Resistance to Blood Flow at Maximal Vasodilatation

To the Editor:

In the April issue of Hypertension, a study by Distler’s group (Schulte et al.), explored whether minimal forearm resistance to blood flow at maximal vasodilatation ($R_{\text{min}}$) is elevated in human primary hypertension by repeating and critically extending the studies published in 1956 and 1958 by Folkow et al. In addition to the methods used by our group (ischemia, exercise, and local heating) to provoke maximal dilatation, they added an infusion of the calcium channel blocker nifedipine. The addition of nifedipine increased blood flow up to 30% in both their normotensive and hypertensive subjects and resulted in $R_{\text{min}}$ values that were apparently lower than those reached in our study. Schulte et al. therefore concluded that 1) complete vascular relaxation was only achieved when calcium channel blockers were added, and 2) $R_{\text{min}}$ was not significantly elevated in their hypertensive group. On closer scrutiny, however, their results seem to confirm the results of our group. As this problem deals with one of the most important principles in primary hypertension, it merits further discussion and clarification.

The $R_{\text{min}}$ values in the study by Schulte et al. can best be compared with those of our study by means of the respective normotensive control groups. These ought to be closely similar, but our hypertensive group seems to manifest more pronounced hypertension than was reported for the hypertensive group in their study. In our normotensive group, mean arterial pressure (MAP) was indirectly measured in the opposite resting forearm at the time of flow recording and was on average 96 mm Hg. Average maximal forearm blood flow was 53 ml·min$^{-1}$·100 g$^{-1}$, and average $R_{\text{min}}$ was 1.81 PRU$_{100}$ (peripheral resistance units per 100 g tissue). In their normotensive group, on the other hand, MAP was intra-arterially measured in the maximally vasodilated forearm during peak flow. After adding the calcium blocker, the average MAP was 70 mm Hg, (versus 80 mm Hg during rest—i.e., a 10-mm pressure drop along proximal arteries at maximal flows). The average $R_{\text{min}}$ in this situation was 1.4 PRU$_{100}$, while it was 1.8 PRU$_{100}$ after ischemic work and heating only (i.e., about 30% higher).

From such data Schulte et al. concluded that complete vascular relaxation was probably not reached in either the normotensive group or the hypertensive group in our study. However, this conclusion overlooks the very important technical differences that exist between the two studies, particularly in relation to the MAP recordings. First, our measurements were made with subjects’ forearms in a 43 °C heated water-filled plethysmograph, which added an external water pressure of 10 cm. For physical reasons, this reduces the effective forearm perfusion pressure by 7 mm Hg. Second, it is known that in humans intra-arterial MAP is 5 to 10 mm Hg lower (assumed to be 7 mm Hg below) than when MAP is measured indirectly in the same limb. Third, the MAP values used by Schulte et al. for $R_{\text{min}}$ deductions excluded the increased (averaging 10 mm Hg in the normotensive group) pressure drop along proximal (subclavian-brachial) arteries during maximal inflows, while our MAP values included the proximal resistance. We measured MAP indirectly in the other resting forearm where the proximal pressure drop during rest is negligible.

At the time of our study (1954–1955), first reported in 1956, it was not possible to perform arterial catheterizations for experimental purposes, but there are reasons to assume that the proximal artery pressure drop was of the same size as in Schulte et al.’s normotensive group (i.e., about 10 mm Hg). In a later study in some additional hypertensive and normotensive subjects in whom arterial catheters were inserted because of various clinical indications, we investigated whether substantially greater pressure drops occurred in hypertensive than in normotensive subjects during peak inflows after ischemic exercise. No major difference was found between the hypertensive and normotensive groups in this respect, and we therefore concluded in our final (1958) paper that the nearly 40% higher $R_{\text{min}}$ in the hypertensive group could not be ascribed primarily to narrowed proximal arteries but must essentially be attributed to the distal “true” resistance vessels.

