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L. Hansson

Elevated systolic blood pressure is nowadays recognized as an even stronger predictor than elevated diastolic blood pressure of cardiovascular morbidity and mortality. Even borderline isolated systolic hypertension is associated with significant increases in cardiovascular risks. Moreover, large prospective intervention trials on the treatment of patients with isolated systolic hypertension have shown significant reductions in the risks of stroke and coronary heart disease. In this perspective it is of interest to note that the new angiotensin II receptor antagonist, the AT_1 receptor selective agent eprosartan, has been shown to effectively reduce systolic blood pressure, both in patients with severe hypertension as well as in other patient groups. *J Clin Basic Cardiol 2001; 4: 131–134.*

Key words: systolic hypertension, cardiovascular morbidity, angiotensin II receptor blockade, eprosartan

A clinically useful way of measuring blood pressure with a sphygmomanometer was introduced in 1896 by Riva-Rocci (Figure 1). By palpating the pulse distal to the cuff, ie usually the pulse in the radial artery, it was possible to assess the systolic blood pressure. In 1905 Korotkoff pioneered the technique of measuring also the diastolic blood pressure by applying a stethoscope to the artery distal to the cuff, ie usually the brachial artery. Following this development it became gradually more fashionable to measure the diastolic blood pressure and in a number of the early intervention trials, such as the Veterans Administration Study and others, the diastolic blood pressure was the main criterion for the definition of hypertension and the target of treatment (Table 1) [1–8].

In more recent years the Hypertension Optimal Treatment (HOT) study used the diastolic blood pressure for the randomization of patients to one of three treatment targets, a diastolic blood pressure of ≤ 90, ≤ 85 or ≤ 80 mmHg [9].

Another reflection of the widespread dependence on diastolic blood pressure in the area of hypertension is the fact that most guidelines for the management of hypertension only provided definitions based on the diastolic blood pressure. As an example: the 1989 recommendations for the management of mild hypertension from the World Health Organization and the International Society of Hypertension (WHO/ISH) stated "No evidence is yet available on the benefits of lowering the systolic blood pressure" [10].

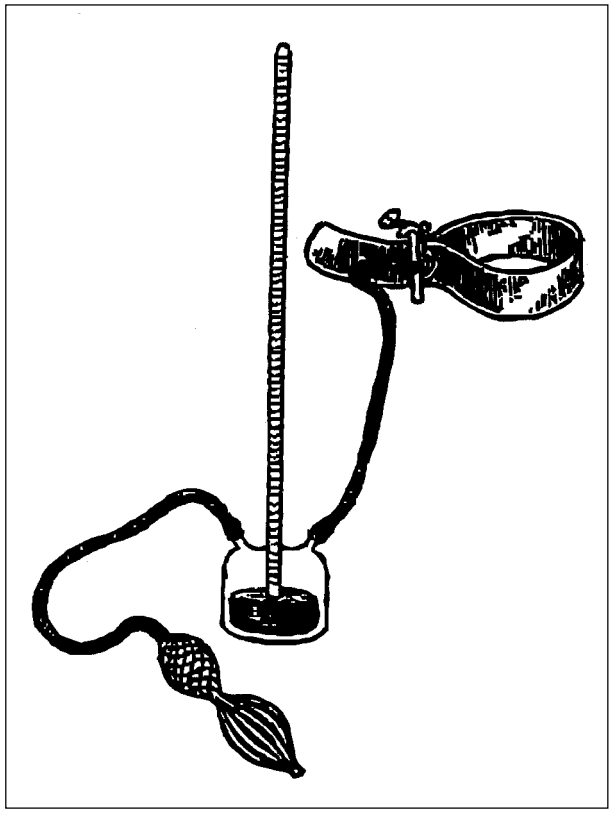

Figure 1. A sphygmomanometer of the kind used by Riva-Rocci in 1896

The Growing Importance of Systolic Blood Pressure

As briefly reviewed above, for several decades the scientific and clinical interest in hypertension was focused on the diastolic blood pressure. This may seem surprising for several reasons. It is, for example, technically more difficult to accurately measure the diastolic than the systolic blood pressure when using the Riva-Rocci and Korotkoff non-invasive technique with a sphygmomanometer and a stethoscope. It is conceivable that doctors during the 1920s, when the Korotkoff technique became more widely employed, were so excited by this new possibility to measure the diastolic blood pressure that the sheer aspect of novelty resulted in a relative over-emphasis of the importance of the diastolic blood pressure.

