Could Different Hydration Protocols Affect the Quality of ^{18}F-FDG PET/CT Images?

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In a group of oncologic patients undergoing ^{18}F-FDG PET/CT, we compared 4 different protocols of hydration to investigate their impact on image quality and to choose the best practice. **Methods:** One hundred twenty subjects undergoing ^{18}F-FDG PET/CT were randomized into 4 groups: group A, receiving free oral hydration; group B, receiving an intravenous injection of 10 mg of furosemide and infusion of 500 mL of saline solution starting 5 min after tracer injection; group C, receiving oral hydration with 500 mL of water; and group D, receiving intravenous injection of 10 mg of furosemide and infusion of 250 mL of the saline solution starting 30 min after the ^{18}F-FDG injection. The maximum standardized uptake value of muscular and adipose tissues, blood pool (aortic and left ventricular cavity), bladder, and renal parenchyma was calculated for each subject. **Results:** These 4 groups were comparable in age, body mass index, blood glucose level, and serum creatinine level. Group A showed the worst results. The controlled hydration protocols (groups B, C, and D) provided lower background activity in the soft tissues and lower urinary activity in the bladder and kidney without significant differences in blood activity. The administration of furosemide produces lower activity in the urinary tract without significant changes in ^{18}F-FDG distribution in the muscle, fat, or blood pool. The best results were in group D. **Conclusion:** Controlled hydration, particularly with standardized parenteral protocols, reduces the background activity in the soft tissues with the potential benefit of increasing the tumor-to-background contrast. Furosemide does not change tracer distribution in normal tissues but improves the quality of PET/CT images, reducing activity in the excretory system, particularly if the furosemide is administered late after ^{18}F-FDG injection.

Key Words: ^{18}F-fluorodeoxyglucose; hydration; furosemide; PET/CT; forced diuresis

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The most frequently used radiotracer in oncologic PET, ^{18}F-FDG, allows evaluation of the glucose metabolism of both normal cells and tumor cells. ^{18}F-FDG is an analog of glucose in which the hydroxyl group in the 2 position has been replaced with a fluorine atom. This change in the molecular structure determines some difference in the biochemical characteristics and in the biologic behavior between glucose and ^{18}F-FDG. In fact, whereas glucose is completely reabsorbed in the proximal tubules of the kidney, ^{18}F-FDG is not, resulting in excretion of radioactivity in the urine (*1,2*). The accumulation of ^{18}F-FDG activity through the urinary system can be mistaken for focal uptake that is due to oncologic processes, and this physiologic accumulation can interfere with the diagnostic evaluation of the abdominal and pelvic regions even if the patients empty their bladders before the scan (*3–6*). Many investigators have demonstrated that hydration and the use of diuretics can eliminate these effects (*7–12*). This evidence has been accepted in the guidelines for PET that some international associations have proposed to improve the quality of PET and have published (*13,14*). Therefore, the intravenous administration of furosemide or the use of oral or parenteral hydration forms part of the ^{18}F-FDG PET and PET/CT protocols in many hospitals. A wide range of solutions relative to hydration are used in current practice, but to our knowledge, no comparative studies have been performed to analyze the results and their effects on the quality of PET and PET/CT examinations. Therefore, this study on oncology patients undergoing ^{18}F-FDG PET/CT compared 4 different protocols of hydration to investigate their impact on image quality and to determine the best practice.

MATERIALS AND METHODS

One hundred twenty consecutive patients undergoing ^{18}F-FDG PET/CT as a part of their oncologic follow-up were enrolled. The study was approved by the local ethical committee, and all patients gave written consent to take part. Weight, height, blood glucose level, and serum creatinine level were measured before ^{18}F-FDG injection. Diabetes or blood glucose levels greater than 8.5 mmol/L, renal failure, and pelvic or obstructive pathology of the urinary tract were the exclusion criteria. The patients were randomized into 4 groups having different protocols of hydration. In group A, each subject received a 500-mL bottle of water and was invited to drink freely. Group B underwent parenteral infusion of 500 mL of saline solution with a 10-mg intravenous bolus of furosemide at the beginning of the hydration (i.e.,

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5 min after tracer injection). In group C, each subject received a 500-mL bottle of water and was asked to drink the entire amount at once (with monitoring during this interval). Group D underwent intravenous injection of 10 mg of furosemide; parenteral infusion of 250 mL of saline solution began later, starting 30 min after the tracer injection. The reduced volume of administered liquids in comparison with group B was chosen to limit the potential risk of urinary discomfort or any urgency during the PET acquisition.

