# Occult Renal Impairment is Common in Patients with Peripheral Vascular Disease and Normal Serum Creatinine

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***Objective****. The incidence of peripheral vascular disease (PVD) and angiography/angioplasty is rising annually. The UK Small Aneurysm Trial and other trials have shown renal function is a predictor of increased mortality and failed infrainguinal bypass despite patent vessels. Renal function is classically assessed by serum creatinine (SCr). However, SCr can be normal despite significant renal impairment. A more sensitive test is creatinine clearance (CrCl) as determined by 24-hour urine collection in combination with SCr. We studied the incidence of renal impairment, as defined by CrCl, in PVD patients with normal SCr.*

***Methodology****. All patients with PVD sufficient to necessitate angiography and normal SCr ($\leq 120 \mu mol/l$ — men; $\leq 97 \mu mol/l$ — women) had their CrCl assessed prior to angiography: using both 24-hour urine collection and the Cockcroft-Gault formula. Various blood tests, a detailed history and examination were performed. A control group of arthritic patients, age and sex-matched with similar SCr, also had their CrCl determined.*

***Results****. 65 of 76 patients (86%) with normal SCr had a subnormal CrCl (<100 ml/min) and 49 (65%) had a CrCl below 60 ml/min. In the control group of arthritic patients, the proportion having impaired CrCl was significantly less — 67% below 100 mls/min ($p = 0.0471$) and only 15% below 60 mls/min ($p < 0.0001$). The median and interquartile range CrCl of 52 [38–81] mls/min for PVD patients was significantly worse than for control patients (80 [68–119] mls/min — $p < 0.0001$). The Cockcroft-Gault formula for calculating CrCl did not correlate well with the urinary CrCl for the control group but did for PVD patients ($p < 0.0001$). Factors associated with a significantly reduced CrCl were age of at least 75 years, SCr of at least 85 $\mu mol/l$ and a history of coronary heart disease (all $p < 0.05$). This had a sensitivity of 88% and specificity of 82% for identifying subnormal CrCl. Statin use was associated with a significantly improved CrCl ($p = 0.040$).*

***Conclusion****. Most PVD patients with normal serum creatinine have occult, significantly impaired renal function as defined by creatinine clearance. Vascular surgeons should include creatinine clearance in pre-operative assessment of renal function especially in patients over 75 years old, with a history of coronary heart disease or a serum creatinine over 85 $\mu mol/l$. The method of determining creatinine clearance could be the Cockcroft-Gault calculation or ideally 24-hour urinary creatinine clearance measurement. This would allow appropriate early referral to a nephrologist for further investigation and management. It is worth noting that statin use seems to be associated with a protective effect on renal function.*

*Keywords: Peripheral vascular disease; Renal impairment; Serum creatine; Creatine clearance.*

## Background

Renal dysfunction is an important risk factor in the outcome of many surgical procedures.[1–3] It has been shown that poor renal function is associated with increased mortality in aneurysm surgery[4] especially endovascular repair[5] and failed infrainguinal bypass

despite patent vessels: especially in diabetics and dialysis-dependent patients,[6–12] although these observations are not universal.[13,14] The incidence of peripheral vascular disease (PVD) and angiography/angioplasty is rising annually.

Renal function is classically assessed by serum creatinine (SCr). Glomerular filtration rate (GFR) is the true reflection of renal function and should be around 125 mls/min in the typical adult. However, SCr does not usually rise until GFR has fallen by 50% or more.[15] Furthermore, SCr depends on lean body weight (LBW), age and sex and is therefore inaccurate in a third of patients aged between 40–49 and 90% in

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the over 70 age group.[16] Three equations have been developed to correct for the inaccuracies posed by weight, age and sex: Cockcroft-Gault, Modification of Diet in Renal Disease and the Bjorssen equation, but the latter two are laborious and impractical.[17]

Direct measurements of GFR include isotope, inulin and creatinine clearance.[18] Of these the most practical for screening purposes is creatinine clearance (CrCl) because it does not require the addition of any marker and is simply determined from a 24-hour urine collection in combination with SCr.

