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Plasma metanephrines in renal failure

GRAEME EISENHOFER, FRANS HUYSMANS, KAREL PACAK, MACCLELLAN M. WALTHER, FRED C.G.J. SWEEP, and JACQUES W.M. LENDERS

Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke; Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development; Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and the Departments of Nephrology, Chemical Endocrinology, and General Internal Medicine, St. Radboud University Medical Center, Nijmegen, The Netherlands

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Background. Diagnosis of pheochromocytoma in renal failure poses a diagnostic dilemma due to lack of reliability of conventional urinary measurements of catecholamine excess. Measurements of the plasma metanephrines, normetanephrine and metanephrine (the O-methylated metabolites of norepinephrine and epinephrine), provide an alternative diagnostic test. The metanephrines may be measured as free metabolites or after a deconjugation step where measurements reflect mainly sulfate-conjugated metabolites. The influence of renal insufficiency states on these various measurements is unclear.

Methods. Plasma free and deconjugated metanephrines and catecholamines in 17 patients on dialysis with end-stage renal disease and 19 patients with renal insufficiency (creatinine clearance, 5–78 mL/min) were compared with levels in 89 hypertensives, 68 healthy normotensives, and 51 patients with von Hippel-Lindau syndrome.

Results. Patients with renal failure had up to two-fold higher plasma concentrations of catecholamines and free metanephrines, and more than 12-fold higher plasma concentrations of deconjugated metanephrines than comparison groups. Plasma free metanephrines and catecholamines were, respectively, within the 95% confidence intervals of reference groups in 75% and 42% of the dialysis patients, and in 74% and 68% of patients with renal insufficiency. In contrast, no dialysis patient and only half the renal insufficiency patients had plasma levels of deconjugated metanephrines within the reference intervals. Plasma levels of deconjugated metanephrines, but not free metanephrines, showed strong inverse relationships with creatinine clearance.

Conclusion. Plasma concentrations of free metanephrines are relatively independent of renal function and are, therefore, more suitable for diagnosis of pheochromocytoma among patients with renal failure than measurements of deconjugated metanephrines.

Key words: normetanephrine, metanephrine, norepinephrine, epinephrine, renal failure, dialysis, pheochromocytoma.

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The metanephrines, normetanephrine and metanephrine, are produced by O-methylation of the catecholamines, norepinephrine and epinephrine [1] (Fig. 1). Further metabolism occurs by deamination or sulfate conjugation. Adrenal medullary chromaffin cells represent the largest single tissue source of circulating metanephrines, accounting for more than 91% of metanephrine and 26% to 40% of normetanephrine [2, 3]. Production of these metabolites within chromaffin cells is continuous and independent of variations in catecholamine release [4], explaining why measurements of these metabolites provide more superior markers for diagnosis of pheochromocytoma than the parent catecholamines [5–8].

Metanephrines in plasma can be measured as the free metabolites or after a deconjugation step that converts the sulfate conjugates to the free metabolites. Although only fractions of the free metanephrines are metabolized to sulfate conjugates (most are deaminated), plasma levels of the conjugates are normally 20- to 30-fold higher than levels of the free metabolites [2]. This difference appears to largely reflect different clearance mechanisms. The free metanephrines are rapidly cleared from the circulation by active uptake mechanisms operative throughout different cells and tissues of the body, while clearance of the sulfate-conjugates is slower and dependent on elimination in urine [3, 4].

Suspicion of pheochromocytoma among patients with impaired renal function is most usually based on the presence of typical symptoms, hypertension or hemodynamic instability. Diagnosis of the tumor in such patients can be troublesome due to influences of impaired renal function on elimination of catecholamines and their metabolites in urine, often making conventional urinary tests of catecholamine excess unreliable. Plasma measurements may also be compromised by increased sympathetic outflow or dependence of catecholamine metabolite levels on clearance by the kidneys [9, 10]. These problems are particularly acute in end-stage renal disease (ESRD), when patients are functionally anephric and on dialysis [11]. There

