

Aortic Input Impedance during Nitroprusside Infusion

A RECONSIDERATION OF AFTERLOAD REDUCTION AND BENEFICIAL ACTION

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ABSTRACT Beneficial effects of nitroprusside infusion in heart failure are purportedly a result of decreased afterload through "impedance" reduction. To study the effect of nitroprusside on vascular factors that determine the total load opposing left ventricular ejection, the total aortic input impedance spectrum was examined in 12 patients with heart failure (cardiac index <2.0 liters/min per m^2 and left ventricular end diastolic pressure >20 mm Hg). This input impedance spectrum expresses both mean flow (resistance) and pulsatile flow (compliance and wave reflections) components of vascular load. Aortic root blood flow velocity and pressure were recorded continuously with a catheter-tip electromagnetic velocity probe in addition to left ventricular pressure. Small doses of nitroprusside (9–19 $\mu\text{g}/\text{min}$) altered the total aortic input impedance spectrum as significant ($P < 0.05$) reductions in both mean and pulsatile components were observed within 60–90 s. With these acute changes in vascular load, left ventricular end diastolic pressure declined (44%) and stroke volume increased (20%, both $P < 0.05$). Larger nitroprusside doses (20–38 $\mu\text{g}/\text{min}$) caused additional alteration in the aortic input impedance spectrum with further reduction in left ventricular end diastolic pressure and increase in stroke volume but no additional changes in the impedance spectrum or stroke volume occurred with 39–77 $\mu\text{g}/\text{min}$. Improved ventricular function persisted when aortic pressure was restored to control values with simultaneous phenylephrine infusion in three patients. These data indicate that nitroprusside acutely alters both the mean and pulsatile components of vascular load to effect improvement in ventricular function in patients with heart failure. The evidence presented suggests that it may be possible to reduce

vascular load and improve ventricular function independent of aortic pressure reduction.

INTRODUCTION

Others have inferred that left ventricular function improves during nitroprusside infusion as a result of afterload or "impedance" reduction in patients with heart failure (1–5). This conclusion is based on the ratio of measurements of cardiac output by indicator dilution and mean arterial pressure, usually obtained from a peripheral artery, to derive peripheral vascular resistance. These resistance data, however, represent only the nondynamic (static) factors related to the steady flow characteristics of the peripheral arterial system. Clearly, the left ventricle does not pump a mean blood flow directly into the peripheral resistance vessels. Only a fraction of the stroke volume is displaced peripherally into the arterioles during each ventricular ejection. The left ventricle ejects pulsatile blood flow into a distensible aorta. To describe and analyze this pulsatile (dynamic) system, the concept of hydraulic input impedance derived from the relationship of pulsatile pressure to pulsatile flow measured at the root of the aorta was used (6). From such measurements, the total aortic input impedance spectrum can be derived. This function takes into account not only the peripheral resistance, but also the distensibility of the aorta, inertial properties of blood, and effects of wave reflections within the arterial tree (6–11). This concept, which has its analogy in other pulsatile hydrodynamic systems and alternating electric current theory, is useful to clarify the behavior of the system and more completely describe the total dynamic load against which the ventricle ejects blood (10–15). In spite of the complexity of pulsatile pressure-flow relationships, study of the aortic input impedance spectrum can provide information about the

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vascular mechanical properties of the circulation (6). For example, a portion of the aortic input impedance spectrum is sensitive to alterations in the wall compliance of large arteries and recent studies indicate that this property can be modified by age and certain disease states that include heart failure (8, 11, 12). A study of the possible effects of nitroprusside on the aortic input impedance spectrum in man has not been reported.

Accordingly, we studied the effect of nitroprusside on the total aortic input impedance spectrum in patients with chronic left ventricular failure. The impedance spectrum was determined from measurements of pulsatile aortic blood flow and pressure made with an electromagnetic catheter-tip velocity transducer. Our results indicate that nitroprusside produces a dose-dependent alteration of the total aortic input impedance spectrum, as a result of changes in compliant, wave reflectance, and resistive terms. Thus, improvement in ventricular function relates to reduction of both pulsatile and steady flow components of vascular load.

METHODS

Patient population

Patients with clinical evidence for congestive heart failure scheduled to undergo diagnostic catheterization studies were invited to participate in the study. The experimental protocol, specifically defining the catheter-tip velocity flow probe and related procedures, was approved by appropriate institutional committees for clinical investigation and informed consent was obtained from all patients. No patients with valvular or congenital heart disease were included. Patients with mitral insufficiency were specifically excluded. The study group consisted of 12 patients (age range, 40–55 yr) including 10 with primary cardiomyopathy and 2 with chronic coronary heart disease. In each patient, dyspnea and cardiomegaly were present for at least 1 yr, and two patients (Nos. 7 and 8) had a history of mild hypertension. All patients were in New York Heart Association functional class III or IV and had a resting left ventricular end diastolic pressure ≥ 20 mm Hg and cardiac index < 2.0 liters/min per m^2 .

Catheterization and measurements

Studies were conducted in a fasting, postabsorptive state without premedication and before administration of angiographic contrast material. Catheterization was performed from a right brachial artery cutdown. Aortic root blood flow velocity was measured utilizing a No. 8 French catheter-tip flow velocity probe (Carolina Medical Electronics, Inc., King, N. C.) This probe has an electromagnetic flow velocity sensor mounted 5 cm from its tip. The tip was advanced through the aortic valve into the left ventricular cavity. The sensing electrodes were positioned fluoroscopically near the upper border of the sinuses of Valsalva. The probe was effectively stabilized at this location in the central axis of the aortic root, eliminating signal artifacts that occur if the probe lays against the vessel wall and minimizing waveform artifacts related to motion (11, 12, 16, 17). According to calibration in our laboratory (11) the dynamic frequency response

of this system, using a Carolina flowmeter (model 601D) was constant ($\pm 5\%$) in amplitude from 0 to 14.5 Hz. The phase shift was linear with frequency. This response is adequate for accurate measurement of pulsatile velocities in the human aorta because $>98\%$ of the variance of the pulsations, at heart rates observed in man, is included in the first eight harmonics (6, 11, 18). Because the blood flow velocity profile in the ascending aorta is relatively flat (19, 20) the product of linear velocity and aortic cross-sectional area is volume of blood flow per unit time. Assuming a constant (mean) aortic cross-sectional area, the velocity signal is the same as a volume flow signal. The mean output signal of the flowmeter was calibrated in cubic centimeters per second by reference to simultaneous cardiac output determinations by indicator dilution technique. In these patients with low cardiac outputs, indocyanine green was injected rapidly into the right atrium with sampling from the main pulmonary artery to minimize effects of a large central volume (21). Using an electromagnetic velocity sensor mounted on a similar catheter, we found (22) excellent correlation (0.93) between mean blood flow measurements obtained by this method and measurements obtained using dye dilution. Before insertion of the velocity catheter, an *in vitro* zero velocity signal was established by submersion of the probe in saline solution. This zero signal was identical to the electrical zero obtained by switching off the magnet current. At the end of each patient study, the catheter was withdrawn until the velocity sensor was in the brachial artery. The artery was then totally occluded by a snare to establish an *in vivo* hydraulic zero.

