Original Article

Effects of Nifedipine on Systemic and Pulmonary Vascular Impedance in Subjects Undergoing Cardiac Catheterization

Toshitaka NODA¹⁾, Toshio YAGINUMA^{2)*}, Michael F. O'ROURKE^{3),4)},
and Saichi HOSODA⁵⁾

Nifedipine 10 mg, administered sublingually to 12 patients following diagnostic cardiac catheterization, caused reduction in systemic resistance, and change of impedance together with alteration in contour of the ascending aortic and left ventricular pressure waves. The substantial reduction in ascending aortic and left ventricular systolic pressure with nifedipine occurred despite an increase in stroke volume and cardiac output, and was associated with similar reductions in mean pressure and indices of wave reflection. In the same patients, there were no significant changes in pulmonary vascular resistance or impedance, nor in pulmonary artery or right ventricular pressure pulse contour. For the systemic circulation, as with nitroglycerin and nitroprusside, reduction in wave reflection appears to be an important factor in the drug's action and for its beneficial effects on cardiac load in the treatment of angina pectoris, systemic hypertension and left ventricular failure. Thus the observed effects of nifedipine were attributed to vasodilatation of the systemic arteries and arterioles. (*Hypertens Res* 2006; 29: 505–513)

Key Words: wave reflection, pressure wave augmentation, vasodilation, peripheral resistance

Introduction

Nifedipine and other dihydropyridine calcium channel blockers (CCBs) are widely used in the treatment of hypertension, ischemic heart disease and cardiac failure with preserved left ventricular systolic function (1–6). Nifedipine is also used in the treatment of aortic valve incompetence (7) and pulmonary hypertension (8). These drugs are effective in lowering arterial pressure, relieving myocardial ischemia, and improving both systolic and diastolic left ventricular function (3, 4, 9). Their beneficial effects have been attributed to peripheral arteriolar dilation, which results in decreases in mean arterial pressure and left ventricular afterload (5, 9). However, there

have been few studies on the effects of nifedipine on pulsatile phenomena, either in the systemic or pulmonary circulations. While nifedipine has been shown to reduce early wave reflection and central aortic systolic pressure (10), the limited studies of vascular impedance have not shown a consistent effect of the drug on the frequency-dependent components of ascending aortic impedance (11, 12). And despite the drug's use in pulmonary hypertension (8), no data are available on the effects of nifedipine on pulmonary vascular impedance.

The purpose of this study was to investigate the effects of nifedipine on pulsatile arterial hemodynamics and systemic and pulmonary vascular impedance in human subjects undergoing cardiac catheterization for known or suspected ischemic heart disease.

From ¹⁾Noda Clinic, Yamaguchi, Japan; ²⁾Omiya Medical Center, Jichi Medical University School of Medicine, Saitama, Japan; ³⁾University of New South Wales, Sydney, Australia; ⁴⁾St. Vincent's Clinic, Sydney Australia; and ⁵⁾Cardiovascular Institute, Tokyo Women's Medical College, Tokyo, Japan.

*Deceased.

Address for Reprints: Michael F. O'Rourke, M.D., Suite 810, St. Vincent's Clinic, 438 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia. E-mail: M.O'Rourke@unsw.edu.au

Received January 24, 2006; Accepted in revised form March 31, 2006.

Fig. 1. Position of the sensors during cardiac catheterization.

Methods

Patients

Twelve patients underwent diagnostic cardiac catheterization for chest pain syndromes at our institution over the study period; five had suffered from myocardial infarction, six had experienced angina pectoris, and one was subsequently diagnosed with neurocirculatory asthenia. No patient had clinical or catheterization evidence of pulmonary disease, valvular disease or heart failure. Vasoactive medications were discontinued 24-h before cardiac catheterization. The study protocol and all procedures were approved by the ethical review committee of Jichi Medical University School of Medicine.

All studies were performed in a fasting, post-absorptive state after premedication with Diazepam 10 mg by intramuscular injection. Routine right-heart catheterization was performed using an antecubital vein cutdown approach. Left-heart catheterization was performed using a brachial artery cutdown approach. After routine coronary angiography and left ventriculography, the standard catheters were replaced by custom-designed high-fidelity transducer catheters (Millar Instruments, Houston, USA) (Fig. 1).

