



Timing of diuretics in diuresis renography

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Abstract

Purpose The aim of this systematic literature review was to obtain an overview of when to administer the diuretics in relation to the radiopharmaceutical during a diuresis renography.

Methods A systematic literature search was performed in three different databases (Embase, PubMed/Medline and Cochrane Library) together with an information specialist. The review question was: when should diuretics be administered in relation to the radiopharmaceutical in a diuresis renography? Studies of adults were included together with guidelines published in collaboration with an organization.

Results Seventeen articles and four guidelines were retrieved in the literature search. The F – 15 method (diuretics administered 15 min before the radiopharmaceutical) was the one that was studied and described most and was compared with other time points for diuretic administration. The retrieved articles and guidelines report of advantages with different time points for diuretics. Both F – 15 and F + 0 are reported to clarify washout in equivocal cases compared to F + 20.

Conclusion No consensus could be found for a preferred time point of diuretics administration during a diuresis renography.

Keywords Renography · Diuresis renography · Diuretic timing · Furosemide

Introduction

A diuresis renography is an examination where a diuretic, commonly furosemide, is administered during radionuclide renography to distinguish between obstruction and prolonged renal drainage [1, 2]. Furosemide increases the urine flow rate and has a rapid onset. Its renal action begins within the first few minutes after intravenous diuretic administration and the maximal urinary flow rate occurs after approximately 15 min [3]. However, in an obstructed kidney, the washout can remain slow even after diuretic administration with a prolonged retention of radiopharmaceutical proximal to the obstruction [4].

There is variability in the methodology of renographies between different Nuclear Medicine departments, mostly concerning the timing of the diuretic administration in relation to the radiopharmaceutical administration.

A study or a method where the diuretic is administered after the radiopharmaceutical is described as F+ and before the radiopharmaceuticals as F–. The F + 20 method, i.e. diuretics given 20 min after the radiopharmaceutical, has been considered to be the traditional method [2].

There have been reports of modified methods of the traditional diuresis renography where other time points for diuretic administration were described. One such method was the F – 15 where the diuretics were administered 15 min before the radiopharmaceutical and another method was F + 0 with the diuretics administered at the same time as the radiopharmaceutical, summarized by O’Reilly [2]. Other time points of diuretics are used as well in diuresis renographies.

Aim

The aim of this literature review was to obtain an overview of when to administer the diuretics in relation to the radiopharmaceutical during a diuresis renography. Is there a preferred time point of diuretics administration during a diuresis renography?

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Materials and methods

This systematic literature review was registered in the Prospero database (CRD42020167484) and followed the method “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) [5]. The PICO method, where four different areas are described (Population, Intervention, Comparison, Outcome) [6] was used to address the review question. The PICO aimed to give an overview of when to administer diuretics in relation to the radiopharmaceutical in diuresis renography, Table 1.

Literature search

The primary literature search was performed in May 2019 in three different databases for published articles and guidelines (Embase, PubMed/Medline and Cochrane Library) together with an information specialist. A secondary search was performed in February 2021 to include newer publications.

Synonyms of the words renography and diuretics were combined and used as search expressions to address the PICO question, Appendix 1. There was no limitation as to the publication year in the literature search process.

Duplicates were removed before two researchers (AKB and HG) individually read the retrieved titles and abstracts from the literature search. Abstracts that were selected by at least one reader were read independently in full text by both readers.

The collected articles and guidelines had to have been published in a paper listed in the Web of Science and written in English to be selected for full-text reading. Guidelines of relevant topics published in collaboration with an organization were also included. The content of the articles and guidelines had to concern diuresis renographies of adults where the timing of furosemide in relation to a radiopharmaceutical were studied or described. Non-original articles, articles on topics not relevant to the study, or articles that only included children were excluded, Appendix 2. Disagreements after full-text reading were resolved by consensus between the two readers. Basic information, such as author, country, year of publication, study type and number of participants were noted for each included article.

The radiopharmaceuticals that were used in the performed renographies and the different timepoints of the administered diuretics were noted as well.