Aortic pressure was measured through the fluid-filled lumen of the velocity catheter with a Millar strain gauge transducer (Millar Instruments, Houston, Tex.) attached directly to the external port. The dynamic calibration of the system was determined after each study using the free oscillation method (6). The resonant frequency of the system ranged from 19 to 33 Hz with a damping ratio of 0.11–0.21. Left ventricular pressure was recorded with an additional No. 4 French micromanometer catheter (Millar model PC340) introduced percutaneously into the left brachial artery (23). We have found that placement of two catheters across the aortic valve of animals does not distort the aortic flow signal recorded from either cuff-type or catheter-mounted velocity probes. Aortic pressure and flow, left ventricular pressure, and a standard electrocardiographic lead were continuously monitored on a multichannel oscilloscopic recorder (model DR12, Electronics for Medicine, Pleasantville, N. Y.).

Procedure

After the catheters were in position and the velocity probe calibrated, as outlined above, pulsatile aortic flow and pressure and left ventricular pressure signals were recorded during a control interval. This interval was defined as a 5-min period during which pressure, peak flow, and heart rate were stable ($\pm 5\%$). Recordings were then made continuously as sodium nitroprusside was infused intravenously by a Harvard pump (Harvard Apparatus Co., Millis, Mass.) at $9 \mu\text{g}/\text{min}$. After peak hemodynamic effects occurred and stabilized, usually between 3 and 5 min, the infusion rate was doubled and recordings continued. This procedure was repeated until systolic aortic pressure declined below 90 mm Hg or peak aortic blood flow decreased. In three patients aortic pressure was transiently increased, during continued nitroprusside infusion, by the intravenous infusion of phenylephrine. The phenylephrine infusion rate was adjusted to restore systolic pressure to control values for 5 min. Recordings were repeated during simultaneous phenylephrine and nitroprusside infusion.

At the conclusion of the above, selective coronary and left ventricular cineangiograms were performed by standard techniques.

Calculations and statistical analysis

Determination of left ventricular pressure, aortic pressure, stroke volume, and heart rate. Pressure, flow, and heart rate measurements were averaged during the control period and with each nitroprusside dose, from at least 10 consecutive beats. Mean aortic pressure, left ventricular end diastolic pressure, stroke volume, and heart rate were tabulated and grouped at the following nitroprusside dose ranges; 9–19, 20–38, and 39–77 $\mu\text{g}/\text{min}$.

Determination of the aortic input impedance spectrum. Aortic pressure and velocity signals were recorded on magnetic tape (model 3960, Hewlett Packard Co., Palo Alto, Calif.) and later digitized at a sampling interval of 10 ms by an analogue to digital converter (model 1015, Biomation Corp., Cupertino, Calif.). To construct the aortic input impedance spectrum, aortic pressure and flow data were converted to a Fourier series and impedance moduli and phase angles computed as a function of frequency according to the method (Appendix) outlined by McDonald (6). The resistive term, peripheral vascular resistance (PVR),¹ was calculated in dyn/s per cm^5 as the ratio of pressure and flow at 0 Hz. From the aortic input impedance spectrum the compliant term, characteristic impedance (Z_0), was calculated in dyn/s per cm^5 as the arithmetic mean of impedance moduli >2 Hz (11). Input impedance moduli are known to oscillate around the characteristic value because of

pressure and flow waves reflected from distal points (6, 7, 11). The reflectance term was quantitated as a wave reflection index calculated as the maximum-minimum impedance modulus difference (12).

Mean values and standard errors of the mean were calculated. From these values for impedance moduli and phase angles composite impedance spectra were constructed for the entire patient group and spectra from control and nitroprusside periods were compared qualitatively. Also, statistical comparisons of mean hemodynamic data obtained from control and nitroprusside infusion periods were made using an analysis of variance. Differences were considered statistically significant when P values were <0.05 .

RESULTS

The influence of nitroprusside on the aortic input impedance spectrum and pertinent hemodynamic data is summarized for all patients in Figs. 1 and 2, and Tables I and II.

Effect of nitroprusside on aortic input impedance spectrum. Composite aortic input impedance spectra (modulus and phase) summarize the findings of the entire patient group in Fig. 1. Alterations in the aortic input impedance spectrum occurred in each patient with only 9–19 $\mu\text{g}/\text{min}$. Comparison of impedance spectra before and during nitroprusside reveals a dose-dependent decline in impedance modulus at each frequency. This decline appeared proportionately greater at the lower frequencies. At the higher frequencies this decline results in a more “flattened”