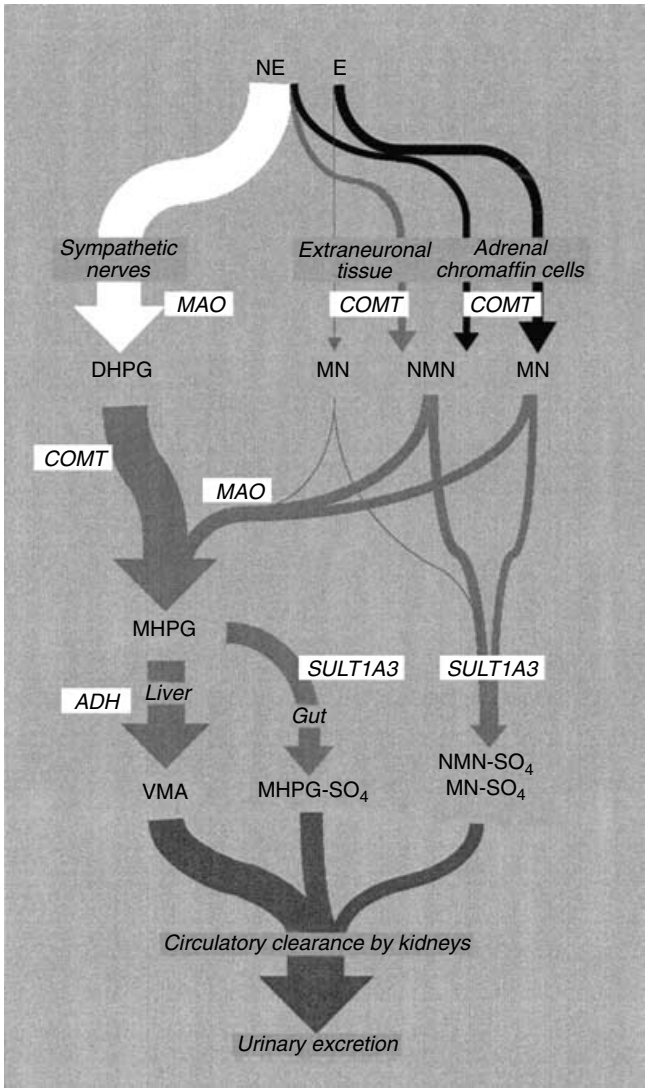

Fig. 1. Diagram showing the main pathways for metabolism of the norepinephrine and epinephrine derived from sympathoneuronal or adrenalmedullary sources. Deamination in sympathetic nerves (white) is the major pathway of catecholamine metabolism and involves intraneuronal deamination of norepinephrine leaking from storage granules, or of norepinephrine recaptured after release by sympathetic nerves. Metabolism in adrenal chromaffin cells (black) involves O-methylation of catecholamines leaking from storage granules into the cytoplasm of adrenalmedullary cells. The extraneuronal pathway (gray) is a relatively minor pathway of metabolism of catecholamines released from sympathetic nerves or the adrenal medulla, but is important for further processing of metabolites produced in sympathetic nerves and adrenal chromaffin cells. The free metanephrines produced in extraneuronal tissues or adrenal chromaffin cells are either further metabolized by deamination or sulfate conjugation. Abbreviations: NE, norepinephrine; E, epinephrine; DHPG, 3,4-dihydroxyphenylglycol; MN, metanephrine; NMN, normetanephrine; MHPG, 3-methoxy-4-hydroxyphenylglycol; VMA, vanillylmandelic acid; MHPG-SO_4, 3-methoxy-4-hydroxyphenylglycol sulfate; NMN-SO_4, normetanephrine-sulfate; MN-SO_4, metanephrine-sulfate; MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; ADH, alcohol dehydrogenase; SULT1A3, phenolsulfotransferase type 1A3.

may also be concerns about influences of renal function on some urinary measures of catecholamine excess in patients with milder forms of renal insufficiency [12, 13].

The presence of pheochromocytoma in hypertensive patients, with or without renal failure, is rare, but should be considered when associated with symptoms of catecholamine excess, or when hypertension is unresponsive to therapy. The risk of pheochromocytoma is higher in several hereditary conditions. Von Hippel-Lindau (VHL) syndrome is one example where there is a high risk of both pheochromocytoma and kidney cancer, and where the former tumor may often need to be considered in the setting of mildly to severely impaired renal function [5].

This study examined the influence of mildly to severely impaired renal function on plasma concentrations of catecholamines and free and deconjugated metanephrines. Because the circulatory clearance of free metanephrines is largely independent of renal function, we hypothesized that plasma concentrations of these metabolites, unlike the conjugated metabolites, would remain largely uninfluenced by renal insufficiency states.

METHODS

Subjects

Patients included 17 with ESRD (renal failure patients) who were on hemodialysis ($N = 16$) or peritoneal dialysis ($N = 1$), and 19 patients with milder impairments of renal function (renal insufficiency) who were not on dialysis (Table 1). These patients were from two sources: (*1*) 24 patients presenting to the Department of Nephrology at St. Radboud University Medical Center for clinical examination of renal insufficiency, dialysis therapy, or consideration for a kidney transplant; and (*2*) 12 patients screened for pheochromocytoma at the National Institutes of Health (NIH).

ESRD in the 17 patients on dialysis was secondary to hypertension ($N = 3$), diabetes mellitus with or without hypertension ($N = 4$), chronic interstitial renal disease ($N = 2$), Alport's syndrome ($N = 2$), focal glomerulosclerosis ($N = 2$), and bilateral nephrectomies due to renal cell carcinoma in VHL patients ($N = 4$). Impaired renal function among the 19 patients with renal insufficiency was due to renal artery stenosis ($N = 8$), unilateral nephrectomies and renal tumors or cysts in remaining kidneys due to VHL syndrome ($N = 8$), chronic or IgA glomerulonephritis ($N = 2$), and polycystic kidney disease ($N = 1$). The mean ($\pm$ SD) creatinine clearance among patients with renal insufficiency was 49 ± 21 mL/min, with a range from 5 to 78 mL/min. These patients included four with ESRD (clearance <25 mL/min) who were not on dialysis.