Data extraction

Data extraction was performed and double-checked by two researchers (AKB and CS). Due to the lack of homogenous numerical results, a meta-analysis could not be performed, and the results are reported in a narrative format.

Quality assessment

A quality assessment form influenced by QUADAS-2 and the Newcastle–Ottawa scale was created and used when assessing the included articles [7, 8]. The quality assessment form contained nine questions in four different domains as well as a domain question which summarized each domain, Table 2.

Each article was graded individually by two researchers (AKB and HG) using a three-grade scale when assessing the different domain questions (low risk or high risk for bias, and unclear). Guidelines were not included in the quality assessment process. No exclusions were made during this process.

Results

There were 17 articles and four guidelines relevant to the review question, Fig. 1.

The included articles were published between the years 1978 and 2020 [9–25]. The number of participants varied between 14 and 320. The radiopharmaceutical ^{99m}Tc -MAG3 was administered in six studies [11, 17–19, 24, 25], ^{99m}Tc -DTPA in five studies [9, 12, 13, 20, 22], ^{123}I -OIH in four studies [15, 16, 21, 23], ^{99m}Tc -EC in one study [10] and one study did not mention which radiopharmaceutical had been administered [14]. Five studies had a retrospective study design [15, 17, 22, 24, 25] and 12 studies had a prospective study design [9–14, 16, 18–21, 23]. Four articles included both children and adults in their studies [16, 17, 20, 22], Table 3.

Table 1 The review question and the four different areas: population, intervention, comparison and outcome

<i>PICO</i>	
Review question	When should diuretics be administered in relation to the radiopharmaceutical in a renography, F + 10, F + 20 or other?
Population	Adult patients with the clinical question of obstruction or split renal function
Intervention	The time of furosemide administration in relation to the radiopharmaceutical administration during a renography
Comparison	Other timepoints for diuretic administration or no administration
Outcome	Optimal differential between obstruction or no obstruction

Table 2 A summary of the quality assessment form

	Domain 1 patient selection	Domain 2 index test(s)	Domain 3 selection of controls	Domain 4 flow and timing
Question 1	Was a consecutive or random sample of patients enrolled?	Was the diuretic method described properly?	Was the comparison between groups performed in the same patients?	Was there an appropriate interval between test(s)?
Question 2	Did the study avoid inappropriate exclusions?	Was there a comparison between groups in the study?	Were all patients included in the analysis?	
Question 3	Could the selection of patients have introduced bias?	Is there a concern that the index test, its conduct, or interpretation differ from the review question?	Is there a risk of bias in the comparison between groups?	Is there a risk that the patient flow could have induced bias?
Domain question	Is there a risk that the included patients could have introduced bias or do not match the review question?	Is there a risk that the conduct of the index test or interpretation could have introduced bias?		

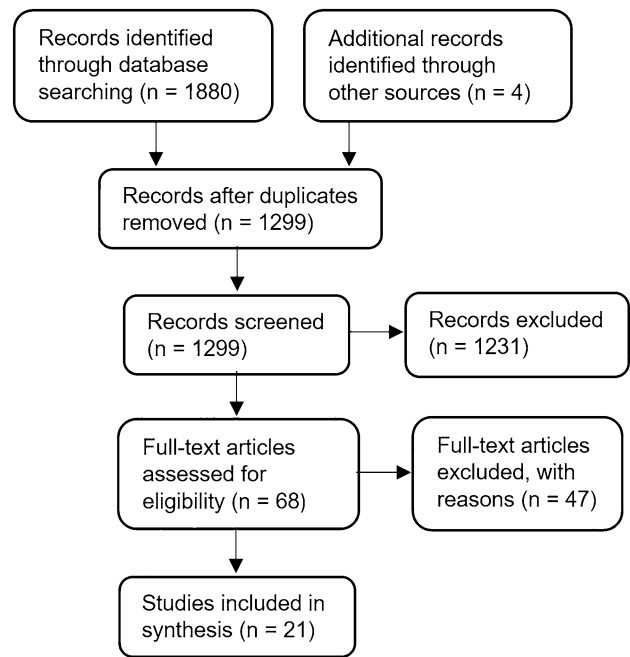


Fig. 1 Study flow diagram

The F – 15 method was the method that was studied and described most in the published articles. Five studies compared the F – 15 method with the standard, F + 20 method [9, 10, 14–16]. The F – 15 method gave fewer equivocal results and led to clarification in cases of equivocal results compared to the F + 20 method [9, 10, 15]. Furthermore, an equivocal response in F + 20 could be converted to a normal response by F – 15 [14]. English et al. reported that the F – 15 method could increase the specificity of diuresis renography in patients with equivocal pelviureteric junction obstruction [16].

