Arterial Vascular Compliance Response to Vasodilators by Fourier and Pulse Contour Analysis

STANLEY M. FINKELSTEIN, V. ROSS COLLINS, AND JAY N. COHN

SUMMARY Vasodilator drugs are widely used in the management of cardiovascular disease. They decrease systemic vascular resistance, but they also may influence vascular arterial compliance. This study evaluated the effects of three vasodilators—nitroprusside, nitroglycerin, and hydralazine—on vascular compliance using impedance parameters determined by pulse contour and Fourier analyses. The open chest study was performed on anesthetized dogs. Mean arterial pressure decreased by a minimum of 20% after vasodilator intervention. The decrease in systemic vascular resistance was significant (p < 0.01) only after hydralazine treatment. Proximal compliance increased after administration of all drugs, but the increase was not statistically significant. Distal compliance determined by pulse contour analysis increased by 60 to 120% after all three drug treatments (p < 0.05 for nitroprusside, p < 0.02 for nitroglycerin and hydralazine). Characteristic impedance from Fourier analysis responded variably, and changes were not statistically significant. The sensitivity of changes in distal compliance as a marker for the vascular effect of these drugs suggests that it might be used as a more reliable guide than blood pressure or vascular resistance in monitoring clinical response to such intervention. The more traditional measure of characteristic impedance provides a vascular measurement that is less sensitive than distal compliance to the effects of these vasodilator drugs. (Hypertension 12: 380-387, 1988)

KEY WORDS • vascular compliance • pulse contour analysis • Windkessel model • input impedance • vasodilators

VASODILATOR drugs are widely used in the management of cardiovascular disease.1-5 Although vasodilators share the ability to decrease systemic vascular resistance (SVR), they also may influence vascular arterial compliance, which may be an important determinant of the hemodynamic effects of the drugs and of left ventricular performance.6-8 Arterial compliance, however, cannot be measured directly in intact subjects. Characteristic impedance, derived from aortic input impedance analysis, provides an indirect measure of compliance and has been used in both animal and human studies.9-14 The determination of impedance requires monitoring instantaneous arterial flow and pressure simultaneously and at the same site. This technique can be used during cardiac catheterization procedures, but it is not feasible in the usual clinical setting. Pulse contour analysis is another indirect method for measuring compliance.15-18 It requires measurement of a peripheral arterial pressure waveform and cardiac output and thus is a less invasive procedure.

Although SVR is a satisfactory indicator of the proportionality between mean pressure and flow, it does not provide information about the dynamic pressure and flow relationship in the cardiovascular system. This dynamic relationship can be expressed as a vascular impedance function, described by a spectrum of moduli and phases at the fundamental frequency (heart rate) and higher harmonics. From this spectrum, parameters that describe properties of the arterial vascular system are obtained. Examples of these parameters are characteristic impedance,19 the frequency of the first impedance minimum,20 and the difference between the maximum and minimum impedance modulus.12 Characteristic impedance is inversely proportional to the square root of total arterial vascular compliance.19 It is calculated by averaging impedance moduli over the high frequency range of interest,
usually from the second to eighth harmonic. This range generally spans 2 to 10 Hz in humans and 4 to 20 Hz in animals studied at higher heart rates.

Impedance properties can also be determined from the shape of the pressure pulse contour, which is determined by the interaction of the heart and the vascular bed. Several investigators have used the basic Windkessel model or a modified Windkessel model (Figure 1) to interpret the dynamic relationship between arterial pressure and flow, particularly in response to vasoactive drug administration and cardiovascular disease.\(^{16-18,21,22}\) The elements of the Windkessel model constitute the impedance load seen by the left ventricle during the cardiac cycle and provide insight into the effects of the compliant (or capacitive) components of this load under various conditions of intervention.

The present study was designed to evaluate the effects of various vasodilator drugs on vascular compliance using impedance parameters calculated by pulse contour and Fourier analyses. A comparison of the effectiveness of the individual vasodilators in altering compliance was not part of the study plan, since that would have required careful dose-response studies. The goal was to compare the sensitivity of these two methods and to determine whether the clinically applicable pulse contour method might be a useful technique for evaluating vasodilator drug effects on compliance.

