

## Can Arterial Stiffness Be Reversed? And If So, What Are the Benefits?

Based on a presentation by Michel E. Safar, MD

### **Presentation Summary**

Systolic and diastolic blood pressure are generally considered to be the exclusive mechanical factors that predict cardiovascular risk in normotensive and hypertensive populations. However, these 2 measures give an incomplete picture when evaluating risk for cardiovascular events. Rather, one must consider the entire blood pressure curve when assessing risk.

The blood pressure curve has 2 components: the mean arterial pressure and the pulse pressure. Both components of the blood pressure curve also vary with age. Abnormalities of the large arteries predominate over abnormalities of the small arteries in the elderly, causing a predominant increase in pulse pressure. This pattern is also observed in persons with diabetes and in those with end-stage renal disease.

As a result of these changes, the shapes of the blood pressure curves from older patients and younger ones are very different, despite the same mean arterial pressure.

Mean arterial pressure has recently been shown to be a predictor of risk for events involving the cerebral vessels, the coronary vessels, and the kidney. Pulse pressure has an additional effect on cardiovascular mortality: it is an independent predictor of cardiac death and, to a lesser extent, stroke death, particularly in women over the age of 55.

It is possible to reverse pulsatile arterial hemodynamics in patients with hypertension, particularly with the use of angiotensin-converting enzyme (ACE) inhibitors. Several techniques are available to measure arterial stiffness, for which pulse pressure is a surrogate.

ACE inhibition with perindopril has been shown to increase the diameter of muscular arteries in patients with hypertension, demonstrating a drug-induced effect on the arterial wall. Furthermore, there was an additional improvement in brachial artery compliance at the end of 12 months with perindopril treatment.

© Medical Economics Company, Inc. **S**ystolic and diastolic blood pressure are generally considered to be the exclusive mechanical factors that predict risk in normotensive and hypertensive populations, according to Michel E.

Safar, MD, Professor of Medicine, Chief, Department of Internal Medicine, Hospital Broussais, Paris, France.

However, if hypertension is viewed as a mechanical factor that

acts upon the arterial wall, where it exerts potentially deleterious effects, then the entire blood pressure curve—not just the systolic and diastolic pressures—should be considered when investigating and evaluating cardiovascular risk, Dr. Safar remarked.

### **Describing the Blood Pressure Curve**

To investigate high blood pressure as a cardiovascular risk factor, he continued, it is necessary to have a better description of the blood pressure curve. Physiologists use the term mean arterial pressure to describe that curve, a good term because the area under the curve for mean arterial pressure represents cardiac work and is exactly equal to the area under the curve for pulsatile pressure. However, when the term mean arterial pressure is used, it generally supposes that the blood flow is constant and the heart is not beating, an inappropriate setting for exploring cardiovascular risk.

A good description of the blood pressure curve must consider not only the mean arterial pressure, but also the fluctuation around the mean; that is, the pulse pressure, which is the difference between the systolic and diastolic blood pressures. An adequate evaluation of hypertension should also consider the status of both small arteries and large arteries, Dr. Safar explained.

The mean arterial pressure, which is the product of cardiac output and vascular resistance and provides information on the status of the small arteries, is the steady component of the blood pressure curve, whereas the pulse pressure is the pulsatile component. The pulse pressure is governed by 3 factors: ventricular ejection, arterial distensibility, and the timing of reflected pulse waves. Thus, pulse pressure at a given ventricular ejection is an indicator mainly of large artery status.

Another important point about the blood pressure curve is that it propagates along the artery so that there is no change in mean arterial pressure from central to peripheral arteries, but there are pronounced changes in the shape of the blood pressure curve. As a result of changes in arterial stiffness and wave reflections, the systolic blood pressure increases from central to peripheral arteries, whereas the diastolic blood pressure tends to decrease.

It is also important to consider the fact that both mean arterial pressure and pulse pressure vary substantially with age. Whereas systolic pressure increases with age, diastolic pressure generally increases with age until age 55 and then decreases with age thereafter.

