



## ***Symposium Report***

**New Strategies for  
Cardiovascular Disease Management:**

# **Blood Pressure & Augmentation Index Monitoring**

**November 10, 2003  
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# 1 Home Blood Pressure Monitoring

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**C**ontrol of hypertension is universally abysmal around the world: the majority of hypertensives are undiagnosed or inadequately treated.

Compounding the problem is evidence demonstrating the inadequacy of the traditional model for detecting and managing hypertension. For example, clinicians rely primarily on office blood pressure monitoring to diagnose hypertension and monitor therapy, but this approach misses important information. Blood pressure is much more than the simple measurement of systolic and diastolic pressure; to reduce morbidity and mortality, we must do more than checking blood pressure in the clinic every few months.

The idea that blood pressure can be characterized by occasional readings in the clinic is absurd when you think about it seriously. This approach assumes blood pressure is mostly stable and can be accurately assessed from one or two office measurements. In fact, blood pressure fluctuates based on time of day, physical activity, emotional state, even physical location, with some people showing higher blood pressure readings in their doctor's office, for example, compared to ambulatory blood pressure monitoring (ABPM). Even where we measure blood pressure may be inadequate. Relying on brachial artery pressure ignores the fact blood pressure varies in different parts of the arterial system, which will be discussed in more detail in the two reports that follow.

Much of our effort in reducing hypertension-related morbidity and mortality is based on preventing target organ damage. In cross-sectional studies, ambulatory blood pressure correlates more closely than clinic blood pressure with organ damage. If occasional blood pressure measurement in the clinic is not very helpful, the question then is: How many readings are needed to accurately determine average blood pressure? According to French investigators (Chatellier, et al. *Hypertension* 1995; 25: 294-301), about 15 blood pressure readings are required to determine average blood pressure for an individual. More than 15 readings provide little additional information, but only a few readings lead to a very high standard deviation between successive measurements.

## Home Monitoring

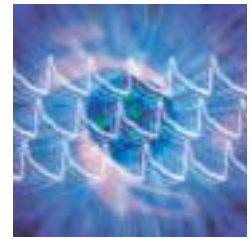
A profound argument can be made for adopting a new model for hypertension diagnosis and management that includes home blood pressure monitoring. According to the seventh Joint National Committee (JNC 7)

guidelines, self-measurement of blood pressure provides important information on the effect of antihypertensive therapy, may improve adherence to therapy, and can reveal white-coat hypertension (**Table 1**).

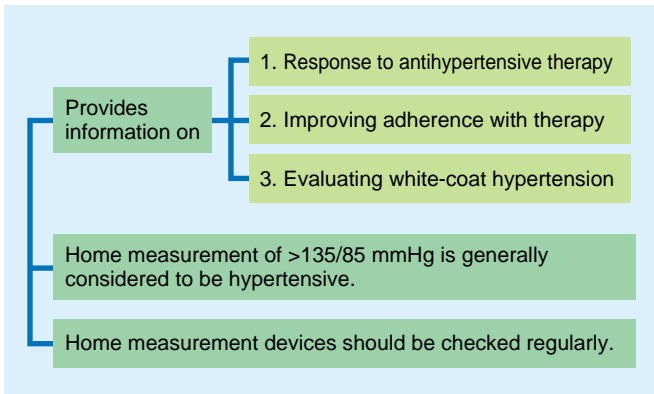
Importantly, a lower cut-off point is used for hypertension at home versus in the clinic; a home measurement of  $>135/85$  mmHg is generally considered hypertensive. However, few patients have been instructed on proper use of home blood pressure monitors, which means doctors must make sure staff members train patients in proper home monitoring techniques and patients must be told that home measurement devices need to be checked regularly for accuracy.

Home blood pressure monitoring avoids the "white coat effect." This effect is not a research artifact; real world studies indicate that physician-recorded blood pressure is a very inaccurate measure of true blood pressure. For example, two years ago, a study of three general practices in the United Kingdom (Little, et al. *BMJ* 2002; 325: 254-59) established that physician-recorded blood pressures average 19/11 mmHg higher than the daytime average measured by ABPM. Blood pressure readings taken by well-trained nurses were comparable to self-monitoring at home, but the most accurate measure of blood pressure – and the best predictor of risk – is blood pressure measured by ABPM. Indeed, data will be published soon demonstrating that if ABPM measurements are known, clinic blood pressure is irrelevant.

