Variability of Arterial Pressure in Normotensive and Spontaneously Hypertensive Rats[1] (36412)

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Excessive variability of arterial pressure, or lability, has been suggested as an intermediate stage in the development of sustained elevated arterial pressure (1–5). However, evidence that excessive fluctuation of arterial pressure is a characteristic of labile or borderline hypertension or a prognosticator of future persistent hypertension is lacking for both man and experimental animals. One of the major problems in this area of investigation is the lack of information regarding the day-to-day variability of arterial pressure in the normal as well as the hypertensive animal (2, 6).

To determine the relationship between long-term variability and height of arterial pressure daily systolic pressures were obtained in normotensive and spontaneously hypertensive (SHR) Wistar rats. This strain of hypertensive rat was developed by Okamoto and Aoki (7) and Okamoto *et al.* (8) by inbreeding rats of the normal Wistar population which exhibited "above the average" arterial pressure.

Methods. Indirect systolic pressures were measured 5 days/week for a 1 month period on each of 20 control and 20 SHR Wistar rats matched for sex and age. The SHR rats are of the F_{20} generation of the Okamoto–Aoki strain, bred in our laboratory from F_{19}. (Our initial breeding stock was generously provided by Dr. Albert Sjoerdsma of the National Heart and Lung Institute.) At the beginning of the study the ages ranged from 11 to 24 weeks and their weights from 150 to 435 g. The animals were indelibly marked, kept in the same cage with their initial "cage mates," and housed in plastic cages in as constant environmental conditions as possible in the same room.

To determine indirect systolic arterial pressures, the unanesthetized rats were placed in plastic restraining cages and a 15 mm wide occlusion cuff was positioned at the base of the tail and pressures were measured by a previously described technique (9). In brief, an electronic plethysmograph (Buffington Clinical Devices) was applied to the tail with masking tape on the ventral surface immediately distal to the occlusion cuff. The animals were warmed with an infrared lamp (to ambient temperatures of 36–39°) until full-scale plethysmographic displacements were obtained on a Grass multichannel recorder (Model 5D). Heating usually required approximately 10 min. If, at the end of this time, the displacement deflections were not sufficiently amplified, the plethysmographic transducer was reapplied. Each determination of systolic pressure consisted of increasing occlusion cuff pressure with an inflation bulb to suprasystolic levels until arterial pulsation displacements were no longer evident. Cuff pressure was slowly reduced until the pulsations reappeared. Through a T-tube connection, the occlusion cuff pressure was simultaneously monitored with an aneroid manometer and by a Statham $P_{23}Db$ transducer attached to the recorder. The cuff pressure at the reappearance of the initial displacement pulsation following occlusion was the systolic pressure. Our previous studies have shown an extremely high degree of correlation between such indirect pressures with directly recorded arterial pressures in

[1] Supported in part, by funds from the Oklahoma Heart Association, NIH Grant HE 12287 and NIH Training Grant IT01HE-05959.

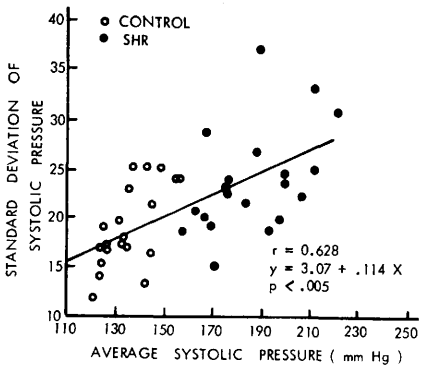

FIG. 1. The relationship of average indirect systolic arterial pressure and standard deviation of the daily average systolic pressures for 20 control (●) and 20 SHR rats (○) during the first month of study.

unanesthetized rats ($r = .975, p < .001$) (9). Five such consecutive indirect systolic measurements were obtained for each rat during every study day.

Because of the apparent day-to-day variability in systolic pressure in some normotensive rats, we chose to increase the number of animals in each group at the conclusion of the first month. Therefore, 20 control Wistar and 10 SHR rats were added to the original study groups, and the same procedure, outlined for the first month, was continued during the second and third months of study for the total 40 control Wistar and 30 SHR rats. However, because of the obvious time involved in obtaining five daily pressure determinations in these 70 rats, only duplicate consecutive daily measurements were obtained for each rat (provided these duplicate daily pressure measurements were within 5 mm Hg).

The five consecutive readings for the first study month were averaged to obtain that day's systolic pressure of each rat. From these daily average systolic pressures, monthly averages and their respective standard deviations were calculated for each rat in order to permit correlations of height of systolic pressure and its respective variability. Thus, by ascribing variability or lability to arterial pressure we specifically exclude variability of pressures obtained for a single day's reading but refer to day-to-day variability. These same calculations were performed for all rats studied during the second and third months.

Since the standard deviation of any group does not follow the normal distribution, nonparametric statistics had to be used. Thus, the Spearman rank correlation coefficient was computed to determine the relationship between average systolic pressure and its standard deviation and for the same reason the Mann-Whitney test was used to compare the standard deviations of two groups of rats (10).

