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Borderline Hypertension

Hypertension Seminars at Östra Hospital, Göteborg, Sweden

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ABSTRACT. Borderline hypertension was the topic of one of the "Hypertension seminars" arranged by the Hypertension Section at the Östra Hospital, Göteborg, Sweden. On that occasion Professor Stevo Julius, Ann Arbor, Michigan, USA, was an invited guest. During the seminar, various aspects of borderline hypertension were discussed, e.g. the natural history, hemodynamics and management of this condition. The present review is based on these discussions.

Key words: borderline hypertension, hemodynamics, epidemiology.

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It has been shown beyond doubt, and there is general agreement today, that arterial pressure in any population is distributed as a continuous variable, the curves being Gaussian in shape when converted to the logarithmic scale. In other words, arterial pressure is a quantity, not a quality. With this in mind, it is not logical to treat arterial pressure as a quality and set up a dichotomy: normotension and hypertension, a fact repeatedly pointed out by Sir George Pickering (75, 76).

The fact that most physicians and scientists still use the terms hypertension and normotension, and also the term borderline hypertension, the topic of this seminar, does not mean that they do not recognize that blood pressure (BP) is a quantitative variable. The use of these terms reflects the realization that individuals with a certain level of BP have several common physiologic and epidemiologic characteristics which often mandate specific investigative and practical approaches. As will become evident during this seminar, the term borderline hypertension signifies not just a certain range of BP between "normotension" and "hypertension", but rather a clinical condition with recognizable and reproducible characteristics.

DEFINITIONS

The WHO has defined hypertension as systolic BP (SBP) ≥160 and/or diastolic BP (DBP)≥95 mmHg and normotension as ≤140/90 mmHg, leaving the range between these two delineations to be called borderline hypertension (101). The Ann Arbor group has previously defined patients with borderline hypertension as those having, out of five indirect casual BPs within the last year, at least one with a diastolic value ≥90 mmHg and at least one ≤90 mmHg (45). Others have defined borderline hypertension as BP intermittently above 150 mmHg systolic or 90 mmHg diastolic (94). Since arterial pressure tends to increase with age in the Western world, all the above definitions have inherent problems, simply because they do not consider the age of the subject. However, the Ann Arbor group has recently taken age into consideration and defines borderline hypertension in the following manner: age 17–40: >140/90, <160/100; age 41–60: >150/90, <160/100 and age >60: >160/90, <175/100 (40). Obviously the intent of all these classifications is to delineate the mildest possible form of hypertension. Consequently, the term borderline hypertension excludes the existence of BP-related target organ damage such as hypertensive retinopathy and left ventricular hypertrophy (with conventional methods) or impaired renal function.

A number of synonyms to borderline hypertension have been proposed. The term labile hypertension is not logical as it implies increased BP variability. Some of the early studies indicating a higher degree of BP variability in subjects with systolic blood pressure above 120 mmHg as compared to those with BPs below this level, are open to serious criticism, e.g. that in the lower BP group the upward variability of the BP was limited by definition (it could reach a maximum of 120 mmHg) whereas no such restrictions existed in the high BP group (78).

Furthermore, several studies have demonstrated that there is no correlation between the level of BP and its variability when repeated measurements are made during 1–3 weeks (10, 26). In addition, BP fluctuates markedly

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even in normotensive individuals (4). It is therefore not surprising to find that an excessive variability of BP has never been established as a characteristic feature of borderline hypertension. Even if the BP variability were increased, the importance of this finding would be questionable. The extreme ranges of BP do not seem to predict the risk of cardiovascular disease. Thus, Sokolow et al. (85) found that the five highest and five lowest BPs during a 24-hour recording did not relate to cardiovascular morbidity, whereas the average BP during that period carried an important predictive power. The term "labile" should be reserved for individuals with extremely variable BPs, irrespective of whether these occur in the normotensive, borderline or hypertensive range.

The term prehypertension indicates a condition which almost invariably leads to established hypertension. Since this is not the case, which will be shown later, the term is not logical. Latent hypertension points to a condition which may develop into hypertension or which may remain latent, and this term is accordingly a useful synonym. Marginal hypertension is also acceptable, whereas early essential hypertension should be avoided for the same reasons as prehypertension. However, borderline hypertension is such an accepted and commonly used expression that any attempt to use synonyms for this condition is likely to cause confusion. For this reason we would recommend that the use of synonyms be restricted.

