Kidney International, Vol. 45 (1994), pp. 384–389

# Relevance of single nephron studies to human glomerular function

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Over the past decades, the search for clues to the understanding of renal function and disease has led to the ongoing development of innovative laboratory techniques to approach these questions on the single nephron level. Development of renal micropuncture techniques has allowed assessment of the single nephron glomerular filtration (SNGFR) and its determinants, as well as of tubular transport characteristics. The history and techniques of micropuncture study have recently been reviewed [1]. This brief review will focus on three specific aspects of how single nephron studies have been used to provide insights into human glomerular function: explication of hemodynamic patterns of disease; definition of effects of hormonal mediators of glomerular function, allowing correlation with hemodynamic disease patterns; and identification of mechanisms contributing to efficacy of therapeutic interventions.

## Hemodynamic patterns in renal disease

In clinical practice, nephrologists are relatively limited in ability to define hemodynamic patterns of disease. Clinical examination of renal function usually consists of measurement of glomerular filtration rate (GFR) by the less than perfectly accurate creatinine clearance method [2]. Clinical investigations can utilize better techniques: more accurate measurement of GFR using inulin or radioisotopic methods; measurement of renal plasma flow using para-aminohippurate or isotopic methods (though usually not corrected for renal extraction); and more sophisticated methods involving dextran modelling [2, 3].

Determination of whole kidney GFR can only reveal whether total filtration function is increased, normal, or decreased; this measurement sheds little light on hemodynamic patterns at the microcirculatory level. Development of a number of different animal models of renal disease, chosen to mimic a variety of human clinical diseases, has allowed elucidation of single nephron hemodynamics using micropuncture techniques in laboratory animals (usually the rat). These studies generally involve measurement of GFR at the whole kidney and single nephron level. The major determinants of SNGFR [the glomerular capillary plasma flow rate, $Q_A$; the glomerular capillary hydraulic pressure ($P_{GC}$) and the transcapillary hydraulic pressure gradient ($\Delta P$); plasma colloid oncotic pressure; and the ultrafiltration coefficient ($K_f$)] are determined. These measurements, together with measurements of mean arterial pressure and postglomerular capillary pressure, allow calculation of the glomerular afferent ($R_A$) and efferent ($R_E$) arteriolar resistances [4].

Such studies in diverse disease models have established that within the three categories of whole kidney GFR (high, normal, or low), substantial variations in the hemodynamic determinants of SNGFR may be found. Representative examples of some prominent patterns of disease are depicted in Table 1 [5–14], and are briefly described here. Elevation of whole kidney GFR ("hyperfiltration") may result from substantial increases in both capillary perfusion and the glomerular capillary hydraulic pressure—a hemodynamic pattern which is associated with progressive injury in a number of disease states. However, hyperfiltration may also result from increased renal perfusion without glomerular capillary hypertension; this benign condition characterizes normal pregnancy [9] and is not usually associated with progressive renal disease. Findings of a normal GFR may reflect normal renal function, or compensatory adaptations leading to hyperfunction in a decreased number of nephrons. In some cases, as in progressive renal disease occurring long after acute renal failure [9], the GFR may be normal, and yet intrarenal adaptations (increased $P_{GC}$ and decreased $K_f$) are found. When GFR is reduced, the cause may be a primary reduction in the ultrafiltration coefficient (due to limitation of hydraulic permeability and/or the surface area available for filtration), as is the case in many forms of experimental glomerulonephritis [9, 13]. Alternatively, a low GFR may represent inability of a reduced number of hyperfiltering functioning nephrons to maintain GFR (despite various intrarenal adaptations), or a primary decrease in renal perfusion, as occurs in severe renal artery stenosis [14].

## Major patterns in experimental renal disease

Though many different hemodynamic patterns may be found, micropuncture studies have revealed that two major maladaptations are particularly prominent, and are most frequently found in studies of experimental renal disease.