The right heart catheter was a #8 F catheter with a #6 F leader that was advanced into either the right or left pulmonary artery. The leader helped to stabilize the catheter. Pressure and flow velocity sensors were located 5.5 cm back from the tip to allow measurement of the main pulmonary artery pressure and flow velocity. A second pressure transducer was

Table 1. Clinical Characteristics of the Study Population

Patient No.	Sex	Age (years)	Height (cm)	Weight (kg)	BSA (m ²)	Diagnosis
1	M	53	155	66	1.67	AP
2	M	54	159	60	1.61	Inf. MI
3	M	43	147	50	1.40	AP
4	M	48	153	48	1.42	AP
5	M	59	165	64	1.70	Inf. MI
6	M	47	156	52	1.47	AP
7	M	62	150	51	1.44	Inf. MI
8	M	53	162	63	1.67	NCA
9	M	55	173	73	1.86	AP
10	M	63	163	64	1.68	Ant. sept MI
11	M	62	159	50	1.49	Inf. MI
12	M	43	171	62	1.73	AP

BSA, body surface area; M, male; AP, angina pectoris; Inf. MI, inferior myocardial infarction; NCA, normal coronary arteries; Ant. sept MI, anterior septal myocardial infarction.

located 5 cm further back to allow simultaneous measurement of right ventricular pressure. The #8 F arterial catheter had a pressure transducer located at the tip. The catheter tip was advanced across the aortic valve to help stabilize the catheter and to keep the sensors in the center of the stream, while also allowing measurement of left ventricular pressure. Pressure and flow velocity sensors were located 5 cm back from the tip to allow measurement of ascending aortic pressure and flow velocity (Fig. 1). The pulmonary artery and aortic flow velocity sensors were connected to two identical Biotronex BL-613 flow meters (Biotronex Laboratories, Chester, USA) whose signals were amplified by two identical, specially constructed, non-inverting operational amplifiers. Each system had a phase lag of 1.3°/Hz, which was accounted for in subsequent calculations.

Before inserting each catheter, the sensors were prewarmed for at least 30 min in saline solution at 37°C. The pressure reading at the end of this period, with the pressure sensor barely submerged in the fluid at atmospheric pressure, was used as the zero pressure reference signal of the study. The flow velocity signals were low-pass-filtered with corner frequencies at 50 Hz. The flow velocity signals together with the four pressure signals and surface ECG were recorded on a TEAC 71 seven-channel analogue magnetic tape recorder (TEAC Corporation, Tokyo, Japan) for subsequent analysis and also on an Electronics for Medicine VR16 recorder (Honeywell, Freeport, USA) as a reference. All signals were fed into a Sanei signal processor 7T17 (Sanei, Tokyo, Japan) to calculate the input resistance, pressure/flow moduli, and phase spectrum by Fourier analysis. The ascending aortic cross-sectional area was estimated by measuring the diameter of the aorta (averaged over a cardiac cycle and both before and after administration of nifedipine) at the upper margin of the sinus of Valsalva. Aortic mean flow was calculated from

Table 2. Hemodynamic Data of the Study Population

Patient No.	EDV (ml)	ESV (ml)	SV (ml)	EF (%)	HR (bpm)	CO (l/min)	LV _{max} d/dt (mmHg/s)	LVEDP (mmHg)	PCW (mmHg)
1	112	21	91	81	78	5.17	1,867	8	2
2	126	54	72	57	81	4.26	1,728	10	13
3	135	72	63	47	65	5.27	1,751	7	6
4	177	42	135	76	60	5.13	1,848	8	6
5	116	53	63	54	58	4.17	1,300	9	10
6	98	21	77	79	61	5.68	2,600	7	10
7	84	34	50	59	61	3.80	1,308	10	12
8	103	27	76	74	86	5.43	2,940	6	8
9	134	40	94	70	59	6.97	1,600	14	13
10	125	59	66	53	76	4.10	1,450	14	14
11	123	49	74	60	78	4.38	820	8	8
12	150	48	102	68	75	6.93	1,680	13	10
Mean±SD	124±24	43±15	80±22	65±11	70±10	5.11±1.00	1,741±543	10±3	9±3

EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; EF, ejection fraction; HR, heart rate; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; PCW, pulmonary capillary wedge pressure.

the flow velocity signal, together with the aortic root area determined from aortic diameter. The correlation between the stroke volume derived from the thermodilution method and that from the aortic flow signal was high ($r=0.97$) (12), but the stroke volume determined from the pulmonary flow velocity probe was somewhat smaller than that determined by thermodilution.