EPIDEMIOLOGY

The prevalence of borderline hypertension has been studied in several population surveys. In the Bergen study, performed in the 1950s, 8% of the males in the age group 20–30 years had borderline hypertension and 13% in the 30–40 years group. The prevalence of borderline hypertension was somewhat lower in women below 50 years of age, but with increasing age this difference disappeared (6). Also in the US the prevalence of borderline hypertension increases rapidly with increasing age (7). The prevalence of borderline hypertension in university students in Michigan has been reported to be approximately 20% (40).

Accurate data about the prevalence of borderline hypertension in Sweden are lacking. However, if the prevalence data from the Alameda County BP study in California were valid also in Sweden, the total number of persons with borderline hypertension would exceed one million (of a total population of 8 millions) (Table I).

For a complete review of available data on the prevalence of borderline hypertension, see Julius and Schork (47). In this context it should be stressed again that the definition of borderline hypertension, and indeed also of hypertension, becomes crucial with advancing age. For example, a population study of 70-year-old women in Göteborg indicated that no less than 48% had hypertension (92), demonstrating the dilemma of arbitrary definitions of hypertension. The incidence of borderline hypertension has repeatedly been found to be quite low, in the order of 1%/year of observation (47, 52).

Table I. *Calculated number of persons with borderline hypertension in Sweden*

Based on population data on Dec. 31, 1976, the total population of Sweden being 8 236 179 (90), and The Alameda County BP study (7)

Age group	Males	Females
18–24	19 900	7 600
25–44	114 200	54 300
45–64	163 100	196 700
>65	106 800	357 400
All	403 800	616 000
All males and females	1 019 800	

NATURAL HISTORY AND RISK FACTORS

The later occurrence of established hypertension has repeatedly been found to be 2–5 times more common in individuals with borderline hypertension than in those with initial normal BP. Still it should be stressed that only a minority of individuals with borderline hypertension later develop established hypertension. An approximate figure for the accumulated overall risk is commonly considered to be around 20% (44, 70, 73).

The morbidity and mortality from cardiovascular disease in the population with borderline hypertension is approximately twice as high as in a normotensive population (47). The increased morbidity in borderline hypertension shows a similar pattern to the morbidity observed in established hypertension. Thus, an excess in myocardial infarction, strokes, congestive heart failure and ECG changes has been reported (32, 51, 57, 62, 88, 96). Consequently it is likely, but not proven, that this higher morbidity occurs in the group (20%) of patients who will later develop established hypertension (hypertension-specific cardiovascular morbidity).

A good example of morbidity in borderline hypertension can be found in the Framingham study, which showed a 50% increase in age-adjusted coronary heart disease (50, 51). Other studies have shown similar or higher (up to 200%) increases in

coronary morbidity in borderline hypertension (39, 47, 57). The Framingham study also found an almost doubled incidence of atherothrombotic brain infarction.

The mortality in borderline hypertension is also increased. One could question the specificity of this mortality since in the report by Levy et al. (57), patients with borderline hypertension had a greater tendency to commit suicide. However, the Framingham study shows that the excess mortality in borderline hypertension is specific.

A 50% increased overall mortality for men and a 75% increase for women with borderline hypertension as compared to normotensive control groups was reported. The increase is largely due to cardiovascular mortality, which was twice the normal rate for men and four times that for women in age group 67–74 (50). In younger age groups the increase in cardiovascular mortality was substantial but not as dramatic as in older ages (50).

As the risks for complications increase with rising BP (85), it is not surprising that a great deal of work and interest have gone into attempts to identify factors that predict future hypertension. As it happens, the best predictor for future hypertension is high BP, i.e. the initial level is the strongest predictor for BP in the future (11, 32, 48, 64, 69, 87). Another, independent predictive factor is tachycardia, which is *not* a benign sign (70, 87). Levy et al. found that when both transient hypertension and transient tachycardia were present, the incidence of later established hypertension was more than twice the incidence when only one of these factors was present (58).

Overweight is also associated with borderline and mild hypertension. High relative weight is a predictor of future hypertension, as is weight gain over a period of years (32, 37, 38, 70, 87, 89).

