Arterial Dilation and Reduced Wave Reflection
Benefit of Dilevalol in Hypertension
Raymond Kelly, Julie Daley, Alberto Avolio, and Michael O'Rourke

We compared dilevalol (an isomer of labetalol), 200–400 mg daily, against atenolol, 50–100 mg daily, in a double-blind, crossover, placebo-controlled trial with respect to effects on arterial distensibility (measured as pulse wave velocity [PWW]) and wave reflection (assessed from carotid pressure wave contour). Twelve patients of mean age 58 years (range 44–73 years) with essential hypertension (supine diastolic blood pressure 95–114 mm Hg) took active therapy for 12 weeks, separated by a 2–4-week placebo period. Carotid pressure waveforms were recorded noninvasively by applanation tonometry with a Millar micromanometer-tipped probe. PWW was measured between carotid and femoral arteries (aortic PWW), carotid and radial arteries (arm PWW), and femoral and pedal arteries (leg PWW). Early wave reflection was calculated from the ratio of the height of the peak of the carotid wave above its shoulder to the pulse pressure and was expressed as an augmentation index. Both drugs were equally effective in reducing brachial sphygmonanometric pressure and PWW in all three regions (active vs. placebo, p<0.001), but there was no significant difference between the two active therapies. However, the augmentation index (averaged during the treatment period) was significantly lower with dilevalol (19%) than with atenolol (28%, p<0.01), corresponding to a greater decrease of 5–8 mm Hg in carotid systolic pressure compared with the brachial artery. Although both drugs were equally effective in reducing arterial distensibility, the vasodilating action of dilevalol gave added benefit in reducing wave reflection, presumably through its vasodilatory effect on peripheral conduit arteries. (Hypertension 1989;14:14–21)

The largest and most detailed epidemiological studies of population groups have demonstrated the importance of systolic rather than diastolic pressure in the etiology of heart failure,1 stroke, 2 and cardiovascular mortality. 3 These data support actuarial statistics4–6 and classic experimental studies based on measurement of systolic pressure7 and call into question the preoccupation of clinicians, until quite recently, with diastolic pressure exclusively in the definition and management of hypertension.

Detailed hemodynamic studies in humans have clarified the role of arterial distensibility, 8 vascular impedance, 9 pulse wave velocity, 10 and pulse wave reflection11 in determination of the amplitude of systolic pressure in systemic arteries. The most recent work has shown that systolic pressure in the central aorta in humans is markedly increased in hypertension and in the elderly as a consequence of early return of wave reflection caused by arterial stiffening and degeneration. 10–12 This phenomenon is not so obvious in peripheral arteries such as the brachial artery where pressure is measured conventionally with a sphygmomanometer.13

The new information, established during the last decade, challenges the current approach to hypertension and its drug therapy, with its emphasis on pressure measurements from the brachial artery and on diastolic pressure, and with the effects of drugs on arterioles and peripheral resistance. New therapies of hypertension should be evaluated with respect to their effect on pulsatile phenomena and on the determinants of systolic pressure in central and peripheral arteries. If drugs are to be used for the treatment of hypertension to reduce death and disability from heart failure, coronary occlusion, and stroke, it is important to understand how these agents damage the heart that fails and the arteries that clog or rupture.

The present study compared the new antihypertensive drug dilevalol (an optical isomer of labetalol)14,15 against atenolol with respect to its effects on the central and major peripheral arteries (measured as pulse wave velocity) and on peripheral wave reflection (assessed from interpretation of pressure wave contour).
**Patients and Methods**

This study was conducted in randomized, double-blind, crossover fashion on five women and seven men of mean age 58 years (range 44–73 years) and mean weight 74 kg (range 63–83 kg) (Table 1). All patients had essential hypertension of mild to moderate severity (supine diastolic blood pressure 95–114 mm Hg). Mean control blood pressure for the group was 169/101 mm Hg, and mean resting heart rate was 72 beats/min (range 56–84 beats/min). All patients gave informed consent to the investigation, which was approved by the Ethics and Research Committee of St. Vincent's Hospital. Patients were studied for a period of 32 weeks, with active therapy periods of 12 weeks preceded and separated by 2–4-week placebo periods. Active therapy was 50–150 mg atenolol once daily or 200–400 mg dilevalol once daily, titrated to control diastolic arterial pressure equal to or less than 90 mm Hg. Maximum doses used were atenolol, 50 mg daily in six patients; atenolol, 100 mg daily in six patients; dilevalol, 200 mg daily in seven patients; and dilevalol, 400 mg daily in five patients.