In any case, it follows from this that the $R_{\text{min}}$ data that Schulte et al. reported for their normotensive group can be directly compared with our data only after 7 + 7 + 10 mm Hg is subtracted from the indirectly recorded MAP of our normotensive group. In other words, our average MAP was really 72 mm Hg (96 – 24 mm Hg) when measured exactly as the 70 mm Hg of their normotensive group was measured. At an average maximal blood flow of 53 ml·min$^{-1}$·100 g$^{-1}$, this changes the $R_{\text{min}}$ value for our normotensive group from 1.81 PRU$_{100}$ to 1.35 PRU$_{100}$; if anything, it is lower than that reported by Schulte et al. (1.4 PRU$_{100}$). In other words, if the normotensive subjects in their study were in a state of maximal dilatation, so in all likelihood, were our subjects.

This, after all, is not surprising because, on the basis of extensive experience in animal experiments, we made a great effort to enforce a complete vascular relaxation by pushing total ischemia with superimposed exercise to the extreme and by using external tissue heating to the border of pain (43 °C),
which, of course, is of crucial importance in studies of this type. It would, however, be strange if the highly potent vasodilator factors produced by the tissues were unable ever to mobilize and utilize the maximal conductance of their nutritional circuits (but only about 75% of the maximum as indicated by the data reported by Schulte et al.). Furthermore, all data from animal experiments or from intense exercise in humans indicate that the organism can indeed fully utilize the local "blood flow reserve," whenever needed, by way of the locally produced vasodilator mechanisms.

In any case, as equally low $R_{\text{min}}$ values were reached in our and their normotensive groups, when compared in the correct way, two conclusions can be drawn. First, the procedures used in our study were really able to induce complete vascular relaxation. Second, as this was the case in Schulte et al.'s study only after the addition of nifedipine, they evidently did not push the ischemia-exercise-heating procedures for vasodilatation quite as far as we did in our study.

When it comes to a correct interpretation of the data presented by Schulte et al. in general, it is remarkable that the spread of the maximal blood flow values in their normotensive group was nearly three times bigger (96-29) than in our normotensive group (62-39 ml min$^{-1}$ 100 g$^{-1}$). In fact, the very lowest as well as the highest maximal flow values in their normotensive group are so far beyond what is ordinarily seen in normal human forearms, that they must reflect some vascular abnormalities or technical artifacts (or both). It should also be stressed that the plethysmographic technique is difficult to use correctly at very high flows.

Moreover, the type of volume-displacement plethysmograph that we used, which directly records the total volume inflow to the entire tissue region studied, must be more reliable than the mercury-in-Silastic strain gauge variant used by Schulte et al., as the latter only records the changes along a single circumference of the studied tissue region. For example, local differences in venous distensibility or capacitance (or both), and hence in the extent of blood that can be accumulated, may, in the mercury-in-Silastic variant, somewhat distort the true inflow values to the total forearm region, whereas during total volume recordings such differences will "equal out" between nearby tissue sections. Furthermore, the 15-cm-long volume plethysmograph includes the tapering distal forearm parts, which have a relatively higher fraction of poorly perfused bone tissue than the more muscle-containing forearm circumference "seen" by the mercury-in-Silastic variant. For this reason, the latter method should, if anything, give higher maximal flow values per 100 g tissue, and hence lower $R_{\text{min}}$ values, than the volume-displacement plethysmograph—other things being equal.

To make the $R_{\text{min}}$ values for our hypertensive group directly comparable with those of the hypertensive group studied by Schulte et al., the average MAP value of 149 mm Hg in our group should first be reduced by about 35 mm Hg (7 + 7 + 21 mm Hg) because their hypertensive group had a bigger proximal pressure drop (21 mm Hg) than their normotensive group (i.e., to 115 mm Hg). Thus, while the average $R_{\text{min}}$ values for their hypertensive and normotensive groups are 1.6 and 1.4 PRU$^{100}$ respectively, the average values for our hypertensive and normotensive groups are 1.9 and 1.35 PRU$^{100}$ respectively (i.e., a 40% difference, which in this context is a highly significant difference).

