

Nuclear medicine: investigation of renal function in small animal medicine

Nucleaire geneeskunde: onderzoek naar de nierfunctie bij kleine huisdieren

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ABSTRACT

Kidney function investigations in veterinary medicine are traditionally based on blood analysis (blood urea nitrogen (BUN) and serum creatinine concentration) and / or urinalysis (urine specific gravity, protein-to-creatinine ratio or fractional excretion). Morphologic information is usually obtained by abdominal radiography or ultrasonography. However, when more specific information on the functionality of the kidneys is needed, nuclear medicine offers various tracers that specifically represent glomerular filtration rate, effective renal plasma flow or functional renal mass, sometimes combining functional and morphologic data. These procedures can be based on blood sampling techniques (non-imaging methods), or data can be obtained using a gamma-camera (imaging methods). The most commonly used radionuclides for the examination of kidney function in small animal medicine are discussed in this review.

SAMENVATTING

Wanneer de nierfunctie bij dieren moet bepaald worden, wordt er gewoonlijk een bloedonderzoek uitgevoerd (voor de bepaling van de ureum- en serum/creatinineconcentratie). Het bloedonderzoek wordt vaak gecombineerd met een urineonderzoek (voor de bepaling van het urinaire soortelijke gewicht, de urinaire eiwit/creatinineratio of fractionele excretie). Morfologische informatie wordt verkregen via de gebruikelijke beeldvormingstechnieken, zoals abdominale radiografie of echografie. Indien er echter meer specifieke informatie nodig is over de nierfunctie, kunnen renale nucleaire merkers gebruikt worden. Afhankelijk van de gebruikte *tracer* bekomt men informatie over de glomerulaire filtratiesnelheid (GFR), de renale doorbloeding (ERPF) of de hoeveelheid functionele niermassa. Sommige van deze *tracers* geven bovendien zowel morfologische als functionele informatie. Sommige onderzoeken zijn gebaseerd op een techniek met bloedstalen (niet-beeldvormend), terwijl men bij andere onderzoeken gebruik maakt van een gammacamera (beeldvormend). In dit overzichtsartikel worden de meest gebruikte merkers voor nierfunctieonderzoek bij kleine huisdieren besproken.

INTRODUCTION

Deterioration of the kidney function is a common disease in older cats and dogs. Although the exact pathogenesis of this disease often remains unknown, the loss of function is mostly contributed to a tubulo-interstitial condition. Clinical signs are often vague and not necessarily related to the kidneys (e.g. weight loss, polyuria, polydipsia). Elevation of serum creatinine (sCreat) and blood urea nitrogen (BUN) does not become apparent until approximately 70 - 75 % of the kidney's functionality is lost (Finco, 1995). Besides blood examination, urinalysis can provide insight in the kidney function, by assessment of the presence of proteinuria or determination of the urine specific gravity.

Plain abdominal radiographs may give some information on the location, size, shape and delineation of the kidneys, although no functional information can be derived. Intravenous contrast urography may give more information on functionality, but is a strenuous proce-

dure and radiographic contrast agents may be nephrotoxic. Therefore these agents must be used carefully in patients suspected of renal disease and must be avoided in patients with severely decreased kidney function. Ultrasound provides more information on the structure and shape of the kidneys and renal tissue, but remains an imaging modality mainly focused on the morphologic features of the kidneys (DiBartola, 2000).

Nuclear medicine techniques have been developed to obtain information on the global kidney function and furthermore, depending on the tracer used, on the individual kidney function. In the early detection of renal disease, the emphasis is mainly put on the estimation of the glomerular filtration rate (GFR) (DiBartola, 2000). However, the scintigraphic evaluation of the different actions carried out by the kidneys is not limited to the GFR. Assessment of functional tubules as a separate entity within the kidney is possible by means of a specific marker reflecting uptake in functional tubular cells. Also, the determination of the effective renal plasma or

blood flow can be accomplished with the appropriate markers.

Kidney function tests with radioactive markers have been historically of great interest in human nuclear medicine. In veterinary medicine, especially cats are prone to kidney disease and eventually kidney failure; it is interesting to apply the findings from human medicine to veterinary medicine. These techniques cannot only be helpful in diagnosing declining kidney function, but also disease progress and the effect of installed therapies, such as a renal diet or surgery, can be monitored. Moreover, many of these tests allow the assessment of the global kidney function as well as the individual kidney function. The latter may be of particular interest, for instance when a surgical procedure (e.g. nephrotomy or nephrectomy) is being considered (Barthez, 1998).

Obviously, due to the use of radioisotopes, these investigations are limited to specialized hospital settings equipped with a nuclear medicine division.

The most commonly used renal radionuclides and their use in dogs and cats are treated in this review. Non-imaging methods (based on blood sampling) and imaging methods (using a gamma-camera) for the measurement of GFR, effective renal plasma flow (ERPF) and assessment of the renal functional mass are discussed.

GLOMERULAR FILTRATION RATE (GFR)

The measurement of the GFR is a good and reliable method to assess the glomerular function of the kidneys. It is directly related to the number of functional nephrons in the kidneys (Gaspari, 1997; DiBartola, 2000), due to the close interaction of the glomerular and tubular mechanisms. Early changes in renal function can be detected by changes in the GFR, even in a non-azotaemic animal (Twardock, 1991; Lees, 2004). It is a suitable method to follow the progression (improvement or deterioration) of kidney function over time or after installment of treatment (Bolliger, 2005), which may be of interest for instance in patients with a low grade of chronic kidney disease. When the individual kidney GFR is obtained, the information may be useful prior to nephrectomy (Barthez, 1998). Global and individual kidney GFR methods have been developed.