We therefore studied the incidence of renal impairment in PVD patients with normal SCr, as defined by both the Cockcroft-Gault equation and urinary CrCl. A control group of patients, age and sex-matched were selected from arthritic patients awaiting joint replacement surgery for comparison purposes.

## Methods and Materials

We invited all patients with peripheral vascular disease (PVD) and normal serum creatinine (SCr) going for elective angiography or angioplasty to participate in this study. In our hospital this normal SCr is up to 120 μmol/l for men or 97 μmol/l for women. Approval was obtained from the Ethics Committee of the Royal Free Hampstead NHS Trust. Calculated Creatinine clearance was done using the following Cockcroft-Gault formula:

$$CrCl(ml/min) = \frac{(140 - age[years]) \times LBW[kg]}{SC[\mu mol/l] \times 0.81}$$
$$\times 0.85[women]$$

$$LBW[kg] = 2.3 \times (Height[inches] - 60) + 50$$
$$- 4.5[women]$$

All patients had a relevant history and examination performed with some specific investigations performed prior to angiography. In particular, creatinine clearance (CrCl) was measured after admission in the ward under the supervision of experienced nurses. Creatinine clearance was done by 24-hour urine collection.

A group of arthritic patients scheduled for hip or knee replacement surgery, but who did not have PVD were selected as controls. These patients were selected to match the age and sex profile of PVD patients and again had their CrCl measured together with other relevant history, examination and investigations.

**Table 1.**

| Criteria | PVD | Controls | p |
|---|---|---|---|
| SCr: μmol/l | 88 [74—100] | 81 [73—96] | 0.2863 |
| Age: years | 75 [64—85] | 65 [62—75] | 0.0543 |
| Gender (M:F) | 50:26 | 18:9 | 1.000 |

Key: SCr: serum creatinine; M: Male; F: Female; PVD: peripheral vascular disease; controls: arthritic patients. Values are creatinine clearances: median [interquartile range]. P-values from two-tail T-test except Fisher's exact test used for gender.

## Statistics

With regard to 24-hour urinary creatinine clearance (CrCl), this is a standard test performed routinely in our Biochemistry Department which is fully and regularly validated. In keeping with other laboratories, the coefficient of variation from repeated 24 h urine collections is between 11—30%. Given almost all measurements were done whilst the patients were in hospital and supervised by experienced nurses, we feel confident that our results are around 11%.

Analysis comparing risk factors between two groups using continuous variables (e.g. - age) was with two-tailed T-tests except where the risk factor used segregation into groups (e.g. - presence or absence of diabetes) - here Fisher's exact test was used. Correlation between continuous variables was done using Pearson's correlation coefficient with two-tailed significance.

For the analysis of risk factors predicting renal dysfunction (as defined by impaired creatinine clearance), a general linear model was applied (SPSS software). Variables which demonstrated significant associations with creatinine clearance in univariate analysis were included in the general linear model.

Results are given as median with interquartile range (IQR).

## Results

76 PVD patients with normal SCr were recruited to this study — 50 male and 26 female. All patients had their

**Table 2A.**

| Criteria | PVD | Controls | p |
|---|---|---|---|
| Urinary CrCl: mls/min | 52 [38—81] | 80 [68—119] | <**0.0001** |
| Urinary CrCl - <100:≥100 | 65:11 | 18:9 | **0.0471** |
| Urinary CrCl - <60:≥60 | 49:27 | 4:23 | <**0.0001** |
| Calculated CrCl: mls/min | 55 [42—73] | 63 [50—79] | 0.2725 |
| Calculated CrCl - <100:≥100 | 68:7 | 27:0 | 0.1850 |
| Calculated CrCl - <60:≥60 | 44:31 | 10:27 | 0.0722 |

Key: CrCl: creatinine clearances; PVD: peripheral vascular disease; controls: arthritic patients. Values are median [interquartile range]. P-values from Fisher's exact test except for continuous variables (measured in mls/min) which use the two-tail T-test.