In evaluating these data, it should be stressed that the $R_{\text{min}}$ values in their normotensive group ranged between 0.8 and 2.6 PRU$^{100}$ (about threefold) while those in our normotensive group (MAP values recalculated as previously discussed) ranged between 1.1 and 1.7 PRU$^{100}$ (about 1.5-fold). Furthermore, the $R_{\text{min}}$ values in their hypertensive group show a much wider range (about ±40% around the mean) than those in our group (about ±20-25%). Moreover, the MAP values in their hypertensive and normotensive groups overlap considerably (72-124 mm Hg versus 56-84 mm Hg), while there was hardly any overlap of MAP between our hypertensive and normotensive groups (see Figure 3 in Reference 2). Therefore, because of the wide spreads and overlaps in the data of Schulte et al., it would, a priori, be next to impossible to trace a $R_{\text{min}}$ difference (e.g., 30-35%) between hypertensive and normotensive subjects. At most, it could be expected to be 30 to 35%, to judge from the many precise $R_{\text{min}}$ measurements performed on SHR and WRY vascular beds at similar MAP differences. However, a 30-35% $R_{\text{min}}$ increase is very important hemodynamically.

Nevertheless, Schulte et al. interpreted their data to indicate that significant $R_{\text{min}}$ differences probably do not exist between hypertensive and normotensive subjects, and therefore that functional excitatory influences must dominate the increased systemic resistance in established primary hypertension. However, to be sure that two groups of biological data are not different requires very uniform data for very large groups. To derive these conclusions from the available data is, in fact, unwarranted. Furthermore, this conclusion disregards the unavoidable geometrically amplifying effects of the well-documented structural increase in the wall/lumen ratio in the resistance vessels. Quite independent of the hemodynamic effects of a structural $R_{\text{min}}$ increase, this structural wall/lumen increase produces a hemodynamically important vascular hyperactivity, whereby bigger increases in resistance are obtained at given smooth muscle activations. It is remarkable that Schulte et al. do not mention the great number of highly relevant and precise measurements of $R_{\text{min}}$ increases and wall/lumen increases in rats with chronic hypertension, where far better controlled analyses can be performed than is possible in humans.

If earlier $R_{\text{min}}$ studies in humans failed to reveal that $R_{\text{min}}$ values in hypertensive and normotensive
persons really do not differ, as Schulte et al. conclude, then the addition of the calcium channel blocker should induce relatively greater final flow increases in hypertensive than in normotensive subjects. However, this was not the case in the study by Schulte et al., because $R_{\text{min}}$ was reduced to equal extents in both their hypertensive and normotensive groups when nifedipine was added to ischemic exercise: by 23% in the hypertensive group (from 2.1 to 1.6 PRU$_{100}$) and by 22% in the normotensive group (from 1.8 to 1.4 PRU$_{100}$). However, the huge spread of these data had a curious statistical consequence: The "significant" difference between 2.1 and 1.8 PRU$_{100}$ ($p < 0.05$) became "insignificant" when these figures were proportionally reduced to 1.6 and 1.4 PRU$_{100}$, respectively.

This finding led Schulte et al. to conclude that the hypertensive and normotensive $R_{\text{min}}$ values did not differ. However, the only safe conclusion that can be drawn is that the wide scatter and overlaps make it impossible to determine whether a difference of 25 to 30% is really present, at least as the data are presented in the published article. Dr. Distler has given me a diagram in which all the MAP and $R_{\text{min}}$ data of their hypertensive and normotensive groups are plotted together in the format that we used in our 1956 article (see Figure 3 of Reference 2). If this diagram had been included in their article in Hypertension, it would have facilitated direct comparisons with our data. Such a diagram would have allowed the reader to explore whether $R_{\text{min}}$ really is independent of MAP, as Schulte et al. concluded. Despite the huge spread of their data I have calculated from this diagram that the probability that $R_{\text{min}}$ is independent of MAP is less than 0.0023 (i.e., 1 in about 400–500)! In my opinion, their data seem to fully support the findings and conclusions of our original study (as do the many detailed animal experiments performed during the last 15–20 years)—namely, that a hemodynamically important upward structural resetting of $R_{\text{min}}$ occurs in primary hypertension, and, indeed, in any type of chronic hypertension.

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References

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