Sultan et al. compared the F – 15 method with the F + 15 method and concluded that the F – 15 method resulted in fewer equivocal results than the F + 15 method did [13]. Turkölmez et al. compared three different methods (F – 15, F + 0 and F + 20) with each other in the same patient group. The reported results were that the F + 0 and the F – 15 methods allowed classification of equivocal F + 20 results. Furthermore, that the F + 0 method is a more practical and shorter technique than F – 15 and therefore a better alternative, especially if there is only one opportunity to confirm or exclude obstruction [18]. Adeyoju et al. included three different methods as well and compared the F + 0 method with the F – 15 method or the F + 20 method in their study. They reported that the F – 15 method had the best record in terms of reducing equivocal results compared to both F + 20 and F + 0. Moreover, that the F + 0 method gave similar results to F + 20 but could reduce the time required compared to F + 20 [11]. Liu et al. compared the F + 0 method

Table 3 Articles and guidelines in PICO

○ = Low risk/Low concern. ● = High risk/High concern. ● = Unclear.

Author [reference] Country or Organisation	Year	Type of study Participants	Study aim	Radiopharmaceutical (described diuretic timepoint(s))	Outcome	Quality Assessment			
						Domain 1	Domain 2	Domain 3	Domain 4
Sachpekidis [25] Switzerland	2020	Retrospective 120 patients	To evaluate the intra- and inter-observer agreement when assessing the renal function in ^{99m} Tc-MAG3 diuretic renographies	^{99m} Tc-MAG3 (F+10)	The reader's experience is important when calculating renal parameters as the assessment of differential renal function and T _{max} . Reader training could be of value. The manual tool was better in assigning regions of interests than the semi-automated tool	○	○		○
Bäck [24] Sweden	2020	Retrospective 320 patients	To discover a cutoff value of residual radioactivity in the kidneys at 7 minutes into the F+10 renography, to use as a threshold in the diuretic decision	^{99m} Tc-MAG3 (F+10)	F+10 renography is feasible and acceptable in clinical practice. The suggested cutoff value to use in clinical practice is 85% of the maximum activity	○	○		○
Kumar [9] India	2018	Prospective 51 patients	To investigate if F-15 can reduce inconclusive results of F+20 in hydronephrotic kidneys	^{99m} Tc-DTPA (F-15 and F+20)	F-15 showed significantly less equivocal results and clarification in cases of equivocal results of F+20 protocol	○	○	○	○
Kandeel [20] Egypt	2013	Prospective 102 patients (including children)	The effect of timing, F+0 or F+10, on the split renal function compared with ^{99m} Tc-DMSA	^{99m} Tc-DTPA (F+0 and F+10)	Discrepancy in split renal function between F+0 and F+10 in favour of F+10	○	○	●	○
Tartaglione [19] Italy	2013	Prospective 36 patients	To compare F+10 with F-15 for diagnosis of obstructive uropathy	^{99m} Tc-MAG3 (F+10 and F-15)	F+10 (seated position) reduces the equivocal findings of F-15. The lower dose and a better timing of diuretics could lead to less bladder filling related problems and therefore improve patients' compliance	●	○	○	○
Taghavi [10] Iran	2007	Prospective 21 patients	To compare F-15 with F+20 in patients with upper urinary tract dilatation	^{99m} Tc-EC (F+20 and F-15)	Obstruction was discovered in more cases by the F-15 method than by the F+20 method. F-15 protocol may reduce the equivocal results of the F+20.	●	○	○	○
Liu [17] USA	2005	Retrospective 85 patients (including children)	To compare if F+0 resulted in more patients able to complete the acquisition without disruption due to voiding than F-15	^{99m} Tc-MAG3 (F+0 and F-15)	More renographies were interrupted because of voiding in the F-15 cohort than in the F+0 cohort	○	○	●	●
Turkolmez [18] Turkey	2004	Prospective 22 patients	To compare the diagnostic impact of F+20, F-15, and F+0 in cases with upper urinary tract dilatation	^{99m} Tc-MAG3 (F+20, F-15 and F+0)	F+0 and F-15 allowed classification in cases of equivocal F+20 studies. F+0 is recommended when equivocal results are obtained by F+20 or when only one opportunity exists to confirm or exclude obstruction	●	○	○	●
Adeyoju [11] UK	2001	Prospective 29 patients	To investigate F+0 with F+20 or F-15 in the effect on assessing split renal function and interpreting upper tract drainage dynamics	^{99m} Tc-MAG3 (F+0, F+20 and F-15)	F+0 gives similar results to the conventional techniques, reduces the time required, but may not be useful in evaluating the grossly dilated upper tract. F-15 has the best record in terms of reducing equivocal results	●	○	○	○
