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Review

Hemodynamic Mechanism of Ventricular Hypertrophy in Hypertension

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Abstract

Arterial hemodynamic assessments with technique of spectral analysis can obtain complete hemodynamic parameters including steady and pulsatile components. The steady parameters include arterial pressure (AP), heart rate, cardiac output, stroke volume and total peripheral resistance (TPR). Parameters of pulsatile hemodynamics are characteristic impedance (Zc), arterial compliance (Cm) and pulse wave reflection (P_b) *etc*. Studies of ventricular hypertrophy (VH) and arterial hemodynamics have disclosed several important findings. Hypertension in spontaneously hypertensive rat (SHR) and human subjects causes functional abnormalities in the resistance and Windkessel vessels. The extent of VH in SHR and hypertensive subjects was not correlated with AP and TPR, but positively correlated with pulsatile hemodynamic factors such as Zc and P_b. Many antihypertensive and vasodilators were capable of reducing the AP, but did not improve the VH. We have also investigated the effects of vasodilatory agents such as nifedipine (a calcium channel blocker), propranol (a non-selective β-adrenergic blocker) and atenol (a selective β-adrenergic inhibitor) on the arterial hemodynamics and VH. In addition, the effects of acute and chronic nitric oxide (NO) deprivation with N^{ω}-nitro-L-arginine methyl ester (L-NAME) on the arterial hemodynamics and VH were evaluated. We compared the endothelium-dependent and -independent vasodilation to acetylcholine, sodium nitroprusside and S-nitroso-N-acetylpenicillanine and the endothelium-dependent or -independent vasoconstriction to norepinephrine and phenylephrine between SHR and normotensive Wistar Kyoto strain. In SHR with long-term administration of L-NAME, VH was associated with decreases in left ventricular cGMP and nitrate/nitrite accompanying increase in collagen content. Coadministration of NO precursor L-arginine improved the VH and fibrosis. In VH caused by long-term L-NAME, the LW/BW ratio, total number, numerical density and size of cardiomyocytes were correlated well with both steady and pulsatile hemodymanics. Aortic stiffness has significant impact on the cardiovascular risks. We simulated aortic stiffness by applying silicon gel embedding of the abdominal and/or thoracic aorta. Aortic stiffness did not affect the blood pressure and the steady hemodynamics. It caused VH associated with increases in the pulsatile hemodynamics. The extent of VH (LVW/BW, total number, numerical density, size of cardiomyocytes and collagen volume fraction) was correlated with the pulsatile hemodynamics (impedance, pulse wave velocity and wave reflection). The finding further supports the contention that blood pressure is not the determinant of VH. The ventricular afterload is the major cause of VH. The hemodynamic consequences of ovariectomy (Ovx), menopause and estrogen replacement were investigated. Ovx increased body weight, LVW/BW ratio, Zc and P_b, but decreased Cm. These changes were reversed by estrogen replacement. For steady hemodynamics, Ovx did not much alter the systolic, mean and diastolic pressure. The pulse pressure was slightly elevated. There was large increase in TPR. Again, these changes were reversed by estrogen supplement. The implication of these findings was that menopause tends to exert vasoconstrictory effects on the resistance and Windkessel vessels. On the contrary, estrogen possesses a vasodilatory influence on the systemic vessels.

Key Words: hemodynamics, ventricular hypertrophy, hypertension, aortic pressure, aortic flow, vascular resistance, impedance, pulse wave reflection

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Introduction

Arterial stiffness after long-term hypertension and aging affects the physical properties of elastic arteries, including arterial impedance, pulse wave velocity and reflection. These Windkessel functional changes have been considered as risk factors leading to cardiac hypertrophy and decompensation (4, 13, 17, 26, 39, 54, 64). The mechanical characteristics of large arterial vessels are important determinants that reflect the ability of an artery to expand and recoil with heart pulsation and relaxation (2, 5, 55). Our laboratory has reported that arterial stiffness impaired the ventricular relaxation in patients with hypertension (11). We applied the arterial impedance analysis technique for hemodynamic measurements in spontaneously hypertensive rats (SHR). Long-term hypertension resulted in increases in arterial impedance and pulse wave reflection with a reduction in arterial compliance compared to normotensive Wistar Kyoto strain (WKY) (21). In animal experimentations, we found that chronic deprivation of nitric oxide (NO) caused ventricular hypertrophy (VH) accompanying with changes in steady and pulsatile hemodynamics. The extent of VH was equally correlated to the increases in arterial pressure (AP), total peripheral resistance (TPR) and pulse wave reflection with reduction in arterial compliance (32).

The major purposes of this review article are to present [1] The methodology of arterial hemodynamic analysis including hemodynamic measurements and analysis of arterial stiffness, arterial impedance, pulse wave velocity, evaluation of VH, determination of steady and pulsatile components of hemodynamics. [2] Arterial hemodynamics in human and animal hypertension. [3] The role of NO. [4] Effects of antihypertensive and vasodilator agents and endocrine factors and [5] Correlation of VH with arterial hemodynamic parameters.