Patients were seen at intervals of 1–2 weeks. At each examination, brachial artery pressure was measured by standard sphygmomanometry after the patient had been recumbent for 5 minutes. Pressures were averaged from three successive recordings. In addition, pulse recordings were made with noninvasive pencil-type probes incorporating a Millar strain gauge transducer in the tip of the probe (model PR-356, Millar Instruments, Houston, Texas). The transducer has a small pressure-sensitive sensor (0.5 × 1.0 mm) with a frequency response of more than 2 kHz coplanar with a larger area (7-mm diameter) of flat surface, which is in contact with the skin overlying the pulse. Flattening (applanation) of the curved surface of an artery balances circumferential stresses in the wall and so allows accurate registration of the pressure waveform with the technique of arterial tonometry as described by Drzewiecki et al. Pressure wave recordings were then taken simultaneously at the carotid and femoral arteries for noninvasive determinations of aortic pulse wave velocity, at the carotid and radial arteries for determination of upper-limb wave velocity, and at the femoral and dorsalis pedis arteries for lower-limb wave velocity. Normal values for pulse wave velocity vary with age and arterial pressure. In a normotensive local population, values for pulse wave velocity in the sixth decade of life were aortic, 945 ± 74 cm/sec; brachial, 1,350 ± 51 cm/sec; and leg, 1,255 ± 54 cm/sec. Wave velocity was calculated as the distance between recording sites measured over the surface of the body, divided by the time delay between the foot of the waves at the two sites. Waves were stored in analog form on magnetic tape. Examinations were conducted 2–8 hours after active therapy; each examination lasted 20–40 minutes.

Particular attention was directed at the contour of the carotid artery pressure wave. The technique of applanation tonometry provides an accurate reproduction of intra-arterial pressure wave contour, but as used here, cannot give an accurate recording of absolute pressure. The technique of measurement records pressure waves that are almost iden-

**TABLE 1. Patient Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement or n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>7 men, 5 women</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44–73 (mean, 58)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63–83 (mean, 74)</td>
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<tr>
<td>Blood pressure (control) (mm Hg)</td>
<td>169/101 (mean)</td>
</tr>
<tr>
<td>Heart rate (control) (beats/min)</td>
<td>56–84 (mean, 72)</td>
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<tr>
<td>Previous myocardial infarctions</td>
<td>4</td>
</tr>
<tr>
<td>Maximum daily dose</td>
<td></td>
</tr>
<tr>
<td>Dilevalol, 200 mg</td>
<td>7 patients</td>
</tr>
<tr>
<td>Atenolol, 50 mg</td>
<td>6 patients</td>
</tr>
<tr>
<td>Dilevalol, 400 mg</td>
<td>5 patients</td>
</tr>
<tr>
<td>Atenolol, 100 mg</td>
<td>6 patients</td>
</tr>
</tbody>
</table>

**Figure 1.** Comparison of simultaneously recorded ascending aortic pressure (mm Hg, upper graph) determined with Millar micromanometer catheter and carotid artery pressure wave (mm Hg, lower graph) determined noninvasively in a 54-year-old man. Recordings obtained in association with Dr. Harry Gibbs.
FIGURE 2. Determination of augmentation index from central pressure pulse as ratio of late systolic peak ($\Delta P = P_{pk} - P_t$) to pulse pressure (PP). $\Delta P_t$, time from onset of wave to return of reflected wave. After Murgo et al.21