It's well established that some patients with elevated blood pressure only in the clinic have a relatively benign prognosis. Much less appreciated is the finding that some patients who are normotensive in the clinic have marked hypertension at home or on ABPM. This "masked hypertension" occurs in about 20% of patients based on our data. Thus, we're missing this entire group of patients if we rely only on conventional screening methods in the clinic. Making the situation worse is evidence expected to be published in the next year showing that patients with masked hypertension have more left ventricular hypertrophy (LVH) and a worse prognosis compared to patients showing hypertension both at home and in the clinic. Therefore, whether hypertension is detected in the doctor's office or not, never dismiss the finding of a high home reading in patients who are monitoring their own blood pressure. Doctors tend to have more confidence in office-based measurements, but due to the white-coat effect, this is



**Table 1**  
JNC 7: Self-Measurement of Blood Pressure



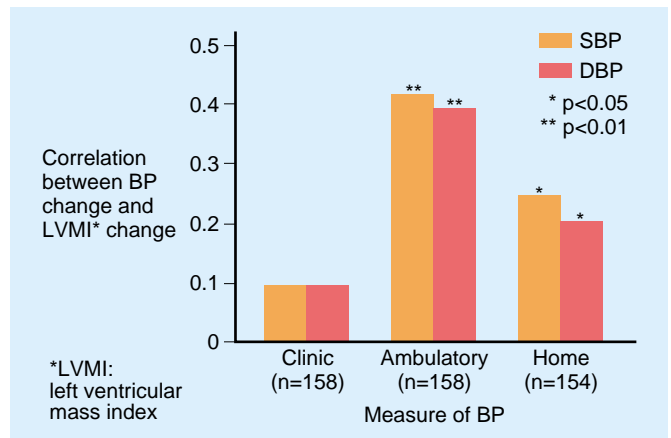
simply not true.

One of the strongest arguments for home monitoring in the evaluation of anti-hypertensive treatment was the Study on Ambulatory Monitoring of Blood Pressure and Lisinopril (SAMPLE) (Mancia, et al. *Circulation*. 1997; 95: 1464-70). In 206 essential hypertensives with documented LVH, regression of LVH was predicted much more closely by treatment-induced changes in ambulatory blood pressure than in clinic blood pressure. ABPM was better than home monitoring for predicting treatment-induced regression, although home monitoring was still significantly better than clinic blood pressure measurement for predicting LVH regression (**Figure 1**). This Italian study is the first longitudinally controlled evidence that ABPM may be clinically superior to traditional blood pressure measurements.

Whether home monitoring improves blood pressure control is unclear, although there is a rationale that patients measuring their own blood pressure may feel more involved in their care and more likely to take their medications. At least one study suggests home monitoring improves blood pressure control and reduces mean arterial pressure compared to usual care (Rodgers, et al. *Ann Intern Med*. 2001; 134: 1024-32).

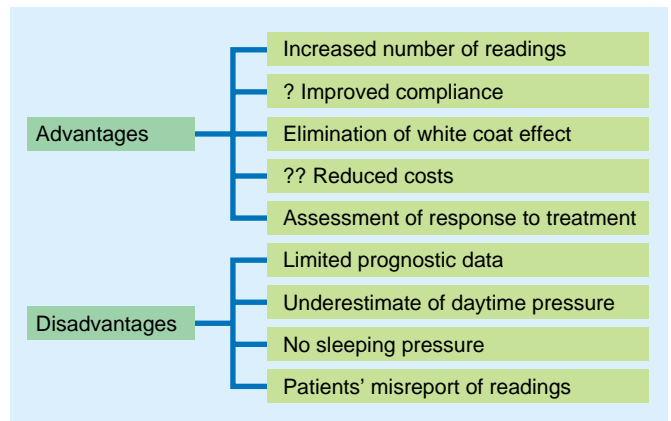
There are potential disadvantages to home monitoring, too, which need to be considered (**Table 2**). Prognostic data are limited, with only one published study from Japan showing that self monitoring predicts outcome, although another study is expected soon by French investigators that may confirm the Japanese data. Patients tend to take readings at home in the evening, although morning blood pressure is very important in predicting morbidity. Finally, there is a tendency for

**Figure 1**  
Change of ABP with Treatment Gives the Best Correlation with Change of LVMI-SAMPLE



Mancia, et al. *Circulation* 1997; 95: 1464-70

**Table 2**  
Advantages and Disadvantages of Self Monitoring of Blood Pressure



patients to misreport their readings, although this will diminish with wider use of devices that store blood pressure readings in memory and perhaps transmit the data over the telephone or the internet.

