Chapter 5
Modulation by Taurine of Human Arterial Stiffness and Wave Reflection

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Abstract Effects of taurine (1000–2000 mg) on hemodynamic function and the arterial pulse wave were investigated for 102 healthy medical and paramedical students. The vascular parameters were generally dependent on aging, with the arterial stiffness parameters, such as baPWV, ABI and AI, are considered the indicators of "vascular aging". Acute administration of taurine decreased BP and HR and attenuated the stiffness parameters derived from the pulse waveform. Thus, taurine can cause significant changes in the cardiovascular system and the arterial pulse wave. However, approximately 5% of the students were non-responders. This may be related to the notion that taurine would be expected to exert greater effects on the vascular functions of unhealthy individuals. Based our previous experiments, therefore, taurine plays a role in the regulation of the cardiac and vascular function.

Abbreviations *ABI*, ankle and brachial pressure index; *AI*, augmentation index; *baPWV*, brachial to ankle pulse wave velocity; *BP*, blood pressure; *CBP*, central arterial blood pressure; *CHF*, congestive heart failure; DBP, diastolic blood pressure; $[Ca^{2+}]_o$, extracellular Ca^{2+} concentration; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; *HR*, heart rate; *MBP*, mean blood pressure; *SBP*, systolic blood pressure

5.1 Introduction

Taurine (a sulfur amino acid) is present in high concentration (around 10 mM) in myocardial cells, but is found at relatively low levels in the plasma. Taurine has been reported to be involved in numerous physiological functions, such as osmoregulation, antioxidant action, and Ca^{2+} modulation. Taurine has been found to produce many electrical and mechanical actions on cardiac muscle cells (Huxtable 1992; Sperelakis and Satoh 1993; Satoh and Sperelakis 1998; Satoh 1998b, 1999; Sperelakis et al. 1992).

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The intracellular taurine content of myocardial cells is reduced during ischemia and hypoxia, leading to calcium overload (an excess of $[Ca^{2+}]_i$ level) (Crass and Lombardini 1978; Schaffer et al. 1980; Satoh 1994a, 1994b, 1994c, 1996). Under those conditions, administration of taurine produces a beneficial effect, as the physiological and pharmacological actions induced by taurine are dependent on $[Ca^{2+}]_i$ and $[Ca^{2+}]_o$ (Satoh 1994a 1994b 1994c). For example, taurine exhibits normalizing activity, which is dependent on $[Ca^{2+}]_i$. Thus, taurine acts to maintain cellular homeostasis via its actions on ion channels, signal transduction pathways and transport systems. At a high $[Ca^{2+}]_o$, taurine inhibits cardiac function, whereas at low $[Ca^{2+}]_o$, taurine enhances it.

In arteries, the pulse wave velocity (PWV) depends on regional large artery stiffness. A high PWV allows the reflected wave to return to the aortic root sooner and to increase systolic pressure of the heart. The arterial pulse wave is formed by combining the ejection and reflection pulses and is altered in atheriosclerosis and hypertension. An augmentation index (AI) depends not only on systemic arterial elasticity but also on arterial geometry and tone (Nichols and O'Rourke 1998; Pannier et al. 2002; Davies and Struthers 2003).

In rat aorta, taurine modulates contractile function in a $[Ca^{2+}]_i$-dependent manner (unpublished data). Like cardiac cells, modulation of aortic function by taurine depends upon modulation of automatic activity, ionic channels and contractile force (Franconi et al. 1982; Satoh 1995a, 1995b 1996, 1998a, 1998b, 1998c, 1999, 2001; Satoh et al. 2002; Satoh and Sperelakis 1998). Thus, clinically, taurine may regulate vascular wall tone, mediating in the process declines in central arterial pressure provided that the tissue is exposed to high $[Ca^{2+}]_i$ with an opposite effect seen at lower $[Ca^{2+}]_i$. The aim of the present study is to investigate the arterial pulse wave. The effect of taurine on hemodynamic properties and on arterial stiffness was examined.

5.2 Materials and Methods

The study was approved by the Ethical Committee of Nara Medical University Hospital, and an informed consent was obtained from all students.