The gold standard to evaluate global GFR is based on a constant rate infusion (CRI) with inulin (Lees, 2004). Urine collection during several hours is required for this method, in order to determine the amount of inulin eliminated from the blood through the kidneys over the course of time. Inulin is highly suited for this purpose, because of its pharmacokinetic characteristics: it is freely filtrated through the glomeruli (and solely excreted from the body through glomerular filtration), binding to plasma proteins is absent, as is tubular secretion or reabsorption, and it is inert when passing through the kidneys. On the other hand, there are some disadvantages to this gold standard method. A CRI is not practical and the collection of urine during several hours is also very laborious and impractical. Furthermore, the determination of inulin concentration in the

urine samples is rather costly and not straightforward.

Alternatives have been developed, using both non-radioactive (e.g. creatinine or iohexol) (Finco, 1991; Rogers 1991; Moe, 1995; Brown, 1996; Miyamoto, 2001) and radioactive tracers (Biewenga, 1981; van den Brom, 1981; Krawiec, 1986; Moe, 1995). All markers have similar favorable characteristics for GFR determination, to a great extent resembling the properties of inulin. In human medicine, the choice of tracer is influenced mainly by the availability of the tracer and by work preferences. In general, iohexol (non-radioactive) and ethylene diamine tetraacetic acid (EDTA) labelled with ⁵¹chromium (⁵¹Cr-EDTA) (radioactive) are considered equivalent for GFR determination. If both are available, the ease of determination of ⁵¹Cr-EDTA may outweigh radioprotective considerations, while sample processing of iohexol (using HPLC) is more costly and cumbersome (Brandstrom, 1998). CRI is replaced by intravenous bolus administration of the tracer, and the clearance of the tracer from the blood can be determined with blood or plasma samples.

For all tracers, whether radioactive or not, it is important to establish a protocol and reference values for each tracer separately. Results from different markers should not be extrapolated to other markers or other species.

Considering the nuclear medicine tracers, the quantification of the GFR can be performed with non-imaging or imaging modalities.

Non-imaging methods

Non-imaging methods are based on (several) blood samples, in which the disappearance of the tracer is measured after a bolus injection of the tracer.

Multiple blood samples are taken at set points in time after tracer injection. In these blood samples, the amount of activity (arising from the presence of tracer in the blood) is determined with a gamma well counter. The disappearance of tracer from the blood is based on clearance by glomerular filtration only, and will give an estimation of the *global* GFR with the contribution from both kidneys. The activity in the blood samples is then plotted against the progression of time, yielding a time-activity curve (TAC). Traditionally, the disappearance of tracer is considered to follow a two-compartmental pharmacological model (the first phase being a period of equilibration with the extracellular fluid, the second being the intravascular phase), and the data are fitted using a bi-exponential function, although other models have been investigated (Sapirstein, 1955; Moe, 1995; Heiene, 1998). Individual kidney GFR cannot be determined with this non-imaging method.

Although this method is already easier to perform than the gold standard inulin method, it still requires multiple blood samples. Therefore, simplified methods – with limitation of the sample number – have been developed, making the estimation of GFR with the appropriate nuclear medicine tracers very feasible

and relatively simple to perform. However, one has to keep in mind that a decrease in sample number implies a loss of accuracy. These simplified methods are generally considered to be acceptable for clinical use, especially when they are established in a group of animals with a wide range of renal functionality (Barthez, 2000). Still, the used method should be carefully chosen, partly depending on the expected level of kidney function. When a very low kidney function is expected, it may be necessary to choose a technique based on more than 1 sample. A severely decreased kidney function, although perhaps not difficult to diagnose, possibly hampers an accurate GFR quantification (Picciotto, 1992; Biggi, 1995; Blaufox, 1996; Barthez, 2000).

The best-known nuclear tracer for global GFR estimation based on plasma sampling is diethylene triamine pentaacetic acid (DTPA), labelled with ^{99m}Tc -DTPA. After intravenous administration of ^{99m}Tc -DTPA, it will quickly disperse over the circulating extracellular fluid. Even though a certain (and variable) percentage of plasma protein binding is reported (up to 10% in dogs, unknown in cats), this does not significantly influence the estimated GFR (Twardock, 1991; Uribe, 1992). In the dog, there is no evidence for tubular secretion or reabsorption of the tracer, making it suitable for GFR measurement (McAfee, 1981). Specific data investigating tubular tracer handling for cats are not available. A good correlation with the gold standard inulin measurements was found using the multi-sampling technique in dogs (Twardock, 1991) and cats (Uribe, 1992).

A validated GFR method was established for both dogs and cats with 12 blood samples, taken between 5 minutes and 300 minutes after the IV injection of the tracer (Barthez, 2000). The animals included in this study had different levels of renal function. Based on the reference method, simplified methods were also determined. The optimal sampling times in a four-sample protocol were 10, 20, 90 and 240 minutes after tracer administration, yielding a good correlation with inulin clearance (Barthez, 2000). For practical reasons, further simplification was investigated with reduction of the sample number to 2 (taken at 20 and 180 minutes after tracer injection) or even 1 (taken at 90 minutes after tracer injection) (Barthez, 2001). Both methods have a good correlation when compared to the 12-sample reference method. Although there is an inevitable loss of accuracy with reduction of sample number, the simplified methods are suited for clinical practice, where the costs, efficiency and inconvenience for the patient need to be taken into account (Barthez, 2001).