There are obviously other reasons as well. Over the years most textbooks on cardiology and internal medicine have presented and emphasized the view that it was mainly the

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Table 1. Improvement of prognosis by antihypertensive therapy in non-malignant hypertension

Authors	Number of patients	Year	Benefits shown at diastolic blood Pressure > (mm Hg)	Reference
Hamilton et al.	64	1964	110 (phase IV)	1
Wolff and Lindeman	87	1966	110	2
Veterans Administration	515	1967 & 1970	105	3, 4
Australian National Study	3,943	1979	100	5
Australian National Study	3,427	1980	95	6
Hypertension Detection and Follow-up Program Study	10,940	1979	90	7
Medical Research Council Study	17,354	1985	90	8

Table 2. Definitions and classification of blood pressure levels in the 1999 guidelines from the World Health Organization and the International Society of Hypertension

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	< 120	< 80
Normal	< 130	< 85
High-normal	130–139	85–89
Hypertension		
Grade 1 (mild)	140–159	90–99
Subgroup Borderline	140–149	90–94
Grade 2 (moderate)	160–179	100–109
Grade 3 (severe)	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90
Subgroup Borderline	140–149	< 90

Based on [16]

Table 3. Long-term cardiovascular morbidity and mortality in subjects who were free of cardiovascular disease at baseline in the Framingham Heart Study

Events	Number of events		Hazard Ratio 95 % CI
	Normal Blood Pressure (n = 2416)	Borderline Isolated Systolic Hypertension (n = 351)	
All CV disease	821	189	1.47 (1.24–1.74)
CHD	557	125	1.44 (1.18–1.77)
Stroke or TIA	208	55	1.42 (1.03–1.94)
CHF	173	55	1.60 (1.15–2.22)
Fatal CV disease	316	102	1.57 (1.24–2.00)
All cause mortality	926	206	1.14 (0.97–1.34)

CV = cardiovascular, CHD = coronary heart disease, TIA = transient ischaemic attacks, CHF = congestive heart failure. From Sagie et al. 1993 [17].

diastolic blood pressure that was worth considering when diagnosing hypertension. The diastolic blood pressure was usually also the only blood pressure worthy of therapeutic considerations.

In recent years the systolic blood pressure has been presented as a stronger risk indicator than the diastolic blood pressure, not the least based on data from the Framingham Heart Study [11]. It could be argued that since the systolic blood pressure can be measured with a smaller error of measurement than the diastolic, as alluded to above, and since the systolic blood pressure encompasses a wider range of values than the diastolic, any application of values of systolic blood pressure in a regression equation would yield higher correlation coefficients than simultaneously obtained diastolic blood pressure values.

However, the recent emphasis of systolic blood pressure as a stronger risk indicator than the diastolic blood pressure is not based just on a technicality. Solid evidence from the Framingham Heart Study shows that the systolic blood pressure is at least as strong a risk indicator as the diastolic blood pressure [11]. Moreover, intervention trials based on the level of systolic blood pressure such as SHEP [12], Syst-Eur [13] and Syst-China [14] have shown at least as good benefits of antihypertensive therapy on "hard endpoints" as studies based on diastolic blood pressure entry criteria.

In particular the impressive results shown in the intervention trials comprising patients with isolated systolic hypertension [12–14] have had a great impact on the present view on the importance of systolic blood pressure. It is also worth noting that the 1993 guidelines from WHO/ISH, for the first time listed systolic blood pressure criteria for the definition of hypertension [15]. This view is augmented in the most recent guidelines from WHO/ISH, issued in 1999, which also include definitions of isolated systolic hypertension and borderline isolated systolic hypertension (Table 2) [16]. That even borderline systolic hypertension leads to increased risks for stroke, coronary heart disease, congestive heart failure and other fatal or non-fatal cardiovascular events was clearly shown in a long-term follow-up from the Framingham Heart Study (Table 3) [17].

In a recent issue of "Blood Pressure", another important aspect of systolic blood pressure was presented. Howes and coworkers showed that the prevalence of isolated systolic blood pressure in patients attending general practice in Australia is 8 %, a percentage that can be expected to increase considerably with ageing [18]. Since most Westernized populations show that the proportion of elderly individuals increases it is to be expected that the management and treatment of systolic hypertension will assume greater importance in the future.

The significant impact of isolated systolic hypertension as a risk factor for cardiovascular morbidity and mortality was recently reviewed [19]. It was emphazised that the benefit of treating isolated systolic hypertension has been proven beyond doubt and that most likely also borderline isolated systolic hypertension, although not yet demonstrated in an appropriate prospective intervention trial, would benefit from treatment [19]. There may be many spin-offs from this. One could be that antihypertensive drugs that have been shown to be especially effective in lowering the systolic blood pressure will appear particularly attractive in the antihypertensive armamentarium.