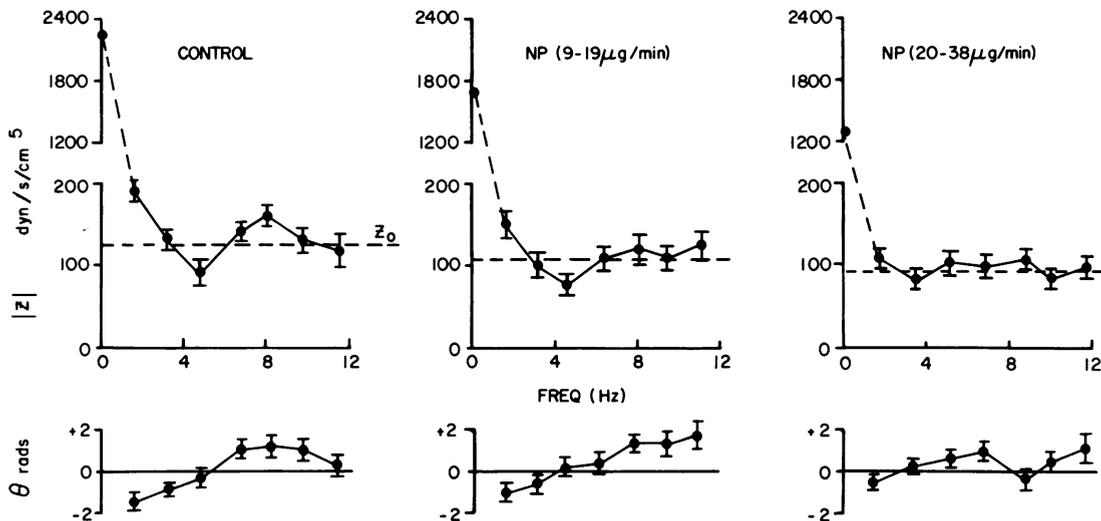


FIGURE 1 Composite aortic input impedance spectra (modulus at top and phase at bottom) during control and nitroprusside infusion periods (NP) derived from all 12 patients. Amplitudes of respective impedance moduli (vertical axis) are plotted as a function of frequency (horizontal axis). Note the reduction in amplitude of impedance moduli with nitroprusside. Z_0 (dashed line) and PVR (term at 0 Hz) decline with nitroprusside indicating that both the pulsatile and mean components of load decreased. The other pulsatile term, representing wave reflections and indicated by impedance modulus oscillations between maximum and minimum values, also decreased with nitroprusside. The strongly negative phase at lower frequencies, indicating that flow leads pressure, becomes less negative and the zero crossing is shifted to lower frequencies with nitroprusside. Circles represent means and bars represent 1 SEM.

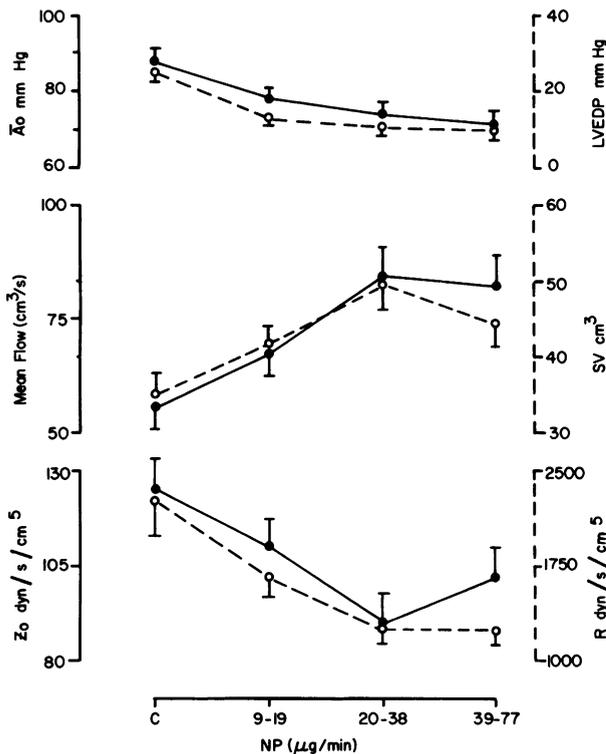


FIGURE 2 Summary of hemodynamic changes during the control period (C) and at several nitroprusside (NP) dose ranges (horizontal axis). Z_o and PVR (R) (solid and dashed lines, respectively) declined significantly with 9–19 $\mu\text{g}/\text{min}$ as a greater decline occurred with 20–38 $\mu\text{g}/\text{min}$. Cardiac output (mean flow) and stroke volume (SV) (solid and dashed lines, respectively) increased as impedance declined. The maximum flow increase occurred at 20–38 $\mu\text{g}/\text{min}$ coincident with the maximum decline in Z_o and PVR. Mean aortic (\bar{A}_o) and left ventricular end diastolic (LVEDP) pressure responses are illustrated (solid, and dashed lines, respectively). Bars represent 1 SEM and circles indicate mean data obtained in 12 patients.

spectral pattern as there is less variation in the magnitude of moduli. Impedance phase, strongly negative in the control period, became less negative and crossed zero at lower frequencies with nitroprusside.

The PVR declined (25%) from $2,256 \pm 221$ to $1,682 \pm 144$ dyn/s per cm^5 (mean \pm SE) as Z_o declined (14%) from 125 ± 8 to 108 ± 7 dyn/s per cm^5 (Fig. 2) at the 9–19- $\mu\text{g}/\text{min}$ dose range (both $P < 0.01$). The maximum-minimum impedance modulus difference (reflection index) also declined at this low dose from 112 ± 7 to 79 ± 6 dyn/s per cm^5 , $P < 0.01$ (Fig. 1). The maximum decline in PVR, Z_o , and reflection index occurred at a dose range of 20–38 $\mu\text{g}/\text{min}$ ($P < 0.001$). Larger doses resulted in no additional statistically significant reduction in these variables (Table I).

Effect of nitroprusside on left ventricular hemodynamic function. Average heart rate did not change significantly at 9–19 or 20–38 $\mu\text{g}/\text{min}$ of nitroprusside.

However, at 39–77 $\mu\text{g}/\text{min}$, heart rate increased 12% ($P < 0.05$), compared to control (Table II). Mean aortic pressure declined from 88 ± 3 to 79 ± 2 mm Hg at 9–19 $\mu\text{g}/\text{min}$ ($P < 0.01$). Stroke volume increased from 35 ± 3 to 43 ± 2 cm^3 at 9–19 $\mu\text{g}/\text{min}$ ($P < 0.01$) and to 49 ± 3 cm^3 at 20–38 $\mu\text{g}/\text{min}$, ($P < 0.001$). No additional increase in stroke volume occurred for the group at 39–77 $\mu\text{g}/\text{min}$. This increase in left ventricular output was evident ≈ 45 s after the infusion began with little change in aortic pressure and became maximal between 60 and 90 s. The increase in output was associated with a reduction in left ventricular end diastolic pressure (26 ± 1 to 16 ± 1 mm Hg, $P < 0.01$). The increase in stroke volume and reduction in end diastolic pressure were both temporally related to changes in the aortic input impedance spectrum. The stroke volume-end diastolic pressure relationship achieved, as vascular load was reduced with nitroprusside, is illustrated in Fig. 3. Cardiac output or mean aortic blood flow (Table I and Fig. 2) increased, as Z_o declined with nitroprusside infusion, ($r = -0.75$, $y = -0.51x + 124$) $P < 0.01$, (Fig. 4). An example of the instantaneous flow and pressure signals recorded from a patient representative of the group is shown in Fig. 5.