**Materials and Methods**

Six mongrel dogs weighing 20 to 25 kg were anesthetized with sodium pentobarbital (25-30 mg/kg), and each heart was exposed through a median sternotomy. An electromagnetic cuff-type flow transducer was placed around the ascending aorta. An additional 18-gauge Teflon catheter was introduced percutaneously into the right femoral artery catheter to the second pressure transducer. The right atrial catheter was connected directly to the transducer. A 6-in. length of Teflon pressure tubing was used to connect the femoral artery catheter to the second pressure transducer. The right atrial catheter was connected directly to the third transducer. The frequency characteristics of both arterial catheter systems were determined by the free vibration method using a step function of pressure ("balloon pop") as described by McDonald.\(^{21}\) The resonant frequency of both systems was consistently greater than 25 Hz, with a damping ratio between 0.4 and 0.5.

All pressure and flow measurements were recorded on magnetic tape using an eight-channel Vetter (Rebersburg, PA, USA) Model A FM tape recorder. A representative set of aortic and femoral pressure and aortic flow waveforms recorded at baseline conditions is shown in Figure 2. Waveforms were recorded for 30-second periods before and during each intervention. Data were digitized using an eight-channel 12-bit analog to digital converter at a rate of 200 samples/sec. The onset and end of diastole were marked manually on six consecutive good beats. Onset of diastole was defined as the closure of the aortic valve, as determined by

![Figure 1. Modified Windkessel model of the arterial vascular load. LV = left ventricle; P1(t) and P2(t) = proximal and distal (femoral) arterial blood pressure (mm Hg), respectively; C1 and C2 = proximal and distal compliance (ml/mm Hg), respectively; L = the inerance of the column of blood between proximal and distal sites (mm Hg/ml/sec^2); R = systemic vascular resistance (dyn · sec · cm^-5).](http://hyper.ahajournals.org/)

![Figure 2. Typical tracings of aortic pressure (A), femoral pressure (B), and aortic flow (C) from one of the study dogs at preblock baseline conditions.](http://hyper.ahajournals.org/)

Cardiac output was determined by integrating the flow signal obtained with a Statham (Gould, Oxnard, CA, USA) SP2202 electromagnetic flowmeter. Static calibrations were obtained by pumping saline through the flow probe at a known velocity. Electronic calibrations of the flowmeter provided by the manufacturer indicated less than a 5% fall in amplitude at a frequency of 25 Hz, with the 3 dB point at 45 Hz. All pressure measurements were made with Bell & Howell (Pasadena, CA, USA) 4-327-I transducers. Aortic root pressure measurements were obtained by connecting the aortic root pressure-monitoring catheter directly to the transducer. The right atrial pressure tubing was used to connect the femoral artery catheter to the second pressure transducer. The right atrial catheter was connected directly to the third transducer. The frequency characteristics of both arterial catheter systems were determined by the free vibration method using a step function of pressure ("balloon pop") as described by McDonald.\(^{21}\) The resonant frequency of both systems was consistently greater than 25 Hz, with a damping ratio between 0.4 and 0.5.

All pressure and flow measurements were recorded on magnetic tape using an eight-channel Vetter (Rebersburg, PA, USA) Model A FM tape recorder. A representative set of aortic and femoral pressure and aortic flow waveforms recorded at baseline conditions is shown in Figure 2. Waveforms were recorded for 30-second periods before and during each intervention. Data were digitized using an eight-channel 12-bit analog to digital converter at a rate of 200 samples/sec. The onset and end of diastole were marked manually on six consecutive good beats. Onset of diastole was defined as the closure of the aortic valve, as determined by
the end of ejection measured by the aortic root flowmeter. End diastole was determined by the upstroke of the femoral pressure pulse. Thus, analysis begins at the onset of true diastole for the entire vascular system, which is the time the fully "charged" system begins its passive runoff through the compliant and resistive components of the connecting pathways. This is consistent with the circuit equation analogy used in the lumped parameter model approach. Good beats were selected manually by the operator as those six consecutive beats with the greatest degree of pattern consistency from beat to beat (e.g., no premature beats). The RR interval was used as the fundamental period, and the pressure and flow curves were expressed as Fourier series while the impedance modulus at each harmonic was calculated as the ratio of pressure and flow moduli at that harmonic. Characteristic impedance (Zc) was calculated as the average of impedance moduli from the second to eighth harmonic.11