Systolic Blood Pressure Control with Angiotensin II Receptor Blockade

Angiotensin II receptor antagonists of the AT_1 subtype have been in clinical use since the mid-1990s. The new, highly selective AT_1 receptor antagonist eprosartan is of special interest in this context since it also induces sympathetic suppression by inhibiting angiotensin II-stimulated presynaptic noradrenaline release [20]. In animal studies eprosartan has been shown to inhibit sympathetic outflow in contrast to several other AT_1 receptor antagonists [21].

In an 8-week placebo-controlled dose-ranging study in 351 hypertensive patients, eprosartan at doses of 400, 600, 800 and 1200 mg daily was found to lower systolic blood pressure significantly at all doses [22]. Of particular importance is that eprosartan was found to be significantly more effective than enalapril in reducing systolic blood pressure in patients with severe hypertension (Figure 2) [23]. Eprosartan was also numerically, although not statistically significant, more effective in lowering the diastolic blood pressure [23]. African-American patients, a group of patients often considered to be relatively unresponsive to antihypertensive therapy based on the blockade of the renin-angiotensin-aldosterone system, have been found to respond especially well to eprosartan, the systolic blood pressure being reduced more in that patient group than in all other patients (Figure 3) [23].

Data of this kind indicate that angiotensin II receptor blockade with the AT_1 receptor blocker eprosartan is very effective in lowering systolic blood pressure. This is of relevance in view of the established importance of systolic blood pressure as a risk indicator of cardiovascular morbidity and mortality.

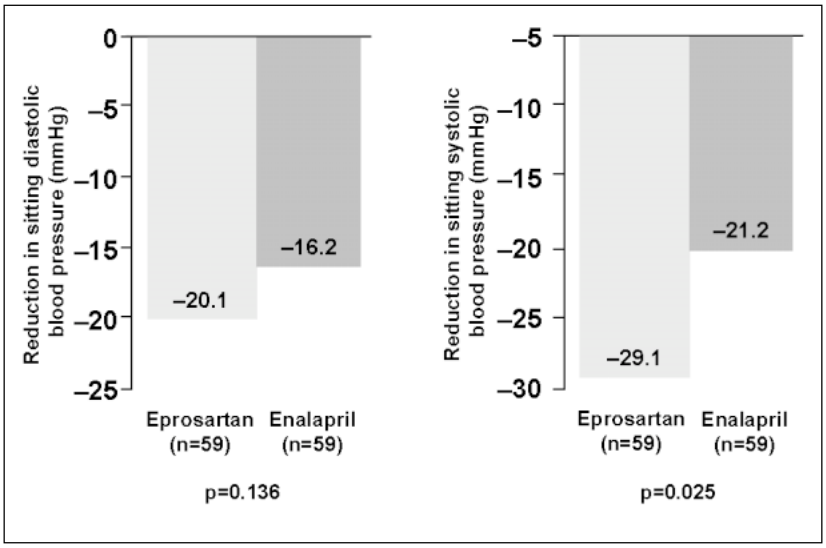

Figure 2. Effect of eprosartan and enalapril on blood pressure in 118 patients with severe hypertension. Redrawn after Hedner T, 1999 [23].

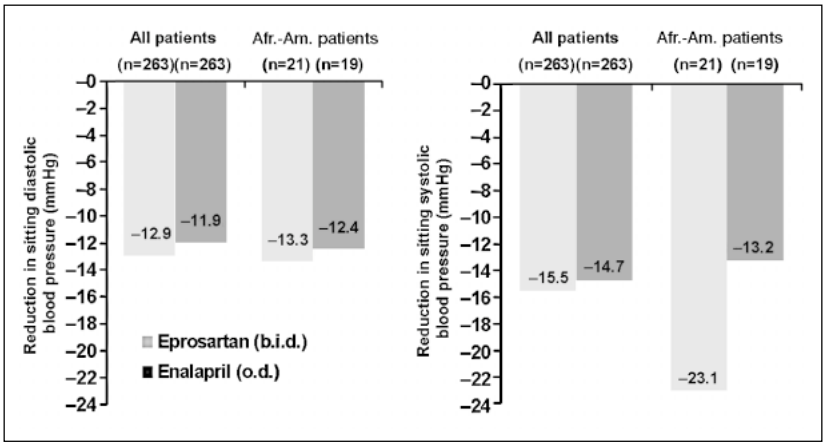

Figure 3. Effect of eprosartan and enalapril on blood pressure in 21 African-American patients and 263 non-African-American patients with hypertension. Redrawn after Hedner T, 1999 [23].

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