“Because of these age-related changes, the blood pressure that is interesting to look at in terms of cardiovascular risk is the pulse pressure, and not only the mean arterial pressure,” Dr. Safar emphasized.

### **What the Blood Pressure Curves Tell Us**

Abnormalities of the large arteries predominate over abnormalities of the small arteries when blood pressure is elevated in the elderly, in people with diabetes, and in those with end-stage renal disease.<sup>1</sup> In fact, Dr. Safar noted, one of his colleagues in Paris has described high blood pressure in patients with end-stage renal disease undergoing hemodialysis as a model of hypertension in the elderly.

To better understand the relationship between arterial alterations and changes in blood pressure in older patients, it is necessary to compare blood pressure curves from older and younger patients with the same mean arterial pressure—that is, the same area under the blood pressure curve. Despite the same mean arterial pressure, the shapes of the blood pressure curves are quite different. In older patients, the blood pressure curve shows a higher peak systolic blood

pressure and a lower diastolic pressure. This is the result of increased stiffness of the arterial wall. The increase in systolic pressure is a dominant factor promoting cardiac hypertrophy, while the decrease in diastolic pressure tends to alter coronary perfusion and may also favor coronary ischemia, Dr. Safar explained.

These pathophysiologic mechanisms are now becoming more and more important in light of recent findings in cardiovascular epidemiology. The mean arterial pressure component of the blood pressure curve has been shown to be a predictor of risk for events involving the cerebral vessels, the coronary vessels, and the kidney, exactly as has been observed for systolic or diastolic blood pressure. However, the pulsatile pressure component—that is, a widening pulse pressure—has been shown to have an additional effect: it is an independent predictor of cardiac death and, to a lesser extent, of stroke death, particularly in women over the age of 55.<sup>2</sup> More recently, investigators have shown that an increase in pulse pressure was an independent predictor of cardiovascular risk, particularly for myocardial infarction, in treated and untreated hypertensives.<sup>3-9</sup>

It has also been shown by investigative groups in Paris, New York, Glasgow, and Boston, that an increasing pulse pressure is not a surrogate for increasing systolic blood pressure because an increase in pulse pressure is due to both an increase in systolic blood pressure and a decrease in diastolic blood pressure.<sup>2-9</sup>

To illustrate this point, Dr. Safar described a meta-analysis of 3 studies in which he and his colleagues divided the study subjects according to level of diastolic blood pressure. They found that at any given level of systolic blood pressure, the 2-year risk for all cardiovascular endpoints was higher when the diastolic blood pressure was lower.<sup>10</sup>

“This demonstrates that it is the increase in pulse pressure, not the

increase in systolic pressure alone, that is independently related to cardiovascular risk,” Dr. Safar emphasized. Such findings strongly suggest that it is important to decrease arterial stiffness in patients with hypertension, particularly the elderly.

### **Effects of Antihypertensive Therapy and ACE Inhibition**

Although there are relatively limited data on whether arterial changes that influence pulse pressure can be reversed, Dr. Safar noted that it is possible to reverse pulsatile arterial hemodynamics in patients with hypertension, particularly with the use of angiotensin-converting enzyme (ACE) inhibitors. He provided support for this data from a number of trials, several of which he performed with colleagues.

One double-blind therapeutic trial evaluating isosorbide dinitrate in elderly patients with systolic hypertension found a selective decrease in systolic blood pressure, but no decrease in diastolic blood pressure, after 8 weeks of treatment.<sup>11</sup> “This is in contrast to the Systolic Hypertension in the Elderly (SHEP) study,<sup>12</sup> which found a decrease in both systolic and diastolic blood pressure with diuretic therapy,” he remarked.

In another study, Dr. Safar and his colleagues used ambulatory blood pressure measurements before and after treatment with the ACE inhibitor perindopril to correlate systolic blood pressure with diastolic blood pressure. They found that the slope of the blood pressure curve after treatment differed from the slope before treatment. At any given value of diastolic blood pressure, the systolic blood pressure was lower after treatment with perindopril than before, a clear demonstration that there is a decrease in pulse pressure at any given value of diastolic blood pressure.