### *Afferent arteriolar vasodilation*

A number of experimental models have in common a primary defect in the afferent arteriole, such that afferent arteriolar resistance is solely reduced, or reduced disproportionately to a smaller decrement in efferent arteriolar resistance. As the ability of the afferent arteriole to dilate or constrict is a critical component of the kidney's defense against changes in renal

**Table 1.** Renal and glomerular hemodynamic patterns

| Clinical | Micropuncture | Disease model/selected references |
|---|---|---|
| ↑ GFR | ↑ $Q_A$ and ↑ $P_{GC}$ | Diabetes [5–7] |
| | ↑ $Q_A$ and ↔ $P_{GC}$ | Pregnancy [8] |
| ↔ GFR | ↑ $P_{GC}$ and ↓ $K_f$ | Post-acute renal failure [9] and normal aging [10] |
| | ↔ $P_{GC}$ and ↔ $K_f$ | Spontaneously hypertensive rat [11, 12] |
| ↓ GFR | ↔ $P_{GC}$ and ↓ $K_f$ | Acute glomerulonephritis [9, 13] |
| | ↓ $Q_A$ and ↓ $P_{GC}$ | Renal artery stenosis [14] |

Abbreviations are: GFR, glomerular filtration rate; $Q_A$, glomerular capillary plasma flow rate; $P_{GC}$, glomerular capillary hydraulic pressure; $K_f$, glomerular capillary ultrafiltration coefficient; ↑ increased, ↓ decreased, ↔ unchanged as compared to normal.

perfusion pressure, this persistent afferent arteriolar vasodilation leads to defective autoregulation. Failure of the afferent arteriole to constrict in the setting of elevated blood pressure can lead to enhanced transmission of systemic pressures into the glomerular capillary network, and glomerular capillary hypertension. Indeed, persistent afferent vasodilation can sometimes lead to glomerular hypertension despite a systemic blood pressure which is normal.

Afferent arteriolar vasodilation is found in a number of experimental models, representing important clinical diseases. A few examples of these include diabetes [5–7], reduced renal mass [15], certain spontaneous models including the Dahl salt-sensitive rat [16], and normal aging [10]. The importance of afferent arteriolar vasodilation in protecting the glomerulus against local glomerular capillary hypertension has been elegantly demonstrated in many studies. For example, Hostetter et al [15] evaluated single nephron function in rats subjected to severe reduction in renal mass. In this model, both afferent and efferent arteriolar resistances are reduced, as compared to values in sham-operated animals (Fig. 1). Since the reduction in afferent resistance exceeds that in $R_E$, the glomerular capillary hydraulic pressure rises. When afferent arteriolar tone is returned to normal (in this case, by dietary protein restriction) glomerular capillary pressure is also normalized [15].

A similar pathogenetic role for afferent vasodilation, and its long-term consequences, was demonstrated by Dworkin and Feiner [11] in a study of the Spontaneously Hypertensive Rat (SHR). This model is characterized by very high systemic blood pressures; however, afferent arteriolar vasoconstriction prevents transmission of systemic pressures into the glomerular capillary network, $P_{GC}$ remains normal, and development of proteinuria (Fig. 2) and glomerular sclerosis is modest. Removal of one kidney in the SHR results in lowering of $R_A$ in the remaining kidney, allowing transmission of systemic hypertension and elevation of $P_{GC}$. This hemodynamic alteration is associated with a sharp increase in proteinuria (Fig. 2), and acceleration of glomerular sclerosis. When the uninephrectomized SHR is fed a low protein diet, the protective afferent arteriolar vasoconstriction is restored, $P_{GC}$ is maintained at normal levels, and proteinuria and glomerular structural injury are prevented [11].

It seems likely that afferent arteriolar vasodilation is present in some of the most prominent clinical renal diseases, including