A global GFR value, determined with the non-imaging ^{99m}Tc -DTPA method, was established between 0.4 and 3.9 ml/min/kg for a group of dogs with varying renal function (normal or decreased renal function), with an average GFR value of 2.0 ml/min/kg (± 0.9 ml/min/kg). No normal values were established in these studies (Barthez, 2000; Barthez, 2001). A GFR

value higher than 2.5 ml/min/kg is considered normal in cats. Decrease of GFR to values between 1.2 and 2.5 ml/min/kg would indicate the presence of a subclinical renal problem, whereas values below 1.2 ml/min/kg often are seen in animals that also have increased levels of BUN and serum creatinine (Russo, 1986).

This methodology was also applied to estimate the effect of radioactive iodine (^{131}I) treatment of feline hyperthyroidism on the kidney function. Hyperthyroidism may temporarily support the kidney function. After treatment of hyperthyroidism, this could result in a decline in kidney function (Graves, 1994; Adams, 1997a). Sixty-eight percent of a group of hyperthyroid cats with GFR values below 2.25 ml/min/kg before treatment developed kidney failure one month after the radioactive iodine treatment (Adams, 1997a). However, hyperthyroid cats may have normal pretreatment ^{99m}Tc -DTPA GFR values (above 2.25 ml/min/kg) (Adams, 1997a) that decrease to abnormally low values after treatment due to the cancellation of the masking effect of excess thyroid hormone on kidney function (Graves, 1994; Adams, 1997b).

As will be discussed further on, ^{99m}Tc -DTPA can also be used for imaging investigations.

Despite the widespread use of ^{99m}Tc -DTPA, ^{51}Cr -EDTA is considered the tracer of choice for (nuclear) GFR studies in human medicine, especially in pediatrics (Chervu, 1982; Blaufox, 1991). The clearance of ^{51}Cr -EDTA has been proven to be similar to that of inulin in both dogs and humans (Favre, 1968). Solely excreted through the kidneys by glomerular filtration, without tubular secretion or reabsorption, and with neglectable plasma protein binding, it is very suitable for GFR studies. Studies in humans and dogs have established a very high correlation with gold standard methods (inulin and urine sampling techniques) (Garnett, 1967; Favre, 1968; Biewenga, 1981; van den Brom, 1981; Gaspari, 1997) and the tracer can be used for follow-up studies after the installment of therapies for kidney related illnesses. Since ^{51}Cr does not emit gamma rays suitable for imaging, it can only be used for non-imaging methods.

Until recently, this tracer had not been used in cats. The use of ^{51}Cr -EDTA in a group of normal and hyperthyroid cats has been investigated. A multiple blood sample (8 samples, taken between 5 minutes and 240 minutes after IV tracer administration) reference method was used (Vandermeulen, 2008). Normal GFR estimation (2.4 ml/min/kg \pm 1.3 ml/min/kg) was very similar to previously reported values obtained with ^{99m}Tc -DTPA (Barthez, 2000). A single and 2-sample method was tested with the 8-sample method as a reference. Both simplified methods (sampling at 48 minutes for the single sample method; first sample taken at 30 minutes after the tracer administration, second sample between 198 and 222 minutes for the two-sample method) gave a good correlation with the reference method ($r^2 = 0.941$ and 0.984 respectively) (Vandermeulen, 2008; Vandermeulen, 2010).

Imaging techniques

The second method for GFR determination is based on imaging techniques.

Contrary to $^{51}\text{Cr-EDTA}$, that lacks gamma-ray emission suitable for imaging, $^{99\text{m}}\text{Tc-DTPA}$ can also be used to visualize the renal handling of the tracer with the aid of a gamma camera. The contribution of the individual kidney to the overall GFR can be obtained, which may be of importance, e.g. prior to a nephrectomy.

The tracer is injected as a bolus at the moment image acquisition is started. The images are acquired in a dynamic way, meaning that several images are obtained during a certain time frame, each lasting for a set time. The bolus of activity can be followed in motion on the images, as it passes through the systemic venous circulation, the heart and lungs, to the arterial systemic circulation, and finally to the kidneys. Part of the injected dose will be briefly accumulated in the kidneys, as the tracer will be cleared from the blood and kidneys by glomerular filtration. The dynamic images of the kidneys are summated, resulting in one composed image. Then, 'Regions of Interest' (ROI's) are applied over each kidney and a background area for background activity correction. Based on the knowledge of the injected amount of activity and the number of counts obtained from the scans, it is then possible to calculate the percentage dose uptake of $^{99\text{m}}\text{Tc-DTPA}$ in each kidney separately (Krawiec, 1986). For dogs, normal global GFR values were estimated to be over 3.0 ml/min/kg (Krawiec, 1986; Kampa, 2003), and the accumulation of tracer correlated well with the clearance of inulin (Krawiec, 1986). Estimated global GFR in normal cats calculated with this technique was found to be 2.91 ml/min/kg (± 0.69 ml/min/kg), which is similar to results from the gold standard technique using a CRI of inuling with both urine and blood sampling (2.64 ml/min/kg ± 1.12 ml/min/kg) (Uribe, 1992; Adams, 1997b). This calculated percentage uptake of injected dose shows a good correlation with the clearance of inulin (Uribe, 1992), which improves even further when a correction is made for activity remaining in the surrounding soft tissue (background correction). The time-activity curves show a peak of activity in the kidneys at approximately 3 – 4 minutes after tracer injection, followed by wash-out of the tracer from the kidney. In cats with clinical signs of renal impairment, it was found that this peak of activity appears only later or not at all (Uribe, 1992). Anaesthesia is often used to restrain the animals during GFR measurements using imaging techniques, and may influence the results, although this remains debated. A study in dogs using different sedative protocols did not reveal significant changes in GFR when compared to GFR measurements in awake dogs (Newell, 1997). However, it has been reported in human medicine (Lessard, 1991) and suspected in cats that anesthesia using isoflurane may increase GFR through systemic hemodynamic changes (Bolliger, 2005). Although this has not yet been investigated thoroughly in cats, one needs to take into ac-