Despite these potential disadvantages, home monitoring of blood pressure is superior to clinic monitoring and ABPM is superior to both home and clinic monitoring. ABPM is the best for predicting morbidity and the most important monitoring strategy for the initial diagnosis of hypertension. Home readings are probably the best technique for evaluating response to therapy. And, of course, ABPM is the only technique that can provide information on blood pressure during sleep, although such data remains more of a research interest than a practical consideration for most patients.

# 2 Augmentation Index, Cardiovascular Risk and Drug Treatment of Hypertension

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**S**tudies evaluating blood pressure as a prognostic factor for cardiovascular (CV) disease usually focus on the levels of diastolic blood pressure (DBP) or systolic blood pressure (SBP). However, blood pressure may be divided into two components: a steady component (mean blood pressure) and a pulsatile component, “pulse pressure (PP).” Mean blood pressure is the product of vascular resistance and cardiac output; PP, the difference between SBP and DBP, is influenced by ventricular ejection, arterial stiffness, and wave reflections.

During ventricular ejection, two different events may be described. The first is an increase in intraventricular pressure, which occurs mainly during diastole. The second event is a shock wave which originates at the beginning of the thoracic aorta and moves along the arterial tree at a given velocity. The level of pulse wave velocity (PWV) is relatively high and approximates 5-7 m/sec physiologically. At each discontinuity of the arterial wall, the pressure wave may be reflected and then returns towards the heart. Thus any blood pressure curve consists in the summation of a forward wave coming from the heart and a reflected wave returning from the arterial sites towards the heart.

PWV varies by age. In younger subjects, arteries are elastic and compliant; so PWV is relatively low; the backward pressure waves return during diastole, boosting coronary perfusion. However, in older subjects, stiffness of the thoracic aorta and high PWV causes the backward pressure wave to return earlier, during systole, reducing coronary perfusion and causing a supplementary increase in SBP, called the augmentation index (AI). In addition, the wave reflections disappear in diastole, causing a steeper slope of diastolic decay and subsequent decrease in DBP. The supplementary increase in SBP contributes to cardiac hypertrophy and congestive heart failure, while the decreased DBP contributes to cause coronary ischemia.

There are three determinants of PP: ventricular ejection, aortic stiffness (or PWV), and wave reflections (or AI). Based on epidemiology, both AI and PWV predict independently CV risk. For example, the enhanced effect of arterial wave reflections on central arteries, like the common carotid artery, which is seen in end-stage renal failure (ESRF) patients, favors myocardial hypertrophy, increases oxygen consumption, and alters coronary blood flow distribution. Moreover, there is direct evidence that in ESRF, increased PWV is an independent predictor of all-cause and CV mortality (London, et al. *Circulation* 2001; 38: 434-38 and Blacher, et al. *Circulation* 1999; 99: 2434-39). Besides ESRF, arterial

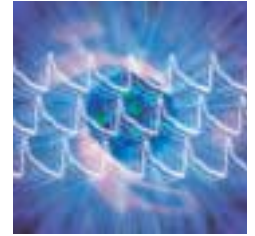
stiffness has a significant predictive value in subjects with essential hypertension and in patients >70 years of age. And this CV risk is not necessarily improved by reduced blood pressure alone. Trials in ESRF patients have shown that there is a decrease in cardiovascular risk only in subjects who exhibit both a decrease in mean blood pressure and a decrease in PWV. Those who have a decrease in mean blood pressure but no change in aortic rigidity generally die from CV diseases.

Given that both AI and arterial stiffness predict CV risk, it seems logical that PP had a similar predictive value. Mean blood pressure, SBP, DBP, and PP all predict CV risk, but PP has classically a lower predictive value. However, this predictive value has been shown to be completely independent from the risk initiated by SBP, DBP, and mean blood pressure. Evidence suggests that mean blood pressure is certainly a strong CV risk factor, influencing renal, cardiac and cerebral complication. As for PP, it appears to be not as powerful a risk factor as mean blood pressure, but it acts independently and only on cardiac complications and mainly on myocardial infarction. This finding has been confirmed by multiple studies, including data from Framingham.

