \quad (22)$$

The conservation of mass at the thoracic vein ( $tv$ ) is:

$$\frac{dP_{tv}}{dt} = \frac{1}{C_{tv}} \left( \frac{P_{mv} - P_{tv}}{R_{mv}} + \frac{P_{ev} - P_{tv}}{R_{ev}} + \frac{P_{sv} - P_{tv}}{R_{ev}} - \frac{P_{tv} - P_{ra}}{R_{tv}} \right) \quad (23)$$

To incorporate the effects of varying thoracic pressure  $P_{thor}$  due to respiration, transmural pressure is calculated by subtracting  $P_{thor}$  from  $P_{tv}$ . Equations for  $P_{thor}$  are provided in later equations:

$$P_{tv-trans} = P_{tv} - P_{thor} \quad (24)$$

The conservation of mass determines splanchnic venous circulation, which assumes total blood volume ( $V_t$ ) is known:

$$\begin{aligned} P_{sv} = \frac{1}{C_{sv}} (V_t - C_{sa} * P_{sa} - (C_{sp} + C_{ep} + C_{mp}) \\ * P_{sp} - C_{ev} * P_{ev} - C_{mv} * P_{mv} - C_{tv} * P_{tv} - C_{ra} \\ * P_{ra} - V_{rv} - C_{pa} * P_{pa} - C_{pp} * P_{pp} - C_{pv} \\ * P_{pv} - C_{la} * P_{la} - V_{lv} - V_u) \end{aligned} \quad (25)$$

Here,  $V_{rv}$  and  $V_{lv}$  are the volumes of the right and left ventricles.  $V_u$  is the total unstressed volume, defined by:

$$\begin{aligned} V_u = V_{u,sa} + V_{u,sp} + V_{u,ep} + V_{u,sv} + V_{u,ra} + V_{u,pa} \\ + V_{u,pp} + V_{u,pv} + V_{u,la} + V_{u,tv} + V_{u,mp} + V_{u,mv} \end{aligned} \quad (26)$$

The model includes a pulsatile model of the heart, again based on conservation of mass and force. Conservation of mass at the left atrium:

$$\frac{dP_{la}}{dt} = \frac{1}{C_{la}} \left( \frac{P_{pv} - P_{la}}{R_{pv}} - F_{i,l} \right) \quad (27)$$

where  $F_{i,l}$  refers to flow into the left ventricle, determined by the mass balance:

$$F_{i,l} = \begin{cases} 0, & P_{la} < P_{lv} \\ \frac{P_{la} - P_{lv}}{R_{la}}, & P_{la} \geq P_{lv} \end{cases} \quad (28)$$

Ventricular volume is calculated as:

$$\frac{dV_{lv}}{dt} = F_{i,l} - F_{o,l} \quad (29)$$

where flow out of the left ventricle ( $F_{o,l}$ ) is calculated from:

$$F_{o,l} = \begin{cases} 0, & P_{max,lv} < P_{sa} \\ \frac{P_{max,lv} - P_{sa}}{R_{lv}}, & P_{max,lv} \geq P_{sa} \end{cases} \quad (30)$$

$P_{max,lv}$  represents the isometric pressure in the left ventricle, which is used to determine ventricular pressure during the cardiac cycle. It is used to determine  $R_{lv}$ , the viscous resistance of the left ventricle:

$$R_{lv} = k_{Rlv} * P_{max,lv} \quad (31)$$

where  $k_{Rlv}$  is a constant parameter. Instantaneous pressure in the left ventricle represents the difference between the isometric pressure ( $P_{max,lv}$ ) and viscous losses, therefore:

$$P_{lv} = P_{max,lv} - R_{lv} * F_{o,l} \quad (32)$$

Isometric pressure is time-dependent and varies throughout the cardiac cycle. The base model by Ursino (1998) assumes that isometric pressure/volume can be characterized by an exponential function during diastole, when the ventricle is relaxed, and by a linear function at the end of systole, when the ventricle is contracted maximally. Thus, isometric pressure transitions between an exponential and linear function over the course of the cardiac cycle:

$$\begin{aligned} P_{max,lv}(t) = \varphi(t) * E_{max,lv} * (V_{lv} - V_{u,lv}) + [1 - \varphi(t)] \\ * P_{0,lv} * (\exp(k_{E,lv} * V_{lv}) - 1) \end{aligned} \quad (33)$$

with  $0 \leq \phi(t) \leq 1$ .

$E_{max,lv}$  is the ventricular elastance at the maximal contraction of the ventricle.  $V_{u,lv}$  is the corresponding unstressed volume of the ventricle and is the  $x$ -axis intercept of the end-systolic pressure/volume function.  $P_{0,lv}$  and  $k_{E,lv}$  are constant parameters that describe the monoexponential pressure/volume function at diastole. The term  $\phi(t)$  represents the 'activation function' of the ventricle. When  $\phi(t) = 1$ , the ventricle is at maximum contraction, when  $\phi(t) = 0$ , it is at complete relaxation. This activation function is defined as:

$$\varphi(t) = \begin{cases} \sin^2 \left[ \frac{\pi * T(t)}{T_{sys}(t)} * u \right], & 0 \leq u \leq \frac{T_{sys}}{T} \\ 0, & \frac{T_{sys}}{T} \leq u \leq 1 \end{cases} \quad (34)$$

$T$  represents the heart period (i.e. inverse of heart rate).  $T_{sys}$  is the duration of systole and  $u$  is a dimensionless variable ranging between 0 and 1 and represents the fraction of the cardiac cycle. A value of  $u = 0$  corresponds to the beginning of systole. This variable has been modelled as an integral pulse frequency modulation function:

$$u(t) = \text{frac} \left[ \int_{t_0}^t \frac{1}{T(t)} d\tau + u(t_0) \right] \quad (35)$$

The fractional part of this equation,  $\text{frac}[\cdot]$ , indicates that the variable  $u(t)$  is reset to zero as soon as the value reaches a value of 1.

The duration of systole is determined by:

$$T_{sys} = T_{sys,0} - k_{sys} * \frac{1}{T} \quad (36)$$

where  $k_{sys}$  and  $T_{sys,0}$  are constant parameters. A separate set of equations analogous to those above are used to describe the right heart as well.

**Afferent input types.** Similar to the baroreceptors, a first-order low-pass filter in series with a sigmoidal static characteristic function is used to model the cardiopulmonary receptors. Because cardiopulmonary receptors depend on transmural pressure at the pulmonary veins, this pressure difference is used as an input to first-order low-pass filter:

$$\tau_{cp} \frac{dP_l}{dt} = -P_l + (P_{pv} - P_{thor}) \quad (37)$$

$$f_{cp} = \frac{f_{max,l}}{1 + \exp\left(\frac{P_{tn} - P_l}{k_l}\right)} \quad (38)$$

Here  $P_{pv} - P_{thor}$  is the transmural pressure at the pulmonary vein or input value to the low-pass filter function.  $P_l$  is the output variable of the low-pass filter.  $f_{cp}$  is the spike frequency of the afferent fibres from the cardiopulmonary receptors and  $f_{max,l}$  is the upper saturation limit of the frequency discharge of these receptors, the lower limit being zero.  $P_{tn}$  represents the pulmonary venous pressure at the central point of the sigmoid curve.  $k_l$  is another constant that determines the slope of the sigmoid curve, or sensitivity of the cardiopulmonary receptors.

Lung stretch receptors are modelled using a first-order lowpass filter where  $f_{lr}$  is the firing rate of the lung stretch receptors,  $\tau_{lung}$  is the time constant of the receptor response to lung inflation,  $G_{al}$  is a gain, and  $V_{lung}$  is the lung volume:

$$\frac{df_{lr}}{dt} = \tau_{lung} * (-f_{lr} + G_{al} * V_{lung}) \quad (39)$$

**Sympathetic efferent outflow.** Sympathetic efferent outflow is modelled to be dependent on the afferent input

$$P_{thor} = \begin{cases} P_{thor, \max} - (P_{thor, \max} - P_{thor, \min}) * \frac{T_{resp}}{T_{insp}} * s & 0 \leq s \leq \frac{T_{insp}}{T_{resp}} \\ P_{thor, \max} - \frac{(P_{thor, \max} - P_{thor, \min})}{T_{exp}} * (T_{insp} - T_{exp} - s * T_{resp}), & \frac{T_{insp}}{T_{resp}} \leq s \leq \frac{T_{insp} + T_{exp}}{T_{resp}} \\ P_{thor, \max} & \frac{T_{insp} + T_{exp}}{T_{resp}} \leq s \leq 1 \end{cases} \quad (47)$$

signals sent by the baroreceptor, cardiopulmonary and lung stretch receptors. Moreover, the combined effects of these input signals affect sympathetic efferent outflow to different effector functions differently. Therefore, a series of calculations are included to determine (i) the afferent firing frequency input, which is then used to determine (ii) the distinct sympathetic efferent outflow signals to the respective effector functions associated with the heart ( $h$ ), peripheral circulation ( $p$ ) and unstressed volumes ( $v$ ):

$$f_{as, h} = G_{ab, h} * f_{br} - G_{al, h} * f_{lr} + G_{ac, h} * f_{cp} \quad (40)$$

$$f_{as, p} = G_{ab, p} * f_{br} + G_{al, p} * f_{lr} + G_{ac, p} * f_{cp} \quad (41)$$

$$f_{as, v} = G_{ab, v} * f_{br} + G_{al, v} * f_{lr} + G_{ac, v} * f_{cp} \quad (42)$$

$G_{ab, j}$ , where  $j$  is a general index for the heart, peripheral circulation, or unstressed volume, represents a constant gain factor indicating how much influence each afferent input has on determining sympathetic efferent outflow. A factor of  $-1$  is used for  $G_{al, h}$  as this provided the best fits for the model. The resulting  $f_{as, j}$  values are then used to determine sympathetic efferent outflow to the respective effector functions using a negative monotonic function to relate afferent activity to efferent neural pathways:

$$f_{es, h} = f_{es, \infty} + (f_{es, 0} - f_{es, \infty}) * \exp(-k_{es} * f_{as, h}) \quad (43)$$

$$f_{es, p} = f_{es, \infty} + (f_{es, 0} - f_{es, \infty}) * \exp(-k_{es} * f_{as, p}) \quad (44)$$

$$f_{es, v} = f_{es, \infty} + (f_{es, 0} - f_{es, \infty}) * \exp(-k_{es} * f_{as, v}) \quad (45)$$