Effect of restoration of aortic pressure. Aortic pressure was restored in three patients by simultaneous phenylephrine infusion (Table III). Hemodynamic responses were similar in each of these patients and mean values are shown for the aortic input impedance spectra (modulus and phase) in Fig. 6. An example of the pressure and flow recordings from one of these

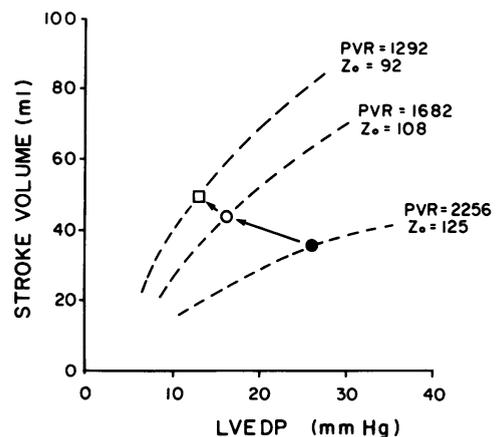


FIGURE 3 Effect of vascular load reduction on left ventricular function. Stroke volume (vertical axis)—left ventricular end diastolic pressure (LVEDP, horizontal axis) relationship as the aortic input impedance spectrum was altered by nitroprusside. Symbols represent mean values observed during control (●) and nitroprusside periods at 9–19 $\mu\text{g}/\text{min}$ (○) and 20–38 $\mu\text{g}/\text{min}$ (□). Hypothetical isopleths (dashed lines) are drawn for mean PVR and Z_o data. The leftward and upward shift in the stroke volume-end diastolic pressure relationship strongly supports improved function as vascular load declines.

TABLE I
Effects of Nitroprusside Infusion on Cardiac Output and Components of Vascular Load

	Patient	Control	Nitroprusside, $\mu\text{g}/\text{min}$			Patient	Control	Nitroprusside, $\mu\text{g}/\text{min}$			
			9-19	20-38	39-77			9-19	20-38	39-77	
Resistance, $\text{dyn}/\text{s}/\text{cm}^5$	1	2,347	1,687	1,250	1,281	Z_0 , $\text{dyn}/\text{s}/\text{cm}^5$	1	145	118	97	107
	2	1,678	1,283	910	938		2	117	107	95	98
	3	1,666	1,281	1,032	993		3	94	90	82	93
	4	3,214	2,539	1,752	1,856		4	146	124	97	107
	5	3,599	2,399	1,717	1,746		5	178	148	128	138
	6	1,862	1,216	965	958		6	88	65	47	58
	7	2,234	1,913	1,268	1,301		7	153	127	128	142
	8	2,841	2,108	1,806	1,821		8	132	104	82	95
	9	3,155	2,023	1,821	1,645		9	140	125	116	127
	10	1,492	1,333	1,069	1,011		10	123	105	94	103
	11	1,479	1,140	897	985		11	99	100	96	104
	12	1,506	1,264	1,018	912		12	97	78	55	72
	Mean	2,256	1,682	1,292	1,287		Mean	125	108	92	104
SD	766	498	374	378	SD	28	23	25	24		
SEM	221	144	108	109	SEM	8	7	7	7		
CO, cm^3/s	1	49	64	81	78	Max-min impedance mod, $\text{dyn}/\text{s}/\text{cm}^5$	1	131	101	85	81
	2	68	81	101	98		2	97	63	28	34
	3	67	78	93	94		3	118	85	81	71
	4	36	42	54	51		4	138	83	31	37
	5	33	45	59	58		5	150	96	41	48
	6	57	80	98	96		6	81	61	26	29
	7	63	62	82	83		7	154	81	36	43
	8	48	55	62	60		8	117	92	68	57
	9	41	56	60	64		9	111	75	30	35
	10	72	75	91	87		10	90	78	27	31
	11	73	83	101	96		11	79	68	24	37
	12	69	78	93	95		12	83	60	23	33
	Mean	56	67	81	80		Mean	112	79	41	45
SD	14	15	18	17	SD	24	18	11	12		
SEM	4	4	5	5	SEM	7	6	3	5		

CO, cardiac output.

patients is illustrated in Fig. 7. Nitroprusside infusion resulted in a decline in impedance modulus at each frequency compared to control. The "flattened" spectral pattern observed with nitroprusside-induced vasodilation is again apparent as PVR and Z_0 decrease (mean from 2,284 to 1,362 and 124 to 87 $\text{dyn}/\text{s}/\text{cm}^5$, respectively). The wave reflection index amplitude also decreased in each patient as the mean value declined from 122 to 78 $\text{dyn}/\text{s}/\text{cm}^5$. Phenylephrine was infused and aortic pressure restored in each of these patients as nitroprusside continued. Mean aortic pressure was increased from 77 to 94 compared to 91 mm Hg observed in the control period. At this similar pressure, PVR and Z_0 increased (to 2,050 and 117 $\text{dyn}/\text{s}/\text{cm}^5$, respectively) and the maximum-minimum modulus amplitude increased to 103 $\text{dyn}/\text{s}/\text{cm}^5$. These values are all reduced compared to control values. At low frequencies, the mean value for

impedance phase is strongly negative, crossing zero at 4.6 Hz and becoming positive at high frequencies. With nitroprusside (38 $\mu\text{g}/\text{min}$) phase is less negative at low frequencies and the zero crossing is shifted to 3.6 Hz. With the addition of phenylephrine phase becomes more negative at low frequencies and crosses zero at 5.2 Hz. With restoration of the pressure term in this subgroup, left ventricular function remained improved in each of these patients compared to control measurements without nitroprusside (Fig. 8).