count that sedative or anesthetic protocols, however necessary, may influence GFR measurements (Twardock, 1991; Uribe, 1992; Newell, 1997; Daniel, 1999; Bolliger, 2005). Regarding the processing of the scans, it seems important that the method used (e.g. for ROI placement on the images) is performed in a manner that is as standardized as possible. The error in calculations will be reduced when the processing is always performed by the same operator, or when a (semi-) automatic computer system can be used (Kampa, 2003; Kampa, 2006). A dynamic $^{99\text{m}}\text{Tc-DTPA}$ scan in a normal cat is depicted in Figure 1A and 1B. The different frames visualize the trajectory of the tracer after intravenous injection (Figure 1A), where the image composed of the different dynamic frames also shows the placement of the different ROI's (Figure 1B).

Besides measurement of GFR, the gross localization and shape of the kidneys can be visualized, although $^{99\text{m}}\text{Tc-DTPA}$ is not the nuclear tracer of choice for morphologic information (cf. infra).

The tracer can also be used for detection and evaluation of ureteral obstruction. Dynamic studies in dogs and cats were performed before and after administration of furosemide, and the obtained TAC's were compared (Barthez, 1999a; Barthez, 1999b; Hecht, 2006; Hecht, 2008). Impaired tracer outflow caused by dynamic problems was reversed after furosemide while it persisted in cases of ureteral obstruction. This is a simple and non-invasive method to diagnose upper urinary tract obstruction, and although it was already known longer in dogs (Barthez, 1999b), it has only recently been described in cats (Hecht, 2010).

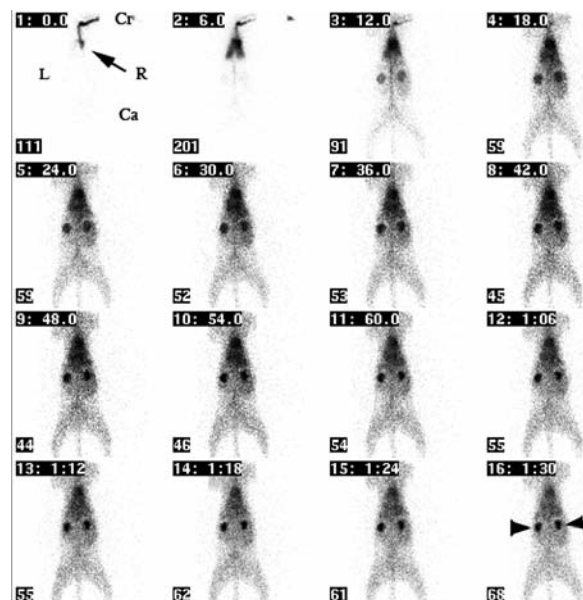


Figure 1A. Fourteen frames of a dynamic $^{99\text{m}}\text{Tc-DTPA}$ scan of a cat (placed in dorsal position, dorsoventral acquisition) allow tracking of the bolus of injected activity. The arrow indicates the arrival of the tracer in the heart. The tracer is distributed over the lungs and further into systemic circulation, and clearly visualizes the kidneys. (arrowheads in the last frame). (Cr = cranial, Ca = caudal, L = left, R = right).

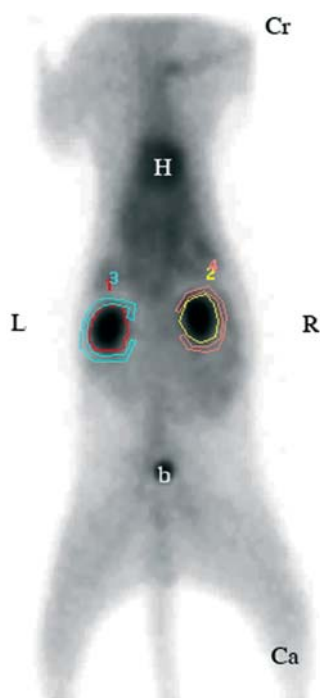


Figure 1B. Summating the separate frames of a dynamic ^{99m}Tc -DTPA scan (cat in dorsal position, dorsoventral acquisition) provides an image on which calculations can be performed by placing ROIs over the kidneys (ROI 1 and 2) and ROIs surrounding for background correction (ROI 3 and 4). Besides activity in the left and right kidney, there is activity in the heart (H), as well as in the urinary bladder (b). (Cr = cranial, Ca = caudal, L = left, R = right).