Comparison groups included 68 healthy normotensive subjects, 89 patients with primary hypertension, and 51

Table 1. Patient characteristics

	Renal failure (dialysis)	Renal insufficiency	Essential hypertension	Normotensive volunteers	VHL syndrome
N	17	19	89	68	51
Age *mean* ± *SD*	54 ± 19	51 ± 13	49 ± 13	48 ± 8	47 ± 8
Male/Female	14/3	8/11	40/49	37/31	21/30

patients with the VHL syndrome undergoing routine screening for pheochromocytoma (Table 1).

Pheochromocytoma in patients screened for the tumor was excluded according to previously reported criteria [7]. All patients with impaired renal function and many of the hypertensives and patients with VHL syndrome were on medications, which, in patients with impaired renal function or hypertension, included calcium channel antagonists, ACE-inhibitors, diuretics, and beta-adrenoceptor blockers. Procedures were approved by the appropriate institutional review boards, and all participants gave written informed consent.

Collection of blood and urine samples

Blood samples were obtained from all patients using an indwelling intravenous catheter inserted into an antecubital vein with patients in the supine position for at least 20 minutes before blood collections. Blood samples were collected after avoidance of medications containing acetaminophen, which, in our liquid chromatographic method of analysis, interferes with measurements of normetanephrine [14]. In the patients on dialysis, blood samples were drawn immediately before the next dialysis. Samples of blood were transferred into tubes containing heparin as anticoagulant or EGTA and glutathione and immediately placed on ice until centrifuged (4°C) to separate the plasma. Plasma samples were stored at −80°C until assayed. Twenty-four–hour urine specimens were collected in patients with renal insufficiency or VHL syndrome into containers containing 30 mL of 6 M hydrochloric acid as a preservative.

Plasma and urinary catecholamines and metanephrines

Plasma concentrations of catecholamines (norepinephrine and epinephrine) were quantified by liquid chromatography with electrochemical detection [15]. Plasma concentrations of free metanephrines (normetanephrine and metanephrine) were determined using a different liquid chromatography procedure after extraction onto solid-phase ion exchange columns [14]. Plasma concentrations of deconjugated metanephrines were determined by the same method after a one-hour incubation (37°C) of 200 μL of plasma with 0.33 units of sulfatase (Sigma, St Louis, MO, USA). Intra-assay coefficients of variation were 1.9% for norepinephrine, 3.0% for epinephrine, 4.2% for normetanephrine, and 3.3% for metanephrine. Interassay coefficients of variation were 3.2% for norepinephrine, 9.9% for epinephrine, 7.1% for normetanephrine, and 5.1% for metanephrine.

Twenty-four–hour urinary excretion of fractionated metanephrines (separately measured deconjugated normetanephrine and metanephrine) in 12 patients with renal insufficiency and the VHL patients was determined by liquid chromatography with electrochemical detection [16].

Data analysis

As described elsewhere [17], logarithmic transformations are required to obtain normal distributions for plasma concentrations of catecholamines and metanephrines. Therefore, data are presented as geometric means with 95% confidence intervals calculated from the antilogarithm of the mean ± 2 SD of the transformed data. Upper reference limits for plasma concentrations of catecholamines and free or deconjugated metanephrines were determined from the 95% confidence intervals for the combined data from the three reference groups. Plasma concentrations of catecholamines in patients with impaired renal function were defined as normal if both norepinephrine and epinephrine were below the upper limit of the 95% confidence intervals in the three reference groups. Similarly, plasma free or deconjugated metanephrines in patients with impaired renal function were defined as normal if both normetanephrine and metanephrine were below the upper limit of 95% confidence intervals in the three reference groups.

Creatinine clearance was calculated by dividing the 24-hour urinary output of creatinine by the serum concentration of creatinine. Similar to calculations of creatinine clearances, clearances of deconjugated normetanephrine and metanephrine (representing almost exclusively the conjugated metabolites) were calculated by dividing the 24-hour urinary output of normetanephrine and metanephrine by the respective plasma concentrations of deconjugated normetanephrine and metanephrine.

Differences in plasma or urinary catecholamines and free or deconjugated metanephrines among groups were assessed using analysis of variance (ANOVA) carried out on logarithmically transformed data, with post-hoc tests of significance determined using Scheffe's method. Similarly, significances of relationships between creatinine clearances and plasma concentrations of catecholamines

Table 2. Plasma concentrations of free and deconjugated normetanephrine (NMN) and metanephrine (MN) and free norepinephrine and epinephrine in patients with renal failure or renal insufficiency compared to hypertensive, normotensive, and VHL comparison groups

	Renal failure (dialysis)	Renal insufficiency	Essential hypertension	Normotensive volunteers	VHL syndrome
Free NMN	96[b,c,d] (26–410)	82[b,c,d] (29–307)	60 (24–148)	47 (18–119)	59 (26–137)
Free MN	41[d] (8–130)	34 (1–142)	28 (11–71)	30 (13–67)	23 (8–64)
Deconjugated NMN	31,477[a,b,c,d] (7,225–101,082)	5272[b,c,d] (1,519–16,949)	2109[c] (783–5,675)	1521 (669–3,451)	2449[c] (988–6067)
Deconjugated MN	14,355[a,b,c,d] (8,266–41,469)	2,089[b,c,d] (409–9286)	809 (324–2023)	822 (346–1954)	889 (326–2427)
Norepinephrine	417[b,c,d] (122–2738)	396[c,d] (88–1131)	268[c] (101–708)	195 (80–475)	246 (101–601)
Epinephrine	56[b,c,d] (5–422)	21 (2–181)	21 (4–124)	18 (3–77)	13 (2–97)