**Table 2B.**

| Patient Group | Pearson Correlation Coefficient | p |
|---|---|---|
| PVD | 0.5918 | <**0.0001** |
| Control | 0.1356 | **0.4748** |

Key: PVD: peripheral vascular disease; controls: arthritic patients.
P-values from Pearson Correlation coefficient.

24-hour urinary creatinine clearance measured and all but one had their creatinine clearance calculated using the Cockcroft-Gault method: the missing patient was an amputee whose height could not be measured. The 27 control patients who had arthritis but not PVD were matched for serum creatinine, gender and age (Table 1).

The CrCl median and IQR for PVD patients was 52 [38−81] mls/min. 65 patients (86%) with PVD had subnormal renal function as defined by 24-hour urinary CrCl (<100 mls/min), with 49 (64%) having CrCl < 60 mls/min representing significant renal impairment − less than half normal GFR. In comparison the control patients had a significantly higher median and IQR CrCl of 80 [68−119] mls/min ($p < 0.0001$). Only 18 of 27 (67%) of the controls had subnormal CrCl ($p = 0.0471$), with only 4 (15%) having significant renal impairment with a CrCl < 60 mls/min ($p < 0.0001$). As can be seen from Table 2A this suggests that PVD patients have statistically significant reduction in renal function compared to age and sex-matched controls. Importantly, these differences cannot be detected by alternative measures of renal function like SCr ($p = 0.2863$) and calculated CrCl ($p = 0.2725$) using the Cockcroft-Gault measurement (Tables 1 & 2A). Indeed Cockcroft-Gault is reliable when correlated with urinary CrCl for PVD patients but not the control arthritic patients (Table 2B).

Univariate analysis shows that only a history of coronary heart disease (CHD) and no history of smoking were associated with decreased CrCl, whereas previous cerebrovascular disease (CVD), hypertension,

**Table 3.**

| Risk Factor | Present | Absent | p |
|---|---|---|---|
| CHD | 44 [36−57] | 57 [37−95] | **0.0073** |
| CVD | 47 [37−68] | 52 [38−84] | 0.3064 |
| DM | 50 [37−72] | 52 [38−82] | 0.3449 |
| HT | 54 [43−82] | 42 [29−62] | 0.2367 |
| ↑ Cholesterol | 56 [42−85] | 45 [28−64] | 0.0954 |
| Overweight (BMI > 25) | 56 [43−81] | 48 [33−81] | 0.8345 |
| Ever smoked | 54 [39−84] | 41 [27−52] | **0.0159** |
| Male gender | 53 [39−86] | 46 [28−67] | 0.1360 |

Key: CHD: coronary heart disease; CVD: cerebrovascular disease; DM: diabetes mellitus; HT: hypertension; ↑ Cholesterol: hypercholesterolaemia; BMI: body mass index. Values are creatinine clearances: median [interquartile range]. P-values from two-tail T-test.

**Table 4.**

| Drug | Not Taking Drug | Taking Drug | p |
|---|---|---|---|
| Anti-hypertensives | 44 [29−63] | 52 [38−82] | 0.4721 |
| Anti-platelets | 53 [29−83] | 47 [36−56] | 0.0554 |
| Anti-diabetic | 52 [39−82] | 46 [32−59] | 0.1130 |
| Statins | 46 [30−61] | 56 [45−91] | **0.0308** |

Key: Values are creatinine clearances: median [interquartile range]. P-values from two-tail T-test.

diabetes, hypercholesterolaemia, gender and being overweight made no difference. (Table 3).

Of the various drugs that patients were taking only statins (Table 4) were associated with a significantly improved CrCl from 46 [30−61] to 56 [45−91] ($p = 0.0308$).