In Europe, the Syst-Eur trial has studied in a large population (>65 years) the level of CV risk as function of systolic blood pressure. Systolic blood pressure predicts CV risk, but when the subjects are subdivided according to DBP level, at any given value of SBP, CV risk is higher when DBP is lower. When combined with other studies including Asia, these data demonstrate a progressive increase in risk as SBP increases and DBP decreases, thus validating PP as an independent predictor of CV risk.

When looking at the relative CV risk associated with SBP, DBP, and PP, evidence suggests that in patients <50 years of age, DBP is the biggest CV risk of these three variables (Franklin S, et al. *Circulation* 2001; 103: 1245-49). Between 50 and 59 years of age, risk is greatest based on DBP and PP, less so for SBP. For patients 60 years of age or older, the best predictor of CV risk is PP, which gives higher value to the AI in these patients, too. So, while most clinicians still focus much of their attention on SBP when estimating risk, relative CV risk at any age is more associated with DBP and mostly PP or AI, either alone or in combination.

Importantly, PP as a CV risk factor is evident in normotensive as well as hypertensive subjects, particularly patients treated for arterial hypertension. For example, in a



large population of men with relatively low CV risk - including a normal mean blood pressure - a wide PP is a significant independent predictor of all-cause, CV, and, especially, coronary mortality. Besides normotensive subjects, PP may suggest great CV risk in hypertensive subjects with “successful” drug therapy, in diabetic patients (mostly type 2 diabetes), in patients with advanced renal failure, and patients with multiple sites of atherosclerosis. For all of these patients, the AI will provide supplementary important informations regarding CV risk.

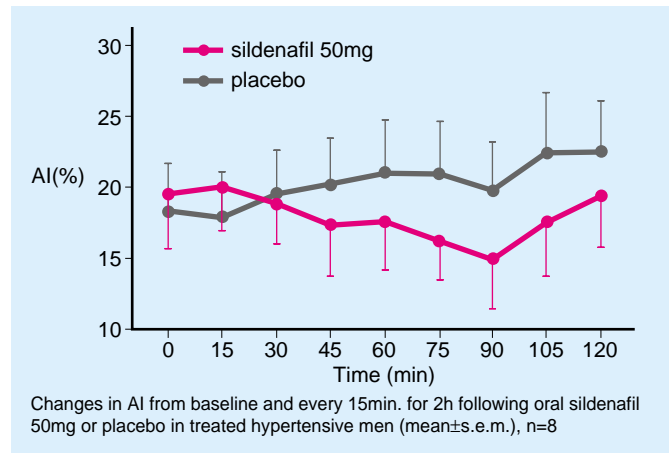
### Therapeutic Implications

Since successful treatment of elevated SBP and DBP does not necessarily affect PP or the AI, these two parameters give therapeutic options that improve those due to the other components of blood pressure, i.e. mean blood pressure.

For example, sildenafil has peripheral vasodilatory effects, possibly related to nitric oxide, which leads to a fall in systemic blood pressure and reduced arterial wave reflection, markedly reducing the AI (Mahmud A, et al. *J Hum Hypertens.* 2001; 15: 707-13) (**Figure 1**). Nitroglycerin can reduce the AI, but only in the ascending aorta and frequently there is a decrease in systolic and pulse pressure in the thoracic aorta but with no measurable effect for the brachial artery. This is a classic demonstration of the effect of pulse wave reflections. Nitrates may be used for treating systolic hypertension in the elderly, and nitrates do reduce SBP better than placebo, but this reduction becomes significant only after at least 8 weeks of therapy and there is practically no effect on DBP.