For the groups with oral hydration (A and C), any residual water not consumed was measured. All protocols were completed within 45 min after the ^{18}F-FDG injection.

PET/CT Protocol

Whole-body PET/CT started 60 min after the intravenous injection of ^{18}F-FDG (4.5 MBq/kg) in subjects who had been fasting at least 6 h. Among patients under oncologic treatment, the examination was scheduled more than 4 wk after the last cycle of chemotherapy and more than 8 wk after the end of external radiotherapy. After injection of the tracer, the patients were asked to lie comfortably in a quiet room during the ^{18}F-FDG uptake period. They were invited to void the bladder, in case of urgency during this period and just before PET/CT. PET was performed caudocephalad with a Biograph 6 HiRez scanner (Siemens). These images were acquired in 3-dimensional mode, corrected for attenuation with a CT-derived map, and reconstructed with a 3-dimensional iterative algorithm (ordered-subset maximum-likelihood expectation). The patients' arms were positioned at the side of the body. Five to 7 emission steps were used to scan the body from the upper thighs to the base of the skull. PET/CT examinations were interpreted independently and in a masked manner by 2 experienced readers. The maximum standardized uptake value (SUVmax) of the muscular and adipose tissues, blood (aorta and left ventricular cavity), liver, bladder, and renal parenchyma was calculated for each subject, using a standardized procedure. Each reader drew standard elliptic or circular regions of interest on the different fixed anatomic regions: bilaterally on the gluteus maximus for the muscular tissue, bilaterally on the lumbar or abdominal subdermal regions for adipose tissue, on the lumen of the descending tract of the thoracic aorta, on the left ventricular and bladder cavities, on the right lobe of the liver, and bilaterally on the parenchyma of the kidneys. Subjects were excluded if they had inflammatory disease or if the anatomic targets showed either pathologically increased ^{18}F-FDG uptake or CT abnormalities interpreted as positive for malignant disease. For the targets, an intraobserver mean value was calculated with bilateral measurements (gluteus maximus, adipose tissue, kidneys). A final interobserver SUVmax was calculated as the mean of the single values obtained by the 2 readers for the same targets.

Statistical Analysis

Quantitative data are expressed as mean ± SD. Differences in clinical parameters for the subjects of the 4 groups and the influence of the different hydration protocols over SUVmax were assessed by 1-way ANOVA. When an ANOVA result was significant, a multiple-pairs comparison was performed using the Newman–Keuls test. χ^2 testing was used to analyze the distribution of variables among the groups, and *t* testing was used to compare the volumes of water drunk by the subjects in the 2 groups with oral hydration. A *P* value of less than 0.05 was considered statistically significant. The analysis was performed using the Winks SDA (version 6.0.4; Texasoft) statistical program.

RESULTS

Age, height, weight, body mass index, blood glucose level, and serum creatinine level were comparable among the 4 groups (Table 1). The mean volume of water drunk was 145 ± 142 mL in group A and 443 ± 75 mL in group C (*t* test, $P < 0.001$). A residual volume greater than 250 mL was found in 21 (70%) of the 30 patients in group A and 1 (3%) of the 30 patients in group C (χ^2 test, $P < 0.001$). All hydration protocols were well tolerated by the patients: 1 patient in group D complained of moderate uri-

TABLE 1
Distribution of Clinical Characteristics in the 4 Groups

Characteristic	Group A	Group B	Group C	Group D	*P*
Age (y)	59 ± 14	60 ± 12	60 ± 11	62 ± 12	NS*
M/F	16/14	13/17	17/13	16/14	NS†
Weight (kg)	69 ± 13	66 ± 13	70 ± 13	68 ± 11	NS*
Height (cm)	169 ± 10	169 ± 11	171 ± 09	171 ± 08	NS*
Body mass index (kg/m^2)	24 ± 2	23 ± 2	23 ± 3	23 ± 2	NS*
Glucose (mmol/L)	5.6 ± 0.7	5.3 ± 0.6	5.1 ± 0.7	5.3 ± 0.9	NS*
Creatinine (mmol/L)	81 ± 11	82 ± 9	80 ± 10	81 ± 9	NS*

NS = not statistically significant.
*ANOVA.
†χ^2 test.
Data are mean ± SD, or *n*.