DISCUSSION

Recent application of vasodilators in the treatment of heart failure has generated widespread interest (1-5). Because determination of the aortic input impedance spectrum requires instantaneous aortic blood flow measurements, only changes in the mean (frequency

TABLE II
Effects of Nitroprusside Infusion on Hemodynamic Variables

	Patient	Control	Nitroprusside, $\mu\text{g}/\text{min}$			Patient	Control	Nitroprusside, $\mu\text{g}/\text{min}$			
			9-19	20-38	39-77			9-19	20-38	39-77	
AoP, mm Hg	1	87	81	76	75	LVEDP, mm Hg	1	20	16	13	12
	2	85	78	69	69		2	25	12	13	13
	3	84	75	72	70		3	28	17	16	14
	4	86	80	71	71		4	25	19	16	15
	5	90	81	76	76		5	32	16	14	13
	6	79	73	71	69		6	30	23	15	12
	7	106	89	78	81		7	20	14	13	13
	8	102	87	84	82		8	27	14	15	13
	9	98	85	82	79		9	22	11	11	11
	10	81	75	73	66		10	23	13	10	10
	11	82	71	68	71		11	29	21	13	12
	12	77	74	71	65		12	25	10	10	10
	Mean	88	79	74	73	Mean	26	16	13	12	
	SD	9	6	5	6	SD	4	4	2	2	
	SEM	3	2	2	2	SEM	1	1	1	1	
SV, cm^3	1	38	45	48	44	HR, beats/min	1	78	85	101	106
	2	45	51	49	48		2	90	95	124	123
	3	36	42	52	40		3	112	111	107	141
	4	20	31	34	33		4	107	81	95	93
	5	20	37	39	36		5	100	73	91	97
	6	39	45	47	45		6	87	107	125	128
	7	33	39	55	45		7	115	95	89	111
	8	29	39	38	37		8	99	87	98	97
	9	27	42	40	34		9	92	80	90	113
	10	43	48	57	49		10	101	94	96	107
	11	42	46	56	50		11	103	103	108	115
	12	49	51	72	70		12	84	92	78	81
	Mean	35	43	49	44	Mean	97	92	100	109	
	SD	9	6	11	10	SD	11	12	14	16	
	SEM	3	2	3	3	SEM	3	3	4	5	

AoP, mean aortic pressure; LVEDP, left ventricular end diastolic pressure; SV, stroke volume; HR, heart rate.

independent) component of vascular load expressed by PVR have been reported with vasodilator therapy in man. In this study, we found that nitroprusside infusion results in stroke volume increases within 45 s with little change in aortic pressure. These early changes in ventricular output relate to significant acute reduction of all components of vascular load expressed by the aortic input impedance spectrum. The pulsatile flow component of vascular load, quantitated by characteristic impedance and the wave reflection index, in addition to the steady flow component, PVR, is promptly reduced. The reduction of Z_0 indicates an action effecting aortic distensibility. In addition, the reduced peripheral resistance implies arteriolar vasodilation in these patients with heart failure. These effects were consistently observed at low nitroprusside doses (9-19 $\mu\text{g}/\text{min}$) and appeared dose dependent over the lower dose range. At larger doses the effects

of nitroprusside on the aortic input impedance spectrum appeared attenuated, possibly because of reflexly mediated increases in sympathetic vascular tone.

Before discussing these results, several limitations of the techniques used require comment. When obtaining volume of blood flow per unit time, with a catheter-tip velocity transducer, certain assumptions are made. The aorta was assumed to be a tube with a constant internal diameter during the cardiac cycle. In previous studies, changes in ascending aortic external diameter during ejection were estimated with an electrical strain gauge caliper (24). The change in external aortic cross-sectional area during systole was $\pm 5.5\%$ of the mean value. This external area change during ejection was greater than previously reported internal area estimates made using angiographic techniques (25). The differences in measurements of cross-sectional area change can probably be attributed to

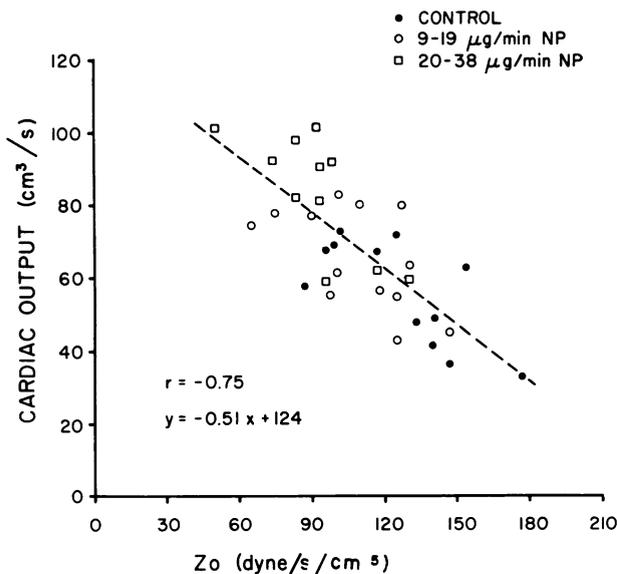


FIGURE 4 Relation between cardiac output (vertical axis) and Z_0 (horizontal axis) is shown for two dose ranges of nitroprusside (NP), compared to control observations. The correlation ($r = -0.75$) between cardiac output and Z_0 was good.

differences in the site of diameter estimation. We found (12, 22, 26) that internal aortic diameter changes are less, inside the pericardial reflection, where angiographic measurements are usually made, compared to outside, where caliper measurements were done (24). Therefore, the effect of cross-sectional area change on calculation of volume flow from velocity flow is probably minimal when velocity is measured near the upper border of the sinuses of Valsalva. Another assumption was that the velocity profile of ascending aorta blood flow is relatively flat. Previous flow velocity measurements over the cross-section of the ascending aorta of man support this assumption (6). Motion artifact present in earlier studies using catheter-tip velocity transducers (27) was minimized in this study by stabilizing the velocity sensor in the central aorta. This was accomplished by placing an extension at the end of the catheter. When the extension is through the aortic valve in the ventricle lateral motion is markedly reduced (16, 17, 22). We found excellent correlation ($r = 0.93$) between cardiac output obtained with an electromagnetic velocity catheter and determinations by dye dilution (22). Although some error is introduced extrapolating catheter-measured blood velocity to volume-flow rate, the error appears relatively small.

Other possible sources of error relate to the methods used for recording and digital conversion of pressure and flow signals and the number of harmonics used to represent them. The sampling theorem for a periodic function states (28, 29) that if $f(t)$ is a function of period

T and if all Fourier coefficients vanish above the N th harmonic, then $f(t)$ has only $2N + 1$ independent sampling values and these have a spacing of $T/(2N + 1)$. This means that if the function to be analyzed, such as aortic pressure and flow, has only eight harmonics (28, 29), 17 samples would be sufficient to obtain its Fourier expansion. In the present study, pressure and flow signals were sampled every 10 ms. With a heart rate of 90 beats/min, 66 samples are provided. To record these signals accurately, the frequency response of the recording system should be flat beyond the eighth harmonic or 10–12 Hz.