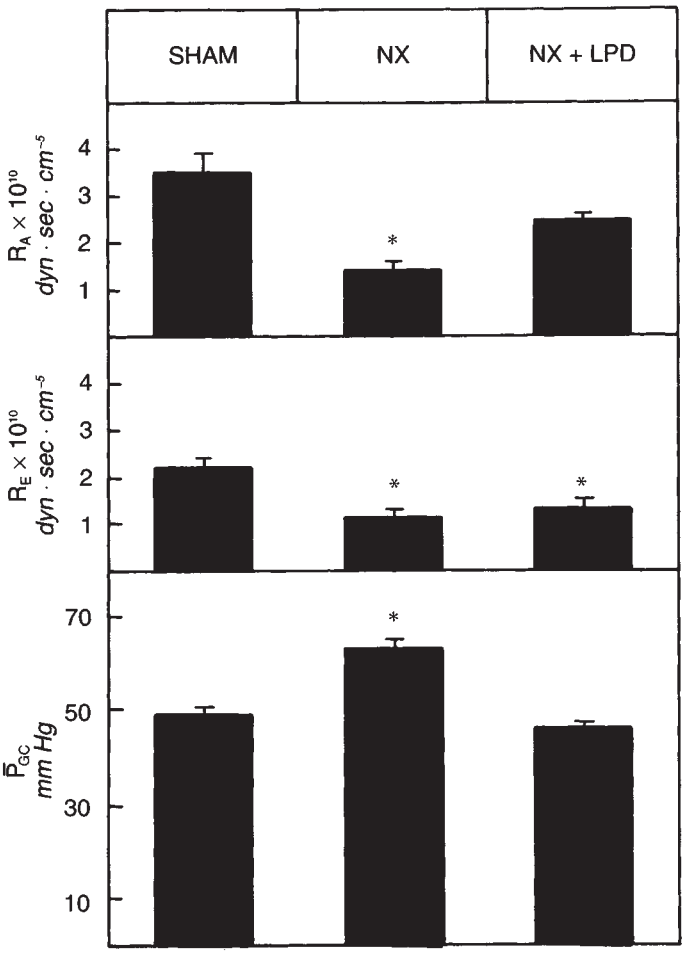


**Fig. 1.** *Effects of subtotal nephrectomy (NX) and low protein diet (LPD) on afferent ($R_A$) and efferent ($R_E$) arteriolar resistances, and glomerular capillary pressure ($P_{GC}$).* In untreated rats, afferent arteriolar vasodilation leads to glomerular capillary hypertension; both are reversed with dietary protein restriction. * $P < 0.05$ vs. Sham. Adapted from data in Ref. 15 with permission.

diabetes, late progressive renal disease after various acute insults, perhaps during normal aging, and in patients with a solitary kidney due to uninephrectomy or renal transplantation.

### *Reduction in the ultrafiltration coefficient*

A completely different set of diseases are characterized by a primary reduction in $K_f$, the ultrafiltration coefficient. In this case, the result is a fall in GFR, with or without changes in plasma flow and the glomerular capillary pressure. The importance of this primary reduction in $K_f$ is demonstrated in Figure 3, where the single nephron GFR and its determinants in an acute model (puromycin nephrosis) are depicted [9]. This model features massive proteinuria, fluid overload, hypoalbuminemia, and other characteristics of the nephrotic syndrome. As is shown in Figure 3, glomerular capillary pressures and flows remain fairly normal. In contrast, however, $K_f$ is markedly reduced, and in consequence, both the single nephron and whole kidney GFR values are significantly impaired [9]. A similar reduction in $K_f$ has been noted in a number of models of glomerulonephritis [13, 17]. Though not amenable to clinical

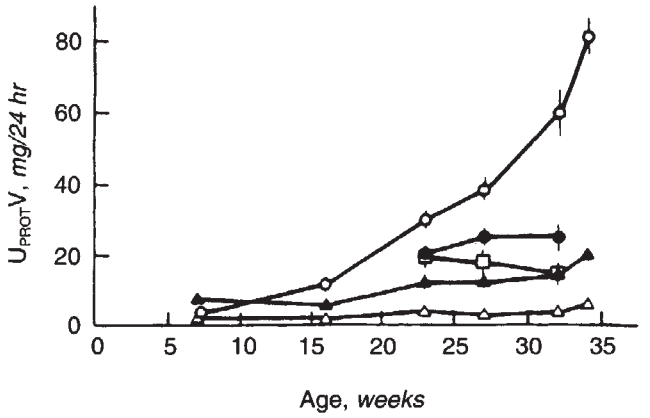


**Fig. 2.** *Effects of systemic hypertension, uninephrectomy (UNX), and low protein (LP) diet on urinary protein excretion ($U_{PROT}V$) in the Spontaneously Hypertensive Rat (SHR) and the Wistar Kyoto rat (WKY).* Symbols are: (□) WKY; (●) SHR; (▲) WKY/UNX; (○) SHR/UNX; (△) SHR/UNX/LP. Intact SHR rats show $U_{PROT}V$ values only slightly higher than those in the intact WKY. UNX dramatically increases $U_{PROT}V$ in the SHR, while feeding a low protein diet abolishes the detrimental effect of UNX. Adapted from Ref. 11 with permission.

measurement, indirect studies using dextran modelling suggest that a decrease in $K_f$ contributes importantly to glomerular dysfunction in patients with lupus nephritis [3], and probably other glomerulonephritides as well.