**Lung volume, thoracic pressure, and abdominal pressure.**

A linear relationship between lung volume and thoracic pressure is used to model lung volume measured by the lung stretch receptors:

$$V_{lung} = V_{lung, 0} - 0.1 * P_{thor} \quad (46)$$

Thoracic pressure varies with time as a result of the effects of the respiratory cycle, which is modelled independently from any autonomic regulation. Parameters were chosen based on experimental work by Moreno et al. (1969). Thoracic pressure varies linearly during respiration between a minimum of  $-9$  mmHg and a maximum of  $-4$  mmHg, which represents steady-state thoracic pressure during the respiratory pause, as modelled by:

where  $T_{resp}$  is the period of respiration.  $T_{insp}$  is the inspiration time,  $T_{exp}$  is the expiration time.  $P_{thor, \min}$  is the value of the intrathoracic pressure at the end of inspiration, and  $P_{thor, \max}$  is the max value of intrathoracic pressure at the end of expiration and throughout the respiratory pause, which takes place in between each respiration period. The parameter  $s$  is dimensionless, varying between 0 and 1, and represents the fraction of the respiratory cycle. A value of 0 represents the beginning of the respiration cycle. Similar to other parameters

representing a fraction of cycle completion, an expression for  $s(t)$  has been developed by introducing yet another state variable  $\epsilon(t)$ , which is determined by:

$$\frac{d\epsilon}{dt} = \frac{1}{T_{resp}} \quad (48)$$

with  $s(t) = \text{frac}(\epsilon)$ .

Abdominal pressure is modelled similarly:

$$P_{abd} = \begin{cases} -2.5 * s * \frac{T_{resp}}{T_{insp}/2} - 4 & 0 < s < \frac{T_{insp}/2}{T_{resp}} \\ -2.5 & \frac{T_{insp}/2}{T_{resp}} < s < \frac{T_{insp}}{T_{resp}} \\ -2.5 * \frac{T_{insp} + T_{exp} - s * T_{resp}}{T_{exp}} & \frac{T_{insp}}{T_{resp}} < s < \frac{T_{insp} + T_{exp}}{T_{resp}} \\ -5 * \frac{T_{insp} + T_{exp} - s * T_{resp}}{T_{exp}} - 4 & \frac{T_{insp} + T_{exp}}{T_{resp}} < s < 1 \end{cases} \quad (49)$$

where  $T_{resp}$  represents the respiratory period,  $T_{insp}$  represents the duration of inspiration and  $T_{exp}$  represents

Inputs to the local circuit neurons are a linear combination of firing frequencies from the baroreceptors ( $f_{BR}$ ), cardiopulmonary receptors ( $f_{CP}$ ), sympathetic efferent firing frequency ( $f_{fesh}$ ) and vagal efferent firing frequency ( $f_{fev}$ ) multiplied by their respective gain values:

$$f_{input, LCN} = K_{LCN_{BR}} f_{br} + K_{LCN_{CP}} f_{cp} + K_{LCN_{fesh, h}} f_{es, h} + K_{LCN_{fev}} f_{ev} \quad (52)$$

**Heart period.** We have modified the original model developed by Ursino (1998) and its subsequent iterations (Magosso & Ursino, 2002; Magosso et al., 2002; Ursino & Magosso, 2000), to account for the differences in the effect vagal activity has depending on when in the cardiac cycle it occurs. The same functions as those of Ursino (1998) (eqns 53–56) are used to calculate the change in heart period from baseline as a result of vagal activity ( $\Delta T_v$ ):

$$\sigma_{T, s}(t) = \begin{cases} G_{T, s} * \ln[f_{es, h}(t - D_\theta) - f_{es, \min} + 1], & f_{es, h} \geq f_{es, \min} \\ 0, & f_{es, h} < f_{es, \min} \end{cases} \quad (53)$$

the duration of expiration.  $s$  is a dimensionless variable, which is the same as eqn (47).

**Respiratory sinus arrhythmia.** A gating function to modulate the outputs of the NTS that go to the NA ( $ff_{NA, input}$ ) based on the phase of the respiratory cycle was added to the extended model to capture RSA. The respiratory phase,  $s$ , varies between zero and 1 and resets to zero at the end of each respiratory cycle. The inspiration and post-inhalation phases of  $s$  are defined using the inhalation time ( $T_{insp}$ ) divided by the total respiratory cycle time ( $T_{resp}$ ). During inspiration, outputs from the NTS ( $ff_{NTS, output}$ ) are decreased by the gain value ( $K_{RSA}$ ), and during exhalation, outputs from the NTS are unaffected to mimic the observed NA input gating behaviour:

$$ff_{NA, input} = \begin{cases} K_{RSA} * ff_{NTS, output}, & s < \frac{T_{insp}}{T_{resp}} \\ ff_{NTS, output}, & s \geq \frac{T_{insp}}{T_{resp}} \end{cases} \quad (50)$$

**Intrinsic cardiac nervous system.** We included in the model a first-order filter on the output of principal neurons that receive direct inputs from the dorsal motor nucleus. This filter is added to represent the slower dynamics of signal transmission due to the muscarinic receptor type that this population of neurons uses. The output, filtered ( $ff_{filtered, PN_{DMV}}$ ) is delayed by  $\tau_{PN_{DMV}}$  compared to the input ( $ff_{out, PN_{DMV}}$ ):

$$\frac{d ff_{filtered, PN_{DMV}}}{dt} = \tau_{PN_{DMV}} (ff_{out, PN_{DMV}} - ff_{filtered, PN_{DMV}}) \quad (51)$$

$$\frac{d \Delta T_s}{dt}(t) = \frac{1}{\tau_{T, s}} * (-\Delta T_s(t) + \sigma_{T, s}(t)) \quad (54)$$

$$\sigma_{T, v} = G_{T, v} * f_{ev, h}(t - D_{T, v}) \quad (55)$$

$$\frac{d \Delta T_v}{dt}(t) = \frac{1}{\tau_{T, v}} * (-\Delta T_v(t) + \sigma_{T, v}(t)) \quad (56)$$

The change in heart period as a result of vagal activity is then modified using a gain value calculated from data on the change in heart period as a function of the timing of vagal activity in the cardiac cycle in dogs by Iano et al. (1973), Levy et al. (1972).

In equation 57, the timing of the stimulus ( $t$ ) was measured as the time which had elapsed between the application of the stimulus ( $t_{fev}$ ) and the midpoint, in time ( $t_{RR, mid}$ ), of that cardiac cycle (Iano et al., 1973). The gain value to be multiplied by the change in heart period was determined using eqn (60), which is a function fit to data from Iano et al. (1973). The constants in eqn (60) were selected to fit the experimental data curve for the relationship between the heart period change and the timing of the stimulus relative to the midpoint of the cardiac cycle as found by Iano et al. (1973). Because vagal activity affects the subsequent cardiac cycle in addition to the current one, the gain values were split into  $k_{RR, t}$  and  $k_{RR, t+1}$  to modify the effect of vagal activity on heart period for the current and subsequent cardiac cycles. For example, if Iano et al. (1973) found that heart period

increased by 10% for vagal activity that occurred at a given point in the cardiac cycle, then the gain value would be 1.1. If the next cardiac cycle started within a time range such that the stimulus still had an effect on it, that gain value was determined from eqn (60) to obtain the gain value  $k_{RR,t+1}$ :

$$t = t_{RR,mid} - t_{fev} \quad (57)$$

$$k_{RR,t} = g(s) | _t \quad (58)$$

$$k_{RR,t+1} = g(s) |_{t+1} \quad (59)$$

$$g(s) = \frac{K_{RR,1}}{(\tau_{RR,1}s + 1)(\tau_{RR,2}s + 1)} - \frac{K_{RR,2}(\xi s + 1)}{(\tau_{RR,3}s + 1)(\tau_{RR,4}s + 1)} \quad (60)$$

$$T = \Delta T_s + k_{RR,t} \Delta T_v + k_{RR,t+1} \Delta T_v + T_0 \quad (61)$$

### Credible practice in modelling

This work followed the Ten Simple Rules of Credible Modelling and Simulation in Healthcare (Erdemir et al., 2020) and the associated rubric is included on GitHub ([https://github.com/Daniel-Baugh-Institute/CardiovascularControl/tree/main/Virtual\\_patient\\_cohorts](https://github.com/Daniel-Baugh-Institute/CardiovascularControl/tree/main/Virtual_patient_cohorts)). The Ten Simple Rules are a conceptual framework for modelling and simulation design, implementation, evaluation, dissemination, and usage in healthcare. The rules cover best practices on model documentation, purpose, limitations and independent reviews. We evaluated our model with the Ten Simple Rules and found that the model complies with each rule adequately to extensively.

## Results

### Generation of an *in silico* patient cohort

To account for the inter-individual variability, we generated a cohort of 59 individual models that produced baroreflex curves within the range of behaviour observed experimentally (Fig. 2) (Mastitskaya et al., 2012; Serebnyński et al., 2021). To generate the cohort, we started with a model based on that of (Gee et al., 2023) that fit the average of the baroreflex curve data from five individuals (Fig. 3B) (Serebnyński et al., 2021). The model includes 51 parameters that represent the neuronal groups in the baroreflex arc as well as left ventricular function. To select parameters that affect HR and MAP, we used a parametric sensitivity analysis known as PAWN. Of the

51 parameters, 28 significantly affected HR and/or MAP (Fig. 3A). These 28 parameter values were then varied simultaneously over a  $\pm 2.5$  fold range from the nominal parameter values to generate 500 potential individual models. Given that a large number of parameters were selected (28) and the possibility of degenerate models, we considered the possibility of overfitting. Thus, the criteria for accepted models were based on neck chamber pressure responses over a range of perturbation pressures. Each individual model prediction of the baroreflex curve was fit to eqn (1) to quantitatively describe each model using parameters representing (1) the response range (maximum-minimum); (2) slope of the sigmoid; (3) centring point of the sigmoid; and (4) minimum response. The models were filtered so that the parameter values for the sigmoid fit are within the 95% confidence intervals based on the data from the five individuals reported in Serebnyński et al. (2021). Additionally, the minimum and maximum RR interval values were required to be within the pre-I/R 95% confidence interval observed for HR and MAP (Mastitskaya et al., 2012) and the maximum RR interval was required to be not greater than 1.2 s (Fig. 3C). Although the range of the values for accepted parameter sets for any individual criterion usually overlaps with the range of the values for the rejected parameter sets, only 59 of the 500 individual patient models generated satisfied these criteria simultaneously (Fig. 3D). Rather than try to fit models any one individual, this method generates a cohort of plausible individuals that cover the range of baroreflex characteristics observed clinically.