Increasing serum creatinine, urea and age were significantly associated with decreased CrCl (Table 5A) with the key cut-off values being SCr of 85 μmol/l, Urea of 6.6 mmols/l and age of 75 years (Table 5B and Figs. 1 and 2).

The factors entered into the general linear model on the basis of univariate analysis were serum creatinine, age, statin use, history of coronary heart disease and smoking. It was decided not to include serum urea in the general linear model as it was simply another measure of renal function that was highly significantly correlated with serum creatinine ($p < 0.0001 -$ Table 5A).

The results of the general linear model (Table 6) showed that statin therapy was significantly associated with improved CrCl ($p = 0.040$), whereas rising SCr ($p = 0.005$) and history of CHD ($p = 0.024$) were significantly associated with impaired CrCl. Smoking and age as a continuous variable did not show any significant association with CrCl. However, age of 75 years and above was significantly associated with impaired CrCl ($p = 0.023$), as was SCr of 85 μmol/l and above ($p = 0.003$).

Overall, renal dysfunction (CrCl < 100 mls/min) is more likely to be found in patients with any of the following risk factors: age 75 years and above, serum creatinine of at least 85 μmol/l or history of coronary heart disease. Having any of these risk factors had a sensitivity of 88%, specificity of 82%, positive predictive value of 97% and a negative predictive value

**Table 5A.**

| Factor A | Factor B | Pearson Correlation Coefficient | p |
|---|---|---|---|
| CrCl | Age | −0.3962 | **0.0004** |
| CrCl | SCr | −0.3445 | **0.0023** |
| CrCl | Urea | −0.3869 | **0.0006** |
| SCr | Urea | 0.4565 | <**0.0001** |

Key: CrCl: Creatinine Clearance; SCr: serum creatinine. P-values from Pearson Correlation coefficient.

**Table 5B.**

| Cut-off Value | Less than | Equal to/greater than | p |
|---|---|---|---|
| SCr of 85 µmol/l | 71 [43−103] | 44 [34−58] | **0.0002** |
| Urea of 6.6 mmols/l | 58 [46−102] | 41 [31−56] | **0.0006** |
| Age of 75 years | 76 [45−99] | 41 [29−54] | **<0.0001** |

Key: SCr: serum creatinine. Values are creatinine clearances: median [interquartile range]. P-values from two-tail T-test.

of 53%. Using the above 3 factors and including non-use of statins as a fourth risk factor for renal dysfunction has a sensitivity of 98%, specificity of 55%, positive predictive value of 93% and a negative predictive value of 86% (Tables 7A & 7B).

## Discussion

This study found that the normal screening tool for assessing renal function, serum creatinine, can be within the normal range even though the vast majority of PVD patients (86%) will have renal impairment (GFR < 100 mls/min) as measured by 24-hour urinary creatinine clearance (UrCrCl).