5.2.1 Taurine Intake

This study investigated the effects of tauirne administration on the hemodynamic properties of 102 healthy paramedical and medical students (averaged 21.5 ± 2.1 years old). The test was performed about 2 h after lunch, and the students took 1000-2000 mg taurine (Waken Co., Kyoto, Japan) with a cup of water. To avoid confounding influences, the students were told not to consume large amounts of beverage at lunch time before the test.

Measurements were obtained every 20 min following consumption of taurine. Significant differences were assessed with ANOVA and Student's *t*-test for paired data followed by gaussian distribution. Values are presented as means ± S.E.M.

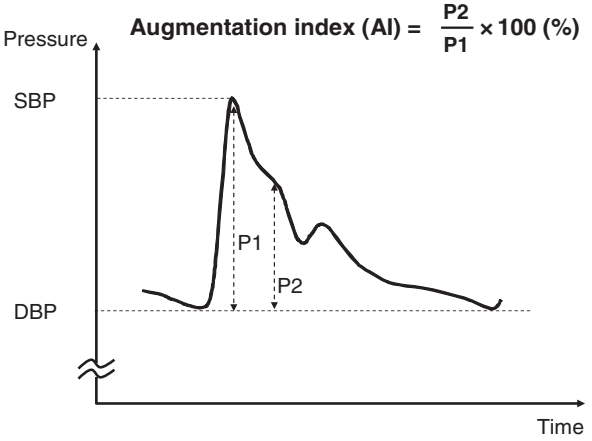

Fig. 5.1 Radial arterial pressure contour. Augmentation index is calculated from the equation; AI = P2/P1 × 100. P1: ejection wave. P2: reflection wave

5.2.2 Measurements of baPWV and ABI

Brachial to ankle pulse wave velocity (baPWV) was measured separately on the right and left sides, using a validated non-invasive device (BP-203RPEII, Omron Healthcare, Kyoto, Japan), with pressure transducers placed at the base of the brachial artery and in the inguinal region on assess the femoral artery. Simultaneously ankle and brachial pressure index (ABI), the ratio of the ankle to the brachial blood pressure, was also recorded on both right and left sides. The value of baPWV was calculated by dividing the distance to the distal site by the transient time for conducted wave.

5.2.3 Measurement of AI

An augmentation index (AI) has been established as a reflection coefficient, a ratio of reflection pressure (P2)/an ejection pressure (P1) (Fig. 5.1). AI is determined by a computer algorithm developed from invasive pressure and flow data (Kelly et al. 1989). AI was measured using automated applanation tonometry (HEM-9000AI, Omron Healthcare, Kyoto, Japan). Simultaneously left brachial HR and BP were recorded. In addition, the central arterial blood pressure (CBP) was estimated from the reflection pulse using automated applanation tonometry.

5.3 Results

Effects of taurine on arterial stiffness and wave reflection were investigated after administration of taurine (1000–2000 mg). The baPWV, the ABI, and the AI, the latter an index of wave reflection, were analyzed using a validated non-invasive

device and applanation tonometry. No students complained of any symptoms following taurine administration.

5.3.1 Blood Pressure

The hemodynamic properties of 79 students were examined before and following taurine administration. The responses were time-dependent and were apparent almost 40–60 min post-administration. Prior to taurine administration, systolic blood pressure (SBP) of brachial and ankle arteries were 114.1 ± 1.0 mmHg and 126.8 ± 1.5 mmHg on the right side, and 115.2 ± 1.3 mmHg and 116.9 ± 1.4 mmHg on the left side, respectively. Brachial and ankle diastolic blood pressure (DBP) on the left and right sides were 65.2 ± 1.5 and 64.1 ± 1.2 mmHg, and 64.8 ± 1.5 and 66.0 ± 1.1 mmHg, respectively. Right and left mean BP (MBP) were 82.3 ± 2.1 and 81.7 ± 1.6 mmHg, respectively, while HR was 73.9 ± 1.7 beats/min before taurine administration.

Approximately 40–60 min after administration of 1000 mg taurine, both SBP and DBP tended to decrease although it was not significant (by approximately 2.5 to 5%). Taurine also tended to decrease HR in a time dependent manner. However, 2000 mg taurine mediated a significant decline in both SBP and DBP (Fig. 5.2).