In addition to the well-known increase in peripheral resistance, previous studies from our laboratory indicate that the pulsatile component of vascular load is increased in patients with heart failure (12). Both

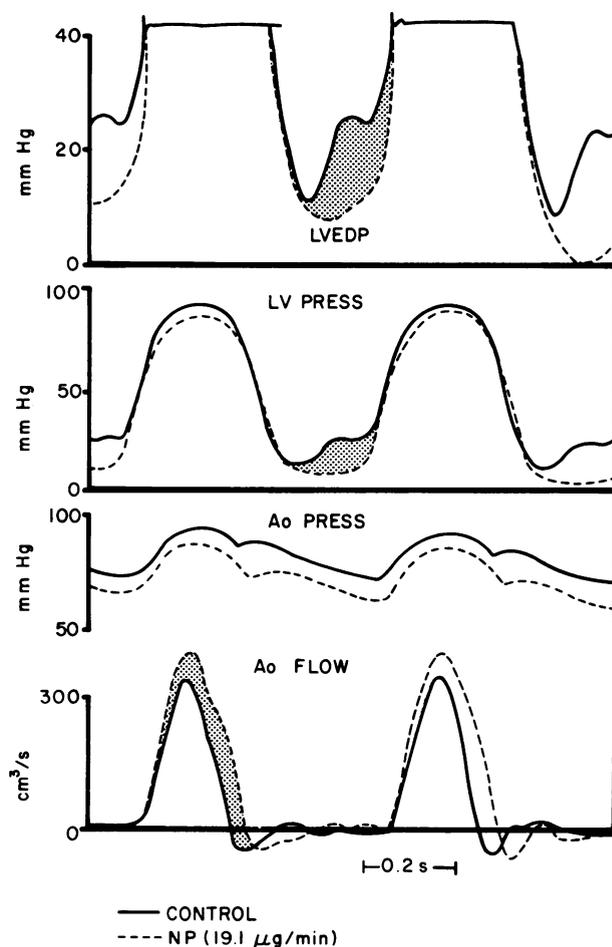


FIGURE 5 A typical example of the tracings obtained as nitroprusside (NP) was infused at $19 \mu\text{g}/\text{min}$ (left ventricular diastolic (LVEDP) systolic (LV) and aortic (Ao) pressures, and instantaneous aortic blood flow). Note the increase in phasic aortic flow occurs throughout the systolic ejection period as left ventricular diastolic pressure declines (hatched areas).

TABLE III
Effects of Restoration of Aortic Pressure during Nitroprusside Infusion

Patient	$\dot{A}oP$, mm Hg			LVEDP, mm Hg			SV, cm ³			HR, beats/min		
	Control	NP	NP + Ph	Control	NP	NP + Ph	Control	NP	NP + Ph	Control	NP	NP + Ph
1	106/78(87)	98/67(76)	111/81(92)	20	13	17	38	48	41	78	101	79
3	101/74(84)	93/64(72)	109/78(90)	28	16	18	36	52	46	112	107	105
8	119/91(102)	102/68(84)	117/88(101)	27	15	16	29	38	36	99	98	94
Mean	109/81(91)	98/66(77)	112/82(94)	25	15	17	34	46	41	96	102	93

Patient	CO, cm ³ /s			Resistance, dyn/cm ⁵			Z_o , dyn/cm ⁵			Max-min impedance mod, dyn/cm ⁵		
	Control	NP	NP + Ph	Control	NP	NP + Ph	Control	NP	NP + Ph	Control	NP	NP + Ph
1	49	81	54	2,347	1,250	2,274	145	97	134	131	85	109
3	67	93	81	1,666	1,032	1,491	94	82	92	118	81	102
8	48	62	56	2,841	1,806	2,388	132	82	125	117	68	98
Mean	55	79	64	2,284	1,362	2,050	124	87	117	122	78	103

$\dot{A}oP$, mean aortic pressure; LVEDP, left ventricular and diastolic pressure; SV, stroke volume; HR, heart rate; CO, cardiac output; NP, nitroprusside infusion at 38 mg/min; Ph, phenylephrine infusion.

Z_o and wave reflections were accentuated in patients with heart failure compared to age- and pressure-matched subjects without heart failure (12). That conclusion is supported by the present findings of increased peripheral resistance (term at 0 Hz), Z_o (mean of terms >2 Hz), and large difference between maxima

and minima impedance moduli, as seen in the composite spectra (Fig. 1). Nitroprusside acutely altered these findings as peripheral resistance, Z_o and wave reflections decreased. The resulting "flattened" spectral patterns, as a result of reduced amplitudes of impedance and phase moduli, suggest that aortic pres-