TABLE 2
Distribution of SUVmax in the 4 Groups

Group	Left ventricle	Aorta	Muscle	Fat	Kidney	Bladder
A	2.22 ± 0.60	1.76 ± 0.41	0.59 ± 0.09	0.34 ± 0.07	2.2 ± 0.41	31.1 ± 12.8
B	2.09 ± 0.51	1.71 ± 0.34	0.52 ± 0.07	0.27 ± 0.06	1.9 ± 0.43	7.9 ± 3.4
C	2.13 ± 0.52	1.73 ± 0.32	0.53 ± 0.10	0.27 ± 0.11	1.8 ± 0.32	10.4 ± 4.4
D	2.12 ± 0.61	1.73 ± 0.31	0.53 ± 0.08	0.27 ± 0.08	1.6 ± 0.34	5.9 ± 1.8
P (ANOVA)	NS	NS	<0.01	<0.01	<0.001	<0.0001

nary urgency, but the imaging procedure was completed without problems. The SUVmax data are summarized in Table 2.

The protocols using controlled hydration (groups B, C, and D) provided a lower background activity in the soft tissues and a less intense urinary activity in the kidneys and bladder than the free hydration protocol (group A; Fig. 1) but not a different SUVmax in the thoracic aorta or left ventricular blood pool (ANOVA, P = not statistically significant) (Fig. 2). Urinary activity was lower with diuretic administration than with oral hydration. The procedure used in group D provided, on the whole, the best results (Fig. 3).

DISCUSSION

The detection of a pathologic finding (hot spot) on a PET/CT scan is related to the degree of metabolic activity in the lesion and, in particular, to the difference in ^{18}F-FDG uptake between the tumor and surrounding normal tissues, or target-to-background ratio. ^{18}F-FDG cellular uptake in tumor tissue is related primarily to a combination of upregulation of glucose receptors (glucose transporters 1 and 3), increased glucose metabolism, and decreased glycolysis of FDG-6-phosphatase (*15–18*) and is substantially independent of variations in the physiologic parameters and condition of the patient, except for acute hyperglycemia or uncontrolled diabetes (*19,20*). Therefore, the only actual possibility of increasing the target-to-background ratio is through lowering the radioactivity in normal tissues as much as possible, the denominator of this ratio.

Many investigations have shown the usefulness of diuretics, generally in association with hydration, in reducing tracer in the urinary tract and thus increasing the specificity of abdominal and pelvic hot spots (*7–12,21–23*). Nevertheless, experimental studies on animal models have demonstrated that the total amount of ^{18}F-FDG excreted is related to hydration level (*16*). Although this evidence suggests hydration to have further potential benefit in reducing