### Effects of hormonal mediators on glomerular function and disease

A second major use of single nephron studies is to allow definition of the glomerular hemodynamic effects of various vasoactive hormones and other mediators in the normal kidney, and delineation of their roles in the pathogenesis of glomerular disease. Dozens of hormone receptors have been identified in glomeruli [4], and *in vivo* studies have confirmed the ability of most of these to significantly influence SNGFR and its determinants. Though by no means comprehensive, a list of some of the recognized mediators is found in Table 2 [4, 18].

Detailed discussion of the literature concerning effects of these mediators is beyond the scope of this review, but consideration of two examples [the venerable hormone, angiotensin II (Ang II), and the relatively newly described hormone, endothelin] is illustrative of the approaches used to identify the actions of a vasoactive mediator, and its contribution to glomerular hemodynamics in disease states. The hemodynamic actions of angiotensin II (elevation of systemic pressure, predominant constriction of the efferent arteriole and consequent elevation of $P_{GC}$, and reduction in the ultrafiltration coefficient, $K_f$) were identified in the 1970's with development of micropuncture methodology [19]. Later in that decade and in the early 1980's, the advent of the relatively nonspecific Ang II receptor antagonist saralasin, and then angiotensin converting enzyme (ACE) inhibitors, allowed investigations into the role of this hormone in mediation of glomerular disease. Studies showing reversal of vasoconstriction in certain states (such as congestive heart failure [20]), were followed by studies showing reduction of blood pressure and efferent resistance, and elevation in $K_f$, even in conditions not characterized by stimulation of the renin-angiotensin system [7, 21]. More recently, specific $AT_1$ angiotensin receptor antagonists have been used, and thus far appear to reproduce many (though not all) of the characteristic effects of ACE inhibition [22, 23]. Finally, though not yet widely available, use of specific renin inhibitors and monoclonal antibodies to Ang II are likely to provide further insight into specific Ang II-mediated effects in the setting of glomerular disease.

Fairly quickly after its initial description in 1988 [24], endothelin was noted to have profound effects on systemic and intrarenal hemodynamics, including dose-related increases in systemic blood pressure and renal vascular resistance, and decreases in renal perfusion and filtration rates [25, 26]. Micropuncture studies in normal rats revealed that at a modestly pressor dose, endothelin infusion produced constriction in the glomerular arterioles, efferent > afferent, as well as a reduction in $K_f$ and increase in $P_{GC}$ [25]. Later, the development of anti-endothelin antibodies and eventually, specific endothelin receptor antagonists, has begun to allow elucidation of the role of this potent vasoconstrictor in the setting of renal disease [27, 28].

Many other hormones have been implicated in control of glomerular function (Table 2), though some of these are not yet well studied in the setting of glomerular disease. Relatively newly available antagonists of the kallikrein-kinin system [29, 30], endothelial-derived relaxing factor [31–33], and leukotrienes [34], just to name a few, are stimulating extensive investigation into mechanisms of disease.

Ongoing investigations into the hemodynamic (and other) effects of hormonal mediators, and their roles in renal disease are to be anticipated. Newly discovered hormones will be studied, and development of more specific and potent blocking agents (monoclonal antibodies, enzyme inhibitors, competitive antagonists, specific receptor antagonists) for each of these will allow more specific implication of their individual roles.

### Identification of therapeutic mechanisms

A third major use of single nephron studies has been to identify mechanisms contributing to the therapeutic efficacy of various interventions. Many of the dietary and pharmacologic therapies which are in use, both clinically and experimentally, exert glomerular microcirculatory effects which may, at least in part, explain their beneficial effect. (It should be noted, of course, that successful therapies are most likely multidimensional in their mechanisms; indeed, for some of the most successful, numerous mechanisms of protection have been postulated). Again, this review will not be comprehensive, but will highlight some of the more prominent hemodynamic effects of commonly used clinical strategies.