Data are shown as geometric mean values (pg/mL) with 95% confidence intervals in parentheses.
[a] $P < 0.001$ higher than in renal insufficiency.
[b] $P < 0.05$ higher than in essential hypertension.
[c] $P < 0.05$ higher than in normal volunteers.
[d] $P < 0.05$ higher than in VHL syndrome.

and free or deconjugated metanephrines were determined using Pearson's correlation coefficient, determined using logarithmically transformed values for catecholamines and metanephrines. Chi-square tests were used to determine differences in proportions of normal and abnormal results for plasma catecholamines, free metanephrines, and deconjugated metanephrines.

RESULTS

Mean plasma concentrations of free normetanephrine were up to two-fold higher in patients with ESRD on dialysis ($P < 0.002$) or milder renal insufficiency ($P < 0.03$) than in groups of normotensive volunteers, essential hypertensives, and patients with VHL syndrome (Table 2). Plasma concentrations of free metanephrine showed little differences among groups, but were higher ($P < 0.01$) in patients on dialysis compared to those with VHL syndrome. In contrast to the free metanephrines, plasma concentrations of deconjugated metanephrines in both groups of patients with impaired renal function were consistently and significantly ($P < 0.0001$) higher than levels in all three reference groups. Plasma concentrations of deconjugated metanephrines were particularly elevated in patients on dialysis. In these patients, mean plasma concentrations of deconjugated metanephrines were more than 12-fold higher than concentrations in the three reference groups, and more than eight-fold higher than those in patients with milder renal insufficiency states. Similar to plasma free metanephrines, mean plasma concentrations of norepinephrine and epinephrine were also up to two-fold higher ($P < 0.04$) in patients on dialysis than in the three reference groups. Higher plasma levels of norepinephrine were also present in patients with milder renal insufficiency compared to normotensives ($P < 0.0001$) and VHL patients ($P < 0.03$), whereas epinephrine levels were not significantly different between groups.

Plasma levels of deconjugated metanephrines were up to 350-fold higher than free metanephrines and, thus, much easier to measure in patients with impaired renal function than levels of free metanephrines or catecholamines. Difficulties with measurements of the much lower plasma concentrations of free metanephrines and catecholamines in patients with impaired renal function were compounded by interferences from unknown plasma contaminants during liquid chromatographic analysis of plasma samples. This was particularly problematic for patients on dialysis, where chromatograms were highly complex with multitudes of additional peaks, suggesting a build-up of multiple contaminants secondary to impaired urinary excretion. The complex nature of chromatograms often necessitated repeated analysis and always required careful inspection and interpretation of chromatograms to avoid erroneously elevated results. Even so, plasma concentrations of free normetanephrine or metanephrine or both could not be reliably measured in five out of the 17 (29%) patients on dialysis compared to none of the patients with milder renal insufficiency, and only one out of the 208 patients in the other three groups. Similarly, plasma concentrations of catecholamines could not be reliably measured in five out of the 17 (29%) patients on dialysis compared to no patients with milder renal insufficiency, and only two out of the 208 patients in the three other groups.

Examination of individual plasma levels of catecholamines and metanephrines in dialysis and renal insufficiency patients compared to normotensives, essential hypertensives, and VHL patients further illustrated the relatively mild effects of impaired renal function on plasma levels of catecholamines and free metanephrines