It is well recognized that calculating GFR using the Cockcroft-Gault method for creatinine clearance (C-GCrCl) tends to underestimate renal function in the elderly, especially over 70 year olds,[16,17] which is the age profile of most PVD patients. This is reflected in the age-matched control group where the C-GCrCl (63 [50−79] mls/min) was significantly lower (p = 0.0004) than the actual UrCrCl (80 [68−119] mls/min), and the C-GCrCl showed all controls had subnormal renal function whereas 9 out of 27 had a UrCrCl within the normal range. However, the
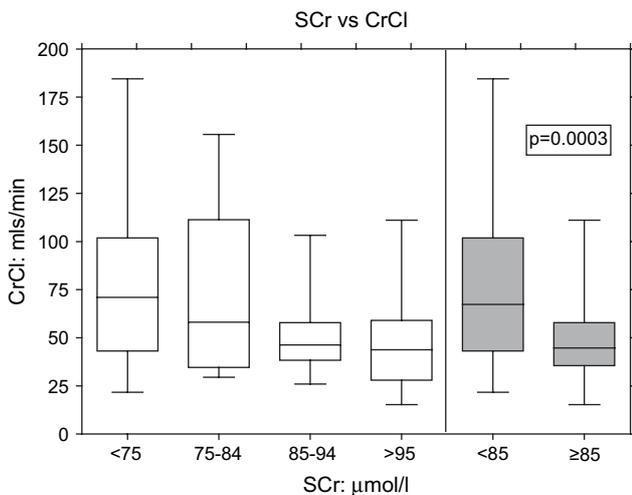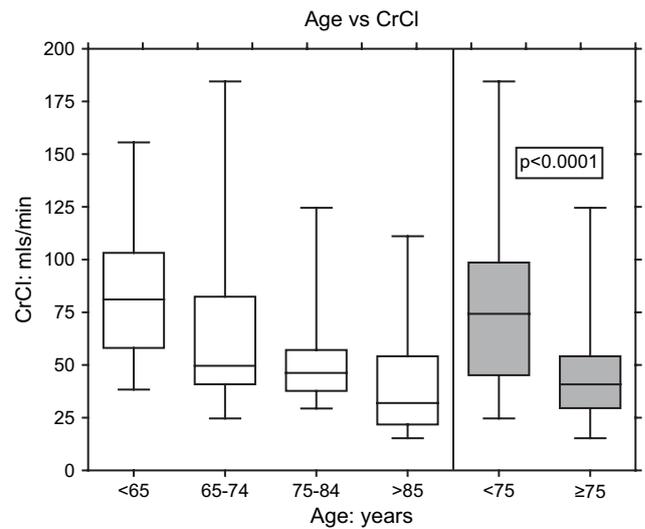


**Fig. 2.** Key: CrCl: Creatinine Clearance. P-value from two-tail T-test.

very poor renal function of PVD patients means that C-GCrCl does predict that the vast majority of PVD patients (91%) have subnormal renal function (GFR < 100 mls/min) and the mean GFR is similar (p = 0.8347) for both UrCrCl (52 [38−81] mls/min) and C-GCrCl (55 [42−73] mls/min).

Theoretically patients with very significant renal impairment − 50% or more decline in normal GFR represented by a value under 60 mls/min[19] - should be picked up by serum creatinine (SCr). However, our study found that 65% of PVD patients with normal SCr had UrCrCl < 60 mls/min. Using C-GCrCl 59% were predicted to have this - again an impressive result. However, 25% of patients with UrCrCl of under 60 mls/min were missed by the C-GCrCl calculation.

The question then is how important is accurate estimation of renal function. As previously mentioned renal function is an important predictor of surgical outcome. However, perhaps more importantly is the fact that renal dysfunction is a critical risk factor in



**Fig. 1.** Key: CrCl: Creatinine Clearance; SCr: serum creatinine. P-value from two-tail T-test.

**Table 6.**

| Risk Factor | Present | Absent | p |
|---|---|---|---|
| SCr | Continuous | Variable | **0.005** |
| Age | Continuous | Variable | 0.106 |
| CHD | 44 [36−57] | 57 [37−95] | **0.024** |
| Statins | 56 [45−91] | 46 [30−61] | **0.040** |
| Ever smoked | 54 [39−84] | 41 [27−52] | 0.078 |
| SCr under 85 µmol/l | 71 [43−103] | 44 [34−58] | **0.003** |
| Age under 75 years | 76 [45−99] | 41 [29−54] | **0.023** |

Key: SCr: serum creatinine; CHD: coronary heart disease. Values are creatinine clearances: median [interquartile range]. P-values from general linear model.