Dietary protein restriction has been advocated for decades as a method to control uremic symptoms and more recently, as a strategy to slow the progression of renal disease [35]. The older observations that limiting protein intake reduces both renal blood flow and GFR have been expanded more recently using micropuncture techniques. The hemodynamic consequences of dietary protein restriction in progressive renal disease were described by Hostetter et al [15] in the remnant kidney rat model (Fig. 1). As described above, the primary hemodynamic maladaptation in this model is afferent arteriolar vasodilation.

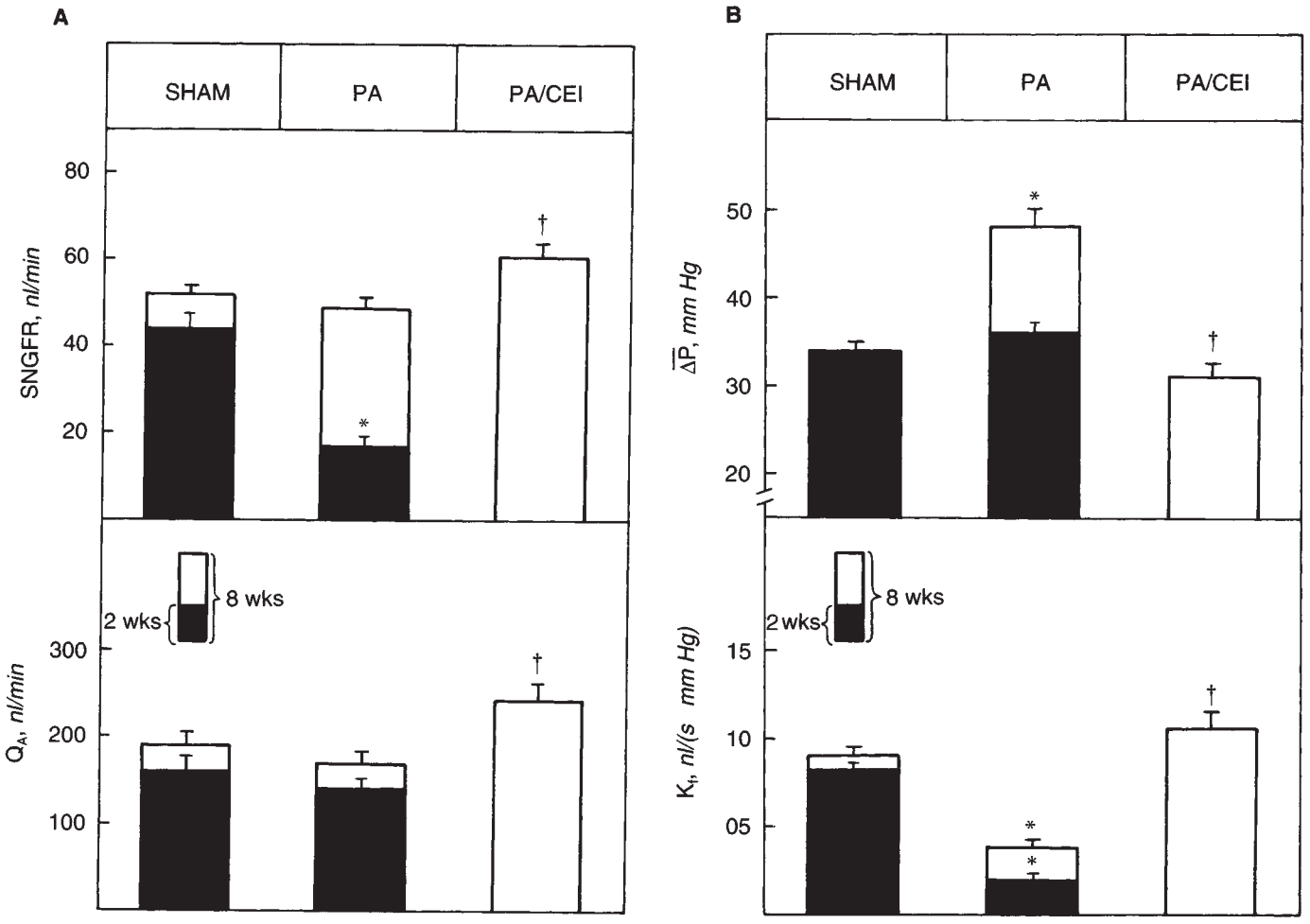


**Fig. 3.** *Glomerular hemodynamic parameters in Sham rats and in nephrotic rats injected with puromycin aminonucleoside (PA).* During the acute nephrotic phase (2 wks, ■), values for the single nephron glomerular filtration rate (SNGFR) were markedly reduced in PA rats, as compared to sham rats. There were no changes in the glomerular capillary plasma flow rate ($Q_A$) or glomerular transcapillary hydraulic pressure gradient ($\Delta P$). The low SNGFR resulted from a significant decrement in the glomerular capillary ultrafiltration coefficient, $K_f$. During the recovery phase (8 weeks, □), SNGFR was normalized, at the expense of glomerular hypertension; these changes were prevented with converting enzyme inhibitor (CEI) therapy. * $P < 0.05$ vs. Sham; † $P < 0.05$ vs. PA. Adapted from data in Ref. 9 with permission.

**Table 2.** Potential mediators in renal disease

| | |
|---|---|
| Angiotensin II | IGF-1 |
| Prostaglandins/thromboxanes | Catecholamines |
| Kinins | Atrial natriuretic peptide |
| Endothelin | Glucagon |
| Endothelial-derived relaxing factor | Leukotrienes |
| Epidermal growth factor | Adenosine |
| Histamine | Insulin |
| Platelet-derived growth factor | Parathyroid hormone |
| Serotonin | Vasopressin |
| Dopamine | Platelet activating factor |