5.3.2 baPWV and ABI

Prior to taurine exposure, the baPWV values for the right and left sides of the 79 students were 1125.9 ± 23.2 and 1167.5 ± 20.1, respectively, while the corresponding measurements of ABI were 1.1 ± 0.2 and 1.2 ± 0.2, respectively. Taurine (2000 mg) reduced right and left baPWV by 4.5 ± 0.3% ($P > 0.05$) and 5.2 ± 0.1% ($P < 0.05$),

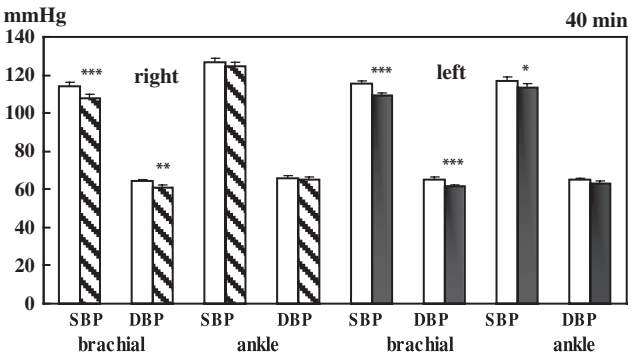

Fig. 5.2 Effects of taurine on SBP and DBP of brachial and ankle on right and left sides (n = 79). White columns: control. Shadow and black columns: 40 min after taking 2000 mg taurine. ∗: $P < 0.05$, ∗∗: $P < 0.01$, ∗∗∗: $P < 0.001$, with respect to control value

Table 5.1 Depressions of baPWV and ABI before and after taurine administration

	n	baPWV		ABI
		right	left	
1000 mg	32	2.8 ± 0.1	3.1 ± 0.3	2.9 ± 0.1
2000 mg	79	4.5 ± 0.3	5.2 ± 0.1[a]	3.1 ± 0.1

Values (%) are represented as means ± SEM. baPWV: a pulse wave velocity of brachial to ankle arteries. ABI: a ratio of ankle vs. brachial BP. [a]: $P < 0.05$, with respect to control value.

respectively, but failed to affect ABI (Table 5.1). At 1000 mg, taurine exerted no significant effect.

5.3.3 AI and CBP

The AI and CBP from radial artery were also measured, and their average values were 57.9 ± 3.1% and 113.8 ± 11.2 mmHg, respectively. Following administration of 1000 mg taurine (n = 32), AI decreased by 3.2 ± 0.3% within 40 min and by 2.9 ± 0.3% within 60 min. By comparison, 40 and 60 min after taurine administration CBP decreased insignificantly by 4.3 ± 0.3% and 4.4 ± 0.3%, respectively. After administration of 2000 mg taurine (n = 63), BP and HR were markedly reduced, with SBP falling 12.7 ± 0.3% ($P < 0.01$), DBP 11.2 ± 0.4% ($P < 0.01$) and HR 10.5 ± 0.8% ($P < 0.05$). Other stiffness parameters were also significantly affected as summarized in Table 5.2.

However, there were non-responders to taurine application for almost 5% students. Taurine did not affect or enhanced the parameters (but not markedly).

5.3.4 Age-Dependent Responses to Taurine

The vascular parameters are generally dependent on aging. The students were divided into three groups: teens, twenties, and thirties. The hemodynamic actions of taurine in the 3 groups were age-dependent. After administration of taurine (2000 mg), the stiffness parameters were reduced. But the coefficients of correlation with aging were not markedly affected, presumably because elder persons were excluded from the study. Taurine decreased the correlation coefficient of AI with respect to aging from 0.365 in the control to 0.283 after 40 min of taurine

Table 5.2 Decreases in stiffness parameters before and after taurine administration

	n	SBP	DBP	HR	AI	CBP
1000 mg	32	4.7 ± 0.2	2.5 ± 0.2	2.4 ± 0.4	3.2 ± 0.3	4.4 ± 0.3
2000 mg	63	12.7 ± 0.3[b]	11.2 ± 0.4[b]	10.5 ± 0.8[a]	10.4 ± 0.4[a]	11.9 ± 0.3[a]

Values (%) are represented as means ± SEM. SBP: systolic blood pressure. DBP: diastolic blood pressure. HR: heart rate. AI: an augmentation index from radial artery. CBP: central arterial blood pressure. [a]: $P < 0.05$, [b]: $P < 0.01$, with respect to control value.

exposure. Also the correlation coefficient of CBP with respect to aging was reduced. The effects on other parameters were not age-dependent.