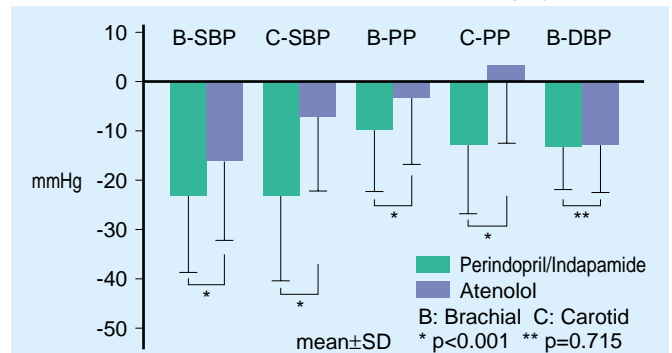
Another possible therapy is the combination of a very low dose of the diuretic indapamide (0.625 mg) and the angiotensin converting enzyme inhibitor perindopril (2 mg). These are subtherapeutic doses of the diuretic indapamide and the ACE inhibitor perindopril, but together they reduce SBP, PP, and arterial function to a significantly greater extent than atenolol for the same decrease of DBP (Asmar, et al. *Hypertension* 2001; 38: 922-6) (**Figure 2**). The improvements associated with this combination were due both to a decrease in PWV, which was the same for both the combination and the atenolol groups, but also to a modification of AI (**Figure 3**) which was particular to the drug combination. Also, the decrease in cardiac mass was much more pronounced using perindopril/ indapamide than atenolol and therefore it is an indirect evaluation of the role of augmentation index in the mechanism of reduction of cardiac hypertrophy.

**Figure 1**  
Sildenafil Effect on AI vs Placebo



Mahmud, et al. *J Hum Hypertens* 2001; 15: 707-13

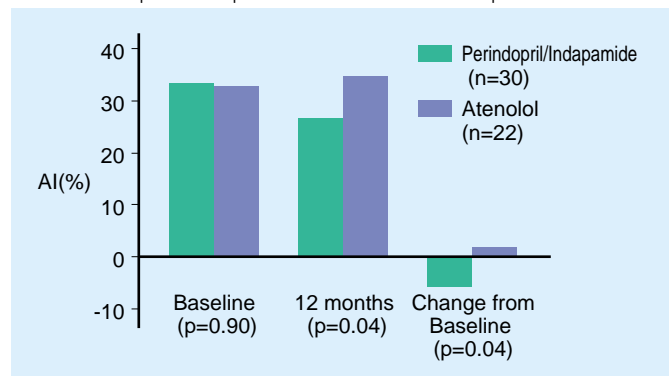
**Figure 2**  
Blood Pressure Changes Comparing After 1-year Drug Treatment; Perindopril + Indapamide Combination and the Blocking Agent Atenolol



Patients entered a 12-month double-blind active treatment period. For brachial measurements, the number of subjects was respectively 204 and 202. For the central measurements, the number of subjects was 65 and 64.

Asmar, et al. *Hypertension* 2001; 38: 922-6

**Figure 3**  
AI (%): Mean Values at Baseline, 12 months and Change from Baseline when Perindopril + Indapamide Combination is Compared to Atenolol



Safar MS. unpublished data, derived from *JACC* 2004; 43: 92-9

# 3 Augmentation Index: Its Role in Elderly Hypertension and Congestive Heart Failure

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The augmentation index (AI) is a noninvasive method of measuring arterial stiffness, a natural process of aging. However, it is unclear which component of central aortic pressure is predominantly influenced by age, thus resulting in age-associated pressure increases. We evaluated the relative contributions of aortic wave reflections to age-associated increases in central systolic blood pressure and left ventricular (LV) remodeling.

The study examined carotid AI (CAI) in 81 healthy nonhypertensive subjects aged 16 to 90 years (systolic blood pressure [SBP] <160 mmHg and diastolic [DBP] <95 mmHg).

Central aortic pulse pressure (AoPP) was estimated assuming age-dependent peripheral amplification. As peripheral and central mean blood pressures are almost identical, systolic and diastolic aortic pressures were calculated from the estimated AoPP; the AI was derived from CAI using a regression equation. Using aortic AI (AAI), aortic pressure was divided into forward (Afor) and backward reflection (Aref) components. Researchers also obtained the putative systolic aortic pressure in the absence of wave reflections (APfor).

When age-dependent peripheral amplification was taken into consideration, age-related increases in estimated aortic systolic and pulse pressures were more marked than those in brachial pressures. Both Aref and Afor positively correlated with age (Figure 1), although the slope of the regression line for Aref was steeper than Afor. However, APfor was not correlated with age. This suggests that the increase in the reflection component of aortic pressure is a predominant determinant of age-associated SBP increases. Reduced aortic distensibility may affect age-associated blood pressure changes

indirectly by altering pulse wave velocity, which results in earlier wave reflections.