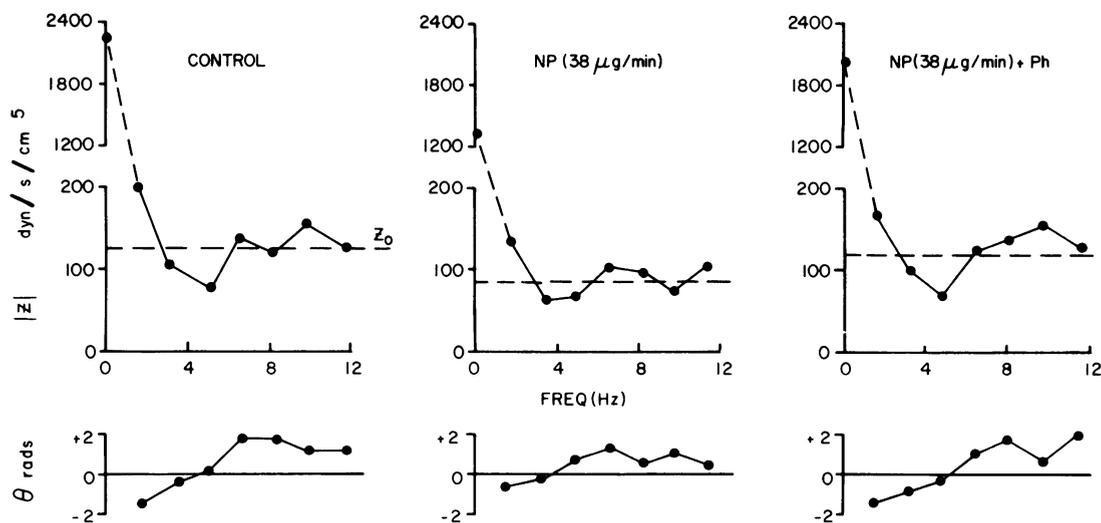


FIGURE 6 Effect of restoration of aortic pressure on aortic input impedance spectra. Mean amplitudes of impedance (top) and phase moduli (bottom, vertical axis) are illustrated at each harmonic frequency (horizontal axis) for the three patients given phenylephrine (Ph) with nitroprusside (NP). Nitroprusside (alone) altered impedance and phase moduli as described in Fig. 1 indicating that both pulsatile and steady flow components of vascular load are reduced compared to control as mean aortic pressure declined. When aortic pressure was restored with simultaneous phenylephrine, the impedance and phase moduli are altered, suggesting some pulsatile and steady flow components of load rise. However, impedance moduli are reduced compared to control values.

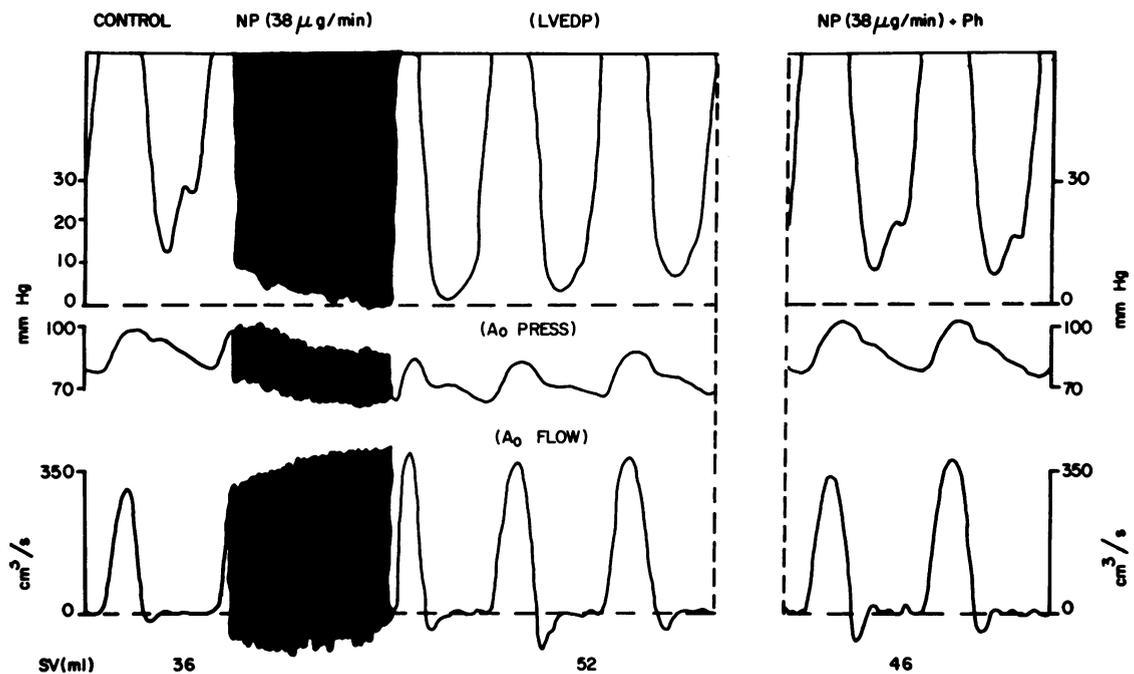


FIGURE 7 Effect of restoration of aortic pressure on ventricular function. Representative high amplification left ventricular (top panel) and aortic (center panel) pressures and phasic aortic blood flow (bottom panel) tracings are illustrated from one of these patients (No. 3). Nitroprusside (NP 38 $\mu\text{g}/\text{min}$) decreased peripheral resistance and characteristic impedance associated with a decline in left ventricular end diastolic pressure (LVEDP) and increase in stroke volume (SV). Restoration of aortic pressure with phenylephrine (Ph) infusion resulted in continued improvement in function reflected by lower end diastolic pressure and increased stroke volume compared to control tracings.

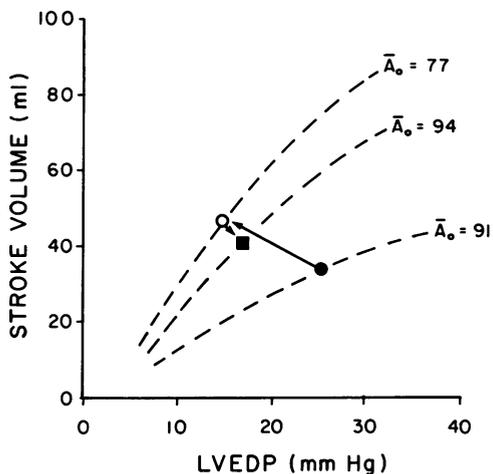


FIGURE 8 Effect of restoration of aortic pressure on ventricular function as nitroprusside-related reduction of vascular load persists. Stroke volume (vertical axis)—left ventricular end diastolic pressure (LVEDP [horizontal axis]) relationship as vascular load is reduced with nitroprusside and mean aortic pressure (\bar{A}_o) increased by simultaneous phenylephrine infusion. Hypothetical isopleths are drawn, to illustrate the mean pressure values achieved in the three patients. Symbols represent mean data during control (●), (38 $\mu\text{g}/\text{min}$) nitroprusside (○), and addition of phenylephrine (■).

sure and flow waves become more similar in shape. Such changes occur when distensibility of the vessel under study is altered. This could result from direct alteration of mechanical properties of the vessel wall like that occurring with smooth muscle relaxation or replacement of collagen by elastic tissue. Alternatively, similar findings could result because of reduction in vessel-distending volume so that the vessel operates over a less steep portion of its pressure-volume curve.