Protocol

Each catheter was manipulated to obtain an optimal flow velocity signal characterized by a steady diastolic level with maximal systolic amplitude and minimal late systolic negative flow. The aim was to position the catheter in the center of the vessel where the velocity profile is relatively flat. Pressure and flow were recorded with the patient resting quietly and breathing shallowly. This initial period, which followed the last injection of contrast material by at least 20 min, constituted the baseline condition. Nifedipine 10 mg was administered sublingually as the contents of a single capsule. After 20–30 min, when the pulmonary artery and left ventricular pressures had reached a steady state, the recordings were repeated.

Calculation and Data Analysis

Aortic pressure and velocity signals were digitized at a sampling interval of 5 ms. The digitized flow velocity signals were displayed on the terminal screen and only beats that had negligible baseline drift and negligible negative dip or secondary rise in diastole were considered acceptable for analysis. Zero flow was assumed to be that in late diastole. The calibration of the flow velocity probes was performed as previously reported (13) (see above). From the calibrated flow

velocity, the aortic volume flow at desired times in the study was calculated by multiplying by aortic cross-sectional area. The main pulmonary artery diameter could not be reliably measured, so the mean pulmonary artery volume flow was assumed to be equal to the mean aortic volume flow. The input impedance modulus (Z_n) and phase angle for each harmonic were calculated as the ratio of the pressure to the flow moduli and the difference of the pressure and flow phase angles, respectively (10). The input resistance, which was the impedance of 0 Hz, was calculated as the mean pressure divided by the mean flow. Pulmonary vascular resistance was calculated as the pulmonary artery pressure divided by the cardiac output.

The characteristic impedance (Z_c) was estimated by averaging the impedance moduli in the frequency range of 2–8 Hz (10, 13). A measure of the reflection characteristics of each vascular bed was obtained by calculating the difference in moduli for frequencies between 1 and 8 Hz, as

$$\left[\sum_{N=1}^{N=8} (|Z_n - Z_c|) \right] \div 8.$$

The first zero crossing of the phase angle was obtained by linear interpolation. For impedance determination, results were averaged over 6–8 pulses to cover one respiratory cycle. Augmentation of the ascending aortic pressure pulse was calculated as the pressure rise from the first systolic shoulder to the peak of the wave, and was expressed in mmHg, and augmentation index was expressed as a percentage of the pulse pressure (10). An effect was considered to be significant at the $p=0.05$ level. Data are presented as the mean±SD. Comparisons between before and after administration of nifedipine were made using paired Student's *t*-test.

Fig. 2. Simultaneous recordings of systemic and pulmonary pressure and flow data in a typical patient before (left) and after (right) administration of nifedipine. The top tracing is an ECG, the second tracing represents aortic pressure (AoPr), the third tracing represents left ventricular pressure (LVPr), the fourth tracing represents aortic flow velocity (AoFV), the fifth tracing represents pulmonary flow velocity (PAFV), the sixth tracing represents pulmonary artery pressure (PAPr), and the seventh tracing represents right ventricular pressure (RVPr). The calibrations for pressure and flow are given at left.

Results

The clinical characteristics of the twelve patients are given in Table 1, and the basic hemodynamic data under control conditions are given in Table 2. All patients were male with an average age of 55.4 ± 6.3 years (age range 43–63 years).

Representative tracings of pressure and flow recorded simultaneously in the left and right ventricles, and in the aorta and pulmonary arteries are shown in Fig. 2, before and after administration of nifedipine. The averaged values of hemodynamic parameters in all patients before and after nifedipine administration are given in Table 3.

Nifedipine administration led to an increase in heart rate from 70 to 84 beats per min (bpm), as well as an increase in stroke volume and, consequently, an even greater (31%) increase in cardiac output. Nifedipine administration resulted in a significant reduction in systemic but not pulmonary vascular resistance (from $1,664$ to $1,126$ dyn s cm^{-5} [$p < 0.001$], and 241 to 182 dyn s cm^{-5} [NS], respectively). There was no significant change in other pulmonary hemodynamic data or in pulmonary vascular impedance with nifedipine, but there

was a very clear change in the systemic vascular impedance (Fig. 3).