Pulse contour analysis was carried out using the method of Goldwyn, Watt, and Burrus16 as modified by Zobel et al. This method uses the diastolic pressure pulse contour measured at the femoral artery to determine the parameters of a modified Windkessel model of the peripheral vasculature. Calculation of model parameters is simplified by assuming that there is no current flow into the model (see Figure 1), corresponding to diastole when there is no blood flow across the aortic valve. The voltages at points P1 and P2 in the model, corresponding to proximal and distal arterial pressure, are simply the solution of a third-order linear differential equation expressed in terms of model parameters: SVR (R), proximal (C1) and distal (C2) compliance, and inertance (L). The general solution to such an equation can also be expressed as

\[ P(t) = A1 \exp(-A2t) + A3 \exp(-A4t) \cos(A5t + A6) \]

where the Ai parameters can be determined from the observed femoral artery pressure waveform by applying a Gauss-Newton parameter-estimating algorithm using minimum least-squares error criteria between estimated and observed pressure to determine the best set of Ai values. Acceptable fits have a least-squares error of 3 mm Hg or less. By equating the Ai coefficients with the comparable coefficients from the circuit equations and solving the resulting algebraic equations simultaneously, the values for proximal and distal compliance and SVR can be determined. According to Watt and Burrus,16 measurements made along the aorta or at a peripheral site such as the brachial or femoral artery will yield the same Windkessel model parameters. Fitted parameters A2, A4, and A5, which are directly related to the system parameters, are essentially independent of the measurement site. Variations in the pressure waveform at different arterial sites are associated with variations in A1, A3, and A6 that are related to system initial conditions.

During instrumentation, all dogs were volume-loaded with normal saline (1.5 to 2 L i.v.). To block sympathetic reflex responses to the vasodilator drugs, an infusion of trimethaphan was initiated at a rate of 0.1 μg/min. Mean arterial pressure (MAP) was maintained near the control level with titrated intravenous doses of phenylephrine starting at a rate of 20 μg/min. The infusion rate of trimethaphan was progressively increased until no arterial pressure rise was observed in response to bilateral carotid occlusion. Once established, the infusion rates of the two drugs were continued throughout the study to maintain a constant baseline arterial pressure. The effect of this pharmacological sympathetic blockade on hemodynamic variables and arterial properties can be estimated from a comparison of preblockade and postblockade data. Postblockade is equivalent in this study to prenitroprusside control studies. Since the infusion of these drugs was maintained at a constant rate throughout the study, the effect of each vasodilating drug intervention on vascular properties is the response from this new but constantly maintained physiological state.

After a control period to allow cardiac output and aortic pressure to stabilize, the drug infusion protocol was initiated. Nitroprusside (NP) infusion was started at 1 to 2 μg/kg/min. Hemodynamic recordings were made and dosage increased at 10-minute intervals until a decrease in MAP of at least 20% was obtained. NP was discontinued, and 30 minutes later nitroglycerin (NG) infusion was started at a rate of 5 μg/kg/min. Every 10 minutes, the hemodynamic data were recorded and the infusion rate was increased by 5 μg/kg/min until MAP fell at least 20%. NG was discontinued, and 30 minutes later a 5 mg/kg bolus of hydralazine was given. Data were recorded after another 30 minutes.

Hemodynamic measurements and vascular parameters for each control and intervention study were determined by averaging the values from the six consecutive beats marked during each study period. Each animal served as its own control for statistical analyses. Statistical comparisons were performed by a paired t test, using the StatPac software package (Walonich Associates, Minneapolis, MN, USA) running on a PC-XT microcomputer (Zenith Data Systems, St. Joseph, MI, USA).