Before describing the effects of ACE inhibition on arterial changes in

detail, he reviewed several techniques used to measure arterial stiffness. One such technique is ultrasound. It measures both pulsatile pressure and pulsatile diameter in each local circulation, and therefore establishes the pressure-diameter relationship, the slope of which may be used as an index of arterial stiffness—ie, compliance or distensibility (Figure 1).

Arterial pulse velocity, which can be measured by computerized techniques, can also be used to evaluate the stiffness of the overall arterial tree. Although the status of the arterial wall in arterial hemodynamics was neglected in the past, it is now possible to measure wall thickness at the site of the carotid artery and the site of the radial artery with a high degree of reproducibility.

Therefore, it is possible to evaluate not only the capacitive change in the arteries, but also the stiffness of the wall material, or the incremental elastic modulus, which is directly

related to the rigidity of the arterial wall. The incremental elastic modulus may be calculated as the ratio between radius or wall thickness and distensibility.

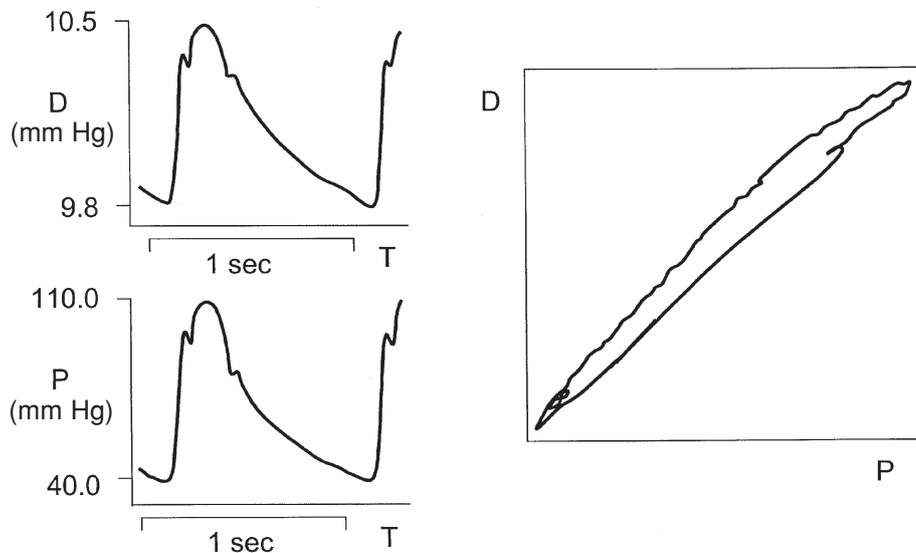
### Perindopril Studies

When an ACE inhibitor such as perindopril is given to a normotensive patient, Dr. Safar explained, there is not only a dose-dependent decrease in vascular resistance at the site of the brachial artery, but also a significant increase in brachial artery diameter. This occurs without any significant change in mean arterial pressure.

“In other words, there is an effect on small arteries and large arteries at the same time,” he pointed out.

This result is more difficult to achieve in subjects with hypertension because the decrease in pressure produced by an ACE inhibitor is followed by an expected passive decrease in arterial diameter, which runs counter to the drug’s effect of relaxation of

**Figure 1.** The Pulsatile Pressure—Pulsatile Diameter Relationship



vascular smooth muscle and improved pressure distention.

Nevertheless, ACE inhibition (in this case, with perindopril) will increase the diameter of peripheral muscular arteries in patients with hypertension (Figure 2), an effect that may also be obtained with nitrates, but not with calcium channel blockers, diuretics, drugs that block the autonomic nervous system, and some centrally acting antihypertensive agents.

When angiotensin II is given intravenously to hypertensive patients, there is no significant brachial artery constriction, as is seen with phenylephrine. Thus, the brachial artery dilation produced by ACE inhibition

is not only due to angiotensin blockade, but also to an endothelial effect.