Arterial Hemodynamics and Stiffness

In collaboration with the Department of Engineering, National Taiwan University, our laboratory developed the technique of arterial hemodynamic analysis. In anesthetized and ventilated rats, the chest was open to insert a Millar catheter with one high-fidelity pressure sensor to measure aortic pressure (AP). An electromagnetic flow probe (internal circumference 7-10 mm) was used. It was placed around the ascending aorta to measure aortic blood flow (AF). AP, flow waves and electrocardiogram (lead II) were continuously recorded on a polygraph recorder and also on a computer for off-line analysis (19, 21, 32, 33). All data were registered after the pressure and flow signals had been stable for more than 10 min.

The pressure and flow were digitized at 1-ms intervals using a 12-bit analog-to-digital converter interfaced to a personal computer. Zero flow was taken at the level of flow in the middle of late diastole. The largest modulus of this portion of the flow was considered to be the noise level. The calibration of the flow velocity signal was performed after the experiment. The flowmeter had a frequency response that was decreased by 3 dB at ~100 Hz. The phase lag was almost linear with frequency (1.2 degrees/Hz). Appropriate corrections were applied at each impedance harmonic to take the phase delay into account. All hemodynamic parameters were calculated beat by beat. The average value of four to six beats was obtained for an individual data point.

Calculations of the hemodynamic components are essentially based on our previous reports (19, 21, 32). The AP and flow waves are subjected to Fourier transform to derive the pressure and flow harmonic. For each beat, the impedance modulus is the ratio of AP harmonic to flow harmonic. The flow phase is subtract from the pressure phase at each harmonic to yield the impedance phase angle. Fig. 1 illustrates a representative recording of AP and flow in WKY and SHR and the calculated impedance modulus and phase.

Systolic, diastolic, mean aortic pressure (MAP), pulse pressure (PP), heart rate (HR), stroke volume (SV) and TPR were also determined for each beat. Cardiac output (CO) was the product of SV and HR.

Arterial Impedance Analysis

In anesthetized rats, the trachea was cannulated to provide artificial ventilation with a tidal volume of 2-3 ml and respiratory rate of 50-60 breaths/min. The femoral artery was cannulated for the recording of femoral AP. The Zc was the average of impedance modulus in the frequency range of 15-45 Hz with coefficients of variation <10%. Because of a curvilinear relation between pressure and intravascular volume in the arterial tree, an acute increase in pressure was associated with reduction in arterial compliance. The arterial compliance at pressure *P* (systolic, diastolic or mean) was obtained from the equation according to previous reports (10, 19, 77) for an exponential pressure-volume relationship:

$$C(P) = \frac{SV}{K} \frac{b \exp^{bp}}{\exp^{bP_s^*} - \exp^{bP_d}}$$

where SV is the stroke volume, *K* is the ratio of total area under the AP curve to the diastolic area, *b* is the coefficient in the pressure/volume relation (-0.0131

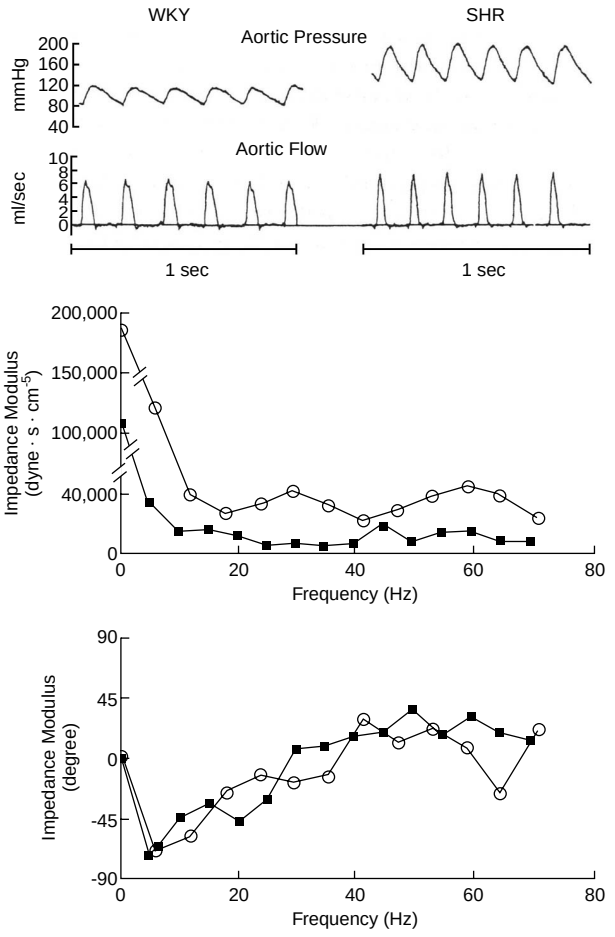

Fig. 1. Aortic pressure, flow waves (upper panels) and impedance spectra (lower panels) in WKY and SHR. The impedance modulus and phase are the average of four beats in the steady sate obtained from a Wistar Kyoto rat (WKY ■) and a spontaneously hypertensive rat (SHR ○).

in the aortic arch).