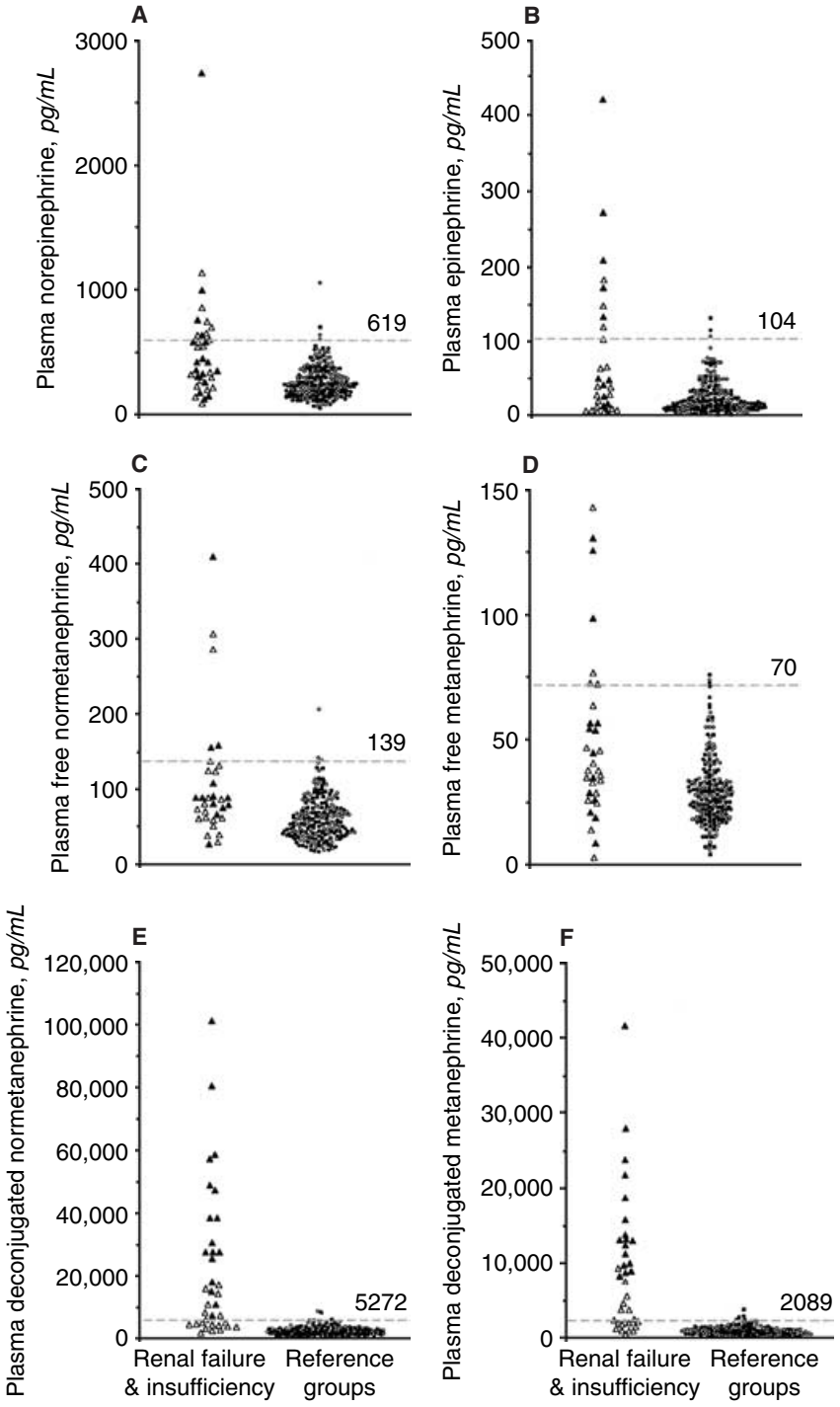

Fig. 2. Plasma concentrations of catecholamines, free metanephrines, and deconjugated metanephrines in individual patients with ESRD on dialysis (▲) and patients with milder renal insufficiency (Δ) compared to individual values in the three reference groups. Horizontal dashed lines represent the upper limits of the 95% confidence intervals for values in the reference population.

compared to the more dramatic effects on deconjugated metanephrines (Fig. 2). Plasma concentrations of norepinephrine were increased above the upper limit of the 95% confidence intervals in the reference groups (619 pg/mL) in 28% (10/36) of all patients with impaired renal function, and plasma concentrations of epinephrine were increased above the 95% confidence intervals (104 pg/mL) in 26% (8/31) of patients where these measurements were possible. Plasma concentrations of free normetanephrine were increased above the upper limit of the 95% confidence intervals (139 pg/mL) in 16% (5/32) of all patients with impaired renal function, and plasma concentrations of metanephrine were increased above the 95% confidence intervals (70 pg/mL) in 22% (7/32) of patients where these measurements were possible. In contrast, plasma concentrations of deconjugated

normetanephrine or deconjugated metanephrine were each increased above their respective upper limits (5272 and 2089 pg/mL) in 72% (26/36) of patients with impaired renal function.

Plasma norepinephrine and epinephrine were normal in 68% (13/19) of patients with renal insufficiency, and 42% (5/12) of the patients on dialysis in whom both analytes were measurable. This compares with plasma free normetanephrine and metanephrine, which were normal in 74% (14/19) of patients with renal insufficiency and in 75% (9/12) of the patients on dialysis in whom both analytes were measurable. In contrast, plasma concentrations of deconjugated normetanephrine and metanephrine were normal in only 53% (10/19) of patients with renal insufficiency and none (0/17) of the patients on dialysis.

Numbers of normal results for plasma free metanephrines were significantly ($P < 0.001$) higher than numbers of normal results for deconjugated metanephrines in patients with ESRD on dialysis and for combined groups of ESRD and renal insufficiency patients. Numbers of normal results for plasma catecholamines were also significantly ($P < 0.02$) higher than numbers of normal results for plasma deconjugated metanephrines in the combined group of ESRD and renal insufficiency patients. There were no significant differences in numbers of normal results between plasma catecholamines and free metanephrines.

Among the patients with VHL syndrome or renal insufficiency there were relatively weak inverse relationships between creatinine clearances and plasma concentrations of norepinephrine ($r = 0.38$, $P = 0.001$) and free normetanephrine ($r = 0.27$, $P = 0.02$), but no relationships with plasma epinephrine or free metanephrine (Fig. 3). In contrast to the weak relationships with plasma free metanephrines, much stronger inverse relationships were present between creatinine clearances and plasma concentrations of deconjugated normetanephrine ($r = 0.63$, $P < 0.0001$) and metanephrine ($r = 0.59$, $P < 0.0001$).