EFFECTIVE RENAL PLASMA FLOW (ERPF)

The indications for ERPF determination are to a certain extent similar to those for GFR determination. However, it does not represent an actual renal function, but reflects the global and / or individual perfusion of the kidneys (Durand, 2002) (global or individual, depending on the method used). It can be used to evaluate the progression of kidney function over time. Amongst others, a special indication is the assessment of kidney perfusion after transplantation, or to detect the presence of an upper urinary tract obstruction (Diethelm, 1980; Dubovsky, 1995; Tulchinsky, 1996).

Similar to the determination of GFR, the ERPF can also be determined by means of a non – imaging and an imaging technique. The first method is based on the disappearance of the tracer from the blood or plasma. The ideal tracer for these studies will be almost entirely cleared from the blood by the kidneys with one circulatory pass. This implies that the tracer should be extracted from the blood by the kidneys in a highly efficient manner, avoiding the recirculation of tracer after passage through the kidneys. The gold standard tracer for these investigations is para-amino hippuric acid (PAH) (Smith, 1945). However, the determination of PAH concentration in blood or urine samples is technically laborious and requires HPLC equipment. A gold standard method would require constant rate in-

fusion and urine collection over several hours. Alternatively, two nuclear medicine tracers, ^{123}I - or ^{131}I -labelled ortho-iodo hippuric acid (^{123}I -OIH and ^{131}I -OIH) and ^{99m}Tc -labelled mercaptoacetyl triglycine (^{99m}Tc -MAG₃), can be used. Both have a good correlation with the ERPF obtained with PAH, are readily available and allow for easy ERPF determination (Chervu, 1982; Blafox, 1996). Contrary to GFR tracers, elimination of the marker must not happen exclusively through glomerular filtration. More important in these investigations is a high renal extraction rate of tracer from the blood, either by glomerular filtration or tubular secretion. A disadvantage of ERPF determination in comparison to GFR measurement is that it is more prone to physiologic variability. Moreover, as mentioned above, it does not represent a specific kidney function.

After tracer injection, a two-compartmental pharmacokinetic model can be seen, with a first phase of equilibration with the extracellular fluids, and a second intravascular phase.

^{123}I - or ^{131}I -OIH

^{123}I - or ^{131}I -OIH is considered the (nuclear) tracer of choice for the determination of the effective renal blood (or plasma) flow (ERBF or ERPF) through the kidneys (Stadnik, 1980; Blafox, 1991; Blafox, 1996). Its chemical characteristics are very similar to those of PAH. The extraction rate of OIH however is not 100% with each circulatory pass, but goes up to approximately 95% (Daniel, 1999). The majority of the injected OIH is excreted through tubular secretion (up to 80 %), with the remaining 20 % being excreted through glomerular filtration (Daniel, 1999).

Due to the presence of the iodine in the molecule, this tracer can easily be labeled with a radioactive iodine isotope, such as ^{131}I or ^{123}I . A single injection method using ^{131}I -OIH has been investigated for the determination of ERPF based on blood sampling, in dogs as well as in cats (Barthez, 2000). Similar to the GFR measurements, a 12-blood samples method was used as the reference against which methods with a reduced number of samples were compared. For dogs, the mean ERPF determined with ^{131}I -OIH was 134.6 ml/min (\pm 43.5 ml/min) or 7.0 ml/min/kg (\pm 3.3 ml/min/kg) when normalized for bodyweight (Barthez 2000; Barthez, 2001). The mean ERPF for cats was found to be 28.2 ml/min (\pm 11.5 ml/min) or 8.7 ml/min/kg (\pm 4.5 ml/min/kg) (Barthez, 2000; Barthez, 2001). These studies were performed in animals with variable levels of kidney function (including both normal, increased and decreased values) to evaluate the method for a wide range of measurements. Another study in normal cats obtained an average value of 10.12 ml/min/kg (\pm 3.76 ml/min/kg) (Adams, 1997b).

Although the standard error increased with the reduction of samples, still a very high correlation ($r^2 = 0.998$) was found when only 4 samples were taken (at 10, 20, 45 and 150 minutes after tracer injection) (Barthez, 2000). ERPF calculation with only 2 or one blood

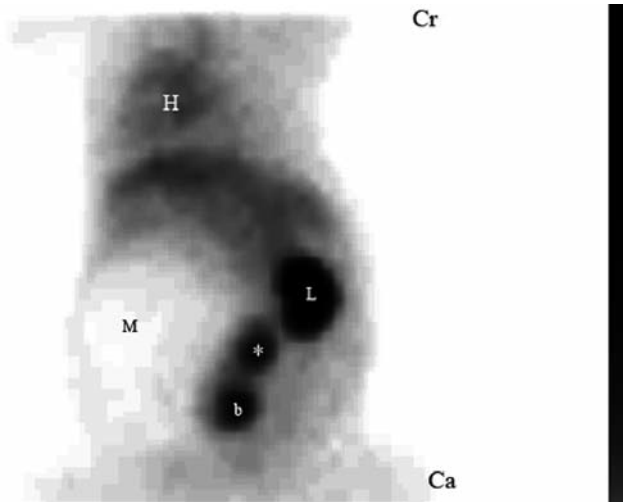


Figure 2A. On the summated image of a dynamic ^{99m}Tc -MAG₃ scan of a dog (ventral position, ventrodorsal acquisition) with a renal mass, the left kidney (L) is clearly visible. The tracer has already been cleared to the urinary bladder (b), and is still visible in the heart (H). The right kidney contains a large non-perfused mass (M) and is not readily identified, although some remnant kidney tissue may be present (*). (Cr = cranial, Ca = caudal).

sample (taken at 20 and 180 minutes after tracer injection for the 2 sample method, and at 20 minutes after tracer injection for the one sample method) still yielded good correlation with the reference method ($r^2 = 0.994$ and 0.965 respectively) (Barthez, 2001).