The increase in cardiac output with nifedipine was associated with a decrease in mean pressure from 102 to 90 mmHg, signifying a decrease in peripheral systemic resistance. Accompanying this, there was a fall of 25 mmHg ($p < 0.0001$) in systolic pressure but only 9 mmHg ($p < 0.02$) in diastolic pressure. The substantial fall in systolic pressure was associated with and largely caused by a reduction in the amplitude of the late systolic peak (Fig. 2). Measured aortic systolic pressure wave augmentation was determined as the pressure difference between the first systolic shoulder and the pressure peak (14, 15). This fell from 22 to 10 mmHg ($p < 0.0001$). Despite the 8% increase in stroke volume, the pulse pressure actually decreased by 30% ($p < 0.0001$). Such a decrease in pressure fluctuation despite an increase in flow fluctuation suggests either a decrease in wave reflection or a decrease in arterial stiffness. The change in shape of the pressure wave, with a reduction in augmentation after the first systolic shoulder, suggests a reduction in the peripheral wave reflection (12–14). This was supported by the 43% reduction (from 193 to 110 dyn s cm^{-5} [$p < 0.0001$]) of the modulus of impedance

Table 3. Hemodynamic Data before and after Administration of Nifedipine: Systemic Circulation Data at Left; Pulmonary Circulation Data at Right

Nifedipine	Left heart		Right heart	
	Before	After	Before	After
HR (bpm)	70±10	84±10**	70±10	84±10**
CO (l/min)	5.11±0.30	6.67±0.17†	5.11±0.30	6.67±0.17†
EDP (mmHg)	9.5±2.7	7.7±2.9	5.8±2.5	7.2±2.5
Mean pressure (mmHg)	102±9	90±7**	15±1	15±1
Systolic pressure (mmHg)	134±13	109±11‡	23±2	23±2
Diastolic pressure (mmHg)	80±7	71±7*	11±2	10±1
Pulse pressure (mmHg)	54±13	38±10‡	13±3	13±2
Augmentation (mmHg)	22±10	10±7‡		
Augmentation index	0.40±0.09	0.27±0.09‡		
IR (dyn s cm ⁻⁵)	1,664±70	1,126±52†	241±20	182±18
Z _c (dyn s cm ⁻⁵)	103±12	80±9	37±4	33±4
Z ₁ (dyn s cm ⁻⁵)	193±72	110±40‡	46±18	35±13
$\left[\sum_{N=1}^{N=8} (Z_n - Z_c) \right] \div 8$ (dyn s cm ⁻⁵)	47±5	29±4**	11±1	7±1

HR, heart rate; CO, cardiac output; EDP, end diastolic pressure; IR, input resistance; Z_c, characteristic impedance; Z₁, impedance modulus at frequency of the first harmonic; Z_n, input impedance modulus. **p*<0.02; ***p*<0.01; †*p*<0.001; ‡*p*<0.0001.

Fig. 3. Modulus of impedance in the ascending aorta (left) and main pulmonary artery (right) before (closed circles, solid lines) and after (open circles, dashed lines) administration of nifedipine. Bars: $\pm$ SD.

at the frequency of the first harmonic of the pulse and by the reduction in

$$\left[\sum_{N=1}^{N=8} (|Z_n - Z_c|) \right] \div 8$$

from 47 to 29 dyn s cm⁻⁵ (*p*<0.01); this is a measure of the fluctuation of modulus around its characteristic value. Characteristic impedance fell by 22% from 103 to 80 dyn s cm⁻⁵, but this change did not reach the level of statistical significance. Any decrease in characteristic impedance could have been due to a passive fall in the distensibility of the proximal

Fig. 4. Phase of impedance in the ascending aorta (upper) and main pulmonary artery (lower) before and after administration of nifedipine. Symbols are as described in the legend for Fig. 3.

aorta with the reduction in arterial pressure.

The steady component of external left ventricular work did not increase significantly after nifedipine administration, the increase in cardiac output being offset by a fall in mean pressure. The decrease in impedance modulus more than offset the increase in stroke volume and pulsatile flow, such that the pulsatile component of external work did not change, and neither did the ratio of pulsatile to total external work.