Altarac [12] UK	1998	Prospective 28 patients	To introduce and evaluate an obstruction score, based on the F-15 renographic washout curve analysis	^{99m} Tc-DTPA (F-15)	The obstruction score system is a sophisticated interpretation approach to the renographic washout curve	●	○		○
Sultan [13] Pakistan	1996	Prospective 52 patients	To compare the role of F+15 and F-15 in the evaluation of ureteropelvic junction obstruction	^{99m} Tc-DTPA (F+15 and F-15)	F+15 gave a reliable assessment of the upper tract drainage. Equivocal cases were resolved by the F-15 and were more conclusive in assessment compared to F+15	●	○	○	●
Upsdell [15] UK	1992	Retrospective 50 patients	To report the results of a long-term follow-up study of patients investigated by the F-15 method compared with F+20	¹²³ I-OIH (F-15 and F+20)	F-15 agreed in unobstructed cases, confirmed unobstruction in some hypotonic washout cases and clarified washout in most equivocal washout cases compared to standard method	○	○	○	●
Upsdell [14] UK	1988	Prospective 14 patients	To report the relation between urinary flow rates induced by diuretics and creatinine clearance levels. Also, the differences in split renal function and washout curves between F+20 and F-15 in a separate study	Not mentioned (F+20 and F-15)	There was no statistical difference in the split renal function between F+20 and F-15. An equivocal response in F+20 was converted to a normal response by F-15 in 4 of 14 washout curves	●	●	○	●
English [16] UK	1987	Prospective 30 patients (including children)	To report a modification of the standard diuresis renography	¹²³ I-OIH (F-15 and F+20)	F-15 increases the specificity of diuresis renography in patients with equivocal pelviureteric junction obstruction	●	○	○	●
Arap [21] Brazil	1984	Prospective 32 patients	To differentiate between obstructed and atonic ureters with diuretic stimulus	¹²³ I-OIH (F+15)	Diuretic stimulus allows differentiation between obstructive and hypotonic processes by stimulating the washout of the radiopharmaceutical from the nonobstructed urinary tract	●	○		○
Koff [22] USA	1979	Retrospective 41 patients (including children)	To present the methodology and results of diuretic radionuclide urography	^{99m} Tc-DTPA (F+10-20)	The three different and clinically significant patterns of radionuclide uptake and excretion were described: Normal, dilated non-obstructed and obstructed	●	●		○
O'Reilly [23] UK	1978	Prospective 52 patients	To describe a non-invasive method of investigating equivocal upper tract obstruction with diuretic provocation	¹²³ I-OIH (F+30)	The function and drainage capability can be assessed with this method and is recommended in all states of equivocal obstruction before proceeding to more invasive procedures	●	○	○	○
Taylor [26] SNMMI and EANM	2018	Guideline	Recommending, performing, interpreting and reporting diuretic renal scintigraphy in the setting of suspected renal obstruction in adults	^{99m} Tc-MAG3, ^{99m} Tc-DTPA, ^{99m} Tc-L/LU D.D-ED, or ¹³¹ I/123I-OIH (F+30, F+20, F+10, F+0, F-15, Fmax)	F+0 is most convenient and minimizes imaging time, F-15 and F+10sp allow better discrimination between obstructed and nonobstructed kidneys. F+20, F+30, Fmax, dual-acquisition protocols allow observation of natural urinary drainage kinetics				
British Nuclear Medicine Society [27]	2011/2018	Guideline	Recommending, performing, interpreting and reporting the results of dynamic renal radionuclide studies	^{99m} Tc-DTPA, ^{99m} Tc-MAG3 or ^{99m} Tc MDP (medronate) (F+20, F+0, F-15)	F+20 can be used when the kidneys have not emptied satisfactorily during the first 20 minutes of acquisition, F-15 when knowledge or suspicion of obstruction exists beforehand, F+0 is commonly used in paediatrics				
François [28] EANM (Technologist guide)	2009	Technologist guide	A technologist guide that focuses on dynamic imaging techniques in obstructive renal pathology	^{99m} Tc-DTPA or ^{99m} Tc-MAG3 (F-15, F+0, F+10, F+15, F+20)	There is no consensus as to the time of furosemide administration in renographies				
O'Reilly [29] International Consensus Committee	1996	Consensus report	To standardize the technical aspects, performance and interpretation of diuresis renography	^{99m} Tc-MAG3, ^{99m} Tc-DTPA, ¹²³ I-OIH (F+20, F+0, F-15)	F-15 is recommended when the F+20 is equivocal, or as a one-stop maximal-diuresis renogram instead of the traditional F+20 technique				