The forward and backward pressure (P_f and P_b) and flow wave ($\dot{Q}_f$ and $\dot{Q}_b$) were analyzed by spectral analysis through a computer program for the calculation of hemodynamic parameters (19, 21, 32).

Pulse Wave Velocity

In addition to the measurement of central AP, a catheter was inserted into the femoral artery to record the peripheral AP. Pulse wave velocity (PWV) was calculated as the distance (centimeters) between the central and peripheral catheter tips divided by transit time (milliseconds). The distance between the two catheter tips was measured *in situ* after postmortem fixation by sticking cotton thread onto the two catheter tip sites. Transit time from the central to peripheral pressure signals was measured on-line for each 5-s period by detectors of the software that systematically shifted in time the peripheral pressure waveform with respect to the central pressure wave and determined the value of the time. These procedures followed those described previously (25, 73).

Evaluation of VH

After the experiment, the rats were euthanized with an overdose of intravenous sodium pentobarbital (100 mg/kg). The heart was removed and the left ventricle dissected with removal of the atrium and aorta to obtain the left ventricular weight (LVW). The LVW to body weight (BW) ratio (LVW/BW) was used as an index of left VH (5, 19, 33). To perform morphological examination, part of the left ventricle was cut into small pieces and immersed in 10% formaldehyde for 24 h. The tissue was then rinsed with tape water to remove formaldehyde and embedded in paraffin at 60°C. A series of microsections (5 μm) was stained with hematoxylin and eosin for histological examination of cardiomyocytes. The total number, density and size of cardiomyocytes were evaluated using a video microscopic system (71, 76, 79).

Steady Components of Hemodynamics

Systolic, diastolic, MAP, PP, HR, SV and TPR were also determined for each beat. Cardiac output (CO) was the product of SV and HR. TPR equals to the MAP divided by CO. The relationship of these steady hemodynamic components followed the Poisseuile's principle (15, 27, 61).

Arterial Hemodynamics in Human and Animal Hypertension

The technique of arterial impedance analysis requires placement of high-fidelity microsensor for AP measurement and electromagnetic flow sensor for AF recordings. The methods are difficult to apply in small animals like rats. It is for this reason that most of these studies were undertaken in human subjects with normotension and hypertension (10, 11, 44-46, 53, 56, 58, 59). Zuckerman and Yin (80) were the first to use a 3-Fr micromonometer designed for high-fidelity recording of AP in the rat. They studied the arterial compliance and impedance in renovascular hypertensive rats with salt and corticosteroid administration. The results revealed that the arterial compliance was reduced and impedance was elevated in their hypertensive rat model.

Because SHR is a genetic model of hypertension extensively used for the study of primary hypertension (70, 78), our laboratory (33) began to apply the same technique as Zuckerman and Yin (80)

for studies in SHR and the normotensive counterpart WKY. We used a relatively large sample size of SHR and WKY and found that the major determinant of VH following long-term hypertension was the impedance factors instead of the AP and peripheral resistance. Our laboratory first measured the AF and pressure waves in anesthetized, open-chest and ventilated rats. Arterial impedance spectral analysis was employed to obtain steady and pulsatile hemodynamic parameters in SHR and WKY. The study has performed a comprehensive analysis of arterial hemodynamics in rats with established hypertension. The SHR had higher AP (50% increase over the control) than WKY. The TPR was elevated by 57%. Stroke volume was decreased by 23% and HR increased by 18% without a significant change in CO. The Z_c was increased by 43%, while arterial compliance was decreased by 52%. There were also big rises in ventricular work and wave reflection. The results provide quantitative analysis of the alteration in arterial hemodynamics of steady and pulsatile components in rats with established hypertension. In long-term hypertension, the hemodynamic changes reflect functional abnormalities in the resistance and Windkessel vessels (7, 8, 11, 15, 21).

The cardiac sequelae of hypertension have been generally attributed to the afterload imposed on the heat. Long-term ventricular loading leads to cardiac hypertrophy, decompensation and finally to heart failure (43, 72). However, the ultimate mechanisms and causal factors leading to hypertrophy still remain obscure (5, 39, 65, 67). Mechanical, neural and endocrine influences appear to be involved to a certain extent (49, 66, 67). Concerning the mechanical factors imposing increased stress on the heart, one of the perplexing findings is the poor correlation between cardiac hypertrophy and blood pressure in animals and patients with sustained hypertension (5, 10, 11, 13, 32, 39, 67, 68). In addition, regression of cardiac hypertrophy does not always follow normalization of blood pressure after antihypertensive treatment. Some antihypertensive drugs are not effective in the reversal of cardiac hypertrophy despite reduction of AP to the same degree as other agents (51, 67-69).