**Results**

The underlying effect of the combination of pharmacological sympathetic blockade (trimethaphan) and pressure maintenance (phenylephrine), kept at a constant level throughout the experiment, was to increase baseline vascular load by increasing SVR and decreasing proximal and distal compliance (Table 1). Because of individual variability, only the change in distal compliance reached statistical significance. The increase in MAP and decrease in cardiac output were not significant, while mean heart rate increased from 126 to 162 beats/min (p < 0.05). Characteristic impedance after blockade was also significantly elevated.
Nitroglycerin and hydralazine both exhibit a decrease in vascular compliance during vasodilator therapy. The decrease in MAP was statistically significant for each vasodilator, with drops of 40% for NP, 26% for NG, and 51% for hydralazine. Both systolic and diastolic pressures decreased proportionately after each intervention. Calculated SVR tended to fall in response to all three vasodilator drugs, but because of individual variation in the cardiac output response, no change in heart rate was observed in response to any of the drugs despite the profound fall in arterial pressure. All subsequent vasodilator drug responses indicate changes from this new physiological and pharmacological baseline condition, which was designed to protect against reflex changes in the vasculature induced by the vasodilator drugs.

The vasodilator infusion rates varied from 2 to 8 µg/kg/min for NP and from 5 to 20 µg/kg/min for NG. Hydralazine was always given as a single 5 mg/kg bolus. Hemodynamic measurements and vascular resistance, compliance, and characteristic impedance parameters are shown in Table 2.

The decrease in MAP was statistically significant for each vasodilator, with drops of 40% for NP, 26% for NG, and 51% for hydralazine. Both systolic and diastolic pressures decreased proportionately after each intervention. Calculated SVR tended to fall in response to all three vasodilator drugs, but because of individual variation in the cardiac output response to the drugs the changes in SVR were insignificant during the NP and NG infusion. SVR fell significantly after administration of hydralazine. As evidence of the background drug-induced ganglionic blockade, no change in heart rate was observed in response to any of the drugs despite the profound fall in arterial pressure.

A significant increase in distal compliance was observed in response to all the vasodilator drugs; the increase ranged from 60 to 120%. Proximal compliance also tended to increase in response to the three drugs, but the changes were not statistically significant. Characteristic impedance should exhibit a decrease if vascular compliance is increased and if vascular compliance and characteristic impedance are inversely proportional to each other, as calculated from a transmission line analogy or direct application of the Moens-Korteweg equation. Characteristic impedance decreased insignificantly only after NP treatment and increased insignificantly in response to NG and hydralazine. Inertance response was variable in all cases and was not statistically significant. The individual responses of distal compliance, SVR, and characteristic impedance to each drug intervention are shown in Figure 3.

The impedance spectrum from 0 to 20 Hz was also determined for each dog before and during each drug infusion. Impedance at 0 Hz is equivalent to SVR, which decreased after each vasodilator intervention, as indicated. Impedance moduli minimum values occurred between 2 and 4 Hz, with a slow rise followed by an oscillatory response pattern. There were, however, no consistent qualitative changes in the impedance spectrum during any drug intervention. Impedance moduli during control and drug interventions are shown in Figure 4.

### Discussion

Two methods for determining vascular impedance, Fourier and pulse contour analyses, were used to study the vascular response to vasodilator administration. The first method, the calculation of characteristic impedance by Fourier analysis, has been a standard method of evaluating impedance for over 20 years. Wave reflections may be
PRE POST

FIGURE 3. Vascular response of each dog to vasodilator intervention with nitroprusside (NP), nitroglycerin (NG), and hydralazine (HY) compared with baseline control (CTL) conditions. $C_2$ (mllmm Hg) = distal compliance; $R$ (dyn · sec · cm$^{-5}$) = systemic vascular resistance; $Z_c$ (dyn · sec · cm$^{-5}$) = characteristic impedance. The effects of reflex blockade are shown in the top panel.

responsible for the shape of both the impedance spectrum and the pulse contour. Maxima and minima in the impedance spectrum are probably due to these wave reflections. Impedance moduli between the second and eighth harmonic frequently are used to calculate characteristic impedance.$^{11}$