5.4 Discussion

Taurine exhibits numerous physiological and pharmacological actions in various tissues. Taurine administration mediates relaxation of smooth muscle, stimulation of skeletal muscle, and diuresis (Rall 1990) Furthermore, in isolated hearts, taurine modulates the ionic currents and the action potentials, and affects the developmental tension and sinus rhythm (Satoh 1994d, 1995a, 1995c, 1998a, 2001, 2003; Satoh and Sperelakis, 1998; Satoh et al. 2002). The intracellular taurine level (10-20 mM) of myocardial cells is reduced in the ischemic heart and hypoxia, leading to a calcium overload (an excess of $[Ca^{2+}]_i$ level) (Suleiman et al. 1997; Song et al. 1998; Satoh et al. 2002). Calcium overload in turn elicits triggered activity and provokes arrhythmias. Under those conditions, taurine administration would be expected to improve cardiac function. Indeed, taurine treatment actually mediates a beneficial effect in congestive heart failure (CHF). On the other hand, taurine stimulates cardiac function under low $[Ca^{2+}]_i$ conditions. Thus, the actions of taurine have been demonstrated to be dependent on $[Ca^{2+}]_i$ and $[Ca^{2+}]_o$11 (Satoh and Sperelakis 1992; 1993; Satoh and Horie 1997).

Pulse waveform is generated by the superposition of the reflected backward wave on the incident forward wave (Nichols and O'Rourke 1998). Pulse waveform depends on two factors; arterial stiffness with increased PWV and a progressively earlier wave reflection. The pressure wave-contour analysis is a key indicator of arterial elastic properties and a prognosticator of cardiovascular risk.

The baPWV is a modality to assess arterial stiffness non-invasively, and also expresses the tone of the peripheral muscular arteries (Asmer et al. 1995; Munakata et al. 2004). Normal PWV value is approximately 950 to 1200 individuals ranging in age from teenagers to the thirties. Values of PWV increase with arterial stiffness induced by aging, hypertension, diabetes, smoking and stress. On the other hand, normal ABI values range from 0.9 to 1.3. Higher ABI values are predictive of arterial occlusive diseases, such as arteriosclerosis obliterans and Raynoud's disease.

The augmentation index has been recently established as a reflection coefficient (Kelly et al. 1989). It is determined by a computer algorithm developed from invasive pressure and flow data. Central aortic augmentation has been evaluated non-invasively by mathematically transforming the radial artery pulse waveform to the aortic pulse waveform (Chen et al. 1997; Gallagher et al. 2004). Recent technical progress makes non-invasive measurements of AI possible. The normal AI value is approximately 50% in teens, 55% in twenties, and 62% in thirties. Reflected pressure waves are also responsible for raising CBP (Karamanoglu et al. 1994). Cardiac afterload depends on the central aortic BP (or CBP) rather than on the peripheral brachial BP. Central arterial stiffening causes the pulse pressure (systolic-diastolic) to widen and leads to the syndrome of isolated systolic hypertension (Wang and Parker 2004).

After administration of taurine, a significant decrease in BP occurs within 40–60 min. In our laboratory, in rat aorta, taurine dilates the NE-induced constriction, due to mainly Ca^{2+} channel inhibition. As a result, taurine can reduce vascular wall tone and might therefore decrease baPWV and AI. But ABI may be unaffected, since taurine reduces both the brachial and ankle BP to almost a similar extent.

In the clinical treatment of CHF, the aims are to achieve several endpoints: (1) reducing workload of the heart, (2) protection of the cardiomyocyte, and (3) restriction and control of volume and sodium. In order to reduce both preload and afterload in cases of elevated filling pressure, arterioles and veins need to be dilated and cardiac output needs to decrease. Taurine might be clinically beneficial through its ability to modulate ion channels of cardiac cells and regulate blood vessel tension.