In studying ACE inhibition with perindopril at the site of the brachial artery, Dr. Safar and his colleagues measured the brachial artery diameter before and after wrist occlusion at the beginning and end, respectively, of 3 months of active treatment, 1 month of placebo, and an additional 8 months of active treatment. With occlusion, both the flow velocity and the arterial diameter were decreased (Figure 3),<sup>13-14</sup> a classic example of the mechanism of endothelial-dependent flow constriction.

With long-term treatment, the same decrease in blood flow velocity could be seen after wrist occlusion, but there was also less constriction, suggesting a pressure-independent effect on endothelial function, he explained.

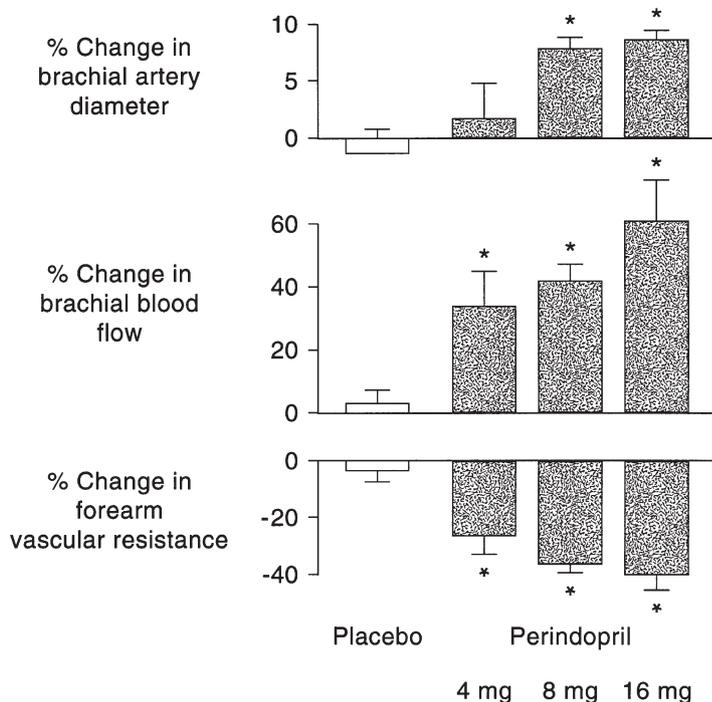
Decreases in blood pressure paralleled the improvements in brachial artery compliance at the end of both active treatment periods, but blood pressure levels returned to baseline at the end of the placebo period. In other words, there was an improvement in compliance when blood pressure decreased, he observed.

Although there was the same decrease in blood pressure at the end of both active treatment periods, he continued, there was an additional improvement in brachial artery compliance at the end of 12 months, suggesting that there are both pressure-dependent and pressure-independent effects on this parameter.

This finding was recently confirmed in a study evaluating the ACE inhibitor trandolapril<sup>15</sup> At the same time, Dr. Safar and his colleagues demonstrated an increase in compliance at the site of the brachial and radial arteries and a decrease in radial artery hypertrophy with perindopril treatment in elderly patients with systolic hypertension.<sup>16</sup>

This is an important point, he said, because radial artery hypertrophy, a marker of conduit artery hypertro-

**Figure 2.** Hemodynamic Changes with Perindopril vs Placebo



\*P < 0.05 versus placebo.

phy, is often present in patients with hypertension.

He then described a 12-month study he did with his colleague Dr. London.<sup>17</sup> They compared the effects of perindopril with those of the calcium channel blocker nitrendiprine in patients who were on hemodialysis because of end-stage renal disease. Both drugs produced the same decrease in blood pressure, as measured at the brachial artery (a peripheral artery), but an even more pronounced decrease in systolic and diastolic pressure, as measured at the carotid artery (a central artery), thus causing a greater decrease in pulse pressure in central arteries than in peripheral arteries. While this effect has been seen with acutely administered nitrates, it has never been demonstrated with other antihypertensive agents, he pointed out. This

improvement in pulse pressure amplification is a clear demonstration of the effect of ACE inhibition on the conduit arteries.