Institution of a low protein diet restores $R_A$ to the normal range (Fig. 1), thereby controlling glomerular capillary hypertension. Subsequent studies have confirmed this beneficial effect on afferent arteriolar tone in other models, including experimental diabetes [6] and hypertension [11].

Antihypertensive therapy has received serious attention in recent years. A number of studies have confirmed that the various antihypertensive drugs available to the clinician exert very dissimilar effects on intraglomerular hemodynamics. While many drugs are as yet unstudied, certain drugs have been sufficiently studied to draw some conclusions as to their effects. Most intensively studied have been the ACE inhibitors, which almost universally lower blood pressure, efferent resistance, and $P_{GC}$ in models with glomerular hypertension, and increase the glomerular capillary coefficient. Accordingly, a beneficial hemodynamic effect (that is, control of glomerular capillary hypertension), is obtained by both dietary protein restriction and ACE inhibition, albeit by different mechanisms. The effects of these two interventions on arteriolar resistance in experimental diabetes are illustrated in Figure 4, representing data from two studies by Zatz and coworkers [6, 7]. Dietary protein restriction acts to limit $P_{GC}$ by increasing $R_A$, whereas ACE inhibition accomplishes the same goal by lowering $R_E$ (Fig. 4) [6, 7]. While the potential additive benefit of these two interventions has been little studied, preliminary evidence showing an additive antiproteinuric effect of protein restriction and ACE

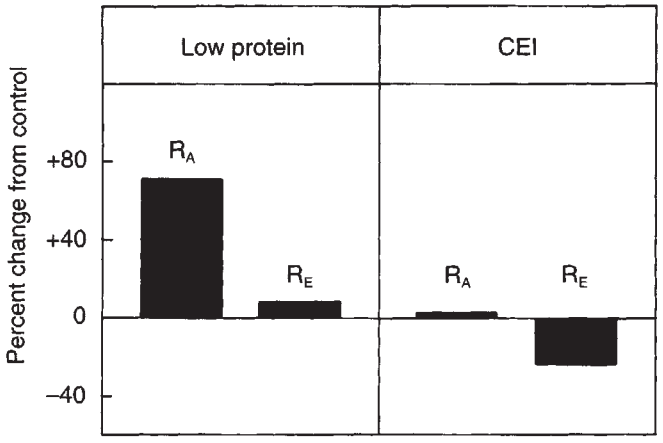


**Fig. 4.** *Effects of a low protein diet or converting enzyme inhibition (CEI) on afferent ($R_A$) and efferent ($R_E$) arteriolar resistances in diabetic rats.* Protein restriction induced afferent arteriolar vasoconstriction, whereas CEI resulted in predominant efferent arteriolar vasodilation. Both responses lowered glomerular capillary pressure. Adapted from data in Refs. 6 and 7 with permission.