MAG₃

MAG₃ can be labeled with ^{99m}Tc , making it a very suitable tracer for imaging procedures. Similar to ^{123}I (or ^{131}I)-OIH, it can be used for calculation of the renal blood / plasma flow in veterinary medicine (Itkin, 1994; Drost, 2000). ^{99m}Tc -MAG₃ is mainly excreted through tubular secretion (up to 90%), with the remainder being cleared from the blood through glomerular filtration. A high percentage of the injected ^{99m}Tc -MAG₃ is bound to plasma proteins, although this is mainly reversible. Even though the clearance of ^{99m}Tc -MAG₃ is lower than the clearance of ^{123}I - OIH, still a very high level of agreement between both tracers was found when screening ^{99m}Tc -MAG₃ for ERPF calculation in human medicine (Eshima, 1992; Daniel, 1999). Normal ERPF as determined with MAG₃ in dogs was found to be 7.0 ml/min/kg (Lora-Michiels, 2001), which is similar to the aforementioned findings using labelled OIH. For cats, this was set at 5.3 ml/min/kg (Drost, 2003), a lower value than the findings with labelled OIH. In patients with severely impaired renal function, ^{99m}Tc -MAG₃ can be used, rather than ^{99m}Tc -DTPA for individual kidney function assessment because of its faster clearance and higher extraction fraction (Taylor, 1990; Eshima, 1992; Drost, 2000). It will render better images even when the kidney function is low, because of lower remaining activity in the surrounding soft tissue.

When imaging procedures are performed, ^{99m}Tc -

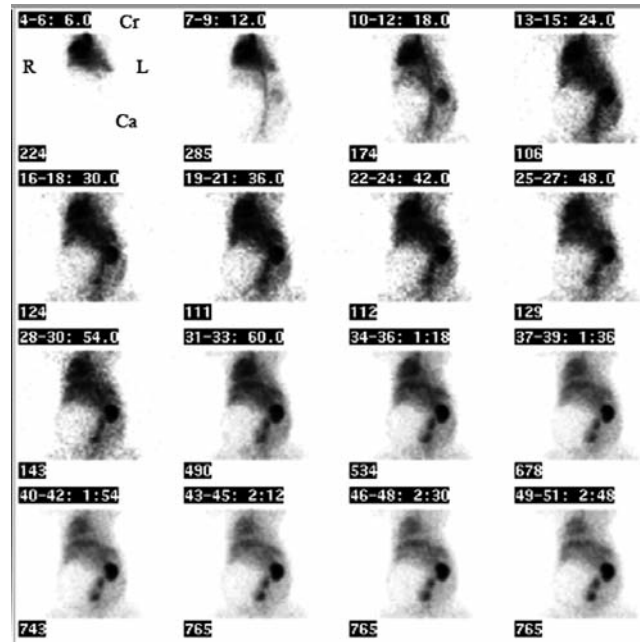


Figure 2B. The different frames of a ^{99m}Tc -MAG₃ scan of a dog (ventral position, ventrodorsal acquisition) with a renal mass. At no point in time, the mass seems to be perfused. (Cr = cranial, Ca = caudal, L = left, R = right).

MAG₃ is preferred over ^{123}I (or ^{131}I) - OIH, due to the superior imaging qualities of ^{99m}Tc , and also due to the high cost of the ^{123}I used for labelling. Figure 2A depicts the summated frames of a ^{99m}Tc -MAG₃ scan of a dog with a renal mass; the separate frames of the start of the scan can be seen in Figure 2B. This scan was performed prior to nephrectomy in order to evaluate the perfusion of the renal mass, and to estimate the viability of the remaining kidney.

In cats it has been demonstrated that up to 16% of the ^{99m}Tc -MAG₃ clearance occurs by the liver (Drost, 2000; Drost, 2003), which may interfere with the calculation of ERPF (Drost, 2003) and may be responsible for the lower ERPF values with MAG₃ in cats when compared to results from OIH studies. It has therefore been recommended not to use ^{99m}Tc -MAG₃ for ERPF calculation based on blood sampling techniques, since no distinction can be made between tracer cleared through the kidneys or through the liver. Imaging techniques are a better choice in cats, since they allow correction for extra-renal activity (Drost, 2003).

A general remark that can be made for imaging methods for ERPF measurement, similar to the remark for GFR estimation using ^{99m}Tc -DTPA scans, is that image processing should be as much standardized as possible in order to reduce errors in the measurements (Kampa, 2003; Kampa, 2006).