In the pulmonary circulation, mean pressure did not change after administration of nifedipine (15 mmHg both before and after), and neither did characteristic impedance (37 and 33 dyn s cm^{-5} before and after). Nifedipine administration did not affect end-diastolic pressure of the left or right ventricle, and did not alter the timing of wave reflection, as gauged by the zero crossing of the impedance phase (Fig. 4). For the ascending aorta, this frequency was 3.3 ± 0.6 Hz before, and 3.4 ± 0.6 Hz (NS) after nifedipine administration; for the pulmonary artery, this frequency was 2.5 ± 0.8 Hz before, and 2.8 ± 1.2 Hz (NS) after nifedipine. This frequency corresponded to the minimal value of the impedance modulus, but could be measured more accurately.

Discussion

To our knowledge, this paper is the first to simultaneously determine the pulsatile hydraulic load presented to the left and right ventricle, before and after use of an orally effective vasodilator agent in human subjects. Input impedance is composed of three components: resistance (mean pressure $\div$ mean flow), stiffness of proximal arteries (ascending aortic or main pulmonary artery characteristic impedance) and reflectance (augmented pressure or impedance fluctuation) (10). The results are intriguing in that they show no significant effect on pulmonary impedance and right ventricular pulsatile load, but considerable effect on left ventricular pulsatile load. The observed effects on the systemic circulation were largely attributed to the decreased peripheral resistance and decreased wave reflection induced by nifedipine.

Ascending aortic impedance is widely accepted as an expression of left ventricular load (15–26), and pulmonary vascular impedance as an expression of right ventricular load (27–29). Studies have been undertaken in patients with chest pain syndromes but without definite cardiovascular disease, in patients with hypertension, in patients with cardiomyopathy, and in patients such as those described here, with coro-

Table 4. Values of Characteristic Impedance under Control Conditions and with Pharmacological Intervention for the Systemic Circulation (A) and Pulmonary Circulation (B), and Expressed as dyn s cm^{-5} , in Human Subjects

Author	Year	Subjects	Value	Value with intervention
A. Ascending aorta				
This study		CAD	103	80 (nifedipine)
Chang <i>et al.</i> (11)	1990	HT	208	187 (nifedipine)
Ting <i>et al.</i> (26)	1991	NT	78	71 (propranolol)
		HT	83	84 (propranolol) 78 (propranolol/ phenolamine)
Ting <i>et al.</i> (25)	1986	NT	112	
		NT	165	
Yaginuma <i>et al.</i> (24)	1986	CAD	78	75 (nitroglycerin)
Fitchett <i>et al.</i> (23)	1986	CAD	127	142 (nitroglycerin)
Laskey <i>et al.</i> (21)	1985	CF	97	87 (nitroprusside)
			88 (Ex)	80 (nitroprusside + Ex)
Merillon <i>et al.</i> (19)	1982	HT	101	
		HT	134	
Merillon <i>et al.</i> (20)	1984	CF	112	
Gundel <i>et al.</i> (18)	1981	CAD	88	99 (isoprenaline) 76 (nitroprusside)
Murgo <i>et al.</i> (15)	1980	N	47	
Nichols <i>et al.</i> (17)	1977	N	53	
		CAD	95	
		CAD, HT	202	
Fujita <i>et al.</i> (38)	1999	CAD	103	87 (nicorandil) 92 (nitroglycerine)
Pepine <i>et al.</i> (36)	1978	CF		
B. Pulmonary artery				
This study		CAD	37	33
Yin <i>et al.</i> (29)	1983		49	
Murgo <i>et al.</i> (28)	1980	N	20	
Milnor <i>et al.</i> (27)	1969	Congenital/ Rheumatic	14	

N, normal subjects; CAD, coronary artery disease; HT, hypertensive subjects; NT, normotensive subjects; CF, cardiac failure. Ex, during exercise.

nary atherosclerosis (Table 4). In past studies of vasodilator action, most attention has been directed to the zero frequency component of impedance modulus—the peripheral resistance. In the late 1970s and early 1980s, the attention began to shift to the changes in characteristic impedance and aortic stiffness resulting from the underlying disease or from drug therapy (16–20). The values of the systemic and pulmonary resistance described here are similar to those reported earlier; the values of aortic and pulmonary characteristic impedance are also in the range of those reported before (Table 4).

