The heterogeneity of vascular findings in the kidneys of patients with benign essential hypertension

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Abstract As the interlobular arteries of the ageing kidney progressively accumulate intimal fibroplasia, these fibroplastic changes appear to introduce strictures upon the interlobular arteries. These strictures are expected to generate nephron heterogeneity, which is a uniquely disturbed setting peculiarly suited to sustaining both high and low renin forms of hypertension. Fibroplastic renovasculopathy accumulates with age at varying rates in different human populations, and these rates closely parallel the rise of blood pressure with age, as documented by community surveys. Here, I introduce the expression type 1 for hypertension in subjects with mild or minimal renovasculopathy, and type 2 for those with severe vasculopathy. Data reviewed here imply that variations in prevailing blood pressure levels between populations can be attributed entirely, or almost entirely, to type 2 hypertension. No practical test is available to detect nephron heterogeneity clinically. Tests for this purpose have not been and are not now in development. The reason for this deficiency is probably the general lack of suspicion regarding the existence of this pathological entity. Once the entity becomes the target of attention, a variety of tests for measuring its severity in clinical patients should follow readily.

Key words: ageing; arteriolosclerosis; human; nephrosclerosis; vasculopathy

Introduction

Subjects with essential hypertension often reveal at autopsy the kind of kidney seen in Figure 1B. This is usually called ‘granular’ or ‘red granular’ kidney. It is marked by a surface with fine roughening, frequently accompanied by course pits of various numbers and sizes. It is useful to emphasize that this kind of kidney cannot be recognized in the living patient, because standard renal function tests typically give results within normal limits. Normal test results invite false-negative diagnoses, even though autopsy later demonstrates that conspicuous structural abnormalities are in fact present.

Fibroplastic strictures on renocortical arteries

Casts of the arterial tree (Figure 1C and D), constructed by injecting plastic into the renal artery, offer a general sense of the distinctive vasculopathy in the granular kidney. Casts of hypertensive interlobular arteries exhibit strictures, in contrast with the smooth contour and uniform calibre of normal interlobular arteries (Figure 2B contrasted with A). Histological sections reveal the kind of tissue that accounts for the appearance of strictures (Figure 2C). Smooth muscle cells of the arterial wall wither, to be replaced with neointima composed of dense collagen in bulky layers. Although that kind of tissue commonly is called ‘arteriolosclerosis’, this report favours the more precise term ‘renocortical arterial intimal fibroplasia’ which shortens to ‘fibroplastic renovasculopathy’. The latter name preserves the distinction of this condition from hyalinization of arterioles (hyaline renovasculopathy), a wholly different entity often deceptively called by the same name ‘arteriolosclerosis’.

Fibroplastic vasculopathy is sometimes viewed as a consequence of high blood pressure. By analogy with arterial injury effected in malignant hypertension, the mysteriously slow and ‘benign’ fibroplastic deterioration is attributed to high blood pressure, even though ‘malignant’ features are unapparent. Before considering this possibility, it helps first to consider another perspective [1].

Nephron heterogeneity

As the interlobular arteries of the ageing kidney progressively accumulate fibroplasia [2,3], it is easy to envisage that these fibroplastic changes gradually introduce ever worsening strictures upon the interlobular arteries. The effect of this hypothetical process would be to generate nephron heterogeneity. Some (isch-
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Fig. 1. Compared with normal (A) the kidney of hypertension often has the ‘red granular’ pattern, (B). Injection of plastic into the renal artery produces casts of the arterial tree of the normal (C) and red granular (D) specimens.

Fig. 2. (A) is magnified from Figure 1C, and (B) is from 1D. Intimal fibroplasia of renocortical arteries (arrow in C) accounts for strictures seen in plastic casts (arrow in B). The variable of interest is $R = 100 \frac{t}{o.d.}$, where $t$ is the thickness of the neointima at the arrow and o.d. is the outer diameter at this position in the PAS-stained paraffin section (C).

Aemic) nephrons deprived of adequate blood flow would send out renin, thereby increasing blood pressure. Other (hyperaemic) nephrons would suppress their own renin production, but would act to increase blood pressure by retaining salt and water in response to excessive renin from other sources. Seally et al. [4] have elaborated the way in which this uniquely disturbed setting, nephron heterogeneity, is peculiarly suited to sustaining both high and low renin forms of hypertension. Data reviewed elsewhere [5] generally tend to support the conclusion that nephron heterogeneity exists in essential hypertension.