Urinary excretions (mean ± SD) of deconjugated normetanephrine were 246 ± 107 μg/day in the patients with renal insufficiency and 281 ± 133 μg/day in the VHL group. Urinary excretions of deconjugated metanephrine were 142 ± 51 μg/day in the patients with renal insufficiency and 85 ± 80 μg/day in the VHL group. Mean ± SD clearances of creatinine, normetanephrine, and metanephrine were 49 ± 21 mL/min, 36 ± 10 mL/min, and 37 mL/min in patients with renal insufficiency, and 110 ± 34 mL/min, 75 mL/min, and 60 ± 21 mL/min in VHL patients. Among these patients, there were strong positive relationships between the clearances of creatinine with clearances of deconjugated normetanephrine ($r = 0.81$, $P < 0.001$) and metanephrine ($r = 0.78$, $P < 0.001$) (Fig. 4).

DISCUSSION

The present study establishes that measurements of plasma free metanephrines are more suitable than measurements of plasma deconjugated metanephrines for diagnosis of pheochromocytoma among patients with impaired renal function. This conclusion is based on the finding that among all patients with impaired renal function, plasma concentrations of free metanephrines were much less frequently elevated above the upper reference limits compared to plasma-deconjugated metanephrines. In particular, only one out of four patients on dialysis showed increased plasma free metanephrines, while all showed substantially increased plasma concentrations of deconjugated metanephrines, and more than one out of two patients had increased plasma concentrations of catecholamines. Plasma concentrations of free metanephrines, therefore, seem to be least dependent on renal function compared to plasma deconjugated metanephrines or plasma catecholamines. This conclusion is supported by the strong inverse relationships between creatinine clearance and plasma concentrations of deconjugated metanephrines, the weaker relationships between creatinine clearance and plasma catecholamines, and the even weaker relationships between creatinine clearance and plasma free metanephrines. The important contributions of renal elimination to the circulatory clearance and resulting plasma concentrations of deconjugated metanephrines are further supported by the strong positive relationships between the clearance of creatinine and clearances of deconjugated metanephrines.

Diagnosis of pheochromocytoma among patients with ESRD is an important but difficult clinical challenge. The importance of the diagnosis is underscored by considerations that hypertension, and in particular, hemodynamic instability and wild swings in blood pressure, occur in both patients with renal failure and pheochromocytoma. Moreover, some of the other varied signs and symptoms that occur in patients with pheochromocytoma, such as headaches, palpitations, and pulmonary edema, can also be present in patients with renal failure. Although pheochromocytomas are rare, numerous case reports of the tumor in patients with renal failure further attest to the importance of differential diagnosis of the tumor among such patients [11, 18–25]. As reviewed elsewhere [26], there are also numerous case reports of coexistence of renal artery stenosis with pheochromocytoma. In some patients, not only the hypertension, but also impaired renal function, may result from an undiagnosed tumor [18–20, 22]. Left untreated, such tumors are invariably fatal, but once diagnosed are usually cured by surgical resection.

Although important to diagnose, the possible association of a pheochromocytoma with renal failure poses