A positive family history of hypertension is more common in patients with borderline BP elevation (42), and established hypertension occurs more often in patients with a positive family history (29). The inheritance of arterial pressure is considered to be multigenetic but the exact mechanisms are not well known (80, 97).

Interest has recently been focused on possible interactions between environmental and genetic-immunological factors in the development of hypertension (12, 93). The question has been asked whether there are genetic indicators—e.g. certain HLA types—at least in some subpopulations in essential hypertension. If so, it might be possible to predict the prognosis or the risk for, e.g., vascular damage more reliably than is presently possible (27, 53). However, to our knowledge no such studies have been performed systematically in individuals with borderline hypertension.

In the overall US population the prevalence of borderline hypertension is very similar for black and white persons of both sexes, but established hypertension is twice as frequent in blacks, indicating that race may be considered as a risk factor and that blacks carry a greater risk for progression from borderline to sustained hypertension (40).

Using multiple logistic function to discern the quintile of the population with the highest risk of developing hypertension within 5 years, Stamler et al. (87) could identify at most 55% of all expected hypertensives in that quintile.

A number of tests have been designed and employed in attempts to identify persons with an augmented risk of developing future hypertension, e.g. cold pressor test, salt loading, reaction to mental arithmetic, digital vascular reactivity to noradrenalin, apparent noradrenalin secretion test and tritiated noradrenalin test as well as different combinations of these. By and large such tests have proved to be of no predictive value, or alternatively they cannot be employed in practice or the needed long-term follow-up is still lacking (40, 91). This holds true also for a new and most interesting approach: the abnormal Na+ and K+ net fluxes in erythrocytes of essential hypertensive patients (also in relatives to hypertensive patients and in some women with hypertension during pregnancy) (25). Whether these abnormalities can really be used as markers for hypertension remains to be confirmed.

HUMORAL FACTORS

Catecholamine concentrations in urine or plasma are frequently used as indicators of sympathetic activity. It is, however, doubtful that patients with established hypertension have increased sympathetic activity as reflected by increased release of catecholamines (8, 15, 18, 19, 23, 34, 55, 59, 68, 74, 81). Age is of importance in this setting, since plasma concentration of noradrenalin is positively correlated with age (23, 34, 74, 81). Activation of the cardiac sympathetic neurones increases urinary catecholamine excretion (9), whereas moderate activation of the peripheral sympathetic nervous

Table II. *Hemodynamics in borderline hypertension*

	Controls ($n=29$)	Whole patient group ($n=44$)	Hyperkinetic subgroup ($n=20$)	Normokinetic subgroup ($n=24$)
Blood pressure (mmHg)				
SBP	120	137***	138***	136***
DBP	71	75**	76**	74*
Mean	88	95***	97***	94***
Heart rate (beats/min)	65	69	76***	△ 65
Stroke volume (ml)	98	111**	119***	△ 104
Cardiac output (l/min)	6.1	7.3***	8.6***	△△△ 6.2
Cardiac index (l/min · m²)	3.33	3.81*	4.55***	△△△ 3.19
Total peripheral resistance (mmHg/l/min)	14.8	13.4*	11.2***	△△△ 15.2
Minimal vascular resistance in the hands (mmHg/(ml/min · 100 ml))	1.69	1.87*	1.71	△ 1.99**
Body weight (kg)	65.9	73.8***	71.4*	75.8***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ in comparison with controls. △ $p<0.05$, △△ $p<0.01$, △△△ $p<0.001$ in comparison with hyperkinetic subgroup (Sivertsson et al.: Unpublished data).

system does not increase plasma concentrations of adrenalin or noradrenalin (1, 61). Some patients with established hypertension appear to have a true neurogenic hypertension and their BP can be normalized following total autonomic blockade (16). Hypertensive patients showing higher noradrenalin levels are usually young (23, 34, 81) and have also been reported to have increased plasma renin activity (16).

In comparison with normotensive individuals, borderline hypertensives usually have normal resting plasma and urinary catecholamine concentrations (8, 67). Physical exercise induces elevation of both noradrenalin and adrenalin plasma concentration but patients with borderline hypertension do not behave differently from normal controls in this respect. Patients with borderline hypertension have increased excretion of urinary catecholamines during mental stress (19, 67) and also an increased catecholamine response to upright posture (19, 54). Poststress plasma catecholamines have recently been shown to be increased also in individuals with a genetic risk of developing hypertension as well as in borderline hypertensives (20).