**Renovasculopathy as a correlate of blood pressure**

The pathological variable of central interest, as illustrated in Figure 2C, is the thickness of the fibroplastic neointima in renocortical arteries. The variable $R = 100t/o.d.$ reports the magnitude of the pathological
intimal thickening, \( t \), as a percentage of the outer diameter, o.d. \([6]\). The average of such measurements in arteries of o.d. 80–149 \( \mu \text{m} \) is \( R_e \) and for o.d. 150–300 \( \mu \text{m} \) is \( R_c \). The mean of \( R_e \) and \( R_c \) is \( R_a \).

Figure 3 depicts some findings from a series of autopsies previously reported \([6]\). The hospital records of those subjects included numerous readings of blood pressure taken at outpatient visits. The mean blood pressure (MBP), derived from systolic (S) and diastolic (D) values by \( \text{MBP} = (S + 2D)/3 \), is used to avoid the effects of pulse pressure widening that accompany stiffening of the aorta as it ages. Figure 3 makes use of MBP averaged over the most recent outpatient visits, thus avoiding large transitions from levels of the remote past, as explained elsewhere \([7]\). This series of cases is overweighted purposely with many hypertensive subjects because they are of special interest and because they often have the requisite lengthy records of blood pressure.

Each spot in Figure 3 represents an autopsy, closed circles for men and women of ages 35–54 years, and open circles for ages 55–92 years. Maltese crosses depict the means of the two age groups. The sloping straight line is the regression line fit to all data (separate lines for the two age groups are rejected as statistically not significant). The horizontal line at the level of 110 mmHg for MBP determines the arbitrarily chosen cut-off for defining ‘hypertension’. This could represent S/D of 140/95, 150/90, 160/85 mmHg or other values with variable pulse pressure that might be influenced by aortic stiffness.

Two types of benign essential hypertension

The grey zone labelled ‘type 1’ in Figure 3 represents the region of the chart that contains ‘hypertensive’ subjects with mild or minimal fibroplastic renovascularopathy, \( R_e \). The zone labelled ‘type 2’ represents ‘hypertensive’ subjects with severe degrees of vasculopathy. Spots in the upper range of the ‘type 2’ zone can be viewed as showing both types of hypertension coexisting. Type 1 is a large vertical departure from the regression line. Type 2 is a large diagonal departure along the regression line.

Some of the subjects in Figure 3 fall in the ‘type 1’ grey zone, having hypertension with mild or minimal renovascularopathy. The existence of such subjects has often inspired far reaching conclusions. Heptinstall \([8]\), for instance, reports findings from renal biopsies in hypertensive patients ‘The fact that no less than 30 of the biopsies showed only slight vascular changes is evidence in favour of the hypertension preceding vascular changes in essential hypertension.’ Also reporting similar biopsy results, Sommers et al. \([9]\) note ‘Although two thirds of the cases revealed advanced renal arteriolar sclerosis, the presence of even a few individuals with apparently normal renal vessels is consistent with the view that hypertension precedes structural changes in the kidney vasculature.’ However, these and other authors fail to offer any reason to conclude that subjects in the ‘type 1’ zone will ever move into the ‘type 2’ zone. Those subjects were not followed at a later time for repeat biopsy. Indeed, no case report can be found of a hypertensive patient with minimal vasculopathy who subsequently acquired the vasculopathy. The absence of such case reports raises doubts about the existence of such cases. It seems plausible to suggest that type 1 hypertensives might remain type 1 throughout their course. Direct evidence on this matter will be reviewed later.

Type 2 variation between groups of subjects

In Figure 3, Maltese crosses locate mean values for the two broad age groups. It happens that the older group is shifted somewhat towards the right, but this is not necessarily a measure of the ageing effect, because these groups were selected intentionally to overweight hypertensive cases. The Maltese crosses, however, do serve to show that the means fall close to the regression line. This illustrates a general principle that will be explored later in some detail: in variously designed studies, group means vary along the regression line, whether the groupings reflect age, race, cause of death or geographic region. Group means are expected to fall along the regression line when type 2 hypertension varies between groups.