In long-term hypertension, the ventricular afterload is definitely increased following hemodynamic alterations in the systemic circulation. However, blood pressure per se, or even vascular resistance, is not adequate to describe the ventricular afterload. These parameters reflect only the non-pulsatile component of the left ventricular afterload. The arterial system has two functions: to convey blood from the left ventricle to different organs and to smooth flow oscillations so that pulsatile input from the left ventricle becomes nonpulsatile at the level of arterioles. The arterial system thus serves both conduit and cushion functions at the same time (41, 42, 46, 56). The pressure generated by the ventricle acts to distend the compliant aorta and to move blood forward. Measurement of "mean pressure" allows no complete description of afterload, because it omits all information about time and frequency dependence. Therefore, a complete assessment of afterload, *i.e.*, arterial impedance spectra including characteristic impedance (Z_c), arterial compliance and wave reflection take into account all of the external factors that oppose the ventricular ejection of blood (10, 40, 46, 52, 62, 68). The theoretical effects on the ventricular afterload has been supported by a few clinical and experimental studies. Bouthier *et al*. (3) and Safar *et al*. (65) have evaluated cardiac hypertrophy by echocardiography and arterial distensibility by pulse wave velocity in patients with essential hypertension and reported that the greater the reduction in arterial distensibility, the higher the degree of cardiac hypertrophy. In a preliminary study on the SHR, Levy *et al*. (40) have found that the degree of left VH did not correlate with blood pressure (systolic, diastolic or mean), but correlated significantly with Z_c.

Correlation analysis requires more information to establish the cause-effect relationship between one parameter and the others. In these studies, one of the problems is the lack of comparison with data from normotensive controls. If a good correlation between the cardiac mass and the arterial distensibility or Z_c exists in normotensive animals or subjects as a consequence of natural aging process, the effects of the hypertensive load on the cardiac mass should be reevaluated. Another problem related to the study in SHR is the use of LVW-to-body weight ratio (LVW/BW) as a measure of left ventricular hypertrophy (LVH). In both SHR and normotensive WKY, the LVW/BW was shown to change with age. It was initially high before the age of 3 weeks, then declined rapidly before 10 weeks and became stable after 20 weeks (67, 68, 70). A definite LVH in SHR was not determined by the LVW/BW alone, but by a significant increase of the ratio over the age-matched WKY. Although LVH developed in early-stage hypertension in SHR (70, 78), a number of reports have indicated that the heart reached a stage of established hypertensive hypertrophy without signs of overt cardiac failure at an age of 20-25 weeks (50, 51). In this connection, the early report by Levy *et al*. (40) on the correlation of the LVW/BW with the $Z_c$was performed in 12-week-old SHR, an age at which the LVW/BW is quite unstable and the LVH only about half maximal.

In order to correlate the VH with the non-pulsatile and pulsatile components, we carried out experiment in SHR with established hypertension (6-8 months with a

tail-cuff pressure above 190 mmHg). Control data were obtained from age-matched normotensive WKY. Animals were anesthetized with pentobarbitone sodium (40 mg/kg i.p.) and artificially ventilated with a respirator. A Millar catheter with a high-fidelity pressure sensor was used to record the AP and an electromagnetic flow transducer to monitor the AF. The pressure and flow signals were subjected to Fourier transformation for the analysis of the arterial impedance spectrum. TheLVW/BW was taken as a measure of the degree of VH. The measured hemodynamic parameters in these anesthetized, open-chest SHRs were systolic pressure (SP) (means ± SE) 172 ± 4 mmHg, diastolic pressure (DP), 120 ± 3 mmHg, PP 52 ± 2 mmHg, peripheral resistance (R_p) 344,032 ± 8,012 dyne/s/cm^{-5}, characteristic impedance (Z_c) 6,442 ± 313 dyne/s/cm^{-5}, the impedance modulus at the first harmonic (Z1) 26,611 ± 1,061 dyne/s/cm^{-5}, mean arterial compliance (C_m) 0.87 ± 0.04 μl/mmHg and LVW/BW 3.092 ± 0.026 mg/g. These parameters were significantly greater than the corresponding values in WKY, except that C_m was much decreased. In SHR, the LVW/BW was not significantly correlated with the SP, DP, R_p and steady external power. In contrast, the degree of CH was positively correlated with Z_c ($r = 0.66$, $P < 0.001$), Z1 ($r = 0.62$, $P < 0.001$) and pulsatile external work ($r = 0.41$, $P < 0.05$). It was also positively correlated with the backward pressure wave ($r = 0.42$, $P < 0.05$) and negatively correlated with C_m ($r = -0.72$, $P < 0.01$). Such correlations of LVW/BW with pulsatile hemodynamics were not found in the normotensive WKY. The results indicate that the degree of cardiac hypertrophy in hypertensive rats, with a high blood pressure, and increased stiffness of the arterial tree, is more closely related to pulsatile arterial hemodynamics than to the nonpulsatile components (32).