tical to those recorded in the ascending aorta (Figure 1). Like the ascending aortic pressure wave, the carotid wave in the mature adult human typically shows an early systolic shoulder and late systolic peak,20-22 with the late systolic peak attributable to early return of wave reflection from the periphery of the body. This (undesirable) effect of wave reflection augments systolic pressure in the ascending aorta, in the left ventricle, and in central but not always in peripheral arteries.13 The degree of augmentation can be expressed as an index (Figure 2) as used by Murgo et al21 and Takazawa22 for the ascending aorta. This augmentation index is defined by the ratio of the height of peak pressure above the shoulder ($\Delta P$ in Figure 2) to pulse pressure (PP in Figure 2). Use of this index necessitates identification of the early systolic shoulder that divides the initial pressure rise from the late systolic peak. Because this identification can be very subjective, we chose to identify the shoulder from the third derivative of the pressure wave, a technique we have found that identifies the point in ascending aortic pressure waves that corresponds closely to the peak of simultaneously recorded flow23 (R. Kelly, unpublished observations) and thus, to the peak of the initial input wave into the vasculature before the effects of wave reflection.

Wave analysis was performed with an IBM AT computer with a modification of asyst software (A Scientific System, Macmillan Software Company, New York). At each analysis, a series of 8–10 successive pressure waves, previously recorded on magnetic tape, were digitized with an acquisition rate of 1 kHz and averaged into a composite waveform.16 From this wave, the augmentation index (Figure 2) was derived. With this analysis method in short-term studies in normal aging subjects, intraserver variation was 11.6%. In long-term studies of hypertensive patients, the coefficient of variation was 19.4%.

Data from all patients was analyzed and tabulated before the treatment code was broken to avoid any subjective bias. Sixteen patients entered the study. Three failed to meet the entry criteria during the 4-week placebo preliminary phase, while another was withdrawn after the first active drug phase because of unsatisfactory compliance with therapy. Twelve patients completed the trial.

Statistical Analysis

Time-related variations among the placebo and drug intervention phases were assessed by analysis of variance. Differences between the treatment groups were assessed by the paired $t$ test with a two-tail value for $p$ and Bonferroni correction for multiple testing. Reproducibility of augmentation index measurements in hypertensive subjects was measured by calculation of coefficient of variation during placebo periods.

Results

Brachial Pressure

Six patients commenced active therapy on atenolol and six on dilevalol. Arterial pressure (recorded by sphygmomanometry from the brachial artery) was well controlled in all patients during dilevalol therapy and in all but one during atenolol therapy. This patient developed frank congestive cardiac failure in association with systolic hypertension (pressure consistently greater than 200 mm Hg) and bradycardia (heart rate less than 50 beats/min). Brachial artery pressure measurements (Figure 3) were similar during dilevalol and atenolol therapy. Systolic pressure was slightly lower during dilevalol therapy (145 mm Hg compared with 152 mm Hg), but the difference was not significant ($p<0.1$ by paired $t$ test). There was no difference in diastolic pressure (85 mm Hg for dilevalol compared with 86 mm Hg for atenolol).

Pulse Wave Velocity

Pulse wave velocity in all three regions (aorta, upper limb, and lower limb) was higher during the placebo period than in either period of active drug therapy ($p<0.001$). However, there was no significant difference in pulse wave velocity during atenolol therapy compared with dilevalol therapy in the aorta, upper limb, or lower limb (Figure 4). Lower wave velocity during active compared with placebo therapy was attributable to lower arterial pressure per se rather than to any direct effect of active therapy on the conduit arteries.23

Carotid Wave

While brachial artery pressure and arterial pulse wave velocity did not differ between the periods of dilevalol and atenolol therapy, carotid pulse wave contour showed changes that suggested a particular
Figure 3. Plot of mean sphygmomanometric brachial artery pressure (mm Hg) recordings determined during first placebo phase (P, ◊), atenolol phase (■), second placebo phase (P, △), and dilevalol phase (▲). Mean heart rate for all patients during phases of trial were: first placebo period, 72 beats/min; atenolol, 58 beats/min; second placebo period, 74 beats/min; and dilevalol, 66 beats/min.