Increase in blood pressure with age

Autopsies do not provide a random sample of a living population. However, in the study of hypertension, a subset of autopsies can be selected so that the causes of death have no known correlation with hypertension or hypertension-linked cardiovascular diseases. These causes include violence, infectious diseases, cancers and many other conditions.
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Autopsies in these basal categories offer an approximate representation of the living population [10]. Figure 4 (left chart) gives results obtained from autopsies in such basal cases for black and white men of New Orleans, USA [11], Tokyo, Japan (unpublished results), and Bombay, India [12]. Renofibroplasia, \( R_c \), increases with age somewhat more quickly in black men than in white men of New Orleans, but increases in both groups much more quickly than in the men of Bombay. The Japanese men fall generally near the levels of New Orleans men.

Data are available to assess the prevailing levels of blood pressure in the US [11], Japan (unpublished results) and India [12], and the mean BP can be derived from the published values of systolic and diastolic levels. Data obtained in this way are plotted in Figure 4 (right chart). This chart shows striking similarities to the comparable chart of renofibroplasia (left).

**Calculating blood pressure from renovasculopathy**

Measurement of fibroplastic renovasculopathy offers a way of estimating blood pressure in the averages of grouped subjects. The regression line in Figure 3 illustrates how this is done. Each position along the horizontal axis maps to a position on the diagonal, and this in turn maps to a blood pressure level on the vertical axis. The regression line in Figure 3 is adequate for the central regions of the data scatter, but polynomial equations offer better precision for the peripheral parts of the scatter [12]. For further use here, mean blood pressure is estimated as follows: in the kidney obtained at autopsy from each basal case, measurements are taken of \( R_c \) and \( R_r \). These measurements are introduced into the polynomial regression equations [12] and the two resulting estimates of MBP averaged. This operation acts as a change of units. Vasculopathy is expressed in units of mmHg blood pressure.

**Type 2 variation between populations**

Figure 5 is a restatement of the data in Figure 4. Measurements of renofibroplasia in the left chart of Figure 4 and survey data on blood pressure from the right chart are plotted against each other in Figure 5. For this purpose, the units of measure for renofibroplasia are transformed into mmHg. This graph also introduces similar results for women. The dashed line in Figure 5 reproduces the regression line from Figure 3 to allow comparison of this line with data on population averages taken from published sources.

The group averages tend to cluster along the dashed diagonal line in Figure 5. This outcome has an interesting consequence: substantial group differences occur along the diagonal, but only minimal departures from the regression line are seen on the vertical. This pattern implies that type 2 hypertension varies between groups. Vertical departures that could reflect type 1 hypertension produce an erratic pattern that might portray nothing more than method error. Type 1 hypertension varies between individuals within groups, and these individual variations cancel each other, leaving the group averages to fall near the regression line. (A technical detail of Figure 5 perhaps calls for comment. Data points tend to depart consistently upward or downward from the dashed line near its two ends, especially for groups of women. These departures expose flaws in the polynomial equations used for estimating MBP from renovasculopathy. These flaws call for refinement by further studies.)

**Blood pressure increases with age in proportion to renofibroplasia**

Figure 5 offers a dynamic image of how hypertension progresses: starting at ages 20–29 years, data points fall near the lower left end of the dashed line. As the
men and women of New Orleans grow older, their data points move upward and rightward along the dashed line, faster for the blacks than the whites. Subjects in Tokyo follow a similar trail to that of New Orleans whites. The men and women of Bombay progress more slowly; it takes them to ages 50–59 years before they overtake the New Orleans subjects of ages 30–39 years. In all circumstances, the progression with age is predominantly along the regression line, without important vertical departures from it. This outcome implies that type 2 hypertension accounts for the increase of blood pressure with age, and for the variations between populations in the rates of this increase.

**Hyalinized arterioles**

The close relationship of MBP to fibroplastic renovascularopathy, seen in Figure 5, is not reproduced by arteriolar hyalinization. This result is seen in Figure 6, constructed as in Figure 5, substituting measurements of hyaline renovascularopathy for the fibroplastic form. The patternless scatter of data points in Figure 6 arises chiefly from the discordance between Japan and the US. Hyalized arterioles were substantially less frequent in Tokyo than in New Orleans. (Data were unavailable for Bombay, and India is not represented in Figure 6.)