### Cardiac remodelling alone partly accounts for post-MI baroreflex control

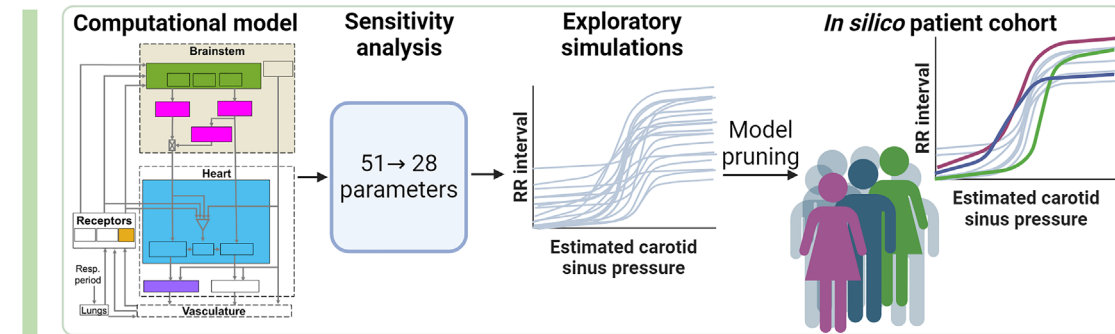
The cardiac parameters identified via sensitivity analysis were used to develop post-I/R models from each of the 59 pre-I/R models (Fig. 4A). Post-I/R RR interval and MAP were modelled to represent the time point following 30 min of myocardial ischaemia and 120 min of reperfusion (Fig. 4B). One hundred post-I/R models were generated for each pre-I/R model using Sobol sampling in a  $\pm 1.5$  fold range from the respective pre-I/R parameter values, for a total of 5900 post-I/R models. The post-I/R models were filtered based on the following criteria calculated from the 95% confidence interval of clinical data: (1) heart rate between 58 and 116 beats  $\text{min}^{-1}$ ; (2) systolic pressure between 96 and 142 mmHg; and (3) RR interval response to neck chamber pressures of 8, 13.2, 18.5, 23.7, 30 and 37.5 mmHg (Osculati et al., 1990). If multiple plausible post-I/R models were found for a single pre-I/R model, they were all included in the analysis. Of the 5900 parameter sets sampled, 85 post-I/R parameter sets met the criteria.

## Adaptation in neural loci after ischaemia

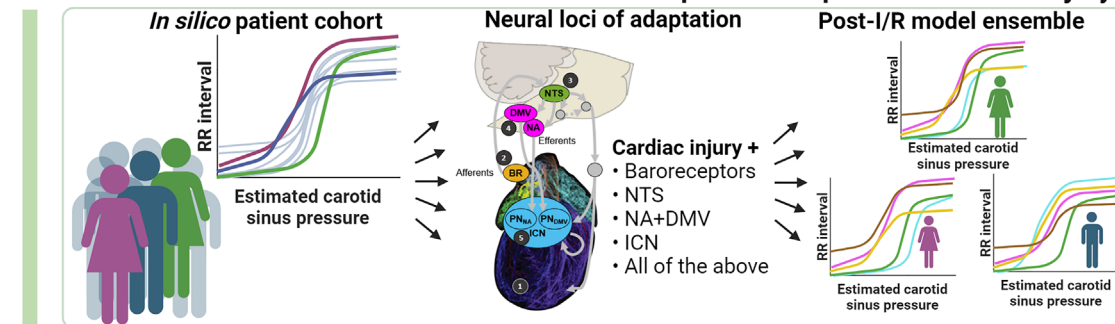
Because autonomic changes accompany myocardial remodelling in acute MI, we developed alternative computational models (Fig. 1) to represent cardiac changes coupled with autonomic changes at different loci in the baroreflex arc (baroreceptors, NTS, NA/DMV, ICN). We start peripherally at the baroreceptors (Fig. 5A)

and proceed through the baroreflex arc to the brainstem nuclei, then back down to the ICN. Baroreceptor adaptation coupled with cardiac changes yielded 88 out of 5900 post-IR models that matched the criteria involving baseline MAP (Fig. 5B) and RR interval (Fig. 5C) ranges, as well as the baroreflex curve (Fig. 5D). The final number of accepted models for cardiac remodelling combined

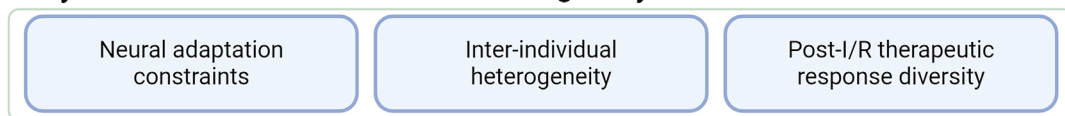
### 1. *In silico* patient cohort generated from mathematical modelling



### 2. Post-I/R models with alternative loci of neural adaptation coupled with cardiac injury

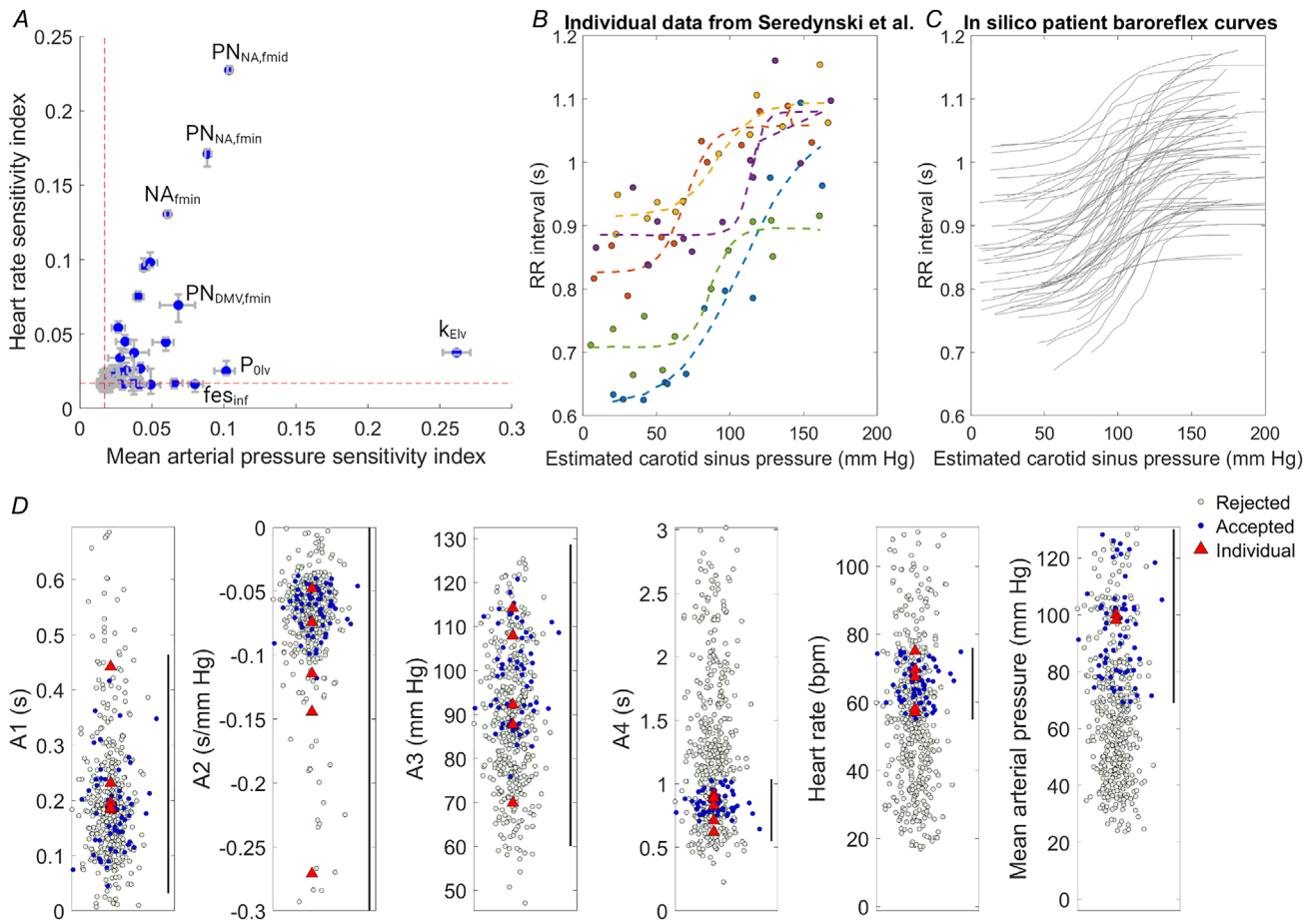


### 3. Analysis of intra- and inter-individual heterogeneity



**Figure 2. Creation of *in silico* patient cohort to explore inter-individual heterogeneity and neural loci of adaptation coupled with cardiac injury**

(1) An *in silico* patient cohort was generated from a previously published baroreflex model (Gee et al., 2023). Fifty-one parameters representing neural loci of adaptation along the baroreflex arc and characterizing left ventricular function were identified. Of the 51 parameters, 28 have a significant effect on heart rate (HR) and/or mean arterial pressure (MAP) based on sensitivity analysis. The significant parameters were Sobol sampled over a 1.5-fold range to generate parameter sets representing different individuals. Simulations were performed using these parameter sets, then selected based on experimental observations of the baroreflex curve response and baseline HR and MAP. (2) Post-ischaemia/reperfusion (post-I/R) models were generated from the pre-ischaemia/reperfusion (pre-I/R) models for each locus of neural adaptation coupled with cardiac injury. Four neural loci were identified: baroreceptors, nucleus tractus solitarius (NTS), nucleus ambiguus (NA) and dorsal motor nucleus of the vagus (DMV) and intrinsic cardiac nervous system (ICN). A model with only cardiac injury and a model with all neural loci coupled with cardiac injury results in a total of six model alternatives. Post-I/R models were generated from each pre-I/R model for each model alternative, then screened based on experimental bounds on the HR and MAP change from pre- to post-I/R (Mastitskaya et al., 2012) and the post-I/R baroreflex curve (Osculati et al., 1990). (3) Model analyses and predictive simulations were performed to identify neural adaptation constraints based on the neural locus, inter-individual heterogeneity, and post-I/R therapeutic response diversity. BR, baroreceptor; PN<sub>DMV</sub>, principal neuron with inputs from the DMV; PN<sub>NA</sub>, principal neuron with inputs from the NA; LCN, local circuit neuron. Created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]