As a group, borderline hypertensives have higher plasma renin activity than normotensive individuals and patients with established hypertension (24). Patients with borderline hypertension have been subdivided by their renin status (17) and approximately 35% are in the "high renin" group, 45% in the "normal renin" group and 20% in the "low renin" group (17). Patients with "hyperkinetic circulation" usually have high plasma renin activity (65).

Total autonomic blockade with propranolol, atropine, and phentolamine normalizes the BP both in patients with high renin borderline hypertension and in high renin established hypertension (16, 17). However, in patients with normal or low renin hypertension the BP remains elevated also following total autonomic blockade (17). This would seem to indicate that the high renin hypertensives have a neurogenic type of BP elevation. Obviously, the plasma renin activity per se does not induce the BP elevation in these patients, since β-adrenoceptor blockade with propranolol, which causes a marked decrease in plasma renin levels, does not reduce the elevated BP (43).

PERSONALITY TRAITS

A few reports indicate that patients with borderline hypertension differ from normal controls in a number of psychological ways (28, 30). Thus, they are more submissive and have more suppressed hostility (28). They also more often exhibit disturbances in sexual roles and have difficulties in interactions with other people (49). These aspects indicate that borderline hypertension could be regarded as a psychosomatic disease.

HEMODYNAMICS

Cardiac output

It is well documented that cardiac output at rest is increased in patients with borderline hypertension as a group, in comparison with normotensive indi-

viduals (47). However, this does not mean that all individuals with borderline hypertension have an increased cardiac output. But in 30–50% the cardiac output exceeds the value found in control subjects by 2 S.D. or more. This difference between borderline hypertensives and normotensives seems to decrease with increasing age (41, 60). Some studies indicate that the high output is caused by an elevated heart rate (24, 41, 60, 63, 79), others that it is due to an increased stroke volume (3, 21) while still others have demonstrated that both factors are involved (13, 78, 100) (Table II).

The elevation of cardiac output is maintained by an increased sympathetic and a reduced vagal activity to the heart, which points to an altered central nervous activity in these individuals. Thus, cardiac output normalized after autonomic blockade with propranolol and atropine (45). Since the sensitivity of the β-adrenoceptors in the myocardium is decreased rather than increased in borderline hypertension, the high output state was not caused by local cardiac effects (43).

Blood volume

Most studies show that blood volume or plasma volume is normal or slightly reduced in borderline hypertension (2, 21, 24, 63) while a few studies show significantly reduced values (22, 46, 78). Cardiopulmonary blood volume is probably normal in patients with borderline hypertension (78). In relation to total blood volume, cardiopulmonary blood volume has been found to be normal (79) or increased (78). In patients with hyperkinetic borderline hypertension, the cardiopulmonary blood volume appears to be increased both in absolute and in relative terms (14). This centralization of blood from the periphery is probably a consequence of an increased vasomotor nerve tone on the capacitance vessels (78). Such a redistribution of the blood pool might influence stroke volume and cardiac output by increasing the venous return. Although there is a positive correlation between cardiac output and cardiopulmonary blood volume (14), this does not prove a causal connection since vasomotor nerve activity may influence both these variables. On the contrary, some data indicate that the two factors are not causally related. Thus, autonomic nerve blockade normalizes cardiac output but not the central blood volume (14). A changed relation between central blood volume and stroke volume or cardiac index (increased stroke volume in relation to central blood volume) supports the idea that vasomotor nerve activity is the main determinant of the increased cardiac output in patients with borderline hypertension (14).

Peripheral vessels and vascular resistance

At rest, total peripheral resistance in borderline hypertension is within normal limits, or in fact slightly reduced (Table II). It has been pointed out, though, that in relation to cardiac output, vascular resistance is increased (46). The vascular resistance can be brought into the normal range by means of phentolamine in about 30% of patients with borderline hypertension (43). During intense physical exercise, total vascular resistance in borderline hypertension remains elevated (60, 79). Moreover, during infusion of dextran, the vascular resistance in borderline hypertension fails to adjust to the increased cardiac output (45).