Results. A positive correlation was obtained between average monthly systolic pressures and their standard deviations for the first ($r = .628, p < .005$; Fig. 1) and second and third months ($r = .699, p < .005$; Fig. 2). Thus, the higher the average monthly systolic pressures the greater was the variability (lability) for each rat, whether he was of the control or SHR groups ($r = .365, p < .0125$ and $r = .540, p < .0025$, respectively; Spearman-Rank correlation coefficient).

Thirty-six of the 40 control rats had one or more *daily* average systolic pressures above 150 mm Hg; and of the 30 SHR rats 12 had at least one *daily* average systolic pressure less than 150 mm Hg (Table I). However, when *weekly* averages were compared, only 11 of the 40 control rats had at least one average greater than 150 mm Hg, and none of the SHR rats had even one weekly average

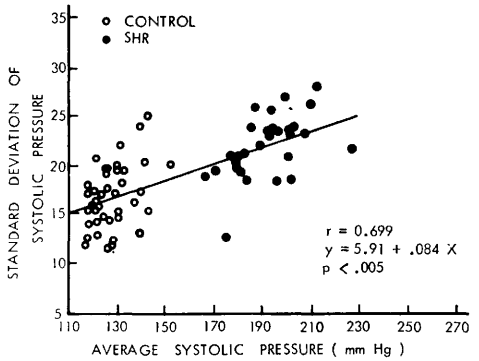

FIG. 2. The relationship of average indirect systolic arterial pressure and standard deviation of the daily average systolic pressures for 40 control (●) and 30 SHR rats (○) during the second and third months of study.

TABLE I. Comparison of Control and SHR Rats Using 150 mm Hg Systolic Pressure as Dividing Line for Hypertension.

At least one Av systolic pressure	Control (40 rats; 150 mm Hg)	SHR (30 rats; 150 mm Hg)
Daily	36 (90%)	12 (40%)
Weekly	11 (28%)	0

systolic pressure less than 150 mm Hg.

The standard deviations of the daily average systolic pressures (the variability index) of the 11 control rats having at least one weekly average pressure greater than 150 mm Hg were compared to those of the remaining 29 control rats (Mann-Whitney test). The 11 former rats had greater standard deviations (variability) than the latter 29 controls ($p < .01$).

Discussion. The results of this study show that, whether normotensive or hypertensive, the higher the systolic pressure in the Wistar rat the greater its variability. Moreover, even in the normotensive (control) group those rats having greater lability of arterial pressure had "borderline hypertension"; that is to say, their weekly systolic pressures were at times above the level usually accepted as "normotensive." This is a crition frequently used clinically to classify patients as having labile or borderline hypertension (2, 4).

The present study, as are most chronic studies involving rats, is concerned only with measurement of systolic arterial pressure. This is because diastolic pressures cannot be measured accurately with indirect methods in the rat (11). In contrast, indirect systolic pressures measured in the tail accurately reflect direct arterial pressures (9).

In characterizing the arterial pressure of a rat as normal or hypertensive a single day's measurement is insufficient. To minimize the chance of erroneously classifying normotensive and hypertensive rats, the present data suggest that duplicate daily pressure should be obtained for at least 1 week. Nevertheless, the long-used, empiric dividing line for hypertension in the rat of 150 mm Hg appears valid in terms of weekly average systolic pressure.

Twenty-eight percent of control animals had weekly average systolic pressures that at least once exceeded 150 mm Hg during the 2 to 3 months of study. Because these animals had pressures that were at times above, and at other times below, an arbitrary dividing line for hypertension they are termed "borderline hypertensives." Conway (2) distinguished between borderline and labile hypertension by suggesting that lability indicates excessive variability of arterial pressure. Thus, borderline hypertensives may or may not have labile arterial pressure.

The present study provides direct evidence that, whether normotensive or hypertensive, animals with higher arterial pressures have greater variability (and hence lability) of pressure. These data, then, provide the first evidence that animals with "borderline hypertension" do, in fact, have a greater variability (lability) of arterial pressure than their normotensive counterparts. We continue to follow our surviving animals to learn whether the "borderline hypertensives" of the control group will ultimately convert to persistent or sustained hypertension.

Summary. Daily indirect systolic pressure was measured, without anesthesia, for 3 months to determine the relationship between variability and height of pressure in individual normotensive and spontaneously hypertensive (SHR) rats. Average systolic pressure correlated with its standard deviation indicating the higher the pressure the greater its variability. The empiric dividing line for hypertension in the rat of 150 mm Hg was reexamined and found appropriate. No SHR rat had an average weekly pressure less than 150 mm Hg and 28% of the controls had at least 1 weekly average above 150 mm Hg; we have termed these rats as "borderline hypertensives." Daily variability of pressure of borderline hypertensives was greater than the remaining controls. Therefore, borderline hypertensives have greater lability of arterial pressure.

The authors gratefully acknowledge the statistical advice of Drs. John McCoy (of the Veterans Administration Southern Research Support Center, Little Rock, AR) and Donald Parker (of the Universi-

ty of Oklahoma Medical Center), the technical assistance of Mrs. Janice Pfeffer and Mr. Philip Barrett, and the secretarial work of Mrs. Irene Smith.

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Received Dec. 27, 1971. P.S.E.B.M., 1972, Vol. 140.