**Figure 3. Generation of pre-I/R patient cohort models**

A, twenty-eight of 51 parameters representing baroreflex and left ventricular function had significant effects on heart rate and/or MAP. A PAVN global sensitivity analysis was used to quantify which parameters have a significant effect on haemodynamics. Heart rate was measured as the average over a 15 s period and MAP was measured as the average of a 30 s period. Sensitivity indices range between 0 and 1, with 0 indicating that the model parameter has no impact on the output, and 1 indicating that the parameter of interest has a major influence on the output. Parameters with a sensitivity index greater than the red line are significant based on the use of a dummy parameter known to have no influence on the output. Parameters were varied over a  $\pm 2$  fold range from the nominal value and six conditioning intervals were used. Each error bar represents the 95% confidence interval of the sensitivity index based on bootstrapping tests that involved 40,000 iterations of a random sampling of the simulated output. B, baroreflex curves of individuals from Serebrynski et al. (2021). Dotted lines representing baroreflex curves for each patient were fit to these data using the sigmoidal function:  $RRinterval = \frac{A1}{1 + \exp[A2(ECSP - A3)]} + A4$ . The parameter A1 represents the response range (maximum–minimum). A2 represents the gain coefficient of the slope of the sigmoid. A3 represents the centring point for the horizontal shift of the sigmoid. A4 represents the minimum response. C, accepted patient cohort models that were generated by simultaneously varying the parameters over a  $\pm 2.5$ -fold range using Sobol sampling. The criteria for model acceptance into the patient cohort were: (1) coefficients A1–A4 within the 95% confidence interval observed in individuals in Serebrynski et al. (2021), (2) RR interval and MAP within the converted 95% confidence interval observed in Mastitskaya et al. (2012). Conversion between rat and human RR interval and MAP was performed by assuming a mean model RR interval of 0.87 s and a MAP of 91 mmHg. All values were then converted using percentage changes. D, distribution of sigmoidal parameters A1–A4 and baseline heart rate and MAP for accepted (blue) and rejected (green) models compared to individual data in the absolute value of the slope parameter (A2) of the sigmoidal function fit to the baroreflex curve. Black bars represent the 95% confidence interval of the experimental data that were used to filter the models. Of the 6000 pre-I/R candidate models generated, 59 models met the criteria.  $PN_{NA,fmid}$ , midpoint firing rate for principal neurons that receive inputs from the nucleus ambiguus ( $PN_{NA}$ );  $PN_{NA,fmin}$ , minimum firing rate of  $PN_{NA}$ ;  $NA_{fmin}$ , minimum firing rate of nucleus ambiguus neurons;  $PN_{DMV,fmin}$ , minimum firing rate of principal neurons that receive inputs from the dorsal motor nucleus of the vagus;  $P_{Olv}$ , left ventricular pressure at diastole;  $k_{Elv}$ , gain for volume effects on pressure changes in left ventricle;  $fes_{inf}$ , constant describing sympathetic efferent tone. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

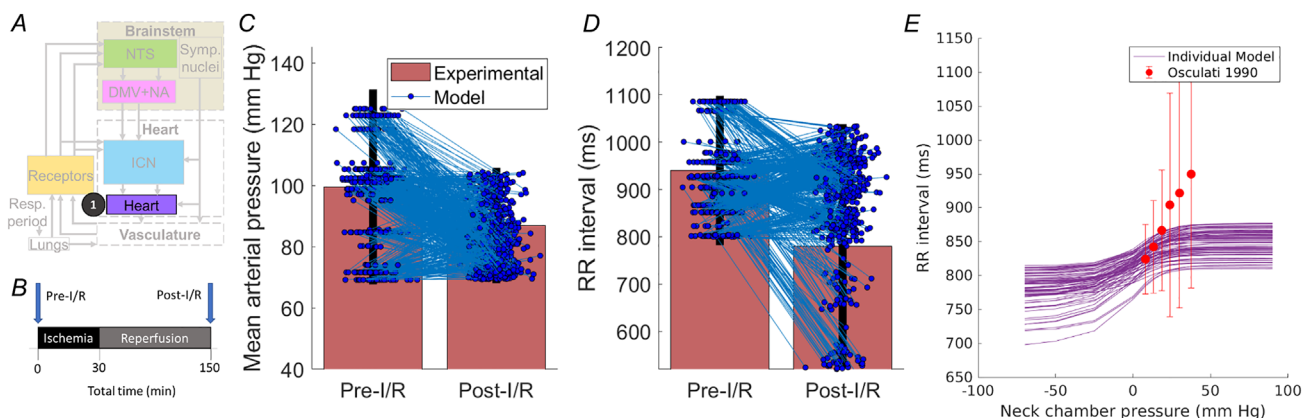
with baroreceptor adaptation is similar to the number of accepted models for only cardiac remodelling. These results suggest there are many degenerate ways in which the baroreflex can adapt. There is a significant amount of diversity in baroreflex behaviour that still remains within the bounded space for baroreflex function and there are several loci that can adapt to account for the haemodynamics observed post-I/R.

Comparison of the baroreceptor adaptation coupled with cardiac remodelling pre- and post-I/R baroreflex response curves reveals significant overlap (Fig. 5E). The baroreceptor response curves vary in the gain value representing the incremental increase in firing rate for a given arterial pressure increase. Although there is a decrease in the baroreceptor gain from pre- to post-I/R due to the parametric constraints enforced during model development, the range of pre- and post-I/R baroreceptor responses overlaps. These results suggest that decreases in baroreceptor sensitivity post-I/R can be responsible for heart rate and blood pressure changes in some individuals, but in others the afferent pathway is intact and the defect is in cardiac dysfunction.

### Central vs. peripheral adaptation post-MI

The post-I/R cohort of models representing central adaptation in the NTS and NA/DMV coupled with cardiac remodelling yield similar numbers of accepted models (Fig. 6A). Of the 5900 post-I/R models screened for each model alternative, 75 NTS adaptation models and 86 NA/DMV adaptation models met the screening criteria for MAP (Fig. 6C), RR interval (Fig. 6D) and baroreflex curve (Fig. 6B). The number of accepted models is comparable to that for other loci of adaptation, suggesting that adaptation in any of these loci are plausible or that there are many degenerate ways in which the baroreflex can adapt post-I/R. These *in silico* patients are within the clinically observed baroreflex behaviour, but it is apparent that the individuals that adapted via the NTS neuronal group pathway have a more limited range of baroreflex curves. NTS adaptation may not be as suitable for maintenance of baroreflex function as a result.

Cardiac remodelling coupled with peripheral ganglionic adaptations in the ICN could also account for the haemodynamic changes observed post-I/R (Fig. 7A). Of the 5900 post-I/R models sampled, 93 models



**Figure 4. Adaptation of cardiac parameters produces physiological post-I/R models**

Starting from 59 pre-I/R models that yielded 5900 post-I/R models, we filtered to obtain 85 models within the acceptable range of physiological behaviour. The criteria for filtering the post-I/R models were (1) heart rate between 58 and 116 beats  $\text{min}^{-1}$ ; (2) systolic pressure between 96 and 142 mmHg; and (3) RR interval response to neck chamber pressures of 8, 13.2, 18.5, 23.7, 30 and 37.5 mmHg within the 95% confidence interval found in (Osculati et al., 1990). A, model schematic highlighting modified heart parameters:  $C_{la}$ , left atrial compliance;  $P_{0lv}$ , left ventricular pressure at diastole;  $k_{Elv}$ , gain for volume effects on pressure changes in left ventricle;  $V_{ulv}$ , left ventricular unstressed volume;  $f_{es_{inf}}$ , constant describing sympathetic efferent tone. B, Experimental procedure with pre-ischaemia/reperfusion (pre-I/R) and post-ischaemia/reperfusion (post-I/R) time points. C, comparison of experimental and model mean arterial pressure (MAP). Error bars represent the SD. Experimental data were collected in rats and converted to human HR and arterial pressure by assuming that the pre-ischaemia rat and baseline human cardiovascular metrics were analogous (Mastitskaya et al., 2012; Seredyński et al., 2021). Experimental values for post-I/R HR and MAP were converted using the percent change from pre-ischaemia. Paired pre- and post-I/R models are connected by a line. D, RR interval experimental data and models corresponding to MAP data. E, baroreflex curve predictions for post-I/R models with cardiac parameter adaptations filtered based on the criteria that the RR interval response be within the 95% confidence interval of the experimental data (Osculati et al., 1990). Each purple line represents one model that met the criteria. The experimental mean and 95% confidence interval are plotted in red. (A) and (B) were created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

recapitulated the experimentally observed MAP decrease (Fig. 7B) and RR interval changes (Fig. 7C) in addition to the baroreflex curve (Fig. 7D). Because the central vs. peripheral contributions to neural adaptation post-I/R have been of interest, we investigated the shift in balance between central and peripheral neural loci before and after cardiac injury in all post-I/R models. To quantify the contribution of central and peripheral model parameters, we use Shapley values, which are used in game theory to calculate the contribution of each player in a coalition game. The average pre-I/R Shapley values are higher for parameters representing peripheral loci compared to central loci. This balance shifts post-I/R so that the contributions of central loci to heart rate regulation are greater.