The second method of impedance analysis used in this study was pulse contour analysis. The systolic pulse contour is determined by the interaction of the left ventricle and the vasculature. During diastole, however, in the absence of aortic insufficiency the vasculature is separated from the heart by the closed aortic valve, and the shape of the diastolic pulse contour can be viewed as the passive response of the vasculature to arterial loading during systole. The method developed by Goldwyn and Watt$^{21}$ views the arterial vasculature as a lumped parameter system and uses the diastolic pulse contour and stroke volume to determine vascular properties such as compliance. This approach assumes an infinite pulse wave velocity and thus cannot specifically separate the influence of reflected waves from the effect of compliance and inerterance on the pulse wave contour.

Each analysis technique relies on a specific model for interpretation of the mathematically derived parameters in terms of physiological properties such as compliance. A reflectionless electrical transmission line is the model usually used to demonstrate that characteristic impedance is an indicator of vascular compliance. A modified Windkessel model was used by Goldwyn and Watt$^{21}$ to express pulse contour data in terms of proximal and distal compliance properties. Both models therefore allow calculation of parameters representing lumped compliance properties of the circulation.

Characteristic impedance and total vascular compliance are inversely related, so that a decrease in characteristic impedance indicates an increase in vascular compliance. This is the indicator of compliance obtained from Fourier impedance analysis. In the pulse contour method, using a modified Windkessel model for parameter interpretation, both proximal and distal vascular compliance can be estimated. In this study, as well as others in the dog and human, distal compliance is at least an order of magnitude smaller than proximal compliance. The proximal value ($C_1$) is associated with the compliance of the aorta and large arteries, whereas the distal value ($C_2$) is associated with the compliance of the more distal vessels, probably down to the arteriolar level. Since the model views these as being almost parallel elements, the total compliance looking into the system (at $P_1$ in Figure 1) appears to be preponderantly $C_1$. It is this element that is physiologically equivalent to the compliance component of characteristic impedance. $C_2$, the distal compliance, is so much smaller that it is completely obscured by any analysis that simply looks at the vasculature from an aortic input impedance perspective. Baseline values for characteristic impedance before each drug intervention were somewhat greater than those reported in the literature, but this was due to the continuing effect of the phenylephrine used to maintain blood pressure after trimethaphan sympathetic blockade, as seen in Table 1. Characteristic impedance did not change consistently from
these baseline values after any of the vasodilator interventions. Although proximal compliance and characteristic impedance are not numerically equivalent, neither indicator of total vascular compliance exhibited a statistically significant response to vasodilator administration in this open chest study in anesthetized dogs. On the other hand, distal compliance, while much smaller than proximal compliance, did increase significantly in response to the three different vasodilators. This distal compliance response is consistent with previous closed chest studies of vascular compliance in dogs, as well as with clinical studies investigating the compliance response to vasoactive drug intervention in healthy subjects and subjects with congestive heart failure and hypertension. This study has shown that distal compliance, as determined by pulse contour analysis within a Windkessel model interpretation, is a more sensitive indicator of vasoactive drug effect than is either proximal compliance or characteristic impedance. The study was not designed to demonstrate the underlying physiological basis for these differences, although the structural differences of arterial wall composition in proximal and distal arteries and arterioles may contribute to the observed differences between responses of proximal and distal compliance and characteristic impedance. A shift in the operating point along the compliance curves for proximal and distal arteries, rather than a structural change, may also account for these differences. Finally, the pharmacological sympathetic blockade also may have contributed to the quantitative differences for each vasodilator if, for example, there were interactions between the blockade drugs and any one of the vasodilating agents. Otherwise, these effects should be similar throughout the study and may have shifted the operating point along each compliance curve, but this factor should not have any effect on the difference in response to each drug as measured by characteristic impedance or distal compliance derived measures of arterial vascular compliance.