In human essential hypertension, the increase in systemic AP is associated with elevations of steady hemodynamics such as TPR and vascular tone of arterioles. Arterial stiffness was also observed. The pulsatile hemodynamic parameters such as characteristic impedance and pulse wave reflection were increased. The arterial compliance is reduced (10, 38, 44, 55, 57, 74, 75). In hypertensive subjects, sublingual administration of nifedipine, a Ca^{2+} channel blocker, reduces the AP and peripheral arteriolar tone, but does not affect the arterial stiffness. The decrease in total external ventricular power in hypertensive patients treated with nifedipine results from a reduction in the steady, but not the pulsatile (oscillatory) components of hydraulic ventricular power (10). Later study in patients with essential hypertension, we find that the pulse wave reflection is enhanced. The early return of the reflection wave may profoundly impair left ventricular relaxation function. The prolonged isovolumic relaxation and unaltered CO suggest that relaxation abnormalities may have a tendency to precede systolic dysfunction in hypertensive subject (11).

Hemodynamic Effects of NO

NO, a simple gas molecule found in smoke, smog, and other waste gases, is an environmental pollutant, destroyer of ozone, precursor of acid rain, and suspected carcinogen. Furchgott and Zawadzki discovered the endothelium-derived relaxing factor (EDRF) in 1980 (28), using endothelium denudation, sandwich, and cascade bioassay methods to confirm that substances released from the endothelial cell account for the vasorelaxation to acetylcholine (ACh). In fact, the discovery of endothelium derived vasoactive factors or substances such as protanoids (eicosanoids) including prostaglandins, thromboxanes and leukotrienes extend from 1930 to 1983. Many important studies have contributed to the biomedical sciences and created a number of Nobel laureates. EDRF was later identified as NO by Ignarro *et al*., Moncada and Higgs, Palmer *et al*. in 1987 and 1988 (36, 47, 60). Extensive studies on the physiological, pathophysiological and pharmacological aspects of NO have revealed that this gas molecule plays a key role in various organ systems (16, 17, 22, 48). In 1992, an issue of *Science* elected NO as the molecule of the year (24). Because of the contribution to the investigations of NO, Furchgott, Ignarro and Murad earned the Nobel Prize in 1998.

In 1997, our laboratory studied the acute effects of NO blockade with N^{ω}-intro-L-arginine monomethyl ester (L-NAME) on the arterial hemodynamics of steady and pulsatile components (16, 20, 22, 34). Acute blockade of the endogenous NO increased the AP and TPR with a decrease in HR, but only slightly influenced the pulsatile hemodynamics such as characteristic impedance and pulse wave reflection. Aminoguanidine, a relatively specific inducible NO synthase (iNOS) inhibitor essentially did not exert significant effect on the steady and pulsatile hemodynamic parameters, suggesting that blockade of constitutive NOS (cNOS), but not iNOS was involved in these changes. As mentioned before, the complete assessment of arterial hemodynamics requires methods using Fourier transformation or frequency analysis. It happened that several students (K. C. Chang and C. T. Hu) from the Department of Engineering, National Taiwan University joined the laboratory work and introduced the mathematic methodology for the complete hemodynamic studies (9, 10). We used L-NAME to elucidate the role of endogenous NO in arterial hemodynamic changes in normotensive and spontaneously hypertensive rats (SHR). Our research showed that L-NAME altered the steady hemodynamics, but not the pulsatile parameters in both

normotensive Wistar Kyoto rats (WKY) and SHR (34). In contrast to the earlier work indicating that EDRF or NO was impaired in hypertension, we found higher elevations of AP and TPR following L-NAME in SHR than in WKY, which suggests that NO release or function is enhanced, rather than impaired in rats with hypertension (20, 22, 34). Since 1992, chronic NO blockade to elevate the AP has become a new model of hypertension (1, 63). One medical student, H. R. Chang, conducted his animal experiments during the winter and summer vacation. He found that early deprivation of NO in SHR at an age of 5 wks (prehypertensive stage) facilitated the hypertension to malignant phase within 4 wks. The magnitude of increase in AP was much greater in SHR than that in WKY. Inhibition of iNOS with aminoguanidine did not affect the changes of AP in SHR and WKY. Accordingly, the enhanced NO release of function through the eNOS, not the iNOS in SHR is a compensatory mechanism to keep the blood pressure at a lower level in SHR. Chang *et al*. also observed when the blood pressure level of SHR reached the malignant phase, the rat developed signs of stroke (7). He and other coworkers continuously extended the experiment using an isolated and perfused mesenteric vascular bed in rats between 12 and 15 wks of age with established hypertension and normotensive WKY (6). ACh and NO donors (sodium nitroprusside or S-nitroso-N-acetyl penicillamine) produced dose-dependent vasorelaxation in WKY and SHR, while the magnitude of endothelium-dependent or -independent vasodilation was greater in SHR than that in WKY. In addition, SHR demonstrated higher vasoconstrictory responses to norepinephrine or phenylephrine than WKY. The results further support that endothelium-dependent or -independent vasoconstriction and vasodilation is enhanced in SHR compared with normotensive WKY.