In studies of renal biopsies of patients with essential hypertension, Katafuchi and Takebayashi [13] noted: ‘These data suggest that intimal thickening of the small arteries, and not hyaline change, leads to atrophy of the renal parenchyma … hyaline change causes less severe or no luminal occlusion of the arterioles.’ This agrees with our own unpublished observations. Other authors have also noted the discordance of MBP with arteriolar hyalinization [2,8].

**Does high blood pressure accelerate the progression of renovascularopathy?**

It has long been presumed, both implicitly and explicitly, that high blood pressure always exerts a harmful influence upon the microvasculature, just as it is known to do upon the grossly visible arteries. This clearly occurs in malignant hypertension [1,14], but is an unresolved issue for benign hypertension [15,16].

A randomized prospective study would offer a clear test of this hypothesis. Such a study would assemble a series of cases with type 1 hypertension, such as those within the type 1 grey zone of Figure 3. These would then be assessed by repeat biopsy at a later date to evaluate their acceleration of vasculopathy after a period of exposure to high blood pressure. No such study has yet been reported, and is unlikely to be undertaken for practical reasons. Figure 7 offers an approximation to that kind of study.

The autopsy cases reported in Figure 3 included data documenting 36 cases during periods of transition from low levels of blood pressure into hypertensive levels (MBP > 110 mmHg). Figure 7 plots the duration of the acquired hypertension on the horizontal axis against the fibroplastic renovascularopathy on the vertical, as determined from autopsy at the end of each clinical course. Nine type 1 hypertensives are represented. Those nine cases revealed mild or minimal vasculopathy after varying periods of hypertension, and are the ones falling below the horizontal dashed line in the graph.

The duration of the hypertension had no discernible effect on the severity of fibroplastic renovascularopathy in Figure 7. These provisional results support the view that type 1 hypertensives will probably remain type 1 indefinitely, because they are not on a track toward acquiring renovascularopathy or nephrosclerosis.

Studies of this kind are less than ideal, because they fail to document the condition of the renal microvasculature at the beginning of the hypertensive course. Nevertheless, such studies are practical. Replication of

![Fig. 6. As in Figure 5, with data on hyalized arterioles substituted for fibroplastic renovascularopathy.](image)

![Fig. 7. Fibroplastic renovascularopathy averaged over arteries of sizes 80–300 μm diameter is plotted against duration of recent blood pressure levels in 36 subjects with documented onset of hypertension. The dashed horizontal line arbitrarily separates the type 1 hypertensives with mild to minimal $R_F$ from the type 2 with moderate to severe $R_F$. Zero on the horizontal axis represents the date of onset of hypertension.](image)
data like those of Figure 7 is readily done, and could offer valuable insights into the possible evolution of type 1 into type 2 hypertension.

**Renal deterioration in hypertensives**

Whether high blood pressure promotes vasculopathy is not the same question as whether high blood pressure promotes renal deterioration and progression toward end-stage renal disease. Friedman *et al.* [17], for instance, identify four ways that high blood pressure could promote renal deterioration without affecting the fibroplastic vasculopathy. These mechanisms include (i) the direct effects of hypertension on the pre-glomerular microvasculature and/or increased glomerular capillary hydraulic pressure; (ii) unsuspected primary diseases affecting glomeruli, renal interstitium or renal arteries; (iii) undetected episodes of accelerated hypertension; and (iv) primary renal microvascular disease with resultant renal insufficiency and hypertension. Mechanism iv in this list refers to scleroderma, panarteritis and similar specific entities. That kidney function deteriorates progressively in many hypertensives [18] does not necessarily mean that the deterioration derives from progression of the vasculopathies under discussion here.

**Conclusions**

Observations reviewed here offer reasons to suspect that nephron heterogeneity exists in the kidneys of most subjects with essential hypertension, and that this heterogeneity could be the source of high blood pressure in subjects with type 2 hypertension. No practical test is available to detect nephron heterogeneity clinically. Tests for this purpose have not been and are not now in development. The reason for this deficiency is probably the general lack of suspicion for the existence of this pathological entity. Once the entity becomes the target of attention, it should not be difficult to devise a variety of tests for measuring its severity in clinical patients.

**References**