The table also visualizes the quality assessment in four different domains graded in three different colors: ○ = low risk/low concern, ● = high risk/high concern, ● = unclear

with F – 15 method and reported that a greater part of the patients could complete the diuresis renography with the F+0 method since more examinations were reported to be disrupted with the F – 15 method due to voiding issues [17].

Three articles reported results concerning administering the diuretics 10 min after the radiopharmaceutical i.e., the F+10 method [19, 20, 24]. Tartaglione et al. reported that the F+10 method (in seated position) could reduce the equivocal findings of the F – 15 method (in supine position) and lead to fewer bladder filling related problems. However, a lower dose of diuretics was administered in the F+10 method compared to the F – 15 method in this study [19]. Kandeel et al. compared F+0 with F+10 and reported a discrepancy in split renal function between F+0 and F+10 and in favor of F+10 [20]. Bäck et al. compared a modified F+10 method (with a cut-off value for diuretic decision) with the F+20 method and reported the F+10 method to be a feasible and acceptable method in clinical practice [24].

Five studies did not compare different methods with each other; instead, they addressed a certain question and described which of the different methods they had used in their studies [12, 21–23, 25]. Arap et al. described the F+15 method and reported that diuretic administration allowed differentiation between obstructive and hypotonic processes [21]. Koff et al. presented a methodology and results of diuresis renography where the diuretics were administered 10–20 min after the radiopharmaceutical [22]. O'Reilly et al. described the F+30 method and reported the method to be a method of investigating equivocal urinary upper tract obstruction with diuretic provocation [23]. Altarac S. introduced and evaluated an obstruction score system based on the F – 15 method [12]. Sachpekidis et al. evaluated the intra- and inter-observer agreement when assessing the renal function in diuresis renography when using the F+10 method and, reported that the reader's experience is important when calculating renal parameters and that reader training could be of value [25].

Four guidelines published between 1996 and 2018 were found in the literature search process [26–29], Table 3. The different methods concerning time points for diuretic administration that are described in all four guidelines are F – 15, F+0, and F+20 [26–29]. The F+10 method is described in two guidelines [26, 28]. The F+30 method and the Fmax (diuretic administration when the activity in the collecting system appears to have reached a maximum) are described in one guideline [26] and the F+15 method is described in one guideline [28].