In general, the values of BP and the stiffness parameters are age-dependent (Marchais et al. 1993). In this study, the values increased with age. Therefore, the stiffness parameters, such as baPWV, ABI and AI, are considered indicators of "vascular aging". In 102 students, acute administration of taurine (1000–2000 mg) produced hemodynamic effects. The AI value was reduced by taurine, but the reduction was not marked because only young people were studied. Taurine concentration in the blood reached a peak ∼40–60 min post-administration. In rat, the serum taurine level is 36.3 ± 1.0 μg/g wet ($n = 20$) (Satoh et al. 2002). Taurine content in the aorta is usually high (∼120–130 μg/g wet) (Song et al. 1998). This high concentration is likely required for its physiological function in arterial vessels. The present finding illustrates the response to pharmacological doses of taurine.

In this study, some students did not respond to taurine, which is consistent with pharmacological non-responders in clinical treatment using herbal medicine (Kampo Medicine). The present results indicate that taurine (at the relatively high concentration of 2000 mg) reduces vascular wall tone, slows baPWV and leads to declines in AI and CBP.

5.5 Conclusion

Administration of taurine (1000–2000 mg) mediated significant hemodynamic changes in healthy students. Thus, even acute administration of taurine can cause beneficial effects; namely, a decline in BP and alterations in the pulse waveforms. Based on our previous findings, taurine would be expected to exert greater effects on vascular function of unhealthy individuals, with greater depressions occurring in the presence of high $[Ca^{2+}]_i$, and an enhancement under low $[Ca^{2+}]_i$ conditions. This hypothesis is supported by the existence of non-responders. This pattern would lead to cytoprotection against cardiovascular diseases. Irrespective, taurine exerts hemodynamic actions, resulting in effective actions on the heart and vascular tissue.

References

Asmer R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy B (1995) Assessment of arterial distensibility by automatic pulse wave velocity measurement:validation and clinical application studies. Hypertension 26:485–490

Chen CH, Nevo E, Fetics B, Pak PH, Yin FCR, Maughan WL, Kass DA (1997) Estimation of central aortic pressure waveform by mathematical transformation of radial tomometry pressure Validation of generalized transfer function. Circulation 95:1827–1836

Crass MF, Lombardini JB (1978) Release of tissue taurine from the oxygen-deficient perfused rat heart. Proc Soc Exp Biol Med 157:486–488

Davies JI, Struthers AD (2003) Pulse wave analysis and pulse wave velocity:a critical review of their strengths and weakness. J Hyertens 21:463–472

Franconi F, Martini, Stendari I, Matucci R, Zilleti L, Giotti A (1982) Effect of taurine on calcium level and contractility in guinea pig ventricular strips. Biochem Pharmacol 31:3181–3185

Gallagher D, Adji A, O'Rourke MF (2004) Validation of the transfer function technique for generating central from peripheral upper limb pressure waveform. Am J Hypertens 17:1059–1067

Huxtable RJ (1992) Physiological actions of taurine. Physiol Rev 72:101–163

Karamanoglu M, Gallagher DE, Avolio AP, O'Rourke MF (1994) Functional origin of reflected pressure waves in a multibranched model of the human arterial system. Am J Physiol 267:H1681–H1688

Kelly R, Hayward C, Avolio A, O'Rourke M (1989) Noninvasive determinstion of age-related changes in the human arterial pulse. Circulation 80:1652–1659

Marchais SJ, Guerin AP, Pannier BM, Levy BI, Safar ME, London GM (1993) Wave reflections and cardiac hypertrophy in chronic uremia Influence of body size. Hypertension 22:876–883

Munakata M, Nagasaki A, Nunokawa T, Sakuma T, Kato H, Yoshinaga K, Toyota T (2004) Effects of varsartan and nifedipine coatcore on systemic arterial stiffness in hypertensive patients. AJH 17:1050–1055

Nichols WW, O'Rourke MF (1998) McDonald's blood flow in arteries: theoretical experimental and clinical principles. Edward Arnold, London

Pannier BM, Avolio AP, Hoeks A, Mancia G, Takazawa K (2002) Methods and devices for measuring arterial compliance in human. Am J Hypertens 15:743–753

Rall JA (1990) Sixty years of investigation into the foundamental nature of muscle contraction. Prog Clin Biol Res 327:1–15

Satoh H (1994a) Antagonistic actions of taurine on Ca^{2+-}induced responses in cardiac muscle cells. Jpn Heart J 35:457–458