RENAL FUNCTIONAL MASS

Renal nuclear medicine imaging techniques offer a combination of information on the morphologic aspects of the kidneys, as well as their functionality. Although other imaging techniques (e.g. abdominal ultrasonography, magnetic resonance imaging) give a more de-

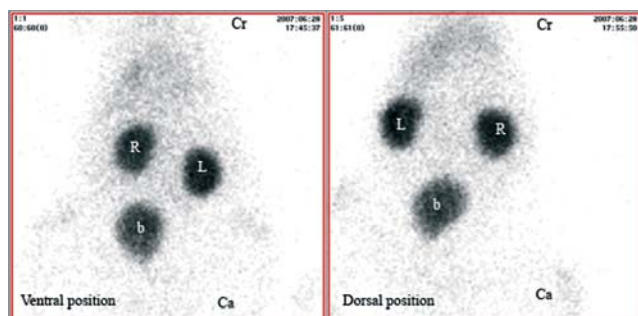


Figure 3A. Two acquisitions using ^{99m}Tc -DMSA of a cat, 4 hours after tracer injection. On the left image, the cat was placed in ventral position (ventrodorsal projection); on the right image, the cat was placed in dorsal position (dorsoventral projection). Due to flexibility of the kidneys in the cat's body, their position may change notably, urging for particular care in positioning of the animals on the camera. (L=left kidney, R=right kidney, b=urinary bladder). (Cr = cranial, Ca = caudal).

tailed image of the kidneys, each nuclear tracer suitable for imaging gives an idea of the shape, size, outline, position or homogeneity of the kidneys. ^{99m}Tc -labelled radiopharmaceutica in particular are highly suitable for this purpose, because of their superior imaging qualities, reasonable price and excellent availability. The low energy and especially the relative short half-life of ^{99m}Tc keep the radiation burden low for patient and practitioner. Although ^{99m}Tc -DTPA or ^{99m}Tc -MAG₃ can be used for imaging studies, their presence in the kidneys is very variable over time because of the constant clearance from the body through the kidneys. The renal nuclear medicine agent of choice in human medicine for obtaining morphologic information is the chelating agent dimercaptosuccinic acid (DMSA) (Blaufox, 1991).

^{99m}Tc -DMSA

^{99m}Tc -DMSA accumulates in the kidneys, mainly in the proximal convoluted tubules. The renal handling mechanisms are not entirely clarified, although a glomerular and a tubular component are involved. Because of the specific tubular localization - leaving the lower tubules and collecting ducts void of tracer - ^{99m}Tc -DMSA scans reflect the amount of functional renal mass, primarily located in the renal cortex (Enlander, 1974; Kawamura, 1979). After accumulation, static image acquisition is possible several hours after tracer injection. In dogs, the static scans are generally obtained 3 to 6 hours after tracer administration (Daniel, 1999; Kerl, 2005). The high quality scans give excellent information on the position and morphology of the kidneys, and the relative renal function (or individual kidney function) can be calculated (Blaufox, 1991). The presence of a renal mass, cysts or scar after trauma or urinary tract infection can be identified, as they will not contain normal renal tissue and thus will not accumulate the tracer.

This tracer has only recently been introduced in feline nuclear medicine. The optimal methodology for

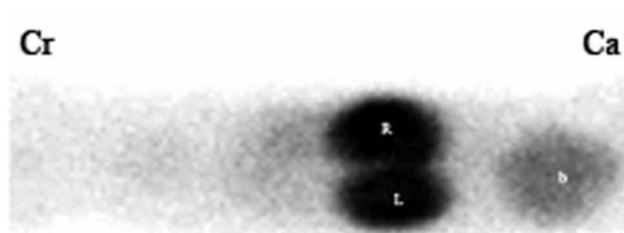


Figure 3B. A ^{99m}Tc -DMSA scan (4 hours after tracer injection) of a cat in left lateral recumbency (dorsoventral acquisition). The activity of the kidneys overlaps, making quantification of the separate kidney function unreliable. (L = left kidney, R = right kidney, b = urinary bladder). (Cr = cranial, Ca = caudal).

use of ^{99m}Tc -DMSA and the feasibility of applying the tracer in cats were investigated (Vandermeulen, 2010, unpublished data). Due to the high flexibility of the organs in the feline abdomen, the correct positioning of the cats is imperative to obtain reliable results. Figure 3A is a dorsoventral ^{99m}Tc -DMSA scan of 1 healthy cat in 2 different positions (ventral and dorsal position) and shows the movability of the kidneys in the feline body. Although the kidneys seem to move more laterally when the cat is positioned in dorsal position, both dorsal and ventral position allow clear distinction between both kidneys. It was also demonstrated that quantification of kidney function from scans with the animals in lateral recumbency (with different imaging tracers) is unreliable, although several studies describe this position (Uribe, 1992; Drost, 2003). Due to the flexibility of the feline kidneys, activity from one kidney may be superimposed onto the other kidney to a certain degree (Figure 3B).

When knowledge about the relative (or split) renal function is needed, there are some options to choose from. However, they all require imaging modalities. Based on the cumulative images of a ^{99m}Tc -DTPA (Drost, 2000) or ^{99m}Tc -MAG₃ scan (Eshima, 1992), the individual contribution of the kidneys to the GFR or ERPF can be calculated. Changes in renal activity occur rapidly, implying that the split renal function calculations also may vary over time. For instance, a study in normal dogs reported an average day-to-day variability of GFR estimation using ^{99m}Tc -DTPA of 8.45 % (\pm 4.9 %) (Kampa, 2003). ^{51}Cr -EDTA is the nuclear tracer of choice for GFR estimation in human medicine, and allows the application of simplified plasma clearance methods. Since it is not suited for imaging studies, it can be combined with a ^{99m}Tc -DMSA scan, a good representative of the functioning kidney mass. Combining the overall estimated GFR from the ^{51}Cr -EDTA investigation and the relative uptake of ^{99m}Tc -DMSA yield the relative estimated GFR for the individual kidneys (Arnello, 1999; Piepsz, 2006).