**Table 7A.**

| RF / CrCl | CHD/Age≥75/SCr≥85 | | CHD/Age≥75/SCr≥85/No statin | |
|---|---|---|---|---|
| | ≥1 RF | No RF | ≥1 RF | No RF |
| Normal | 2 | 9 | 5 | 6 |
| Impaired | 57 | 8 | 64 | 1 |

Key: RF: Risk Factor; CHD: coronary heart disease; SCr: serum creatinine; CrCl: Creatinine Clearance; Impaired: CrCl < 100 ml/min. Values are number of patients in each group.

the development of acute renal failure (ARF).[20] ARF occurs in between 2–7% of hospital patients[21–23] with a mortality if uncomplicated of between 5–10% rising to over 50% if another organ system has failed: an outcome that has not improved over several decades.[24]

Given that measuring renal function is important the next question is how best to measure it. The ''gold standard'' for determining GFR is by measuring the clearance of exogenous substances such as iohexol, inulin, $^{51}$Cr-EDTA, $^{99m}$Tc-labelled diethylenetriamine pentaacetic acid (DTPA), or $^{125}$I-labeled iothalamate. Unfortunately, these techniques are time-consuming, labor-intensive and expensive.[25]

For the last few decades, serum or plasma creatinine (SCr) has become the most commonly used serum marker of renal function. SCr is a metabolic product of muscle tissue which circulates in the blood unbound and is freely filtered by the glomerulus, but also secreted in small amounts in the proximal tubules. Intraindividual variability is low though SCr blood concentrations are affected by age and gender, with interindividual variation. As plasma concentrations increase, tubular secretion of SCr increases, leading to an overestimation of GFR in patients with moderate to severe decreases in GFR.[25–29]

Measurement of creatinine clearance (CrCl) by determining its concentration in timed urine collections and simultaneously in blood correlates with gold standard exogenous methods better than SCr.[26] However, this can be cumbersome and prone to error in the outpatient setting. Fortunately all our patients had

**Table 7B.**

| RF | CHD/Age≥75/SCr≥85 | CHD/Age≥75/SCr≥85/No statin |
|---|---|---|
| Sensitivity | 88 (77-94) | 98 (92-100) |
| Specificity | 82 (48-98) | 55 (23-83) |
| Positive Predictive Value | 97 (88-100) | 93 (84-98) |
| Negative Predictive Value | 53 (28-77) | 86 (42-100) |

Key: RF: Risk Factor; CHD: coronary heart disease; SCr: serum creatinine; Impaired = Creatinine Clearance < 100 ml/min. Values are % with 95% confidence intervals in brackets.

UrCrCl measured under the supervision of experienced nurses whilst inpatients.

Cystatin C offers a potentially superior option to creatinine. However, a recent review found 15 studies showing cystatin C to be superior but 9 were equivocal.[25] Furthermore, there is intraindividual variability[30] and the immunoassay measurement method makes this test prohibitively expensive.

The conclusion that can thus be drawn is that serum creatinine is unreliable as an assessment of renal function in patients with peripheral vascular disease. The Cockcroft-Gault formula is a reasonably good estimation of renal function in PVD patients, though creatinine clearance determined by 24-hour urine collection is a relatively simple and cheap method to determine renal function more accurately.

This methodology may still be prohibitive to some and therefore we attempted to determine which patients are most at risk of renal dysfunction and who would thus benefit from this extra investigation. We suggest patients 75 years and above, a serum creatinine above 85 μmol/l or a history of coronary heart disease identifies those at most risk of renal impairment with a sensitivity of 88% and specificity of 82%. Adding non-statin use to the above three risk factors for renal impairment raises sensitivity to 98% but specificity falls to 55%. It would therefore appear that those patients with PVD who do not yet take statins may be missing out on a potentially renoprotective drug, which agrees with a previous study in our department.[31]

Patients discovered to have renal dysfunction and undergoing angiography could have their management altered by specifically looking for renal artery stenosis, the use of renoprotection with hydration,[32,33] agents like sodium bicarbonate[34] and perhaps N-Acetylcysteine,[35–38] or the preferential use of alternative contrast media like iso-osmolar contrast[39] or gadolinium.[40] Further work is now needed on the relative contributions of intrarenal disease, renal artery stenosis and atheroembolism to the decline in renal function in PVD patients.

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