Benefit for dilevalol in reducing central systolic pressure to a greater degree than atenolol.

Before the code was broken, it was documented that one active agent consistently reduced the amplitude of the augmented late systolic peak (Figure 1) to a greater degree than the other agent in 10 of the 12 patients (two showed no perceptible change). After the code was broken, the active agent was found to be dilevalol in nine of the 10 patients.

There was considerable variation in carotid wave augmentation index (Figure 2) between the different patients, from 4% to 54% (mean 25%) during placebo therapy, but in the one patient, augmentation remained constant during each phase of treatment. Augmentation index was significantly lower during dilevalol (mean 19%) compared with atenolol (mean 28%) therapy (p<0.01) (Figure 5). There was no significant difference between augmentation indexes during atenolol therapy compared with placebo therapy.

Carotid pressure waves recorded during dilevalol therapy were averaged digitally into a single composite wave for comparison with a single composite wave for atenolol and placebo (Figure 6). This shows the relative reduction in late systolic pressure peak during dilevalol compared with atenolol therapy (and to placebo). No change was apparent.
in comparing composite radial artery pressure waves during the three treatment phases.

To clarify underlying mechanisms, we supplemented the data for chronic therapy in these 12 patients with an acute study in a 50-year-old normotensive volunteer (one of the investigators). Each morning for 5 days the subject took dilevalol (200–400 mg) or atenolol (50 mg) orally after control measurements of brachial artery sphygmomanometric pressure and determination of carotid and radial artery pressure wave contours. Recordings were repeated 4–5 hours later. In this subject, neither dilevalol nor atenolol caused any consistent change in brachial artery pressure. Atenolol failed to change the contour of either carotid or radial artery pressure waves. Dilevalol, however, showed consistent and reproducible reduction in the amplitude of the late systolic pressure peak in the carotid pulse, and with peak pressure appearing to decrease by 5–8 mm Hg. This change was accompanied by reduction in the amplitude of secondary fluctuation on the falling limb of the radial pressure wave.

**Discussion**

The major conclusions from this study are 1) that dilevalol has an advantage over atenolol by reducing systolic pressure in central arteries and in the left ventricle, and 2) that this relative advantage is not apparent from measurements of arterial pressure taken conventionally from the brachial artery.

Such conclusions arise from the data presented but require consideration of 1) relations between carotid and ascending aortic pressure waves, 2) the mechanism responsible for the secondary systolic pressure rise in central arteries, 3) the effects of vasodilator agents on arterial wave reflection and wave contour, and 4) the different effects of reflected waves on the amplitude and contour of central and peripheral pressure waves and thus on systolic and diastolic pressure in central and peripheral arteries.
**Carotid Pressure Wave Contour and Ascending Aortic Pressure Contour**

In this study, carotid pressure wave contour, recorded noninvasively, was taken to be representative of pressure wave contour in the ascending aorta and other central arteries. In support of this, similarity of noninvasive carotid and invasive ascending aortic pulses in individual subjects has been noted (Figure 2). Other data support this contention. In mature adult humans, the ascending aortic pressure wave typically shows an early systolic shoulder with a late systolic peak and no diastolic fluctuation; the same pattern is seen in the carotid artery. In adolescents and young adults, the ascending aortic pressure wave shows a high, early systolic wave and a small, lower, late systolic wave with secondary diastolic fluctuation; the same pattern is seen in the carotid artery. With aging in humans, there is progressive increase in the late systolic wave, both in the ascending aorta and in the carotid artery. The degree of increase is greater in the ascending aorta than in the carotid artery, so that the change in the carotid wave probably underestimates the change in amplitude of the late systolic wave in the ascending aorta.

Further, mechanisms that increase or decrease peripheral wave reflection have similar effects on the contour of the ascending aortic and carotid pressure waves; vasodilation reduces the late systolic peak in each, while vasoconstriction causes little change or a slight increase in this peak.