CONCLUSION

When there is a need for information on a specific renal function, various nuclear medicine tracers can be used. Routine methods have been developed in human

and veterinary medicine. Depending on the desired level of accuracy, it is possible to use more simplified methods – with a small loss in accuracy but gaining time and effort – or more elaborate methods, mostly used in research settings. Certain investigations do not even necessitate the use of a gamma-camera for imaging, but can be performed by simple blood sampling. Information on the GFR, ERPF and the estimation of relative renal function can thus be easily obtained in any clinical environment equipped for nuclear medicine studies. In clinical practice, the most applicable study for kidney function investigation, for evaluation of kidney disease progression or for pretreatment screening is GFR measurement. For this purpose, either the combination of a reduced sampling $^{51}\text{Cr-EDTA}$ GFR estimation and $^{99\text{m}}\text{Tc-DMSA}$ scan (for individual kidney function) or a $^{99\text{m}}\text{Tc-DTPA}$ scan are the most practical methods. Only when the kidney function is expected to be very low, it may be advisable to perform a $^{99\text{m}}\text{Tc-MAG}_3$ examination, due to its favorable characteristics in cases of low kidney function. For dogs, this can then be performed by either blood sampling or imaging. For cats, only the imaging method should be used. It is important that, although both investigations supply similar information, the same method should be maintained for patient follow-up.

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Uit het verleden

REIN EN ONREIN VOEDSEL

Van oudsher waarden allerhande menselijke maatschappijen de dieren in termen van wild en tam, nuttig en nutloos of zelfs schadelijk, maar vooral als eetbaar en oneetbaar. Dit laatste onderscheid werd dikwijls in een religieuze context ingebed, waardoor het een dwingend karakter kreeg. Zeer bekend zijn de oudtestamentische regels zoals die in het boek Leviticus (hoofdstuk 11) worden uiteengezet: *En de Heere sprak tot Mozes en tot Aäron, zeggende tot hen; spreek tot de kinderen Israëls, zeggende: dit is het gedierte dat gij eten zult uit alle beesten die op aarde zijn.* De voorschriften zijn zeer gedetailleerd en expliciet. Zijn acceptabel: beesten met in twee gespleten klauwen die ook herkauwen (exclusief dus varkens die niet herkauwen, of herkauwers zoals kamelen en caecotrofe konijnen en hazen die geen gespleten klauwen hebben), in het water levende dieren met vinnen en ook schubben en zelfs sommige insecten, zoals sprinkhanen. Niet eetbaar zijn een twintigtal met naam opgesomde vogelsoorten waaronder arenden, haviken, kraaien, raven en verder ook nog gedierte dat op of onder de aarde kruipt. Uiterst streng is het verbod op het eten van aas (doodgevonden dieren) en alles wat daarmee in aanraking komt.

Deze verboden en regels leven in varianten en aanvullingen nog door in de voorschriften voor het kosjer en halal voedsel (rein in religieuze zin), de wijze van slachten inbegrepen. In het christendom verdween het onderscheid tussen rein en onrein voedsel mettertijd. In de vroege middeleeuwen vervaardigde de kerk nog verboden uit op het eten van kraaiachtigen, ooievaars, hazen, bevers en paarden. Vooral het taboe op het eten van paardenvlees is welbekend. Het zou gebaseerd zijn op de betekenis van dit dier in sommige heidense rituelen. Het is zoals ook andere taboes sterk geografisch gedetermineerd. Zo is paardenvlees in Japan een delicatess (basashi).

Van belang voor de lokale West-Europese tradities is vooral het volgende. Tijdens de reformatie en haar katholieke tegenhanger, de contrareformatie (jaren 1500–1600), veranderde de houding van de kerken. Voedingsgewoonten hadden voortaan niets met religie te maken. Het onderscheid tussen rein en onrein was door de komst van Christus opgeheven, zo werd gesteld. Voor de reinen van geest waren immers alle dingen rein. Alleen sommige sektariërs hielden vast aan de leer dat het bijvoorbeeld zondig was varkensvlees te eten. Ze steunden hiervoor op het verbod uit het oude testament of op het verhaal van Jezus die boze geesten in varkens had doen varen.

Dit betekende echter geenszins dat de voedingsgewoonten meteen veranderden. Naast inertie en gewoonte bleven immers heel wat andere subjectieve factoren onverkort een rol spelen in de aanvaardbaarheid van diverse dieren (of van dieren in het algemeen) als voedselbron, maar dat is een ander verhaal.

Bronnen

Bijbel, dat is de gansche Heilige Schrift (Staten-bijbel) en Thomas, K., *Man and the Natural World, changing attitudes in England (1500 – 1800)*, Lane, London, 1983. Vertaald als *Het verlangen naar de Natuur*, Agon, Amsterdam, 1990.

Zie ook: Devriese L. (2008). Varkensvlees: taboe of schaars. *Vlaams Diergeneeskundig Tijdschrift* 77, 455.

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