In another study that applied the pulse contour analysis technique to the study of vasodilator drug effects in dogs, Zobel et al. found distal compliance to be a sensitive indicator of NP and NG effect, but to be less sensitive than SVR for detecting the hydralazine effect. In their closed chest study in anesthetized dogs, sympathetic reflexes were not specifically inhibited. Therefore, an effect of hydralazine on distal compliance could have been obscured by reflex sympathetic discharge that could have counteracted a vascular relaxing effect of the drug. In the present study in ganglionic blocked dogs, an effect of hydralazine on distal compliance could have been obscured by reflex sympathetic discharge that could have counteracted a vascular relaxing effect of the drug. In the present study in ganglionic blocked dogs, an effect of hydralazine to increase small vessel compliance emerged. Similar effects of hydralazinelike compounds on the vasculature of patients with essential hypertension have been reported recently by Safar and his group. They reported on the different hemodynamic and vascular effects of diltiazem and

FIGURE 4. Impedance moduli (dyn · sec · cm⁻²) during control and vasodilator interventions with nitroprusside (NP), nitroglycerin (NG), and hydralazine (HY). Each curve represents the average of the individual impedance moduli for all study dogs. The upper left panel shows preblockade and postblockade states.
dihydralazine and showed that dihydralazine decreased peripheral vascular resistance (presumably by vasodilation) and at the same time decreased brachial artery diameter. In another study, the same group showed that cadiralazine reduced blood pressure by dilating the small arteries while reducing brachial artery diameter and slightly reducing brachial artery compliance. One conclusion was that vasodilating antihypertensive drugs might have different effects on small and large arteries.

No significant vasodilator drug effects on characteristic impedance could be demonstrated in the present study. Although to our knowledge there are no comparable animal studies, there are human studies of the effects of NP on the impedance spectrum. In a study of patients with congestive heart failure, NP infusion at 9 to 19 µg/min decreased characteristic impedance by 14%. In another group of patients with coronary artery disease, some of whom had congestive heart failure, no significant change in characteristic impedance was noted during NP infusion at 40 to 100 µg/min. In both human studies, the change in characteristic impedance was small. In another recent study on human subjects without heart failure it was shown that glycerol trinitrate did not change characteristic impedance, although both SVR and total vascular compliance increased slightly but not significantly.

In the present study, the responses to NG and NP had similar patterns, with no significant changes in characteristic impedance, SVR, or proximal compliance. Yaginuma et al. used the Simon method, based on a Windkessel arterial model, to determine total compliance, which is equivalent to proximal compliance in the modified Windkessel model used in the present study.

The use of vasodilator drugs to normalize blood pressure in hypertensive patients and to improve left ventricular performance in patients with heart failure has generally been monitored by observing changes in SVR. Since changes in SVR represent predominantly a net change in arteriolar caliber, this measurement does not provide insight into the other vascular actions of vasodilator drugs. Indeed, in the present study the SVR often was not decreased by a vasodilator drug despite a profound reduction in arterial pressure. In contrast, the distal compliance appeared to be a far more sensitive marker for the vascular action of the vasodilator drugs used in this study.

The importance of distal compliance effects in determining the overall circulatory effects of these vasodilator drugs cannot be determined from these studies. Nonetheless, the sensitivity of distal compliance changes as a marker for the vascular effect of these drugs suggests that this measurement could be used as a more reliable guide than blood pressure or SVR in monitoring the clinical response to these drugs. Furthermore, the data indicate that the more complex analysis of characteristic impedance provides a vascular measurement that appears to be insensitive to the effects of these vasodilator drugs. Thus, pulse contour analysis appears to provide a sensitive measure of vasodilator effect as well as a potentially useful technique for selecting patients most likely to benefit from a particular vasodilator drug and for monitoring their response to treatment.

References

17. Zobel LF, Finkelstein SM, Carlyle PF, Cohn JN. Pressure pulse contour analysis in determining the effect of vasodilator drugs on vascular hemodynamic impedance characteristics in dogs. Am J Cardiol 1980;88:69-75


Arterial vascular compliance response to vasodilators by Fourier and pulse contour analysis.
S M Finkelstein, V R Collins and J N Cohn

doi: 10.1161/01.HYP.12.4.380

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/12/4/380

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/