This is an important finding because central and systolic blood pressures may be different and because it is necessary to decrease systolic blood pressure at the site of the heart, not the brachial artery, he continued.

Moreover, while both drugs had the same effects on mechanical factors in terms of pulsatile arterial and mean arterial pressure, they also produced a decrease in cardiac mass, which was significantly more pronounced with perindopril.

“This is a fair demonstration that there is a non-pressure-related decrease in cardiac hypertrophy in people with hypertension,” he said.

Patients with end-stage renal disease are an important subgroup to

**Figure 3.** Hemodynamic Changes With Perindopril vs Placebo Before and After Wrist Occlusion

		Active Treatment		Placebo	Active Treatment	
		T0	T3	T4	T12	
Brachial blood-flow velocity (cm/s)	(B)	7.0 ± 0.7   **	7.8 ± 0.7   **	6.2 ± 0.7   **	7.5 ± 0.9   **	
	(A)	3.5 ± 0.4 	3.6 ± 0.6 	3.0 ± 0.4 	2.8 ± 0.2 	
Brachial artery diameter (cm)	(B)	0.46 ± 0.01   **	0.49 ± 0.01   *	0.47 ± 0.01   *	0.49 ± 0.01   **	
	(A)	0.43 ± 0.02   NS	0.46 ± 0.01   NS	0.43 ± 0.02   *	0.47 ± 0.02 	

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B = before wrist occlusion; A = after wrist occlusion.  
 \*P < 0.05.  
 \*\*P < 0.01.

look at for several reasons. They have a predominant increase in pulsatile pressure, they constitute a very homogeneous population with high cardiovascular risk, their hemodynamic changes can be related to cardiovascular morbidity and mortality, and they serve as an excellent model for demonstrating the link between changes in pulsatile arterial hemodynamics and cardiovascular morbidity and mortality.

Specifically, the carotid incremental elastic modulus, a marker of increased stiffness of wall material, has been shown to be a predictor of cardiovascular mortality,<sup>18</sup> and an increase in aortic pulse wave velocity (above 12 M/sec) has been shown to be a strong predictor of cardiovascular mortality independent of age and mean arterial pressure.<sup>19</sup> In fact, a pulse wave velocity above 12 M/sec was a stronger index of early mortality in patients with end-stage renal disease than was pulse pressure itself, Dr. Safar said.

Such findings probably extend to hypertensive patients without chronic renal failure, he noted, since an increased pulse wave velocity in this population is strongly associated with a higher incidence of cardiovascular death at 10 years, as calculated from Framingham equations.<sup>20</sup>

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... DISCUSSION HIGHLIGHTS ...

**Dr. Weber:** In discussing arterial perindopril, you mentioned that there was a pressure-dependent and a pressure-independent aspect. How did you figure the pressure-independent aspect?

**Dr. Safar:** The pressure-dependent aspect refers to a modification of the set-point along the same pressure-diameter curve, while the pressure-independent aspect refers to the same modification but in a shifted pressure-diameter curve.<sup>13,14,21</sup> This was

shown by Dr. Lévy in Paris in numerous experimental studies<sup>21,22-24</sup> and it was shown in several of the studies that I mentioned, which were done 10 years ago. This was also clearly demonstrated to occur with several kinds of ACE inhibitors.

**Member of the Audience:** From the data you have, do you see a role for the use of drugs that change arterial structure and function before patients develop hypertension, much like we use them in patients with diabetes to prevent diabetic nephropathy? Do you have any data that show that there are changes in arterial structure and function in normotensive diabetics who have been treated with ACE inhibitors?