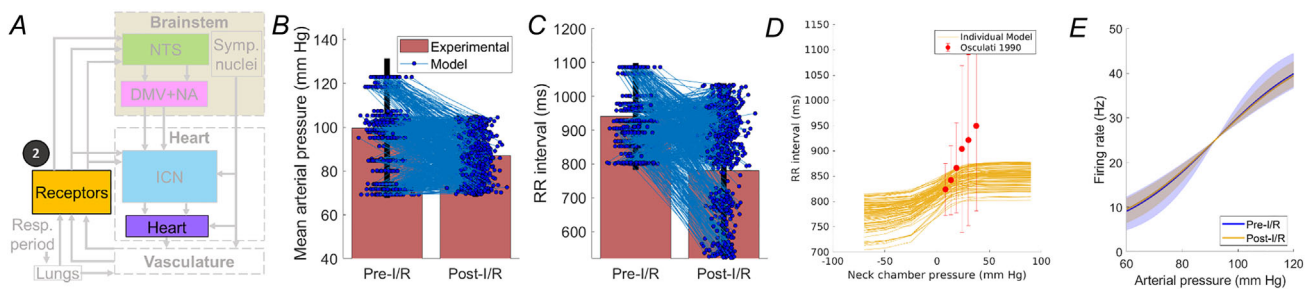
### Combinatorial adaptation in all neural loci

Although we had hypothesized that adaptation in a subset of neural loci was sufficient to maintain baroreflex function post-I/R, it is also possible that cardiac remodelling is coupled with simultaneous adaptation in all neural loci (Fig. 8A). Of the 5900 post-I/R models considered, 72 of the models met the criteria (Fig. 8B and C) in addition to the baroreflex curve requirements (Fig. 8D). These results suggest that simultaneous adaptation in these neural loci coupled with cardiac changes are sufficient to match the experimentally

observed haemodynamic and autonomic changes. The possibility of a baroreflex-wide response to ischaemic injury could not be ruled out.

### Adaptation along vagal efferent pathway can compensate for cardiac injury

A t-distributed stochastic neighbor embedding (t-SNE) was performed to visualize the output characteristics of each post-I/R model (Fig. 9). These characteristics include vagal afferent activity, vagal efferent activity, and baroreceptor responsiveness. The clustering analysis revealed a subgroup of post-I/R individuals in the virtual cohort with high baroreflex sensitivity (Fig. 9A). These individuals tended to adapt via the ICN, NA and DMV comprising peripheral and central vagal efferent pathways (Fig. 9B). The individuals in the virtual cohort with high baroreflex sensitivity also stemmed from a subgroup of pre-I/R individuals with high baroreceptor responsiveness (Fig. 9C). Taken together, these results suggest that central or peripheral vagal efferent adaptation and preserved baroreceptor gain may be sufficient to maintain high baroreceptor sensitivity (BRS) post MI. No trends between baroreflex sensitivity and the ratio of central vs. peripheral contributions to heart rate were identified, reinforcing the idea that vagal efferent dysfunction contributes to poor baroreflex sensitivity post-I/R rather than central vs. peripheral imbalance.



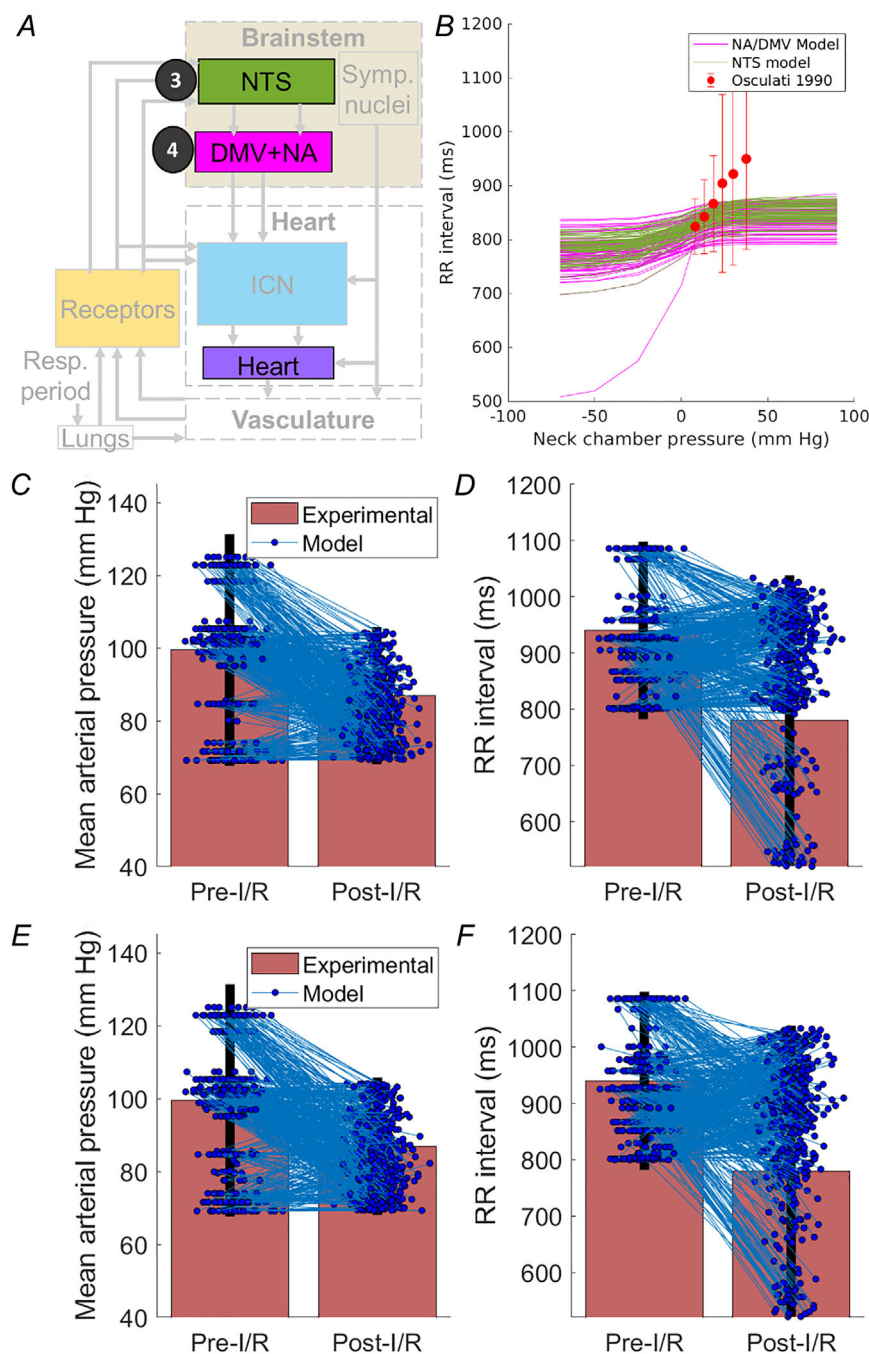
**Figure 5. Baroreceptor adaptation coupled with cardiac adaptation produced models that match experimental observations**

Starting from 59 pre-I/R models that yielded 5900 post-I/R models, we filtered to obtain 88 models within the acceptable range of physiological behaviour. The filtering criteria were the same as what were used for the cardiac adaptation model. A, model schematic highlighting the neuronal group adapted to represent the baroreceptor remodelling coupled with cardiac changes; see eqns (2) and (3) for equations represented by this block. B, comparison of experimental and model mean arterial pressure (MAP). Error bars represent 1 SD. Experimental data were collected in rats and converted to human HR and arterial pressure by assuming that the pre-ischaemia rat and baseline human cardiovascular metrics were analogous (Mastitskaya et al., 2012; Serebyński et al., 2021). Experimental values for end-ischaemia HR and MAP were converted using the percent change from pre-ischaemia. C, RR interval experimental data and models corresponding to MAP data. D, baroreflex curve predictions for post-I/R models with cardiac parameter adaptations filtered based on the criteria that the RR interval response be within the 95% confidence interval of the experimental data (Osculati et al., 1990). Each yellow line represents one model that met the criteria. The experimental mean and 95% confidence interval are plotted in red. E, comparison of pre-I/R (blue) and post-I/R (yellow) baroreceptor response curves. Shaded regions represent 1 SD from the average for both model ensembles. (A) was created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

## Discussion

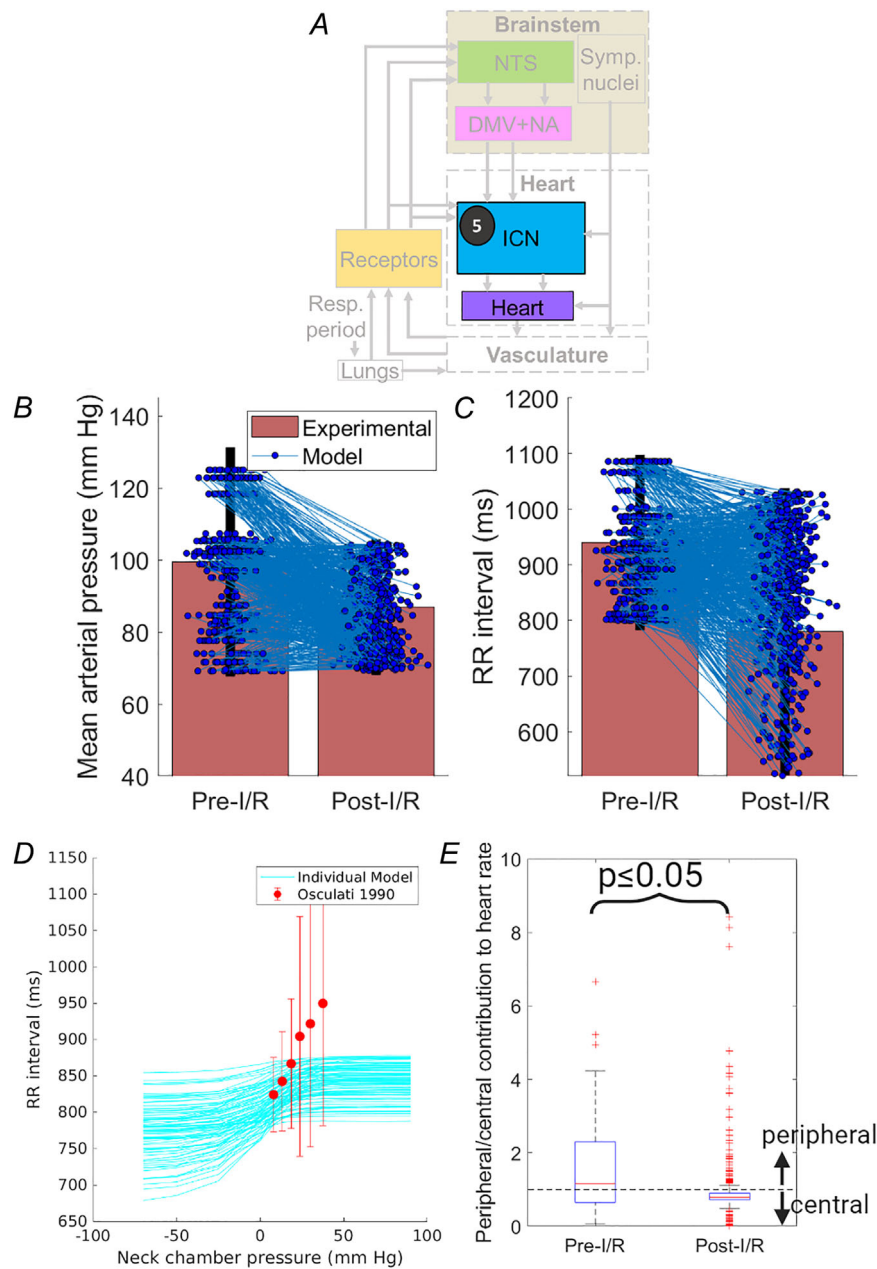
We developed an ensemble of *in silico* patient models of the baroreflex capturing cardiac and autonomic physiology pre- and post-I/R to address the question posed in the white paper by Herring et al. (2025) on how localized pathology in the heart affects adaptation in specific regions of the neural hierarchy and the influence on the behaviour of the system as a whole. Because autonomic adaptation is known to occur to compensate for lost cardiac function, we tested alternative models