Hsieh *et al*. (30, 31) employed chronic NO deprivation with L-NAME in 5-week-old WKY and SHR. He and coworkers used various histopathological and immunohistochemical techniques to observe the structural changes in cerebral arteries. The studies revealed that early NO deprivation accelerated the hypertension. Chronic treatment with L-NAME decreased the BW, but increased heart weight in SHR. Immunohistochemical stain with antibody against macrophage/monocyte (ED1) demonstrated severe perivascular inflammation, and Periodic acid-Schiff (PAS) staining revealed arteriolar hyalinosis and increased arteriolar injury score (Fig. 2). The perivascular inflammatory changes and hyalinosis were observed at only 2 wks following L-NAME, intensifying with continuous administration. The lumen diameter and medial cross-sectional area in SHR were smaller than those in WKY, and further reduced in SHR and WKY following NO deprivation. An analysis of the vascular remodeling indicates eutrophic vascular smooth muscle cells (VSMCs) with hypotrophic medial changes in untreated SHR, but not in untreated WKY. Hypertrophic VSMCs and eutrophic medial changes developed in SHR following L-NAME treatment. Hypertrophic VSMCs and hypotrophic medial changes occurred in all L-NAME treated rats, but not in untreated WKY. The vascular remodeling is significant in reducing the intravascular tension. In the kidney, NO deprivation resulted in severe glomerular sclerosis, arteriolar hyalinosis and impairment of renal funciotn, revealing severe proteinuria, eye fundus, and brain lesions in SHR. However, TUNEL assay did not disclose significant apoptotic changes following L-NAME administration for 4 wks. The use of nonspecific and specific NOS inhibitors suggests that the blockade of the cNOS (possibly eNOS) is the major culprit to cause these structural and functional changes. The study also has revealed an important that chronic NO blockade results in appearance of interacting leukocytes. The number of interacting leukocytes predicts atherosclerosis and restenosis (29).

Studies to examine the effects of NO on the VH continue to-date. Chang *et al*. (8) observed reductions of VH and fibrosis in SHR through chronic L-arginine administration, while Hu *et al*. (32) found that chronic NO deprivation causes severe VH with decreases in left ventricular cGMP and nitrate/nitrite and increase in collagen content. The extent of VH in terms of left ventricular weight to body weight ratio, total number, numerical density and size of cardiomyocytes were correlated well with steady hemodynamic parameters, such as AP and TPR, as well as with pulsatile hemodynamics like artertial impedance, compliance and pulse wave reflection.

Chen *et al*. found that intraperitoneal injection of pancreatic juice in rats caused increases in plasma NO. Immunohistochemical stain revealed enhanced endothelial and inducible NO synthase (eNOS and iNOS) expression. Pancreatic juice resulted in low reactivity of mesenteric bed to phenylephrine. NO blockade with L-NAME restored the vascular response to vasoconstrictor. The results indicate that intraperitoneal injection of pancreatic juice decreases the mesenteric vascular reactivity. Overproduction of NO is responsible for the low vascular reactiveness (12).

Effects of Antihypertensive and Vasodilator Agents and Endocrine Factors

Early work in our laboratory has involved the effect of nitrosovasdilators such as nitroglycerine and nitroprusside on the resistance, exchange and