Satoh H (1994b) Cardioprotective actions of taurine against intracellular and extracellular Ca^{2+}-induced effects. In: Huxtable RJ, Michalk D (eds) Taurine in health and disease. Plenum Press, New York, pp 181–196

Satoh H (1994c) Taurine-induced hyperpolarizing shift of the reversal potential for the fast Na^+ current in embryonic chick cardiomyocytes. Gen Pharmacol 26:517–521

Satoh H (1994d) Regulation of the action potential configuration by taurine in guinea-pig ventricular muscle. Gen Pharmacol 25:47–52

Satoh H (1995a) Regulation by taurine of the spontaneous activity in young embryonic chick cardiomyocytes. J Cardiovasc Pharmacol 25:3–8

Satoh H (1995b) A dual actions of taurine on the delayed rectifier K^+ current in young embryonic chick cardiomyocytes. Amino Acids 9:235–246

Satoh H (1995c) Electropysiological actions of taurine on spontaneously beating rabbit sino-atrial nodal cells. Jpn J Pharmacol 67:29–34

Satoh H (1996) Direct inhibition by taurine of the ATP-sensitive K^+ channel in guinea pig ventricular cardiomyocytes. Gen Pharmacol 27:625–627

Satoh H (1998a) Modulation by taurine of the spontaneous action potentials in right atrial muscles of rat. Gen Pharmacol 30:209–212

Satoh H (1998b) Inhibition by taurine of the inwardly rectifying K^+ current in guinea pig ventricular cardiomyocytes. Eur J Pharmacol 346:309–313

Satoh (1998c) Inhibition of the fast Na^+ current by taurine in guinea pig ventricular myocytes. Gen Pharmacol 31:155–158

Satoh (1999) Taurine modulates I_{Kr} but not I_{Ks} in guinea pig ventricular cardiomyocytes. Br J Pharmacol 126:87–92

Satoh H (2001) $[Ca^{2+}]_i$-dependent actions of taurine in spontaneously beating rabbit sino-atrial nodal cells. Eur J Pharmacol 424:19–25

Satoh H (2003) Electropharmacology of taurine on the hyperpolarization-activated inward current and the sustained inward current in spontaneous beating rat sino-atrial nodal cells. J Pharmacol Sci 91:229–238

Satoh H, Horie M (1997) Actions of taurine on the L-type Ca^{2+} channel current in guinea pig ventricular cardiomyocytes. J Cardiovasc Pharmacol 30:711–716

Satoh H, Sperelakis N (1992) Taurine inhibition of Na^{+}current in embryonic chick ventricular myocytes. Eur J Pharmacol 218:83–89

Satoh H, Sperelakis N (1993) Taurine effects on Ca^{2+}currents in young embryonic chick cardiomyocytes. Eur J Pharmacol 231:443–449

Satoh and Sperelakis N (1998) Review of some actions of taurine on ion channels of cardiac muscle cells and others. Gen Pharmacol 30:451–463

Satoh H, Nakatani A, Tanaka T, Haga T (2002) Cardiac functions and taurine's actions at different extracellular calcium concentrations in forced swimming stress-loaded rats. Biol Trac Ele Res 87:171–182

Schaffer SW, Kramer J, Chovan JP (1980) Regulation of calcium homeostasis in the heart by taurine. Fed Proc 39:2691–2694

Song D, O'Regan MH, Phillis JW (1998) Mechanisms of amino acid release from the isolated anoxic/reperfused rat heart. Eur J Pharmacol 351:313–322

Sperelakis N, Satoh H (1993) Taurine effects on ion channels of cardiac muscle. In: Noble D, Earn Y (eds) Ionic channels and effect of taurine on the heart. Kluwer Academic Publishers, Boston, pp 93–118

Sperelakis N, Satoh H, Bkaily G (1992) Taurine's effects on ionic current myocardial cells. In: Schaffer SW, Lombardim B (eds) Taurine: new dimensions on its mechanisms and actions, pp 129–143

Suleiman MS, Dihmis WC, Caputo M, Angelini GD, Bryan AJ (1997) Changes in myocardial concentration of glutamine and aspartate during coronary artery surgery. Am J Physiol 272:H1063–H1069

Wang JJ, Parker KH (2004) Wave propagation in a model of the arterial circulation. J Biomech 37:457–470