The British Nuclear Medicine Society state in their guideline that when an obstruction is known beforehand, the F – 15 or the F+0 methods could be used and that the F+0 method often is used in pediatrics [27]. The International Consensus Committee reported in their guideline that the F – 15 method is recommended when the F+20

is equivocal, or as a one-stop maximal-diuresis renogram instead of the traditional F+20 method [29]. Another guideline by European Association of Nuclear Medicine in collaboration with Society of Nuclear Medicine and Molecular Imaging states that the F – 15 method could allow better discrimination between obstructed and nonobstructed kidneys. Furthermore, that the F+10 method (in seated position) has been reported to give comparable or superior results to the F – 15 method and, that the F+0 method could minimize imaging time and, therefore, be the most convenient method [26].

As a summary, all the described different renography methods can be used when the function and drainage capability are to be assessed. The F+20 method can be used when the kidneys have not emptied satisfactorily during the first 20 min of acquisition [22, 26, 27]. The F – 15 method has been reported to agree with F+20 in unobstructed cases and show less equivocal results and clarification in cases of equivocal results with F+20 [9–11, 14–16, 26, 29]. The F+0 method can be used when only one opportunity exists to confirm or exclude obstruction [18]. Furthermore, it can minimize the examination time and make less examinations interrupted because of voiding issues than the F – 15 method [17, 26]. The F+10 method in seated position could reduce the equivocal findings of the F – 15 method. This method has a shorter examination time than the F – 15 and gives information about baseline state [19].

None of the guidelines recommended one single method concerning an optimal time point as to when the diuretics should be administered in relation to the radiopharmaceutical.

Quality assessment

The quality assessment revealed that some studies could introduce bias in more than one domain. However, no exclusion was made during this process. The quality assessment revealed a low risk of bias when assessing the conduct of the index test or its interpretation (domain 2) as well as when the comparison between groups was assessed (domain 3). The highest risk of bias was found in the domain where the flow and timing were assessed (domain 4). The domain where the patient selection was assessed (domain 1) had the most unclear issues, Table 3.

Discussion

A systematic literature review has been performed in three different databases to achieve a broad search. The authors chose to not set a limit in the publication year of the articles in the literature search, which resulted in articles published as early as 1978 and as late as 2020. However, not

many published studies could be found in the literature search process. Some studies were included in this study despite the fact that they did not compare different diuresis renography methods with each other. Instead, they studied a certain issue and described a method with a specific time point for diuretic administration in relation to the radiopharmaceutical, these studies are reported separately in the result section.

No exclusions were made during the quality assessment process as we wanted to report results from all included articles found in our literature search. Domain 1 had more unclear issues than the other domains as several of the included studies did not clearly describe how the selection of the study subjects had been performed. Furthermore, a higher score was achieved in domain 3 if the comparison between groups involved the same patients. A higher score was also given when the comparison between groups was performed close to each other (within 2 weeks).

A limitation of this study is that no meta-analysis could be performed. Furthermore, there were few published studies comparing different time points for diuretic administration in a diuresis renography which could be a future area of research. In addition, articles containing only children as study subjects were excluded in the literature search process but articles involving both adults and children were included.

Conclusion

Both F – 15 and F + 0 are reported to clarify washout in equivocal cases compared to F + 20 but no consensus could be found for a preferred time point of diuretics administration during a diuresis renography.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40336-021-00461-w>.

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Author contributions All authors contributed to the study conception and design. A-KB and HG performed the literature search and the quality assessment. A-KB and CS performed the data analysis. A-KB drafted the work and CS and HG critically revised the work.

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Declarations

Conflict of interest The authors (Anna-Karin Bäck, Christos Savvopoulos and Håkan Geijer) report no conflict of interest.

Declaration of Helsinki The study was performed in accordance with the Declaration of Helsinki. This study was registered with PROSPERO (CRD42020167484, 7 February 2020).

Ethical approval No individual patient data were evaluated during the study and the included primary studies had undergone separate ethics approvals.

Consent for publication All authors (Anna-Karin Bäck, Christos Savvopoulos and Håkan Geijer) read and approved the final manuscript.

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