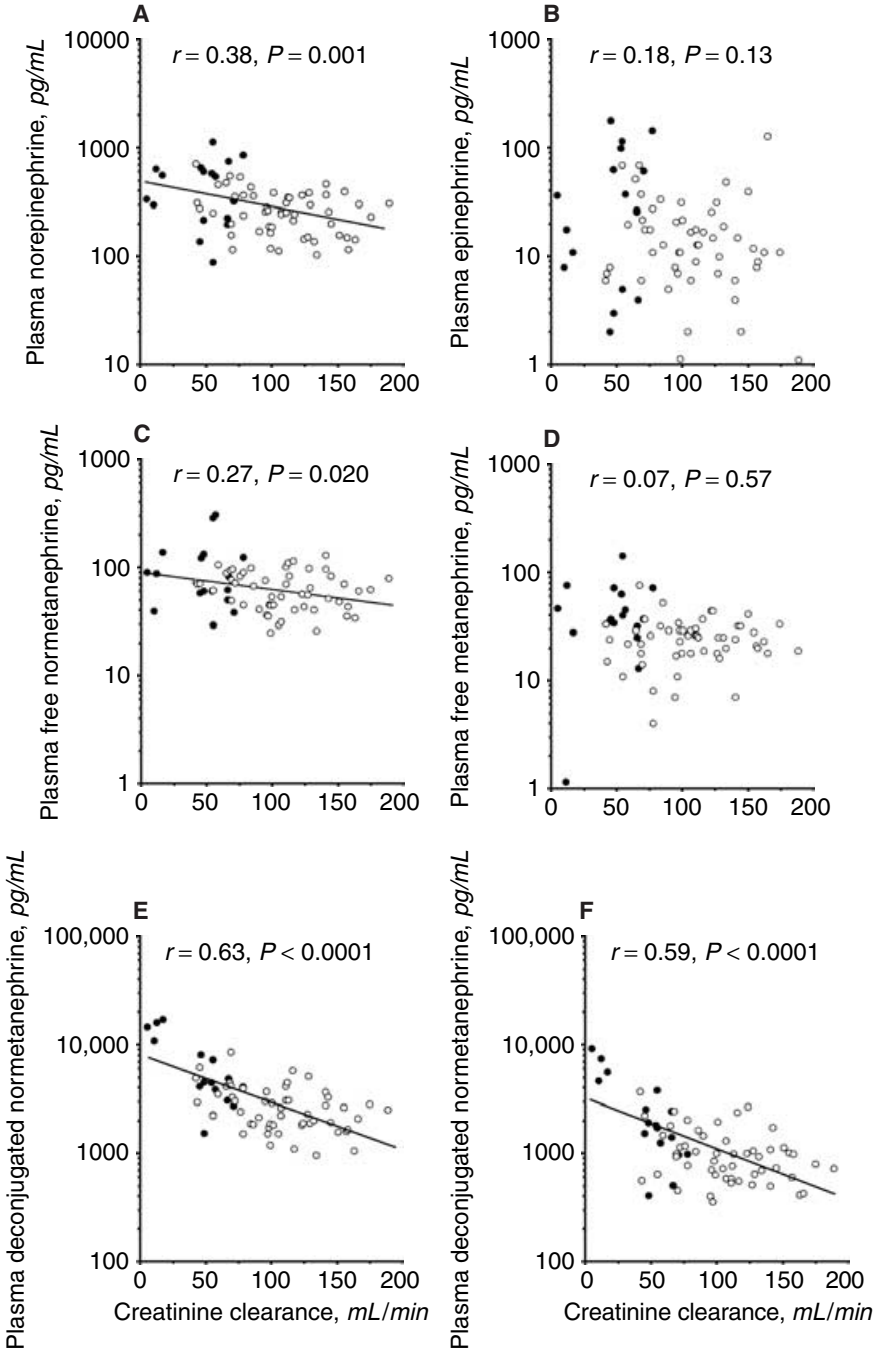

Fig. 3. Relationships between creatinine clearance and plasma concentrations of catecholamines, free metanephrines, or deconjugated metanephrines in patients with renal insufficiency (•) and VHL syndrome (○).

a diagnostic dilemma, particularly acute in patients on dialysis where traditional urinary tests of catecholamine excess cannot be used. Increased sympathetic nervous system activity in renal failure further compounds the difficulty of biochemical diagnosis by leading to increased plasma concentrations of catecholamines [9, 10], this representing the one remaining traditional biochemical test for pheochromocytoma. In the present study, the high proportion of renal failure patients with increased plasma catecholamines illustrates the problem of using these analytes for diagnostic purposes.

Another problem associated with diagnosis of pheochromocytoma among patients with renal failure results from the impaired renal clearance of alternative analytes that may be used for biochemical diagnosis of the tumor. Serum levels of chromogranin A provide one such alternative test for diagnosis of pheochromocytoma. However, the circulatory clearance of chromogranin A depends on renal elimination, so that serum levels of chromogranin A in patients with renal failure are increased well into the range usually observed in patients with pheochromocytoma [27, 28]. Similarly,

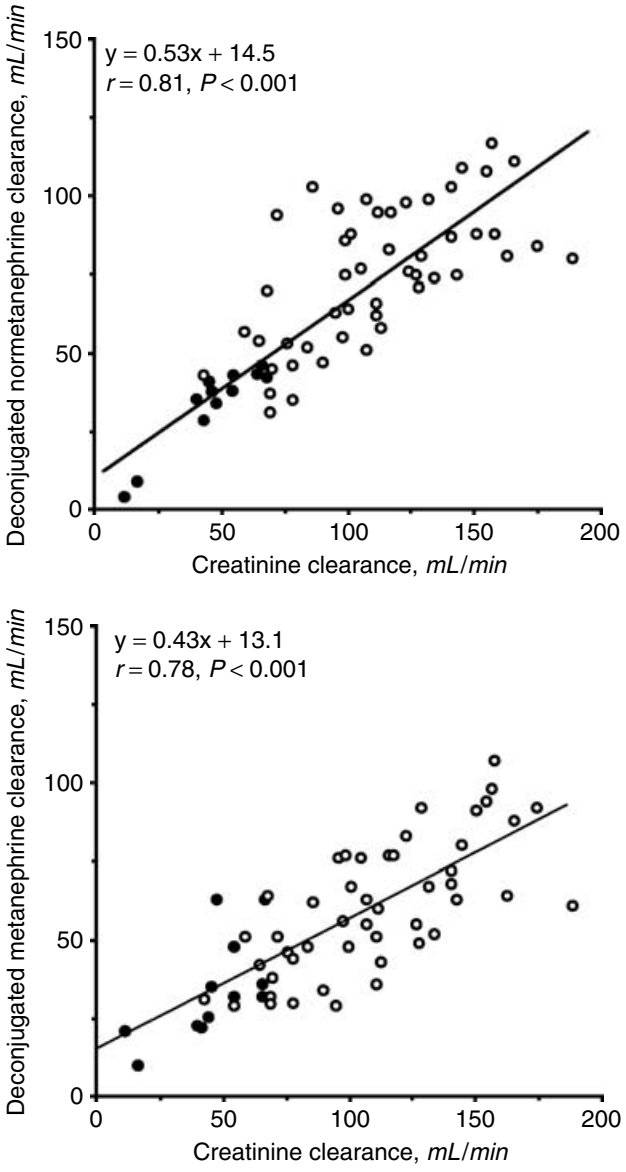

Fig. 4. Relationships between creatinine clearance and clearances of deconjugated normetanephrine and deconjugated metanephrine in patients with renal insufficiency (●) and VHL syndrome (O).

