The true clinical significance of renography in nephro-urology

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Abstract. Isotopic renography is a non-invasive technique used routinely by the clinician to provide information about kidney structure and function. Whilst there is no doubt of its value in the accurate measurement of glomerular filtration rate and in the detection of parenchymal abnormalities, its role in the diagnosis of renovascular disease (especially in patients with renal insufficiency), the exclusion of obstruction and the evaluation of the patient with either acute renal failure or renal transplant dysfunction remains unproven. In part, this reflects a failure to standardise protocols and rigorously evaluate diagnostic techniques. Recent developments in ultrasound, computerised X-ray tomography and nuclear magnetic resonance now present the clinician with rival techniques and emphasise the need for the clinical development of isotopic renography.

Key words: Nephrology – Urology – Renography – Kidney diseases


Introduction

The goal for nuclear medicine in nephro-urology is to yield functional and structural information which is reliable and acquired non-invasively and which provides the clinician with both diagnosis and prognosis. Isotopic renography is in frequent use in the investigation of renal function, renovascular disease, outflow obstruction, reflux nephropathy, renal transplantation and acute renal failure. However, excepting the measurement of glomerular filtration rate and the detection of parenchymal scars, these tests have not become established as gold standards. In part this reflects the failure to standardise procedures, protocols and interpretative criteria and has resulted in a disparate literature from which clear conclusions cannot be drawn. Recent developments in ultrasound scanning, computerised X-ray tomography and magnetic resonance imaging now present the clinician with rival diagnostic techniques although for the moment these are currently limited by operator skill, X-ray dosage and expense, respectively. This review appraises the current status of isotopic renography in nephro-urology and emphasises the need for novel clinical developments.

Measuring and imaging renal function

Effective renal plasma flow

para-Aminohippuric acid is almost completely secreted by the kidney and allows for the most accurate estimation of renal plasma flow. However, the technique is laborious and iodine-131 Hippuran (HIP), which is almost exclusively secreted by the tubule with a clearance of 83% of that of para-aminohippuric acid, can be used in its place. Although handled like HIP, the clearance of technetium-99m mercaptoacetyltriglycine (MAG3) is 30%–40% less due to increased protein binding, lower extraction and a smaller volume of distribution. Effective renal plasma flow (ERPF) can be derived from MAG3 clearance data but MAG3 actually provides more important information about tubular function, which, given the importance of tubulo-interstitial injury as a prognostic determinant, could be developed into a useful measurement [1].

Glomerular filtration rate

Gradual increases in tubular secretion of creatinine, coupled with the difficulty in ensuring accurate 24-h urine collections, in patients with chronic renal failure means that sequential creatinine clearance measurements can be misleading [2, 3] and emphasises the need for more definitive measurement. Although there is a close relationship between ERPF and glomerular filtration rate (GFR), it is easier to estimate the latter and inulin clearance is the most accurate. Ethylene diamine tetra-acetate (EDTA) behaves like inulin and can be labelled with chromium-51, which has a long half-life and is safe. Debate continues regarding the optimal administration and sampling protocol but clearly the more plasma and urine samples taken over the longer duration, the greater the test’s accuracy, particularly in patients with reduced GFR [4]. Recent formulations of 99Tc-diethylene-triamine-penta-acetic acid (DTPA) with minimal protein binding [5] provide another means to measure GFR with...
excellent correlation with $^{51}$Cr-EDTA [6, 7] unless the creatinine clearance is below 30 ml/min, when DTPA is less reliable [8].

Iohexol, a non-ionic, low osmolality iodine-containing contrast medium with little protein binding, is cleared almost exclusively by glomerular filtration and provides a measurement of GFR [9] which is as accurate as $^{51}$Cr-EDTA or DTPA [10] unless GFR is low, when none of these methods is reliable anyway. Concentrations are measured by direct measurement using either high-performance liquid chromatography or radiofluorescence or by labelling iohexol (with $^{131}$I or $^{125}$I) and counting with a gamma counter. Structural information can be acquired by simultaneous urography [11] or computerised tomography [12]. Thus although contra-indicated in patients with known reactions to contrast media, iohexol has much to recommend its routine use.

**Dynamic imaging**

Although clear time-activity curve shapes are obtained with HIP, the two-dimensional images generated on gamma camera are poorly defined. Tracers containing $^{99}$Tc are currently the agents of choice for imaging dynamic function and DTPA is the most frequently used, although the quality of the image, which is high with normal function, deteriorates as renal function falls [13]. MAG3 produces even better images and is of particular benefit when GFR is low [14, 15].

**Static imaging**

$^{99}$Tc-dimercaptosuccinic acid (DMSA) is extracted by tubular cells (by a different mechanism to HIP and MAG3) and defines parenchymal structure and divided function. Parenchymal abnormalities detected by DMSA renography include acute pyelonephritis, scar formation, the presence of non-scarring renal damage, duplex kidneys, tubular dysfunction and renovascular disease in patients on ACE inhibitors. Quantitative DMSA renography, in which planar imaging is used to measure absolute uptake, correlates closely with creatinine clearance [16] and could be used to provide functional data routinely. Unless the patient is significantly obese or the renal position is abnormal, DMSA offers no advantage over either MAG3 [17] or DTPA in the evaluation of divided function.

**New radiopharmaceuticals**

New agents with different kinetics, increased ease of labelling, and improved radiochemical purity and stability, such as $^{99m}$Tc-$N,N$-ethylenedicysteine [18], are available although there is no advantage in terms of activity curves or renogram quality. In patients with systemic pathology, such as atherosclerosis, the use of agents (e.g. $^{99m}$Tc-sestamibi), which can provide information about both the cardiac and the renal vasculature is clearly attractive [19]. Finally, established agents such as gallium-67, previously used in patients with chronic inflammation, may have a role in certain chronic renal diseases, such as IgA nephropathy [20].

**New analytical techniques**

The development of computer-generated analyses, such as deconvolution analysis, which more accurately times parenchymal transit [21], increases the information available from renograms. Single-photon emission tomography (SPET) provides more detailed imaging than planar techniques but requires special computer analysis and prolonged examination time; it is currently best restricted to DMSA rather than the rapidly handled isotopes used for functional assessments [22], although this could change with the advent of the multidetector gamma camera [23]. SPET can accurately quantify absolute renal uptake of DMSA [24] and measure split function [25–27], overcome errors due to body thickness [28] and allow more sensitive and specific detection of structural abnormalities, particularly scarring [29–31].

**Conclusion**

The clinician needs integrated information, preferably from a single test, whereas currently isotopic tests tend to provide information about physiological function or dynamic function or structure separately. At this moment, DTPA could provide simultaneous information about physiological and dynamic function in those patients without severe renal failure and this must become routine. Development of SPET analysis could presumably produce additional structural information as well. The goal for radiopharmaceutical and analytical development should be the maximisation of reliable information from a single test, particularly in those patients with impaired function.

**Renovascular hypertension**

In a minority of patients hypertension is secondary to proximal or segmental renal artery stenosis, often with normal renal function. This may be due to either fibromuscular dysplasia in the young or atherosclerosis in older patients. The challenge is to develop a non-invasive screening test which will exclude those hypertensive patients with normal vessels and identify those with significant renovascular disease amenable to intervention therapy.

Although the area under the HIP time-activity curve is now recognised to be significantly reduced with arteri-