Even though no large comparative study has yet been done, there is every reason to believe that changes in the carotid pressure wave, as recorded noninvasively by applanation tonometry in this study, represent similar changes in the ascending aorta and central cerebral arteries. This point was first made by Fujii et al. Indeed, our own acute intervention studies with nitroglycerin show that the carotid waveform "tracks" the ascending aortic pressure waveform in the baseline state and after reduction of left ventricular afterload.

**Mechanism for Late Systolic Pressure Peak in Central Arteries of Humans**

There is general agreement that the gradual development of a late systolic pressure peak in central arteries with age is due to early return of wave reflection from peripheral terminations. In adolescents, wave reflection in central arteries is apparent as a diastolic wave following the incisura (Murgo's type C wave). With aging, loss of this diastolic wave and appearance of the late systolic peak are attributable to the echo (reflected wave) moving through the incisura into systole as it returns progressively earlier (Figure 1). With aging, duration of cardiac ejection and body length remain relatively constant, but aortic pulse wave velocity doubles between the ages of 18 and 80 years. This mechanism has not been seriously disputed although it has not yet been described with aging in other species that live for shorter lifespans. It appears to be a consequence of arterial degeneration during the many decades of the human lifespan.

**Effects of Vasodilator Agents on Arterial Wave Reflection and Pulse Wave Contour**

Effects of vasodilator and vasoconstrictor agents on wave reflection have been studied from intrarterial injections into peripheral vascular beds. This allows secondary effects of altered arterial pressure to be minimized. Vasoconstriction has little effect on wave reflection from the peripheral vascular bed, probably because wave reflection is already high under control circumstances as a result of high resting arteriolar tone, whereas vasodilation causes profound reduction in wave reflection. Effects of vasodilation on ascending aortic pressure wave contour have been studied by Takazawa, Yaginuma et al, and Fitchett et al. All have shown marked reduction in the amplitude of the late systolic pressure peak in the ascending aorta of human adults with nitroglycerin. Yaginuma et al and Fitchett et al have measured ascending aortic impedance as well and have confirmed that this change in pressure was attributable to reduction of wave reflection from peripheral sites. This has recently been confirmed in dogs by Latson et al. Because the effect of nitroglycerin was seen without reduction in peripheral resistance, all investigators attributed this phenomenon to dilation of small conduit arteries.

We have observed similar effects with diltiazem on the contour of the aortic and the carotid arterial pressure wave. In the present study, diltiazem had a similar effect on the carotid arterial pressure wave. Diltiazem is known to have relatively strong β-agonist effects, causing dilation of arterioles and conduit arteries. In animal experiments, diltiazem has been shown to increase arterial compliance independently of arterial pressure. Hence, its arterial effects are expected to be drug rather than pressure induced. Propranolol and most other β-blocking agents without sympathomimetic activity do not increase compliance. In the present study, we have not been able to demonstrate such an effect because pulse wave velocity was similar during diltiazem and atenolol therapy. The effects of diltiazem on the carotid pressure wave (and undoubtedly on central intra-arterial pressure) thus appear to be attributable principally to its vasodilator properties with reduction in wave reflection.

**Differential Effects of Wave Reflection and of Its Reduction in Central and Peripheral Arteries**

It is accepted that wave reflection is responsible for secondary fluctuations in central and peripheral pulses. Wave reflection, however, has a different effect on contour and amplitude at the central aortic
and carotid pulse on the one hand and on the brachial and radial pulse on the other. It was first described by Salans et al. and is apparent in the data of Remington et al. There is a type of "standing wave" of pressure in the upper limb of human subjects such that pressure wavelets are reciprocal above and below a "node" of pressure in the proximal upper limb. The first reflected wave in the carotid artery and proximal aorta corresponds in time to a dip in the radial wave; the following carotid and aortic dip corresponds to the positive reflected wave in the brachial and radial arteries. These phenomena are what one would expect in a simple resonating system. However, these consequences appear to be of far-reaching significance with respect to pressure wave measurement and interpretation, because in the proximal aorta and carotid artery, wave reflection with aging generates a secondary wave whose amplitude may be as much as one half the total pulse pressure (Figure 1), whereas peripheral brachial and radial arteries, the reflected wave usually occurs later, contributing little or nothing to the systolic peak. In short, the system of wave reflection in humans renders central systolic peak pressure very sensitive to wave reflection but renders peak pressure peripherally in the upper body quite insensitive.