In this study we have shown a decrease in peripheral systemic resistance with nifedipine, in association with an increase in cardiac output and fall in systemic arterial pressure. We have shown, however, that these effects occur without any change in pulmonary characteristic impedance and no significant reduction in systemic characteristic impedance.

We have pointed out that the marked falls in systolic pressure and pulse pressure, and the change in shape of the aortic and left ventricular wave contours, cannot be explained solely by the change in mean pressure and characteristic impedance. However, the decrease in systolic and pulse pressure and the change in waveform can readily be explained on the basis of the decrease in the amplitude of the reflected wave returning from peripheral vascular terminations and consequently on peripheral vasodilation (10, 16, 24). The evidence for this is the reduction in fluctuation of the impedance modulus, and the substantial fall in the ascending aortic impedance modulus at the frequency of the first harmonic of the pulse. Similar changes have been noted with nitroglycerin (23, 24) and with nitroprusside (18–21), and have been attributed to a reduction in pressure wave reflection. These effects on wave reflection have been attributed to arteriolar dilation in the case of nitro-

prusside (21, 22), and in the case of nitroglycerin, to a change in the caliber and compliance of the small conduit arteries immediately upstream from the resistive arterioles (10, 23, 24).

In this study, the change in ascending aortic impedance was associated with a marked reduction in pressure augmentation in the ascending aorta. This fall in augmentation (of 12 mmHg) was of similar magnitude to the degree of fall in mean systemic pressure (12 mmHg) and largely explains the marked reduction in pulse pressure (of 16 mmHg). The reduction of aortic systolic pressure was caused both by a reduction in pressure augmentation and a fall in mean pressure. Both are attributable to peripheral vasodilation, acting in different ways—in the first case through a decrease in wave reflection, and in the second through a decrease in peripheral resistance.

The beneficial therapeutic effects of nifedipine can thus be largely attributed to reductions in the peripheral resistance and wave reflection. In mature adults, high aortic pulse wave velocity, together with structural changes in the region of the abdominal aorta (10, 26, 30) result in wave reflection returning inappropriately early to the heart, and boosting the pressure generated by ventricular ejection in late systole. This pressure boost comprises a substantial component of the left ventricular afterload (10, 13, 14, 31). Its reduction, such as by nitroprusside administration, leads to a reduction in left ventricular load and an improvement in left ventricular function, especially during exercise in patients with left ventricular failure (32). The decrease in systolic pressure by this mechanism also partially explains the benefit of this drug in patients with hypertension and angina pectoris (10, 31).

The effects of nifedipine described here are similar to those previously described for nitroprusside (18, 19, 21, 22) and for nitroglycerin (23, 24), although unlike nitroglycerin, both nifedipine and nitroprusside consistently decrease peripheral resistance (18, 19, 21). It has been stressed, however, that the beneficial effects of nitroglycerin and of nitroprusside may be underestimated when pressure is measured in a peripheral artery (8, 10, 33, 34). The ill effects of early wave reflection, and the beneficial effects of its reduction cannot be properly interpreted or assessed from conventional measurement of the peak (systolic) and lowest (diastolic) pressure in an upper limb artery; they can, however, be assessed from interpretation of the brachial or radial artery pressure wave contour (10, 33, 34). It is quite likely that the same principles also apply to nifedipine. However, no study has yet been conducted to determine the effects of nifedipine on the differences in pressure wave contour between the central and peripheral arteries.

The results presented here for systemic arterial hemodynamics are in line with the report by Ting *et al.* (12), but at variance with those reported by Chang *et al.* (11) in groups of hypertensive subjects. Chang *et al.* (11) found a reduction in systemic vascular resistance, and in the steady component of left ventricular work with nifedipine, but were unable to demonstrate any effect on the frequency-dependent components of ascending aortic impedance. They did show a greater

reduction in systolic than in diastolic pressure with nifedipine, as well as a reduction in amplitude of the first harmonic component of impedance, and a reduction of pulse pressure, but the latter two effects were not statistically significant. The authors studied just seven patients and may have taken control data close to the time of contrast angiography, when the vasodilating effect of the contrast agent was still in evidence. The fact that cardiac output did not increase in that study raises a question as to whether the drug was exerting a pharmacological effect at the time data were taken, *i.e.*, 10–30 min after sublingual administration. Ting *et al.* (12) used a higher dose of nifedipine and showed, as did we, reductions in the measures of wave reflection and in the systemic vascular resistance. Ting *et al.* also showed a reduction in aortic characteristic impedance.

