Quantifying the relationship between hypertension and age-related baroreflex dysfunction

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Hypertension is affecting more than one billion people worldwide, and related complications, including stroke, heart failure and kidney disease, are major sources of mortality [1]. The pathogenesis of hypertension is still not well understood, and a substantial proportion of patients under treatment do not achieve the target levels of blood pressure control recommended by current guidelines. Age is a major risk factor for hypertension, and it is well known that the arterial walls becomes less elastic with advancing age [2]. In this modeling study of the combined baroreflex and circulatory system we show how age-related changes in the viscoelastic properties of the aortic wall may lead to hypertension and baroreflex dysfunction through loss of baroreceptor sensitivity.

The model is based on the the cardiovascular system model from [3] and the baroreflex model from [4], which previously have been combined to form a composite model of the cardiovascular system, downloadable at `www.virtualrat.org/VPR1002`. Here, the aortic wall dynamics and the baroreceptor response of the composite model is changed to account for the age dependency of the pressure-strain relationship of the aortic wall described in [2]. Thus, for the aortic wall pressure-strain relationship we use the original expression from [2], which in Fig. 1 is seen to give aortic strains which are less pressure sensitive with increasing age. In the present model, the baroreceptor is assumed to be directly stimulated by the aortic wall strain, and we suggest a non-linear stimulus-response relationship between the aortic wall strain and the baroreceptor firing rate based on experimental firing rate responses to blood pressure step functions from [5]. In Fig. 2 pressure-strain relationships (row 1) and corresponding baroreceptor firing rate responses (row 2) are shown. With increased age (right columns) both a general loss of strain amplitude and a loss of strain sensitivity in the pressure-strain relationship is obvious, leading to decreased baroreceptor firing rates and decreased baroreceptor sensitivity.

The composite circulatory model with the changed aortic wall and baroreceptor relationship is then run with a Valsalva maneuver as a stimulus. The Valsalva maneuver is an attempted exhalation against closed airways, and it induces a thoracic pressure which initially leads to an increased systemic pressure

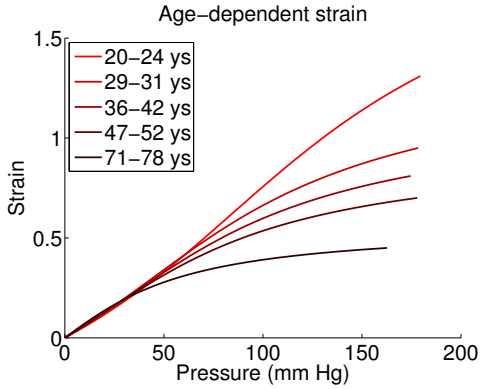

Figure 1: Pressure-strain curves based on the static aortic wall model with age-dependent parameters from [2]. The different age groups are expressed in the legend.