representing adaptation in sensory afferent, central, and peripheral ganglionic loci coupled with cardiac remodelling. The virtual patient cohort was filtered using observed haemodynamic behaviour with baseline MAP, RR interval and baroreflex curves within the 95% confidence intervals (Seredyński et al., 2021) and trends in MAP and RR interval changes before and after I/R (Mastitskaya et al., 2012). We found a subgroup of *in silico* patients that maintained higher baroreflex sensitivity post-I/R. These individuals adapted via central or peripheral vagal efferent neural loci and had preserved



**Figure 6. Adaptation in brainstem (NTS or NA and DMV) neural loci coupled with cardiac remodelling**

Starting from 59 pre-I/R models that yielded 5900 post-I/R models per neural locus of adaptation, we filtered to obtain 75 NTS models and 86 NA/DMV models within the acceptable range of physiological behaviour. The filtering criteria were the same as what were used for the previous alternative models. A, model schematic highlighting the two brainstem models: NTS adaptation coupled with cardiac changes and NA/DMV remodelling coupled with cardiac alterations. B, baroreflex curve predictions for post-I/R models with cardiac parameter adaptations filtered based on the criteria that the RR interval response be within the 95% confidence interval of the experimental data (Osculati et al., 1990). Each green line represents one NTS model and each pink line represents one NA/DMV model that met the criteria. The experimental mean and 95% confidence interval are plotted in red. Pre- and post-I/R MAP and HR changes for each parameter set for NTS models coupled with cardiac remodelling (C) and (D) and for NA/DMV models coupled with cardiac remodelling (E) and (F). Error bars represent the SD. Experimental data were collected in rats and converted to human HR and arterial pressure by assuming that the pre-ischaemia rat and baseline human cardiovascular metrics were analogous (Mastitskaya et al., 2012; Seredyński et al., 2021). Experimental values for end-ischaemia HR and MAP were converted using the percent change from pre-ischaemia. (A) was created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**Figure 7. ICM adaptation combined with cardiac remodelling produces models that match experimentally observed haemodynamic and autonomic changes**

Starting from 59 pre-I/R models which yielded 5900 post-I/R models, we filtered to obtain 93 models within the acceptable range of physiological behaviour. The filtering criteria were the same as what were used for the previous alternative models. **A**, model schematic highlighting ICN remodelling coupled with cardiac changes. **B**, comparison of experimental and model MAP. Error bars represent the SD. Experimental data were collected in rats and converted to human HR and arterial pressure by assuming that the pre-ischaemia rat and baseline human cardiovascular metrics were analogous (Mastitskaya et al., 2012; Seredyński et al., 2021). Experimental values for post-I/R HR and MAP were converted using the percent change from pre-I/R. **C**, RR interval data corresponding to MAP data. **D**, baroreflex curve predictions for post-I/R models with ICN adaptation coupled with cardiac parameter adaptations filtered based on the criteria that the RR interval response be within the 95% confidence interval of the experimental data (Seredyński et al., 2021). Each blue line represents one model. The experimental data and 95% confidence interval are plotted in red. **E**, ratio of peripheral to central contributions to heart rate regulation for all accepted pre- and post-I/R models as calculated using Shapley values that quantify parametric contributions to an output. A ratio above one indicates that peripheral parameters (baroreceptors, ICN) play a larger role in heart rate regulation compared with central (brain-stem) parameters. The distribution of the averaged contribution for central and peripheral parameters, quantified using Shapley values averaged over many points, is shown for pre- vs. post-I/R ( $p = 0.00160$ ). Five outliers were not

shown in the plot for ease of viewing but are included in the analysis. (A) was created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

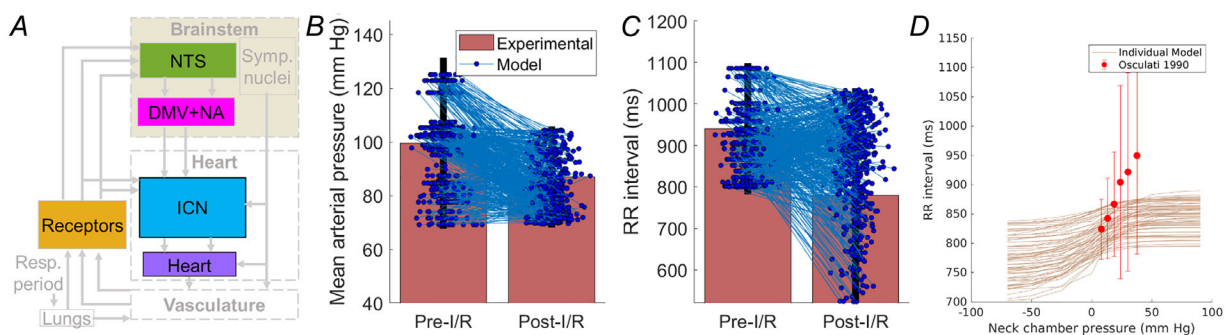
baroreceptor gain. There were also individuals with preserved baroreceptor gain that did not adapt along the vagal efferent pathway who had lower baroreflex sensitivity, highlighting the role of adaptation in parasympathetic efferent nuclei in maintaining cardiac health post-I/R. These model predictions lead to the experimentally testable hypothesis that correlations between post-I/R baroreflex sensitivity and electrophysiological or transcriptomic measurements of neural adaptation may exist.

The model suggests that preserved baroreceptor responsiveness after cardiac injury is necessary for maintaining baroreflex sensitivity. These results are in agreement with several experiments in rats, pigs, and humans. Porcine models have shown that there is both denervation around the infarcted area and functional afferent transmission changes (Kazci et al., 2022; Salavatian et al., 2022). Taken together, these studies point to the importance of afferent function following infarction. Impaired afferent transmission is also associated with decreased vagal tone, which increases the risk of ventricular arrhythmias and heart failure (Salavatian et al., 2022). When performed prior to myocardial infarction, sinoaortic denervation has been found to induce additional impairment of vagal activity in rats (Mostarda et al., 2014). In a porcine model of cardiac ischaemic injury, decreased functional afferent transmission is thought to contribute to vagal withdrawal, further impairing baroreflex function (van Weperen &

Vaseghi, 2023; Vaseghi et al., 2017). Studies in humans have also linked baroreflex sensitivity to vagal tone (Kollai et al., 1994). Similarly, the computational model results suggest that impaired baroreceptor function blunts overall baroreflex sensitivity, which is correlated with vagal tone (Kollai et al., 1994).

Resetting of the baroreceptor firing rate is a well-studied mechanism in baroreflex adaptation (Jezek et al., 2022; Kosinski et al., 2018). Baroreceptors can adapt to a new steady-state blood pressure that shifts the entire curve to the left or right if the arterial pressure is elevated for longer than 3–5 min (Kunze, 1985). This mechanism is probably a major driver of changes in baroreflex control post-I/R. Although this baroreceptor resetting was not explicitly included in the model, it is implicitly included when the parameters are resampled between pre- and post-I/R. The post-I/R baroreceptor parameters reflect the reset baroreceptors. Furthermore, a central component to baroreflex resetting has been suggested (DiCarlo & Bishop, 2001; Kunze, 1985). The resampling of parameters representing central brainstem nuclei post-I/R also implicitly represent baroreflex resetting.

Adaptation in parasympathetic efferent nuclei post-I/R was necessary to maintain baroreflex function in most individuals. Although neural adaptation is difficult to regulate, vagus nerve stimulation (VNS) can restore afferent and efferent vagal tone after myocardial infarction and during the subsequent development of heart failure



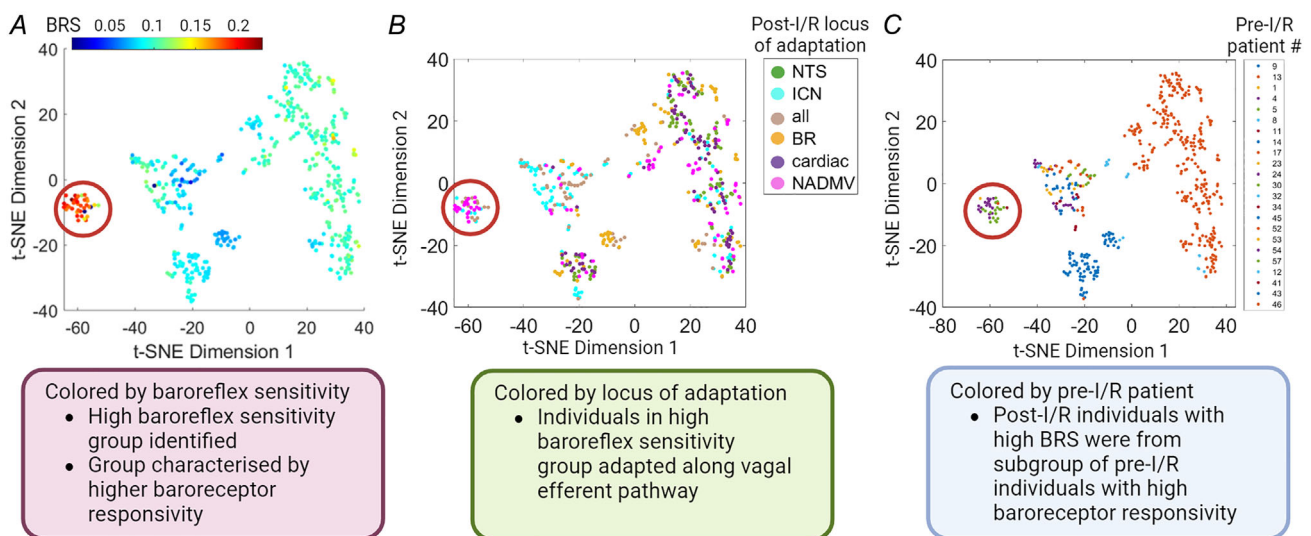
**Figure 8. Simultaneous adaptation in all neural loci combined with cardiac remodelling predicts models that match experimentally observed haemodynamic and autonomic changes**