The data presented here are concordant with those of Ting *et al.* (12) and support the concept that nifedipine is a logical therapeutic agent for management of hypertension or of other conditions (including cardiac failure and coronary disease in older persons) in which the arterial system is stiffened and wave reflection adds to the left ventricular load (24, 31, 34–36). However, one caveat should be made in regard to the use of short-acting nifedipine, such as used here—namely, the decrease in vascular resistance may cause coronary steal and/or tachycardia, which could worsen myocardial ischemia (10). The ideal antihypertensive agent in isolated systolic hypertension (37), and the ideal anti-anginal agent (10) may be one which, like nitroglycerin, reduces wave reflection and aortic systolic pressure while maintaining peripheral resistance and mean arterial pressure (10, 24, 33–35, 37, 38). Long-acting nifedipine is comparable to an angiotensin converting enzyme inhibitor in efficacy and side effect profile (39), and does not induce sympathetic stimulation and tachycardia as can the short-acting preparations used in this study.

References

1. Polese A, Fiorentini C, Olivari MT, Guazzi MD: Clinical use of calcium antagonist agent (nifedipine) in acute pulmonary oedema *Am J Med* 1979; **66**: 825–830.
2. Colucci W: Usefulness of calcium antagonists for congestive heart failure. *Am J Cardiol* 1987; **59**: 52B–58B.
3. O'Rourke RA, Walsh RA: Experience with calcium antagonist drugs in congestive heart failure. *Am J Cardiol* 1987; **59**: 64B–69B.
4. Morrow DA, Gersch BJ, Braunwald E: Chronic coronary artery disease, in Zipes DP, Libby P, Bonow RO, Braunwald E (eds): *Heart Disease*, 7th ed. Philadelphia, WB Saunders, 2005, pp 1281–1341.
5. Opie LH: Calcium channel antagonists, in Opie LH, Gersch BJ (eds): *Drugs for the Heart*, 5th ed. Philadelphia, WB Saunders, 2001.
6. Safar ME, O'Rourke MF (eds): *Handbook of Hypertension*, 23rd ed. Elsevier, Edinburgh, 2006, pp 503–516.
7. Scognamiglio R, Rahimtoola SH, Fasoli G, Nistri S, Dalla Volta S: Nifedipine in asymptomatic patients with severe