To our knowledge, these data represent the first reported pulsatile pressure-flow analysis in patients with heart failure given nitroprusside. A major issue, pertaining to the potential importance of these data, concerns the relative contribution of the steady (PVR) and pulsatile flow (Z_o and wave reflections) components as determinants of ventricular function. Steady and pulsatile components of vascular load have been recognized in the past but not systematically studied to determine their relative importance (30–32). However, recent experiments show that the pulsatile component, described by Z_o and relating to vessel compliance, is at least as important a determinant of ventricular function as PVR. In dogs, O'Rourke reduced the compliance of the systemic arterial system by applying lucite ferrules to the descending thoracic aorta and

brachiocephalic artery (8). The size of these restrictors was controlled to limit systolic expansion of the vessels with only minimal compression during diastole. The change induced in arterial compliance effected a 32% increase in Z_0 and was associated with a 37% decline in stroke volume when PVR was not appreciably altered. More recently, Elzinga and Westerhof (13) used an isolated cat heart model constructed so that resistive (mean pressure/mean flow) and compliant (frequency-dependent impedance moduli) components could be changed independently. They found that a 21% increase in Z_0 was associated with a proportional decline in ventricular output (21% decrease in stroke volume). The potential, independent functional importance of wave reflections, is more difficult to assess. This is because a decrease in peripheral resistance allows pulsatile pressure and flow waves to extend further into the small resistance vessels (6, 33, 34). The distance these waves travel is increased so their reflections are altered reducing the magnitude of oscillation of impedance moduli (6, 33, 34). Because peripheral resistance and arterial compliance influence wave reflections, studies aimed at determining the independent functional importance of wave reflections are lacking. However, a consideration of wave reflection theory in elastic tubes indicates that reflected pressure waves add to the pressure amplitude (6, 33, 34). A rise in blood pressure developed in the ascending aorta during systole would be expected to increase both left ventricular work and tension (8, 35). On the other hand, reflected flow waves subtract from the magnitude of forward flow (6, 33, 34). These factors indicate that both pulsatile components of vascular load (Z_0 and wave reflections) can have important influences on ventricular function and merit further consideration relative to vasodilator therapy.

In these clinical studies, we could not simulate the animal experiments designed to separate the relative contribution of the steady and pulsatile flow components of vascular load. Since this question could not be answered directly, we made the assumption, based on the animal studies outlined, that the pulsatile component was an important independent determinant of left ventricular function. If this were true, a clinical implication would be the possible application of interventions designed to selectively reduce this pulsatile component of load. A major practical limitation of vasodilator therapy at present is the level of arterial pressure tolerated. In theory, it may be possible to selectively alter only the pulsatile load, by increasing arterial compliance, to effect improvement in ventricular function, whereas the level of arterial pressure is preserved. To test this hypothesis, in three patients we examined the effect of artificial manipulation of arterial pressure on ventricular function (stroke volume and end diastole pressure) whereas

arterial compliance was increased, Fig. 8. During nitroprusside infusion, intravenous phenylephrine was used to restore mean arterial pressure to the control level. Invariably, stroke output remained above the control value and end diastole pressure below the control value at essentially the same pressure. Although these data can not be used as evidence for an independent effect of arterial compliance on function, they support the hypothesis that, with alteration of vascular load, improved ventricular function can persist when the arterial pressure term is maintained constant. We feel that these findings underscore the potential importance of a more complete consideration of vascular load to include the pulsatile components.

To summarize, we wish to stress the following observations. Within 45 s after initiation of nitroprusside infusion in heart failure patients, increases in aortic blood flow are observed. Aortic pressure is only minimally influenced. This response occurs with small doses of nitroprusside and appears dose dependent at lower concentrations. Analysis of the pulsatile aortic pressure and flow wave relationship in terms of the aortic input impedance spectrum shows an acute alteration of all components of vascular load. The increased Z_0 , wave reflections, and PVR present in these patients with heart failure are promptly altered by nitroprusside. Improvement in ventricular function, reflected by increased stroke volume and reduced end diastolic pressure, is observed simultaneously with the alteration in the aortic input impedance spectrum. In three patients improved ventricular function persisted during continued nitroprusside infusion when the aortic pressure was increased to control values.

These data indicate that vasodilation with nitroprusside acutely alters the pulsatile flow components of the vascular load in addition to the steady flow component. These changes reflect an acute increase in aortic compliance along with systemic arteriolar vasodilation. Acute improvement in ventricular function is related to changes in both pulsatile and steady flow components of vascular load. Data are presented implying that reduction in vascular load with improvement in ventricular function may be possible independent of aortic pressure reduction.

APPENDIX

The Fourier series representation of aortic pressure $P(t)$, can be written as a finite number of terms (6, 28, 29).

$$P(t) = P_0 + \sum_{n=1}^N P_n \cos(n\omega t - \phi_n),$$

where P_0 = mean arterial pressure; n = harmonic number; N = total number of harmonics; P_n = modulus of the n^{th} harmonic; ϕ_n = phase angle of the n^{th} harmonic; and $\omega = 2\pi f$, where f is heart frequency in hertz. Similarly, aortic flow can be written as,

$$Q(t) = Q_0 + \sum_{n=1}^N Q_n \cos(n\omega t - \alpha_n).$$

The resistive or frequency-independent component, PVR, can be calculated as the ratio of mean ascending aortic pressure and flow, i.e., $R = (P_0)/(Q_0)$.

The frequency-dependent components were expressed as an impedance spectrum where $Z_n = (P_n)/(Q_n)$ is the impedance modulus of the n^{th} harmonic and $Q_n = \alpha_n - \phi_n$ is the impedance phase angle of the n^{th} harmonic.

Because pressure and flow were measured in the ascending aorta, the ratio of these two complex variables determines the input impedance of the entire systemic arterial system (6).

In a hydraulic conducting system (i.e., a fluid-filled elastic pipe) of some length, the ratio of pulsatile pressure and pulsatile flow is termed the characteristic impedance if only centrifugal waves are present at the origin, i.e. if no reflected waves are present, or, if created at the termination of the system, the system is of such a length that the reflected waves are completely attenuated before returning to the origin (6). In this case, characteristic impedance is directly related to the physical properties of the elastic pipe. In both dog and man, since the arterial system is short, input impedance moduli oscillate around the characteristic value because of reflected waves (6, 11, 12). In the ascending aorta, wave reflections exert a prominent influence on impedance moduli at low frequencies (<2 Hz) but for high frequencies input impedance approaches Z_0 (6, 18). Therefore, Z_0 can be estimated as the arithmetic mean of the input impedance moduli above 2 Hz (11, 12, 18). The wave reflection index was estimated as the difference between maximum and minimum input impedance moduli (12).

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