These points are relevant to the effects of vasodilator drugs on pulse contour and on systolic pressure in the carotid artery and ascending aorta compared with the pressure in the brachial and radial arteries. Vasodilator agents reduce wave reflection and the amplitude of secondary fluctuations on the pulse. In the proximal aorta and carotid artery of the mature adult human, a secondary fluctuation from wave reflection is responsible for the pressure peak; hence, reduction in wave reflection reduces, often substantially, peak systolic pressure. In the brachial and radial arteries, on the other hand, wave reflection causes a fluctuation on the descending limb of the pulse, not its peak, so that reduction in wave reflection reduces secondary waves and altered wave contour but usually does not affect peak systolic pressure.

The above can be summarized as follows. Vasodilation reduces wave reflection and can markedly reduce peak systolic pressure in the proximal aorta and carotid artery of mature adult humans without similar reduction in systolic pressure in the brachial or radial arteries; in other words, during vasodilator therapy in mature adult humans, measurements of systolic pressure in the brachial and radial arteries may substantially underestimate the level of systolic pressure in the ascending aorta and carotid artery.

**Explanation of Atenolol and Dilevalol Data**

The previous discussions of hemodynamic mechanisms appear to explain the results obtained in this study. The comparisons of central aortic with carotid pulse contour appear to establish the latter as an index of the former. The 9% decrease in carotid pressure wave amplitude with dilevalol (Figure 5) probably represents a decrease of at least this magnitude in central aortic systolic pressure—a reduction of approximately 5.8 mm Hg (if one assumes central and peripheral pulse pressure to be similar during placebo and during atenolol therapy). This is the type of systolic pressure reduction apparent in the whole group (Figure 6) and is the lower range of pressure change observed in the ascending aorta with nitroglycerin. This systolic pressure reduction occurs during dilevalol therapy without concomitant similar systolic pressure reduction in the brachial or radial artery. In other words, the true reduction in central systolic pressure is greater than that recorded in the brachial artery for dilevalol (Figure 3) and should indeed be 5.5–8.0 mm Hg lower than shown in Figure 3. Although this decrease in systolic pressure may appear trifling, it is similar to the difference between active and control groups in recent major trials of antihypertensive therapy that have shown clear benefit at the lower pressure.

In this study, comparisons of carotid pressure wave contour during atenolol and dilevalol therapy appear to have been much more revealing in terms of important mechanisms than the comparisons of pulse wave velocity, which in this study were among the most detailed yet reported for any therapeutic intervention. Pulse wave velocity is an important parameter of pulsatile arterial phenomena, but it does not bear directly on magnitude of wave reflection. In other studies of vascular impedance, attention used to be directed at characteristic impedance as an index of left ventricular pulsatile load. It is now generally agreed that changes in characteristic impedance are less important than changes of impedance induced by reflection phenomena, particularly at the lower frequencies similar to those of heart rates.

The study presented here represents a framework for understanding how vasodilator drugs, by reducing wave reflection, may substantially reduce central systolic pressure; the study strongly suggests that dilevalol is superior to atenolol through its effects in reducing central systolic pressure. This will, however, need to be confirmed by direct recordings of ascending aortic and brachial artery pressure recorded simultaneously for comparison. The work also opens a new approach to the study of drugs used for treatment of cardiac failure and hypertension and may provide some answers to the question as to why some dilator drugs (those that dilate arteries) are more effective than others in reducing mortality when used for management of cardiac failure and why some are more effective than others in reducing left ventricular hypertrophy when used for arterial hypertension. The approach throws new light on an old field. Ironically, the sphygmomanometer displaced the sphygmograph as a clinical instrument during the early part of this century. Now, the sphygmograph returns to com-
plement and enhance the interpretation of blood pressure recordings obtained from the brachial artery with the sphygmomanometer.

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