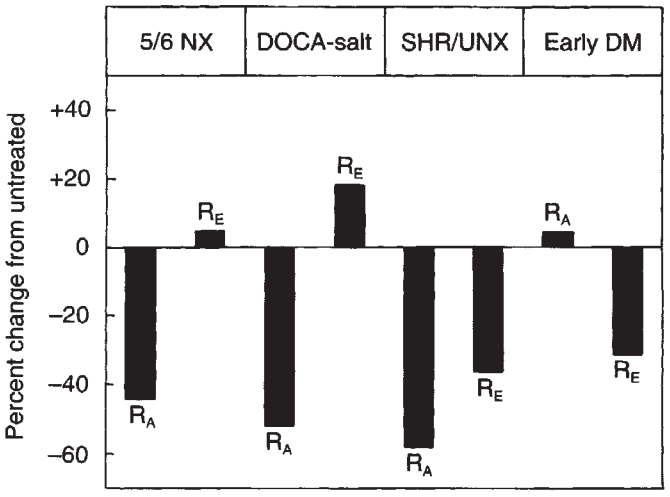


**Fig. 5.** *Effects of combination reserpine, hydralazine and diuretic therapy on afferent ($R_A$) and efferent ($R_E$) arteriolar resistances in four models of experimental renal disease: 5/6 nephrectomy (NX); desoxycorticosterone (DOCA)-salt hypertension; the Spontaneously Hypertensive Rat with uninephrectomy (SHR/UNX); and early diabetes mellitus (DM).* This regimen lowers $R_E$, and thereby $P_{GC}$, in some models, but not in others. Adapted from data in Refs. 21, 38, 39 and 40 with permission.

inhibition in patients with renal disease [36] indirectly supports such a mechanism as a contributor to clinical disease. Similarly, the clinical observation of an additive antiproteinuric effect of nonsteroidal anti-inflammatory drugs (which increase $R_A$ in experimental animals) and ACE inhibition [37] may suggest a similar effect with this combination regimen.

While the results of most (though not all) studies with ACE inhibitors indicate efferent arteriolar relaxation and lowering of $P_{GC}$, less consistency is found in the available studies of other antihypertensive regimens. An older antihypertensive regimen which has been frequently used to control experimental hypertension consists of reserpine, hydralazine, and hydrochlorothiazide. However, while this regimen routinely affords excellent control of systemic hypertension, its effects on arteriolar resistances appear to vary among different experimental models [21, 22, 38–40], for reasons which remain to be elucidated. Some examples of such studies are depicted in Figure 5. The afferent arteriolar response to the reduction in renal perfusion pressure usually consists of a fall in $R_A$. In some models, including uninephrectomized SHR rats [38] and very early (but not late) diabetic rats [39], this regimen also lowers $R_E$ and, thereby $P_{GC}$, whereas in other models, including remnant kidney [21, 22] and mineralocorticoid-salt hypertensive [40] rats, there is no such reduction in either $R_E$ or $P_{GC}$, and consequently no amelioration of progressive renal injury.

Effects of other antihypertensive drugs are much less well studied. Conflicting results have been found in the sparse reports using calcium antagonists [41, 42]. While these agents frequently reduce $R_A$ (either directly, or in response to a reduction in blood pressure), effects on $R_E$ and $P_{GC}$ are variable. These variable hemodynamic effects may explain, at least in part, the similarly variable effect of these agents on clinical proteinuria [41], as reducing proteinuria is consistent with (though by no means diagnostic of) a reduction in glomerular capillary pressure.

## Summary and conclusions

The preceding article has illustrated a few of the many studies utilizing single nephron micropuncture techniques to identify intrarenal hemodynamic disease patterns, to identify the actions of various vasoactive mediators and thereby allow correlation with disease processes, and to explain the mechanisms underlying interventions which benefit the kidney. Many other uses of these techniques have provided insight into clinical disease pathophysiology, including: studies examining the importance of changes in tubuloglomerular feedback; the role of changes in tubular reabsorption; and studies correlating function with morphologic changes and with *in vitro* studies. While this review has concentrated on *in vivo* glomerular micropuncture techniques, a number of other innovative techniques are being used to approach these questions, including studies in isolated perfused tubules, afferent and efferent arterioles, and glomeruli. Accordingly, these studies will continue to provide the hemodynamic context in which other pathophysiologic processes and therapeutic mechanisms are revealed.

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