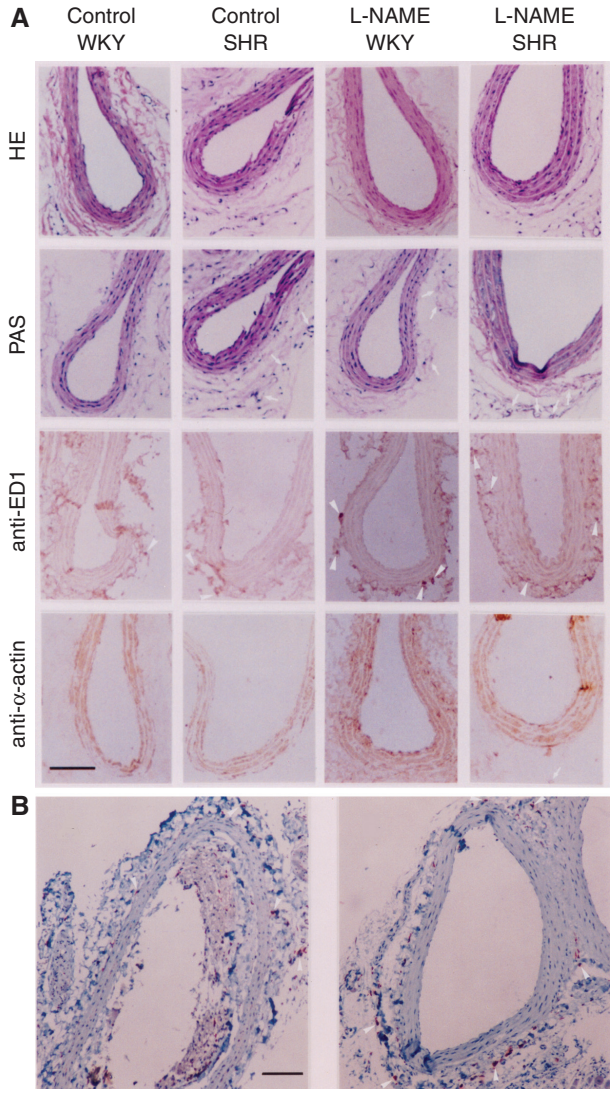

Fig. 2. (A) Histopathological and immunohistochemical examinations of internal carotid artery (ICA) sections stained with hematoxylin-eosin (HE), peridoxic acid Schiff (PAS), anti-ED1 and anti-α-smooth muscle actin (anti-α-actin). Anti-ED1-positive cells (arrow-head), and arteriolar hyalinosis (arrow) are observed in hypertensive rats (B). The micrograph illustrates the vascular changes in hypertensive SHR at 9 weeks old. There were interacting leukocytes in the endothelial layer of ICA in SHR by periodic acid-Schiff's (PAS) stain. The ED1-positive cells (monocytes/macrophage) existed in endothelial layers and intraluminal aspect of endothelium.

capacitance functions and blood volume distribution (14, 18, 23). These studies have revealed that nitroglycerin and nitroprusside act on the arterioles, capillary and venous vessels. The capacitance change caused a decrease in venous return, that may account in part the effect of nitroglycerin to reduce the preload of the heart. In hypertensive subjects with aortic stiffness and increased peripheral arteriolar tone, sublingual administration of nifedipine causes reduction in AP and peripheral vascular resistance. It does not affect the aortic stiffness. In general, nifedipine reduces the total external power and the steady components of hemodynamics. The oscillatory or pulsatile components such as impedance, pulse wave reflection and compliance are not significantly altered (10).

Our previous studies evaluated whether β-adrenergically mediated cardiovascular functions such as AP, HR, SV, CO, R_p, Z_c, C_m and P_b were altered in the SHR compared to the normotensive WKY. In pentobarbital-anesthetized and artificially ventilated rats, the AP wave was recorded with a high-fidelity Millar sensor, and aortic flow wave with an electromagnetic flow probe. The pressure and flow waves were subjected to Fourier transform so as to analyze impedance spectra. Acute β-adrenergic blockade was produced by an intravenous injection of propranolol (nonselective) and atenolol (selective β_1-blocker) at doses of 2 and 5 mg/kg, respectively. Steady-state parameters were obtained 15-20 min after intravenous administration. The SHR had higher AP, HR, R_p and Z_c than the WKY. SV and CO remained unaltered while C_m was lower. In response to propranolol, the mean AP was increased by 7 mmHg in the WKY, but did not change in the SHR. Moreover, significant decreases in HR, CO and C_m occurred in addition to increases in R_p, Z_c and P_b. These changes between the SHR and WKY were only slight. Atenolol caused decreases in AP, HR and CO in both SHR and WKY, but did not significantly alter the R_p, Z_c, C_m and P_b. Again, the atenolol-induced changes in AP, HR and CO did not appear to be significantly different between SHR and WKY. The results indicate that β-adrenergic effects on the heart, Windkessel and resistance vessels are neither greatly enhanced nor impaired during the development of hypertension. In the hypertensive state, significant β-adrenergic mechanisms still exert tonic vasodilatory effects on the large and small arterial system (35).

In collaboration with the pharmacologists, we studied the effects of ovariectomy (Ovx), menopause and estrogen replacement on the hemodynamics. This study employed the technique of arterial impedance analysis to measure and calculate the steady and pulsatile hemodynamics. Our purpose was to determine the hemodynamic consequence of Ovx and estrogen replacement. Ovx was carried out under anesthesia on female Sprague Dawley rats aged 9 weeks. Estrogen (*e.g.* 17β-estradiol or E_2) replacement started 1 week after Ovx for 4 weeks. Ovx increased the BW, while it greatly reduced the uterus weight. LVW was slightly increased, but LVW/BW ratio was significantly reduced. These changes were

reversed after E_2 replacement. Compared to sham group, Ovx with or without E_2 replacement did not significantly affect the systolic, mean and diastolic pressure. In Ovx rats, pulse pressure (PP) and HR were significantly increased, while SV and CO were slightly decreased. TPR was largely elevated, indicating Ovx induced systemic vasoconstriction. These changes all returned to close normal values (sham group) after E_2 replacement, except PP. Ovx increased the Z_c and pulse wave reflection, while it decreased arterial compliance. E_2 treatment reversed these changes, except Z_c. These results demonstrate that Ovx influences both the resistance and Windkessel functions of the artery. E_2 treatment effectively reverses most the effects of Ovx both on the steady and pulsatile hemodynamics (37).