Starting from 59 pre-I/R models that yielded 5900 post-I/R models, we filtered to obtain 47 models within the acceptable range of physiological behaviour. The filtering criteria were the same as what were used for the previous alternative models. A, model schematic highlighting adaptation in all neural loci coupled with cardiac remodelling. B, comparison of experimental and model MAP. Error bars represent the SD. Experimental data were collected in rats and converted to human HR and arterial pressure by assuming that the pre-ischaemia rat and baseline human cardiovascular metrics were analogous (Mastitskaya et al., 2012; Seredyński et al., 2021). Experimental values for post-I/R HR and MAP were converted using the percent change from pre-I/R. C, RR interval data corresponding to MAP data. D, baroreflex curve predictions for post-I/R models with ICN adaptation coupled with cardiac parameter adaptations filtered based on the criterion that the RR interval response be within the 95% confidence interval of the experimental data (Seredyński et al., 2021). Each brown line represents one model. The experimental data and 95% confidence interval are plotted in red. (A) was created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

(Hadaya et al., 2023). Increasing parasympathetic drive with vagus nerve stimulation following myocardial infarction in a chronic porcine infarct model decreased ventricular arrhythmia inducibility (Vaseghi et al., 2017). These results support the idea that augmenting vagal efferent tone after infarction can improve autonomic regulation of cardiovascular function. During pacing-induced heart failure development, cervical VNS was found to improve baroreflex sensitivity, heart rate variability and ejection fraction in a canine model (Zhang et al., 2009). Although cervical VNS stimulates both afferent and efferent vagal fibres, auricular VNS stimulates predominantly afferent fascicles. In a meta-analysis of six auricular VNS studies in humans, only one found a significant effect on BRS, supporting the idea that augmented vagal efferent tone improves BRS (Soltani et al., 2023). However, all six studies were in healthy subjects, who tend to experience less of an effect compared to those with poor autonomic function according to some studies (Soltani et al., 2023). It is also difficult to make a direct comparison between transcutaneous auricular VNS and cervical VNS because of necessary differences in stimulation level to produce similar physiological effects. As a result of limitations in the current literature available, the model prediction that vagal efferent adaptation may be necessary to maintain BRS post-I/R is testable with a dataset that includes post-I/R stimulation of the cervical and auricular vagus normalized based on heart rate

changes to see if afferent *vs.* efferent stimulation improves BRS.

This model captures the progression of cardiovascular physiology from pre-I/R to the acute phase of post-I/R but has several limitations. Because of mismatch of the experimental data used to parameterize the pre- and post-I/R models, the average baroreflex sensitivity, characterized by the slope of the baroreflex curve, is higher post-I/R. It is well known that baroreflex sensitivity decreases post-I/R and that lower baroreflex sensitivity is associated with the progression of cardiovascular disease (La Rovere et al., 1998, 2013; Vaseghi et al., 2017). A large mammal model of myocardial ischaemia and reperfusion with baroreflex response curves, continuous heart rate and blood pressure, electrophysiology recordings and responses to VNS would be useful to further validate and extend this virtual population model. There is also the opportunity to extend this computational model to include a higher-fidelity representation of sympathetic contributions to sympathovagal balance. This model extension could expand our understanding of VNS alternatives including dorsal root ganglion stimulation, which has been shown to reduce sympathetic outflow and long-term blood pressure (Sverrisdottir et al., 2020). Our cohort of models is primed for investigating the effects of heterogeneity in the underlying closed-loop physiology on therapeutic responses following MI.



**Figure 9. Individuals that maintain afferent function and adapt along the vagal efferent pathway are able to compensate post-I/R**

A, t-distributed stochastic neighbour embedding (t-SNE) plot of accepted post-I/R models coloured by baroreflex sensitivity. Each point represents an individual. Each model was characterized by vagal efferent activity, vagal afferent activity and baroreceptor responsivity. Points that are closer together are more similar to each other based on these characteristics. The group with high baroreflex sensitivity is circled in red. B, the same t-SNE plot coloured by the post-I/R locus of adaptation. C, t-SNE of post-I/R models coloured by pre-I/R patient number. Text boxes below the plots were created with BioRender.com. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.com)]

## References

- Achanta, S., Gorky, J., Leung, C., Moss, A., Robbins, S., Eisenman, L., Chen, J., Tappan, S., Heal, M., Farahani, N., Huffman, T., England, S., Cheng, Z. (jack), Vadigepalli, R., & Schwaber, J. S. (2020). A comprehensive integrated anatomical and molecular atlas of rat intrinsic cardiac nervous system. *Isience*, **23**(6), 101140.
- Ajjola, O. A., Yagishita, D., Reddy, N. K., Yamakawa, K., Vaseghi, M., Downs, A. M., Hoover, D. B., Ardell, J. L., & Shivkumar, K. (2015). Remodelling of stellate ganglion neurons after spatially targeted myocardial infarction: Neuropeptide and morphologic changes. *Heart Rhythm*, **12**(5), 1027–1035.
- Argus, F., Zhao, D., Babarenda Gamage, T. P., Nash, M. P., & Maso Talou, G. D. (2022). Automated model calibration with parallel MCMC: Applications for a cardiovascular system model. *Frontiers in Physiology*, **13**, 1018134.
- Ben-Tal, A., Shamailov, S. S., & Paton, J. F. R. (2012). Evaluating the physiological significance of respiratory sinus arrhythmia: looking beyond ventilation-perfusion efficiency: Respiratory sinus arrhythmia function. *The Journal of Physiology*, **590**(8), 1989–2008.
- Berberoglu, E., & Göktepe, S. (2015). Computational modelling of myocardial infarction. *Procedia IUTAM*, **12**, 52–61.
- Chapleau, M. W., & Abboud, F. M. (1987). Contrasting effects of static and pulsatile pressure on carotid baroreceptor activity in dogs. *Circulation Research*, **61**(5), 648–658.
- Cheng, Z., Zhang, H., Guo, S. Z., Wurster, R., & Gozal, D. (2004). Differential control over postganglionic neurons in rat cardiac ganglia by NA and DmnX neurons: anatomical evidence. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **286**(4), 625–633.
- DiCarlo, S. E., & Bishop, V. S. (2001). Central baroreflex resetting as a means of increasing and decreasing sympathetic outflow and arterial pressure. *Annals of the New York Academy of Sciences*, **940**(1), 324–337.
- Erdemir, A., Mulugeta, L., Ku, J. P., Drach, A., Horner, M., Morrison, T. M., Peng, G. C. Y., Vadigepalli, R., Lytton, W. W., & Myers, J. G. Jr. (2020). Credible practice of modelling and simulation in healthcare: ten rules from a multidisciplinary perspective. *Journal of translational medicine*, **18**(1), 369.
- Fadel, P. J., Ogoh, S., Keller, D. M., & Raven, P. B. (2003). Recent insights into carotid baroreflex function in humans using the variable pressure neck chamber. *Experimental Physiology*, **88**(6), 671–680.
- Floras, J. S. (2009). Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *Journal of the American College of Cardiology*, **54**(5), 375–385.
- Gee, M. M., Lenhoff, A. M., Schwaber, J. S., Ogunnaike, B. A., & Vadigepalli, R. (2023). Closed-loop modelling of central and intrinsic cardiac nervous system circuits underlying cardiovascular control. *American Institute of Chemical Engineers Journal*, **69**(4), e18033.
- Gorky, J., Moss, A., Balycheva, M., Vadigepalli, R., & Schwaber, J. S. (2021). Input-output signal processing plasticity of vagal motor neurons in response to cardiac ischemic injury. *Isience*, **24**(3), 102143.
- Hadaya, J., Dajani, A.-H., Cha, S., Hanna, P., Challita, R., Hoover, D. B., Ajjola, O. A., Shivkumar, K., & Ardell, J. L. (2023). Vagal nerve stimulation reduces ventricular arrhythmias and mitigates adverse neural cardiac remodelling post-myocardial infarction. *Journal of the American College of Cardiology: Basic to Translational Science*, **8**(9), 1100–1118.
- Herring, N., Ajjola, O. A., Foreman, R. D., Gourine, A. V., Green, A. L., Osborn, J., Paterson, D. J., Paton, J. F. R., Ripplinger, C. M., Smith, C., Vrabec, T. L., Wang, H. J., Zucker, I. H., & Ardell, J. L. (2025). Neurocardiology: Translational advancements and potential. *The Journal of Physiology*, **603**(7), 1729–1779.
- Iano, T. L., Levy, M. N., & Lee, M. H. (1973). An acceleratory component of the parasympathetic control of heart rate. *American Journal of Physiology*, **224**(5), 997–1005.
- Jezek, F., Randall, E. B., Carlson, B. E., & Beard, D. A. (2022). Systems analysis of the mechanisms governing the cardiovascular response to changes in posture and in peripheral demand during exercise. *Journal of Molecular and Cellular Cardiology*, **163**, 33–55.
- Kazci, Y. E., Sahoglu Goktas, S., Aydin, M. S., Karadogan, B., Nebol, A., Turhan, M. U., Ozturk, G., & Cagavi, E. (2022). Anatomical characterization of vagal nodose afferent innervation and ending morphologies at the murine heart using a transgenic approach. *Autonomic Neuroscience*, **242**, 103019.
- Kember, G., Ardell, J. L., Shivkumar, K., & Armour, J. A. (2017). Recurrent myocardial infarction: Mechanisms of free-floating adaptation and autonomic derangement in networked cardiac neural control. *PLoS ONE*, **12**(7), e0180194.
- Kollai, M., Jokkel, G., Bonyhay, I., Tomcsanyi, J., & Naszlady, A. (1994). Relation between baroreflex sensitivity and cardiac vagal tone in humans. *American Journal of Physiology*, **266**(1 Pt 2), H21–H27.
- Kosinski, S. A., Carlson, B. E., Hummel, S. L., Brook, R. D., & Beard, D. A. (2018). Computational model-based assessment of baroreflex function from response to Valsalva maneuver. *Journal of Applied Physiology*, **125**(6), 1944–1967.
- Kunze, D. L. (1985). Role of baroreceptor resetting in cardiovascular regulation: acute resetting. *Federation Proceedings*, **44**(8), 2408–2411.
- La Rovere, M. T., Bigger, J. T., Jr., Marcus, F. I., Mortara, A., & Schwartz, P. J. (1998). Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *The Lancet*, **351**(9101), 478–484.
- La Rovere, M. T., Pinna, G. D., Maestri, R., & Sleight, P. (2013). Clinical value of baroreflex sensitivity. *Netherlands Heart Journal*, **21**(2), 61–63.
- Levy, M. N., Lano, T., & Zieske, H. (1972). Effects of repetitive bursts of vagal activity on heart rate. *Circulation Research*, **30**(2), 186–195.