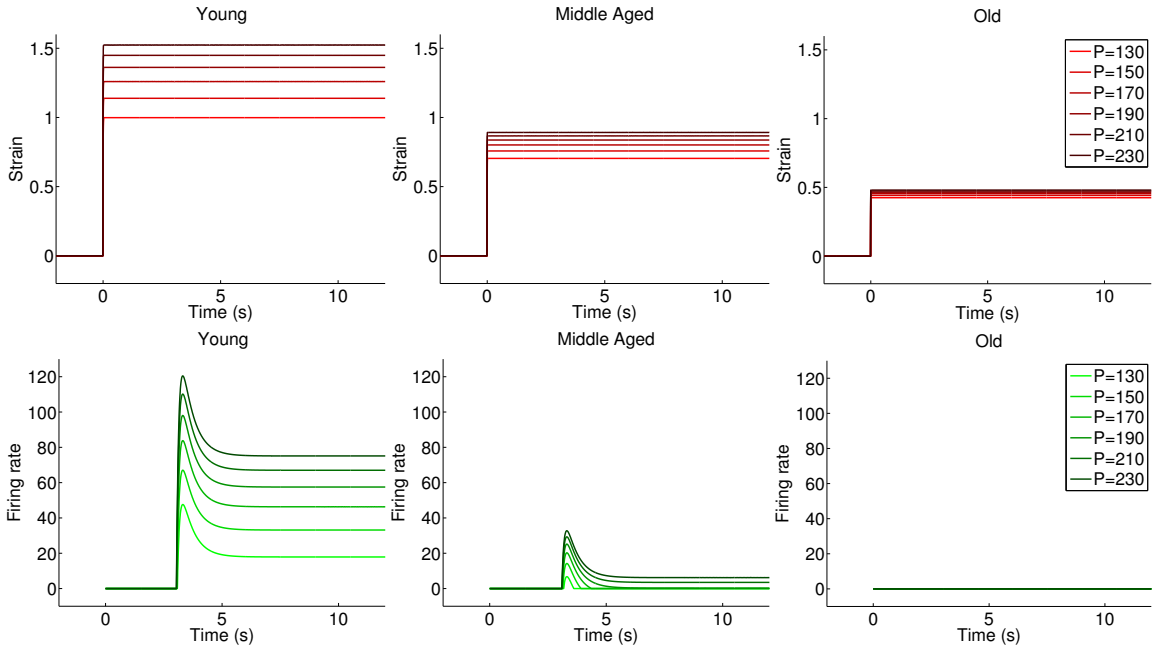

Figure 2: Modeled age-dependent aortic wall strain responses (row 1) and firing rate responses (row 2) to blood pressure step functions of amplitudes 130, 150, 170 190, 210 and 230 mmHg. The firing rates in the left column ('Young', experimental parameters for ages 20-24 years from [2]) resembles the experimental firing rates from [5]. In the middle and right columns the age dependent parameters for the aortic wall pressure-strain relationship are used [2]. *Middle column:* ages 36-42 years. *Right column* ages 71-78 years. The baroreceptor parameters are the same in all columns.

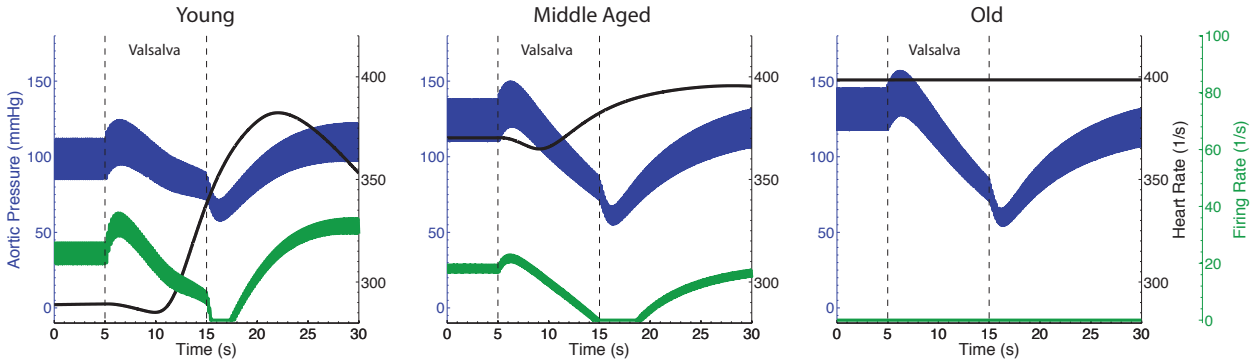

Figure 3: Baroreflex dysfunction with increased age. A Valsalva maneuver is applied in the time interval from 5 seconds to 15 seconds. The aortic blood pressure is plotted in blue, the heart rate in black and the baroreceptor firing rate in green.

through direct mechanical influence on the heart and pulmonary vessels. Fig. 3 shows that the age-induced increase in aortic wall stiffness in the middle and left plots both lead to increased set points for the aortic pressures, as well as baroreflex dysfunction in response to the Valsalva maneuver.

The composite circulatory model has the original rat parameters, see `www.virtualrat.org/VPR1002`, except for the acetylcholine concentration in the heart, which is here set to be constant. A dynamic model for the acetylcholine is expected to further improve the results with respect to experimental traces.

The results from a similar model, based on human parameters, will also be shown. The link to molecular systems biology and more high-resolution models of how hypertension affects kidney and heart processes will be elucidated. We anticipate that our model can become instrumental for changing the current static baroreflex activation therapy - a therapy that uses pre-programmed electrical stimulation of the carotid sinus baroreflex to lower blood pressure - into a dynamic therapy where the carotid sinus baroreflex is continuously regulated with respect to recorded blood pressure.

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