plasma levels of vanillylmandelic acid (VMA), a catecholamine metabolite more commonly measured in urine, are increased about 15-fold in patients with renal failure compared to those with normal kidney function [29]. This is because as an end product of catecholamine metabolism, clearance of VMA is entirely dependent on renal elimination. As illustrated in the present study, and in agreement with previous findings [30, 31], this problem also occurs with measurements of deconjugated metanephrines, which almost exclusively reflect levels of sulfate-conjugated metabolites. Again, as end products of catecholamine metabolism, sulfate-conjugated metanephrines are cleared from the circulation mainly, if not completely, by renal elimination in the urine. Thus, like chromogranin A and VMA, measurements of deconjugated metanephrines in plasma cannot be used for diagnosis of pheochromocytoma among patients with renal failure and are also unreliable in those with milder renal insufficiency states.

The kidneys make a 14% to 16% contribution to the clearance of free metanephrines, and a 15% to 24% contribution to the clearance of circulating catecholamines [3]. Thus, in contrast to the importance of the kidneys for the clearance of VMA and sulfate-conjugated metanephrines, the circulatory clearances of free metanephrines and catecholamines are relatively independent of renal function. Most circulating catecholamines and free metanephrines are actively removed from the circulation by non-neuronal monoamine transporters in other tissues and organs where the amines are subsequently metabolized before excretion [32]. Although decreases in circulatory clearance resulting from impaired renal function may contribute to increased plasma concentrations of free normetanephrine and catecholamines, these increases in patients with renal failure probably mainly result from activation of the sympathetic nervous system.

Previous studies have shown that normal plasma concentrations of free metanephrines are useful for excluding pheochromocytoma, but that occurrence of false-positive results represents a remaining problem [7, 8]. False-positive results can be expected to be particularly troublesome in patients with renal failure, where, as shown here, 25% of patients had elevated plasma levels of free metanephrines. However, judging the likelihood of a pheochromocytoma from an initial positive test result can benefit from consideration of the extent of increase in the abnormal result [33]. In the present series, no patient with renal failure had increases in normetanephrine above 410 pg/mL or of metanephrine above 142 pg/mL, and, as shown elsewhere, most patients with pheochromocytoma have increases well above these levels [7]. Thus, increases in plasma normetanephrine above 410 pg/mL or of metanephrine above 142 pg/mL are highly likely to indicate the tumor. Comparisons with results for plasma catecholamines and responses of plasma normetanephrine to clonidine provide other methods for distinguishing true- from false-positive results [33]. Again, measurements must be accurate. This can be a problem in patients with renal failure.

Accurate measurements of plasma free metanephrines and catecholamines can be particularly troublesome in patients on dialysis, where the circulatory accumulation of blood-borne substances can interfere with biochemical analyses. Apart from medications, our unpublished observations indicate that such interferences can derive from unknown constituents in the diet. In the patient with ESRD on dialysis, dietary-derived substances are likely

to accumulate independent of any fasting state. Possibly, there may be less analytical interferences if blood samples are obtained immediately after, and not before, dialysis. The period immediately after dialysis can be, however, associated with hemodynamic instability, which, through baroreflex-mediated sympathetic activation, may also compromise interpretation of biochemical tests of catecholamine excess. Avoiding analytical problems may also be possible through improvements in sample extraction and purification procedures or use of new analytical methods, such as liquid chromatography with tandem mass spectroscopy [34]. The latter recently developed method offers improved analytical specificity that might be particularly suitable for patients with renal failure.

CONCLUSION

Plasma concentrations of free metanephrines are relatively independent of renal function and, therefore, along with measurements of plasma catecholamines, offer a suitable test for diagnosis of pheochromocytoma in patients with renal failure. Because of the previously published higher diagnostic sensitivity of plasma free metanephrines than catecholamines [5–8], we recommend that the decision to exclude pheochromocytoma should be based primarily on normal results for plasma free metanephrines. Where plasma free metanephrines are elevated, clinicians should be sensitive to the possibility of false-positive results due to influences of sympathetic activation and unrecognized analytical interferences. Due to the latter possibility, consideration should be given to corroboration of positive tests results by repeated testing of plasma free metanephrines, perhaps best achieved using a different testing laboratory and method of analysis.

Reprint requests to Graeme Eisenhofer, Building 10, Room 6N252, National Institutes of Health, 10 CENTER DR, MSC-1620, Bethesda, MD 20892–1620.
E-mail: ge@box-g.nih.gov

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