Adaptive structural changes in the resistance vessels seem to occur already in mild forms of hypertension (83, 84) (Table II). This is in agreement with the echocardiographic observation of left ventricular hypertrophy in borderline hypertensive patients (56). A recent study has shown decreased venous distensibility in borderline hypertension (94). The claim was made that this decreased distensibility was to a certain extent due to structural changes in the veins (94). However, the scientific support for this claim is not convincing and the findings may be explained by increased smooth muscle tone.

MANAGEMENT

It has been pointed out above that borderline hypertension constitutes an important risk factor for future cardiovascular complications. A logical consequence of this would be to lower the BP. However, available data so far, notably the Veterans Administration studies, have shown positive therapeutic effects as regards morbidity and mortality only in patients whose DBPs were 105 mmHg or higher (98, 99). However, the HDFP (Hypertension Detection and Follow-up Program) study (35, 36) demonstrates for the first time a clear reduction in mortality also in patients whose DBPs were 90–105 mmHg. Obviously, these important new results will have a profound effect on management policies for patients with mild hypertension.

Before any kind of intervention is considered in

patients with borderline hypertension, it is obvious that the BP level should be determined with the greatest possible accuracy. Therefore, repeated measurements of BP with a reliable and standardized technique become mandatory.

Borderline hypertensive patients are frequently overweight and since weight reduction lowers BP in obese hypertensive patients (33), it becomes obvious that reduction of body weight should be attempted in borderline patients, too. The BP-lowering effects of weight reduction have been shown to be independent of salt restriction (77). Still, salt reduction of a moderate degree will also lower BP. A reduction of daily salt intake from about 10 to 5 g may reduce the BP approximately 10/5 mmHg (66, 71). Dietary advice may also be beneficial in other ways, e.g. by correcting hyperlipidemia and glucose metabolism disturbances.

In a review of non-pharmacological treatment of hypertension, Blackburn (5) pointed out that "Exercise can be recommended to mildly hypertensive patients, as to the entire public, for its long-term benefit in weight control in a sedentary society. However, it is not established that cardiovascular mechanisms involving autonomic nervous activity which are affected by high level conditioning exercise, have in fact, any independent or long-term antihypertensive effect."

Behavioural methods to reduce high BP include biofeedback, relaxation, psychotherapy, environmental modification and placebo. In an extensive review of this field, Shapiro et al. (82) concluded that "widespread and uncritical application of behavioural methods to the treatment of high blood pressure is premature".

In the management of patients with hypertension, it is obvious that advice and information play important roles. However, such information should be given with care. Canadian steel workers tended to have longer periods of non-attendance when aware of a hypertensive condition than controls who were not aware of having similar BP levels (31).

In conclusion, non-pharmacological treatment and regular check-ups of BP constitute the basis for managing borderline hypertensive patients. Drug therapy is not recommended in cases of truly borderline hypertension, i.e. with DBPs sometimes below, sometimes slightly above 90 mmHg. However, the recent findings of the HDFP group clearly support the opinion that pharmacological treatment should be instituted in hypertensive patients, even in the "mild range", i.e. with DBPs between 90 and 105 mmHg (35, 36). Furthermore, treatment, particularly with a β-adrenoceptor blocking agent, can be considered in borderline hypertensive patients with subjective symptoms related to their condition, e.g. disturbing palpitations or tachycardia.

It also stands to reason that treatment shall be attempted in those patients with borderline hypertension who are at high risk to develop future hypertension due to their family history, race, or uncorrectable other risk factors. Only moderate doses of drugs and only monotherapy are recommended in such cases. It would be unwise to apply the same aggressive stepped-care approach to treatment that is usually used in established hypertension.

CONCLUSIONS

Borderline hypertension refers to that gray zone between clearly normotensive and hypertensive BP values. It is interesting to note that a number of pathophysiological characteristics make it possible to separate borderline hypertension, on the one hand, from normotension and, on the other, from established hypertension. All the available data indicate that borderline hypertension constitutes the first phase in the development of established hypertension, although it should be pointed out that individuals with BPs within the borderline range by no means are bound to develop established hypertension. It is also worth noting that BPs within the borderline hypertensive range are associated with increased risks for cardiovascular morbidity and mortality. The newly published and clearly positive results of the HDFP study regarding antihypertensive therapy in mild hypertension will probably contribute to increased attention of this interesting clinical entity.

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