**Dr. Safar:** I have no data on diabetics. I have data only on end-stage renal disease because I can follow this model. I also have data on normal normotensive subjects where it is easy to show that these effects are independent of blood pressure. I think that high blood pressure may contribute to the expression of some arterial alterations that are already present due to genetic or environmental factors. Of course, there are also arterial alterations that are directly related to high blood pressure as a consequence of Laplace's Law. This is, of course, a complex question.

**Member of the Audience:** The 12-month study showed the pressure-independent changes that developed with the use of the drug perindopril. Did you look to see what happens when you withdraw the drug in terms of these pressure-independent factors and the return to baseline during the intervening placebo period? How long does it take for these changes to occur?

**Dr. Safar:** This work was done mainly by a group of specialists in Maastricht,

the Netherlands, led by Dr. van Bortel.<sup>25</sup>

**Dr. Cohn:** We are going to be presenting data at the American Society of Hypertension (ASH) on a group of normotensive subjects who have reduced small artery compliance. They were given an ACE inhibitor, which did have a favorable affect on the small artery compliance in the absence of any significant blood pressure change. I think that answers the question.

**Member of the Audience:** It is very interesting when you look at some of the data you presented—especially the Benetos study, which looked at 20,000 people—and observed that the double whammy, pulse pressure wider than 65 mm Hg, and mean arterial pressure greater than 107 mm Hg, was worse than either one alone in people between 40 and 64 years of age. However, you also showed a slide that seems to suggest that a higher diastolic pressure and a high systolic pressure may be somewhat protective, at least observationally.

I am concerned that clinicians will look at a narrower pulse pressure with a high systolic pressure as being protective. Until we have studies that either confirm or refute this observation, clinicians could be less than committed to treating patients with high systolic pressure or high systolic-diastolic pressure because they feel that it is protective compared with isolated systolic hypertension.

I am also concerned that this kind of observation will be incorporated into clinical practice and we will lessen our commitment to the treatment of isolated systolic hypertension. Observations without well-designed clinical trials may lead us down the wrong path and divert us from doing what our patients really want us to do for them.

**Dr. Safar:** Let me say something about this difficult topic. When you

look at treated subjects with hypertension, they may have systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg, which corresponds to a pulse pressure of 50 mm Hg or less.

Now, if you consider a patient with 140 mm Hg systolic and 70 mm Hg diastolic after treatment, the decrease in diastolic blood pressure may be due to a related decrease in arterial compliance, and the absence of an increase in systolic blood pressure may be due to associated congestive heart failure or some other cardiac alterations. Yet, this patient has a widening pulse pressure and this may be detrimental.

**Dr. Izzo:** This is a critical point that I tried to raise earlier. We must focus on systolic pressure first in order to answer the questions that were raised. I know that is a big change for many clinicians, perhaps even for some of us at this conference. I think we are better off dealing with the systolic pressure directly because it gets to the pulse pressure argument indirectly.

Moreover, there are no data to speak of from long-term, large-scale trials, and that is another issue. The only data I know that look at 24 months of therapy with an ACE inhibitor are from an angiotensin receptor blocker (ARB) development program in which efficacy was demonstrated with both drugs, typically at 4 and 6 weeks. However, looking at the results at 1 year and 2 years, the diastolic pressure didn't move with either drug, but the systolic pressure continued to go down substantially—by another 8 mm Hg at 2 years—with lisinopril, compared with the ARB.

That is similar to what Dr. Safar has shown with perindopril. If we are right about systolic pressure being the easiest clinical surrogate today for vascular stiffness and hypertension, then we are going to have to do some work to get clinicians to focus on sys-

tolic blood pressure until C2, the augmentation index, pulse wave velocity, or some other measure is available to help us do a better job of assessment.

**Dr. Safar:** I agree with this interpretation.

**Dr. Weber:** So, we are back to regarding systolic pressure as the most simple surrogate for arterial stiffness.

**Dr. Safar:** I agree with this point.

**Dr. Weber:** Yes, we have to rethink and revamp all of our studies because so much of what we have has been based on selecting patients by diastolic blood pressure level and treating that pressure to certain goals.

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