LV mass increased with age, significantly correlating with Aref ( $p < 0.002$ ), the reflection component of aortic pressure. Thus, the increase in wave reflections with age may contribute to an age-associated increase in SBP and a subsequent increase in LV mass. Whether interventions can reduce wave reflection associated with normal aging will require prospective studies.

## Relationship Between Antihypertensive Agents and Wave Reflection

Aortic wave reflection is determined by various factors including BP level and the structural and functional status of the entire arterial tree. Certainly antihypertensive agents lower blood pressure by different mechanisms; we performed a study to determine if different antihypertensive agents might have different effects on aortic wave reflection, an important factor determining LV pulsatile afterload.

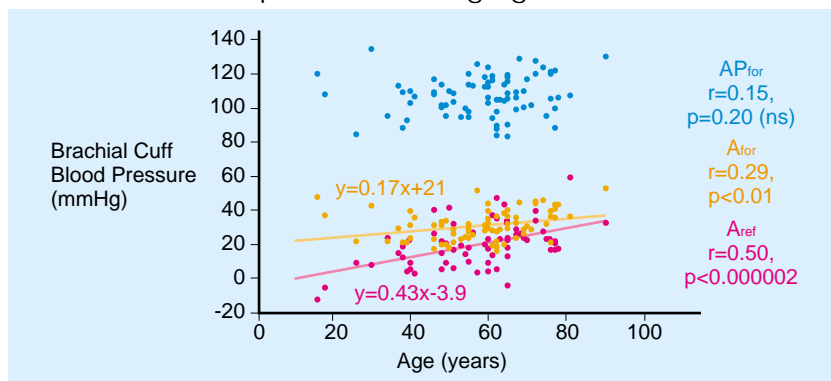
Forty-five hypertensive patients received either enalapril ( $n=23$ ) or nifedipine ( $n=22$ ) for three months as antihypertensive agents. Both agents lowered BP and reduced CAI. Before therapy, an increase in CAI paralleled the increase in SBP. After nifedipine treatment, both CAI and SBP decreased, with the linear relationship between CAI and SBP preserved. In the enalapril group, pre-treatment CAI and SBP also were significantly correlated; however, while both parameters decreased following enalapril therapy, the correlation between CAI and SBP was not seen. Thus, change in CAI was significantly correlated with change in SBP in the enalapril group, but not in the nifedipine arm (Figure 2).

Both nifedipine and enalapril showed comparable BP reductions and comparable change in carotid pulse wave reflections. However, while nifedipine reduced BP independently of the change in aortic wave reflections, enalapril reduced blood pressure in close relation with the attenuation of aortic wave reflections.

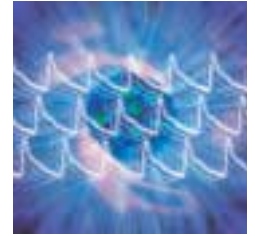
## Wave Reflection and LV Ejection

Based on the principle of pulse wave transmission in the arterial system, we've noted that measured pressure and flow waves are composed of forward and reflected waves. Reflected pressure waves are added to forward waves to determine

Figure 1  
Aortic Wave Components and Aging



Miyashita, et al. J Am Geriatr Soc 1995; 43: 1069-70



wave pressure, while reflected flow waves are subtracted from forward waves; hence, the decelerating portion of the flow wave may indicate wave reflections. Since wave reflection is an important component of central SBP, we looked at developing a clinically useful noninvasive index to evaluate the influence of the aortic wave reflections that impede LV ejection.

In 35 patients with various cardiovascular diseases, the carotid pulse wave and the pulsed Doppler wave in the aortic root (PDW) were recorded simultaneously. The mean ejection fraction was  $47 \pm 13\%$  indicating that most of the patients had LV dysfunction. In 6 of 35 patients, aortic pressure and flow velocity waveform readings were obtained invasively before and after a single dose of nitroglycerin. The investigators defined five Doppler indices that represent the shape of a deceleration curve. With one exception, significant correlations were obtained between CAI and each Doppler index, the highest correlation being with  $DR_{1/3}$  ( $p < 0.001$ ), which best represented the influence of aortic wave reflections on LV ejection fraction (Figure 3).  $DR_{1/3}$  is the ratio of deceleration of flow velocity from the total peak flow velocity at one third of deceleration time ( $DR_{1/3} = \Delta FV_{DT/3} \times 100 / PFV$ ).

