Letter to the Editor

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Response to Renal Function in Primary Aldosteronism: Is Glomerular Hyperfiltration a Hallmark of Primary Aldosteronism? Further Results from the Primary Aldosteronism Prevalence in Hypertension (PAPY) Study

Sechi[1] was challenged by our reporting of no increased glomerular filtration rate (GFR) in primary aldosteronism (PA) patients, as compared with patients with primary hypertension (PH),[2] which deviates from findings of smaller studies[3,4] and raised issues on the mechanisms of renal involvement of PA patients.

A major strength of the Primary Aldosteronism Prevalence in Hypertension (PAPY) Study[5] entails the collection of a large series of PA patients with a conclusive diagnosis of aldosterone-producing adenoma (APA). This was only possible in a multicenter study, where state-of-the art diagnostic criteria and close follow-up after adrenalectomy were prospectively applied at specialized hypertension centers. By contrast, "idiopathic hyperaldosteronism" cannot be reliably distinguished from low-renin PH unless adrenal vein sampling or adrenocortical mineralocorticoid scintigraphy excluded lateralization of aldosterone secretion. Without the systematic use of these strict criteria, which were exploited in the PAPY study,[5] data on idiopathic hyperaldosteronism[4] should be regarded with caution. Hence, we will herein confine our comments to APA patients.

First of all, the limitations and intrinsic inaccuracy of the endogenous creatinine clearance for estimating GFR[3] are well known (reviewed in Reference 6). Nonetheless, these contrasting GFR findings are intriguing. Based on the reported data, it can be calculated (nQuery version 6.0, Statistical Solutions) that, with a 2-group *t* test at a 0.05 two-sided significance level, the studies that documented a hyperfiltration in APA, with sample sizes in the PH and APA groups of 25 and 25[3] and of 100 and 27[4] had only 36% and 66% power, respectively, to detect a difference in means of 12 mL/min/1.73 m^2 between groups, assuming the reported SD. By a similar calculation, our study of 426 PH and 31 APA patients[2] had a power of 80%. Moreover, with the full data set composed of 1125 patients with a final diagnosis (1071 PH and 54 APA patients) and available GFR data, the statistical power of the PAPY study was 96%. Yet, no higher GFR in the APA group could be found, even when patients were stratified by tertile of sodium intake (Table), as suggested.[7] Thus, with a high power, our data do not demonstrate that hyperfiltration is a hallmark of the only subtype (APA) of PA that can be unequivocally identified. This does not contradict the notion that when aldosterone is acutely infused into a normal healthy kidney, an increase of GFR can be seen.

Hall et al,[8] using an electronic servocontroller, elegantly documented a rise of both blood pressure and GFR with aldosterone infusion in dogs; however, holding renal artery pressure blunted the rise in GFR, suggesting that the increase in renal arterial pressure was: (1) involved in the increase of GFR and (2) essential in allowing the kidneys to escape from the chronic sodium-retaining action of aldosterone. Whether under chronic hypertension hyperfiltration occurs simply because of chronic aldosterone excess per se independent of blood pressure elevation is much less certain.

Overwhelming experimental data in models of hyperaldosteronism have documented histopathological changes in the kidney, entailing vascular remodeling, inflammation, necrosis, glomerulosclerosis, and fibrosis, which could be prevented by selective mineralocorticoid receptor blockade with eplerenone.[9,10] Thus, concurrent hypertension- and/or hyperaldosteronism-induced nephroangiosclerosis lead to a progressive loss of glomeruli and could well be accompanied by hyperfiltration in the surviving ones, which can conceivably explain the lack of overall GFR changes (hyperfiltration) and actually the lower GFR of our APA compared with PH patients.[2] To our knowledge, heretofore no study has estimated nephron heterogeneity, which cannot be picked up with measurement creatinine clearance,[4] which estimates the overall GFR.

By definition, single-center studies involve selected PA patients. Moreover, a cross-sectional study design with individual matching of PA with PH patients for demography and duration of hypertension,[4] as we described in the past,[11] is exposed to several potential biases, as discussed.[12] By contrast, multicenter studies composed of a large collection of patients with an unequivocal

GFR in the Patients With PH (n=1071) and APA (n=54) of the PAPY Study

	Tertile of Na Intake					
	First (Na intake <116 mEq per Day)		Second (Na Intake 116 to 177 mEq per Day)		Third (Na Intake >177 mEq per Day)	
Variable	PH	APA	PH	APA	PH	APA
GFR (mL×min^{-1}×1.73 m^{-2})	87±22	84±18	87±22	82±15	89±20	89±19
Adjusted* GFR (mL×min^{-1}×1.73 m^{-2})	87±7	85±9	87±7	85±7	87±7	82±8

Mean±SD. No statistically significant differences between groups or across tertiles were found.
*Adjusted for BMI, age, urinary Na^+ excretion, serum K^+, and mean blood pressure as described.[1]

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diagnosis of APA, their comparison with a large series of prospectively recruited PH patients, and proper covariate adjustments, as done in the PAPY study,[2] minimize the chances for these biases. The gathering of long-term follow-up data[4] might also mitigate these problems, provided that an adequate number of patients is examined. However, the fact that only one third of the patients initially evaluated with GFR measurement in a study completed the follow-up[4] is certainly not reassuring in terms of providing unbiased serial comparisons of GFR over time. The demonstration of regression of microalbuminuria after adrenalectomy[3,4] furnishes compelling evidence for a casual relationship between hyperaldosteronism and hypertension on one side and renal damage on the other. However, the same link might not apply to data obtained with mineralocorticoid receptor antagonists, of which the specificity, at least for spironolactone,[4] is under question. Lack of selectivity and multiple mechanisms of actions can confound the interpretation of results, and only the long-awaited availability of the more selective mineralocorticoid eplerenone might shed novel light in this area in the future.

Based on the finding of partially reversible albuminuria after 6 months of treatment of PA, Sechi et al[4] contended that a "dynamic," rather than structural, renal defect describes the renal dysfunction of PA, of which the elevated microalbuminuria that we documented is a marker. However, not only the functional but also the structural renal changes can be reversed, as documented by an overwhelming amount of experimental and clinical data,[9–11] on removal of the initiating pathogenic mechanisms, for example, hyperaldosteronism.

Thus, we do agree that longitudinal data from a large data set of patients with APA, as those that will come from the ongoing follow-up branch of the PAPY Study, are needed. However, it would be premature at present to attribute only to mineralocorticoid receptor blockade (with ensuing) lowering of GFR the correction of microalbuminuria, as suggested.[4] In truth, available evidences do challenge the "time-honored" notion that PA is "benign" not only on the heart and vessels, as we and others demonstrated,[13] but also in the kidney.

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Disclosures

None.

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