- aortic regurgitation and normal left ventricular function. *N Engl J Med* 1994; **331**: 689–694.
8. Rich S, Kaufmann E, Levey PS: The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; **327**: 76–81.
9. Zusman RM, Christensen DM, Federman EB, Ruddy TD, Miller DD, Boucher CA: Nifedipine but not propranolol improves left ventricular systolic and diastolic function in patients with hypertension. *Am J Cardiol* 1989; **64**: 51F–61F.
10. Nichols WW, O'Rourke MF: McDonalds Blood Flow in Arteries, 5th ed. London, Arnold, 2005.
11. Chang KC, Hsieh KS, Kuo TS, Chen HI: Effects of nifedipine on systemic hydraulic vascular load in patients with hypertension. *Cardiovasc Res* 1990; **24**: 719–726.
12. Ting CT, Chen JW, Chang MS, Yin FC: Arterial hemodynamics in human hypertension. Effects of the calcium channel antagonist nifedipine. *Hypertension* 1995; **25**: 1326–1332.
13. Yaginuma T, Noda T, Tsuchiya M, et al: Interaction of left ventricular contraction and aortic input impedance in experimental and clinical studies. *Jpn Circ J* 1985; **49**: 206–214.
14. Takazawa K: A clinical study of the second component of left ventricular systolic pressure. *J Tokyo Med Coll* 1987; **45**: 256–270.
15. Murgo JP, Westerhof N, Giolma JP, Altobelli SA: Aortic input impedance in normal man: relationship to pressure waveforms. *Circulation* 1980; **62**: 105–116.
16. O'Rourke MF, Taylor MG: Input impedance of the systemic circulation. *Circ Res* 1967; **20**: 365–380.
17. Nichols WW, Conti CR, Walker We, Milnor WR: Input impedance of the systemic circulation in man. *Circ Res* 1977; **40**: 451–458.
18. Gundel W, Cherry G, Rajagopalan B, Tan L-B, Lee G, Schultz D: Aortic input impedance in man: acute response to vasodilator drugs. *Circulation* 1981; **63**: 1305–1314.
19. Merillon JP, Fontenier G, Lerallut JF, et al: Aortic input impedance in normal man and arterial hypertension: its modification during changes in aortic pressure. *Cardiovasc Res* 1982; **16**: 646–656.
20. Merillon JP, Fontenier G, Lerallut JF, et al: Aortic input impedance in heart failure: comparison with normal subjects and its changes during vasodilator therapy. *Eur Heart J* 1984; **5**: 447–455.
21. Laskey WK, Kussmaul WG, Martin JL, Kleaveland JP, Hirschfeld JW Jr, Shroff S: Characteristic of vascular hydraulic load in patients with heart failure. *Circulation* 1985; **72**: 61–71.
22. Pepine CJ, Nichols WW, Curry RC, Conti CR: Aortic input impedance during nitroprusside infusion. *J Clin Invest* 1979; **64**: 643–654.
23. Fitchett DH, Simkus GH, Beaudry JP, Marpole DGH: Reflected pressure waves in the ascending aorta: effects of glyceryl trinitrate. *Cardiovasc Res* 1988; **22**: 494–500.
24. Yaginuma T, Avolio AP, O'Rourke MF, et al: Effects of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. *Cardiovasc Res* 1986; **20**: 153–160.
25. Ting CT, Brin KP, Lin SJ, et al: Arterial hemodynamics in human hypertension. *J Clin Invest* 1986; **78**: 1462–1471.
26. Ting CT, Chou CY, Chang MS, Wang FSP, Chiang BN, Ying FCP: Arterial hemodynamics in human hypertension: effects of adrenergic blockade. *Circulation* 1991; **84**: 1049–1057.
27. Milnor WR, Conti CR, Lewis KB, O'Rourke MF: Pulmonary arterial pulse wave velocity and impedance in man. *Circ Res* 1969; **25**: 637–649.
28. Murgo JP, Westerhof N: Input impedance of the pulmonary arterial system in normal man: effects of respiration and comparison to systemic impedance. *Circ Res* 1984; **54**: 666–673.
29. Yin FCP, Guzman PA, Brin KP, et al: Effect of nitroprusside on hydraulic vascular loads on the right and left ventricle of patients with heart failure. *Circulation* 1983; **67**: 1330–1339.
30. Latham RD, Westerhof N, Sipkema P, Rubal B, Reuderink P: Regional wave travel and reflections along the human aorta: a study with six simultaneous micromanometric pressures. *Circulation* 1985; **72**: 1257–1269.
31. Nichols WW, O'Rourke MF, Avolio AP, et al: Effects of age on ventricular-vascular coupling. *Am J Cardiol* 1985; **55**: 1179–1184.
32. Laskey WR, Kussmaul WG: Arterial wave reflections in heart failure. *Circulation* 1987; **75**: 711–722.
33. Kelly RP, Gibbs H, O'Rourke MF, et al: Nitroglycerin has more favorable effects on the left ventricular afterload than apparent from measurement of pressure in a peripheral artery. *Eur Heart J* 1990; **11**: 138–144.
34. O'Rourke MF: Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. *Hypertension* 1990; **15**: 339–347.
35. Safar ME, London GM: Therapeutic studies and arterial stiffness in hypertension: recommendations of the European Society of Hypertension. *J Hypertens* 2000; **18**: 1527–1535.
36. Pepine CJ, Nichols WW, Conti CR: Aortic input impedance in heart failure. *Circulation* 1978; **58**: 460–465.
37. Safar ME: Epidemiological findings imply that goals for drug treatment of hypertension need to be revised. *Circulation* 2001; **103**: 1188–1190.
38. Fujita M, Takazawa K, Tanaka N, Ibukiyama C: Effects of nicorandil on aortic input impedance—a comparative study with nitroglycerine. *Jpn Circ J* 1999; **63**: 111–116.
39. Yui Y, Sumiyoshi T, Kodama K, et al: Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIB-B) randomized trial. *Hypertens Res* 2004; **27**: 181–191.