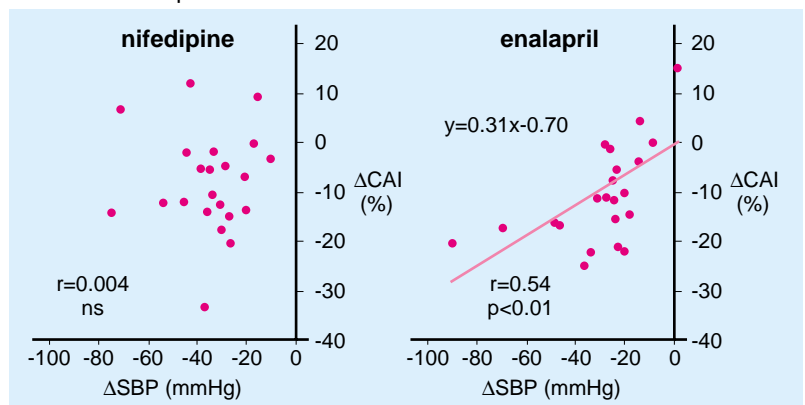
These 35 patients plus 36 other patients were then randomized to either nitrate ( $n=26$ ) or nifedipine ( $n=45$ ) therapy. There were no significant differences in drug-induced  $\Delta DR_{1/3}$  and  $\Delta CAI$  between nitrates and nifedipine. When data were stratified by LV ejection fraction, the relationship between  $\Delta CAI$  and  $\Delta DR_{1/3}$  appeared dependent on LV contractility.

Accuracy of the noninvasive data was demonstrated by the close correlations between CAIs and AAI. Thus,  $DR_{1/3}$  reflects pressure wave reflection or AI; consequently, changes in  $DR_{1/3}$  depend at least in part on changes in pressure wave reflections. So,  $DR_{1/3}$  is sensitive enough to evaluate the acute effect of vasodilators.

## Conclusions

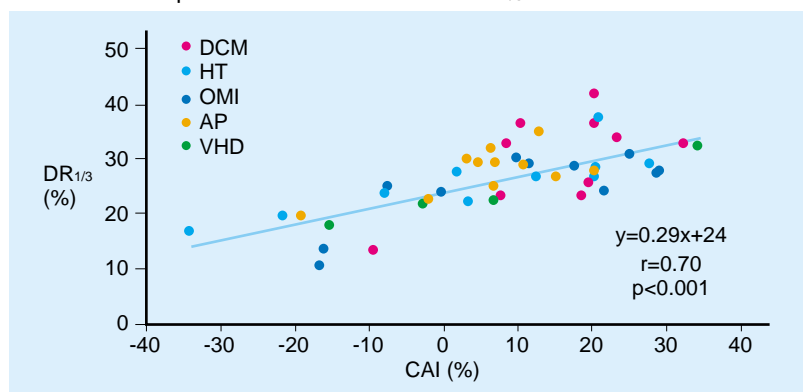
In the normal heart, early wave reflection seen in the elderly causes late systolic pressure augmentation with little change in aortic flow wave. In this setting, the

**Figure 2**  
Relationship between  $\Delta$ SBP and  $\Delta$ AI



Miyashita H, Shimada K. unpublished data, presented at AHA 1993

**Figure 3**  
Relationship between CAI and  $DR_{1/3}$



Miyashita, et al. Heart Vessels 1994; 9: 30-9

strong pumping power of the normal ventricle may be regarded as the flow source. As systolic dysfunction occurs and progresses, wave reflection is still present, but subtracts from the flow wave rather than adds to the pressure wave. In severe heart failure, wave reflection is still present, but cannot be manifest on the pressure wave since the ventricle is incapable of generating such a pressure boost. In that case, the ventricle can only be regarded as the pressure source.

In conclusion, the noninvasive Doppler index,  $DR_{1/3}$ , is useful for assessing the influence of wave reflections and beneficial effects of vasodilator therapy on LV ejection. This approach works in the clinical conditions in which wave reflections are problematic, such as in the elderly or patients with hypertension or congestive heart failure. The relationship between  $DR_{1/3}$  and CAI would indicate dynamic ventricular-vascular coupling to which aortic wave reflections contribute.

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