- Loh, D. R., Yeo, S. Y., Tan, R. S., Gao, F., & Koh, A. S. (2022). Explainable machine learning predictions to support personalized cardiology strategies. *European Heart Journal-Digital Health*, **3**(1), 49–55.
- Ma, W., Liang, Y., Zhu, J., Yang, Y., Tan, H., Yu, L., Gao, X., Feng, G., & Li, J. (2015). Impact of Admission Systolic Blood Pressure and Antecedent Hypertension on Short-Term Outcomes After ST-Segment Elevation Myocardial Infarction: Strobe-Compliant Article. *Medicine*, **94**(34), e1446.
- Magosso, E., Cavalcanti, S., & Ursino, M. (2002). Theoretical analysis of rest and exercise hemodynamics in patients with total cavopulmonary connection. *American Journal of Physiology-Heart and Circulatory Physiology*, **282**(3), H1018–H1034.
- Magosso, E., & Ursino, M. (2002). Cardiovascular response to dynamic aerobic exercise: A mathematical model. *Medical & Biological Engineering & Computing*, **40**(6), 660–674.
- Mastitskaya, S., Marina, N., Gourine, A., Gilbey, M. P., Spyer, K. M., Teschemacher, A. G., Kasparov, S., Trapp, S., Ackland, G. L., & Gourine, A. V. (2012). Cardioprotection evoked by remote ischaemic preconditioning is critically dependent on the activity of vagal pre-ganglionic neurones. *Cardiovascular Research*, **95**(4), 487–494.
- Moreno, A. H., Katz, A. I., & Gold, L. D. (1969). An integrated approach to the study of the venous system with steps toward a detailed model of the dynamics of venous return to the right heart. *IEEE Transactions on Bio-Medical Engineering*, **BME-16**(4), 308–324.
- Mostarda, C., Rodrigues, B., Medeiros, A., Moreira, E. D., Moraes-Silva, I. C., Brum, P. C., Angelis, K. D., & Irigoyen, M.-C. (2014). Baroreflex deficiency induces additional impairment of vagal tone, diastolic function and calcium handling proteins after myocardial infarction. *American Journal of Translational Research*, **6**(3), 320–328.
- Niederer, S. A., Aboelkassem, Y., Cantwell, C. D., Corrado, C., Coveney, S., Cherry, E. M., Delhaas, T., Fenton, F. H., Panfilov, A. V., Pathmanathan, P., Plank, G., Riabiz, M., Roney, C. H., Dos Santos, R. W., & Wang, L. (2020). Creation and application of virtual patient cohorts of heart models. *Philosophical Transactions-Series A, Mathematical, Physical, and Engineering Sciences*, **378**(2173), 20190558.
- Osculati, G., Grassi, G., Giannattasio, C., Seravalle, G., Valagussa, F., Zanchetti, A., & Mancia, G. (1990). Early alterations of the baroreceptor control of heart rate in patients with acute myocardial infarction. *Circulation*, **81**(3), 939–948.
- Park, J., Brureau, A., Kernan, K., Starks, A., Gulati, S., Ogunnaike, B., Schwaber, J., & Vadigepalli, R. (2014). Inputs drive cell phenotype variability. *Genome Research*, **24**(6), 930–941.
- Park, J. H., Gorky, J., Ogunnaike, B., Vadigepalli, R., & Schwaber, J. S. (2020). Investigating the effects of brain-stem neuronal adaptation on cardiovascular homeostasis. *Frontiers in Neuroscience*, **14**, 470.
- Pianosi, F., & Wagener, T. (2018). Distribution-based sensitivity analysis from a generic input-output sample. *Environmental Modelling & Software*, **108**, 197–207.
- Rajendran, P. S., Nakamura, K., Ajijola, O. A., Vaseghi, M., Armour, J. A., Ardell, J. L., & Shivkumar, K. (2016). Myocardial infarction induces structural and functional remodelling of the intrinsic cardiac nervous system. *The Journal of Physiology*, **594**(2), 321–341.
- Sabbah, H. N. (2012). Baroreflex activation for the treatment of heart failure. *Current Cardiology Reports*, **14**(3), 326–333.
- Sáez, P., & Kuhl, E. (2016). Computational modelling of acute myocardial infarction. *Computer Methods in Biomechanics and Biomedical Engineering*, **19**(10), 1107–1115.
- Salavatian, S., Hoang, J. D., Yamaguchi, N., Lokhandwala, Z. A., Swid, M. A., Armour, J. A., Ardell, J. L., & Vaseghi, M. (2022). Myocardial infarction reduces cardiac nociceptive neurotransmission through the vagal ganglia. *Journal of Clinical Investigation Insight*, **7**(4), e155747.
- Seredyński, R., Okupnik, T., Musz, P., Tubek, S., Ponikowska, B., & Paleczny, B. (2021). Neck chamber technique revisited: Low-noise device delivering negative and positive pressure and enabling concomitant carotid artery imaging with ultrasonography. *Frontiers in Physiology*, **12**, 703692.
- Soltani, D., Azizi, B., Sima, S., Tavakoli, K., Hosseini Mohammadi, N. S., Vahabie, A.-H., Akbarzadeh-Sherbaf, K., & Vaseghani-Farahani, A. (2023). A systematic review of the effects of transcutaneous auricular vagus nerve stimulation on baroreflex sensitivity and heart rate variability in healthy subjects. *Clinical Autonomic Research*, **33**(2), 165–189.
- Sverrisdottir, Y. B., Martin, S. C., Hadjipavlou, G., Kent, A. R., Paterson, D. J., FitzGerald, J. J., & Green, A. L. (2020). Human dorsal root ganglion stimulation reduces sympathetic outflow and long-term blood pressure. *Journal of the American College of Cardiology-Basic to Translational Science*, **5**(10), 973–985.
- Ursino, M. (1998). Interaction between carotid baroregulation and the pulsating heart: A mathematical model. *American Journal of Physiology*, **275**(5), H1733–H1747.
- Ursino, M., & Magosso, E. (2000). Acute cardiovascular response to isocapnic hypoxia. I. A mathematical model. *American Journal of Physiology-Heart and Circulatory Physiology*, **279**(1), H149–H165.
- van der Maaten, L. (2013). Barnes-Hut-SNE. *arXiv [cs.LG]*. <http://arxiv.org/abs/1301.3342>
- van Weperen, V. Y. H., & Vaseghi, M. (2023). Cardiac vagal afferent neurotransmission in health and disease: Review and knowledge gaps. *Frontiers in neuroscience*, **17**, 1192188.
- Vaseghi, M., Salavatian, S., Rajendran, P. S., Yagishita, D., Woodward, W. R., Hamon, D., Yamakawa, K., Irie, T., Habecker, B. A., & Shivkumar, K. (2017). Parasympathetic dysfunction and antiarrhythmic effect of vagal nerve stimulation following myocardial infarction. *Journal of Clinical Investigation Insight*, **2**(16), e86715.
- Yang, P.-C., Rose, A., DeMarco, K. R., Dawson, J. R. D., Han, Y., Jeng, M.-T., Harvey, R. D., Santana, L. F., Ripplinger, C. M., Vorobyov, I., Lewis, T. J., & Clancy, C. E. (2023). A multiscale predictive digital twin for neuro-cardiac modulation. *The Journal of Physiology*, **601**(17), 3789–3812.

Zhang, Y., Popovic', Z. B., Bibevski, S., Fakhry, I., Sica, D. A., Van Wagoner, D. R., & Mazgalev, T. N. (2009). Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circulation: Heart Failure*, 2(6), 692–699.

## Additional information

### Data availability statement

All model equations can be found in the Methods and in our prior work (Gee et al., 2023). All model files and nominal parameter values are available on GitHub ([https://github.com/Daniel-Baugh-Institute/CardiovascularControl/tree/main/Virtual\\_patient\\_cohorts](https://github.com/Daniel-Baugh-Institute/CardiovascularControl/tree/main/Virtual_patient_cohorts)) and through the NIH CommonFund SPARC Program Portal (<https://doi.org/10.26275/wabs-qul8>). Simulations can be performed online through the o<sup>2</sup>S<sup>2</sup>PARC platform (<https://osparc.io/study/65a52908-1b13-11ee9cd1-02420a0b1bed>). All data used for model development and validation were publicly available. This work also followed the Ten Simple Rules of Credible Modelling and Simulation in Healthcare and the associated rubric is included in the GitHub repository (Erdemir et al., 2020).

### Competing interests

The authors declare that they have no competing interests.

### Author contributions

M.G. collected and analysed the data and drafted the manuscript. A.L. and J.S. assisted in interpreting the results

and critically revised the manuscript. R.V. conceived the study and critically revised the manuscript. All authors have read and approved the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship and all those who qualify for authorship are listed.

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### Keywords

autonomic regulation, cardiac remodelling, cardiovascular control, computational modelling, myocardial infarction, vagus nerve

## Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

### Peer Review History