Summary: Correlation between VH and Arterial Hemodynamics

Our studies have disclosed several important findings. Hypertension in SHR caused functional abnormities in the resistance and Windkessel vessels. In addition to the increases in AP, TPR, HR and ventricular work, the pulsatile hemodynamics such as characteristic impedance and pulse wave reflection were significantly higher those in normotensive WKY. The cardiac output was essentially not changed. There was decrease in arterial compliance. Similar changes were observed in human hypertension. The extent of VH in SHR and hypertensive subjects was not correlated with AP and TPR, but positively correlated with pulsatile hemodynamic factors such as impedance and pulse wave reflection. Many antihypertensive and vasodilators were capable of reducing the AP, but did not improve the VH.

Nifedipine, a Ca^{2+} channel blocker decreased AP and TPR in human hypertension. However, this agent reduced the external ventricular power, but did not improve the arterial stiffness. Nifedipine exerted more vasodilatory effect on the steady hemodynamics (arteriolar tone) than on the pulsatile hemodynamics (large vessels). It might cause relaxation dysfunction earlier and severer than diastolic abnormality.

Propranol (a non-selective β-adrenergic blockade) reduced the arterial pressure in WKY, but not in SHR. This agent caused decreases in HR, CO, TPR, arterial compliance, impedance and pulse wave reflection. Atenol (a selective β-adrenergic inhibitor) reduced the arterial pressure, HR and cardiac output in both SHR and WKY. It did not alter the characteristic impedance, total preperipheral resistance, arterial compliance and pulse wave reflection. These results indicate the propranol possess effects other than β-receptor blockade. β-adrenergic effects on the heart, Windkessels and resistance vessels play minimal role in the development of hypertension. The atenol effects imply that in hypertensive state, significant β-adrenergic mechanism still exerts tonic vasodilatory effects on the large and small arterial system.

Acute NO deprivation with L-NAME affects predominantly the AP and peripheral resistance. The Windkessel functions such as arterial impedance and pulse wave reflection are slightly increased. Ventricular work are not significantly altered. We also compared the acute NO deprivation between SHR and WKY. In both WKY and SHR, L-NAME resulted in dose-dependent increase in AP with a decrease in HR. Both arterial pressure increase and HR decrease were higher in SHR than those in WKY. With respect to the pulsatile hemodynamics such as impedance, arterial compliance and pulse wave reflection, NO blockade did not significantly alter these parameters in WKY and SHR. Despite higher resting values of AP and TPR in SHR, the magnitude of AP and TPR increments after L-NAME were much higher in SHR than in WKY. The results indicate that NO exerts vasodilatory effects on the peripheral arterioles. This agent plays little role on the large vessels in normotension and hypertension. Furthermore, NO release is not impaired in hypertension. Continuous release of NO appears to be enhanced in SHR as a compensatory mechanism to keep the arterial pressure and peripheral vascular tone at low levels. The endothelium-dependent or -independent vasodilation to acetylcholine, sodium nitroprusside and S-nitroso-N-acetylpenicillanine and the endothelium-dependent or -independent vasoconstriction to norepinephrine and phenylephrine were enhanced in SHR than in WKY.

In SHR with long-term administration of L-NAME, VH was associated with decreases in left ventricular cGMP and nitrate/nitrite accompanying increase in collagen content. Coadministration of NO precursor L-arginine improved the VH and fibrosis. In VH caused by long-term L-NAEM, the LW/BW ratio, total number, numerical density and size of cardiomyocytes were correlated well with both steady and pulsalite hemodymanics.

Aortic stiffness has significant impact on the cardiovascular risks. We simulated with aortic stiffness by applying silicon gel embedding of the abdominal and/or thoracic aorta. Aortic stiffness did not affect the blood pressure and the steady hemodynamics. It caused VH associated with increases the pulsatile hemodynamics. The extent of VH (LVW/BW, total number, numerical density, size of cardiomyocytes and collagen volume fraction) was correlated with the pulsatile hemodynamics (impedance, pulse wave velocity and wave reflection). The finding further supports the contention that blood pressure

is not the determinant of VH. The ventricular afterload is the major cause of VH.

The hemodynamic consequence of Ovx, menopause and estrogen replacement was investigated. Ovx increased body weight, LVW/BW ratio, impedance, pulse wave reflection, but decreased arterial compliance. These changes were reversed by estrogen replacement. For steady hemodynamics, Ovx did not much alter the systolic, mean and diastolic pressure. The pulse pressure and slightly elevated. There was large increase in TPR. Again, these changes were reversed by estrogen supplement. The meaning of these findings was that menopause tends to exert vasoconstrictory effects on the resistance and Windkessel vessels. On the contrary, estrogen possesses a vasodilatory influence on the systemic vessels.

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