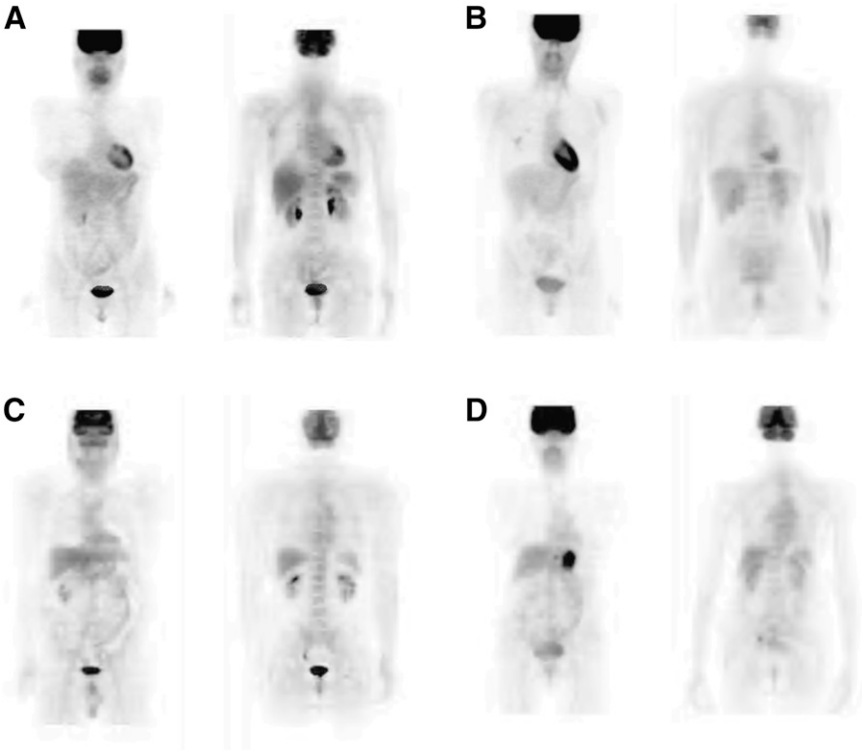

FIGURE 1. Representative cases (2 coronal slices) of mean ^{18}F-FDG distribution for each protocol of hydration: group A (A), group B (B), group C (C), and group D (D).

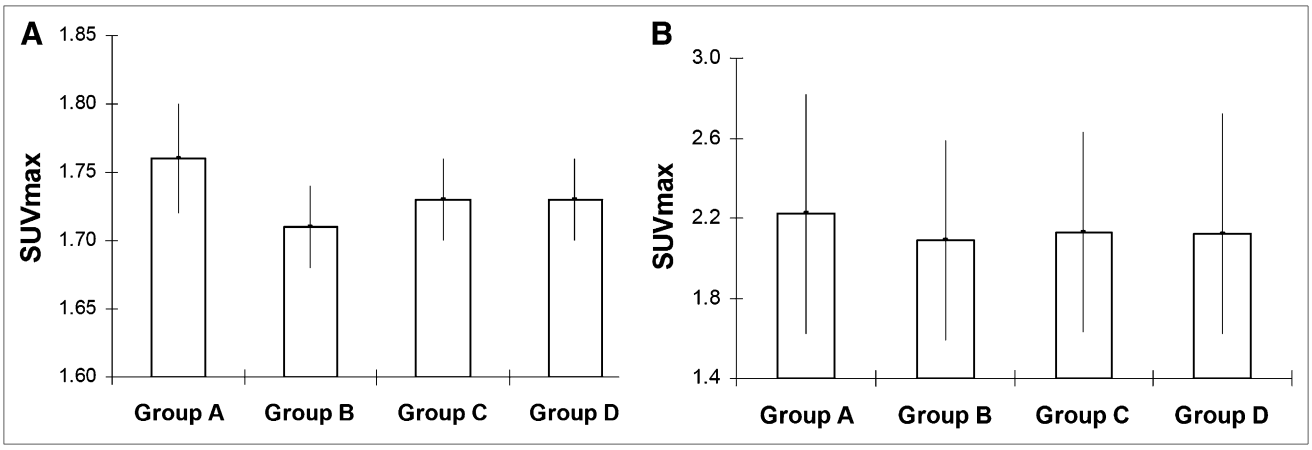

FIGURE 2. Distribution of SUVmax of blood-pool activity calculated in aorta (A) and left ventricle (B) for the 4 groups. For both aorta and left ventricle, P = not statistically significant on 1-way ANOVA.

background radioactivity, decreasing the bioavailability of residual ^{18}F-FDG, and decreasing tracer uptake by normal tissues, to our knowledge no data about this aspect are available yet.

The present study compared 4 protocols of hydration consisting of different combinations of 3 main variables: the volume of liquid administered, the method (oral vs. parenteral) and timing of hydration, and the use of diuretics. These 4 protocols were chosen as representative of the solutions routinely used, with little variation, by many nuclear medicine departments in their clinical practice.

Oral hydration is obviously the simplest and cheapest solution but needs continuous monitoring by the nursing

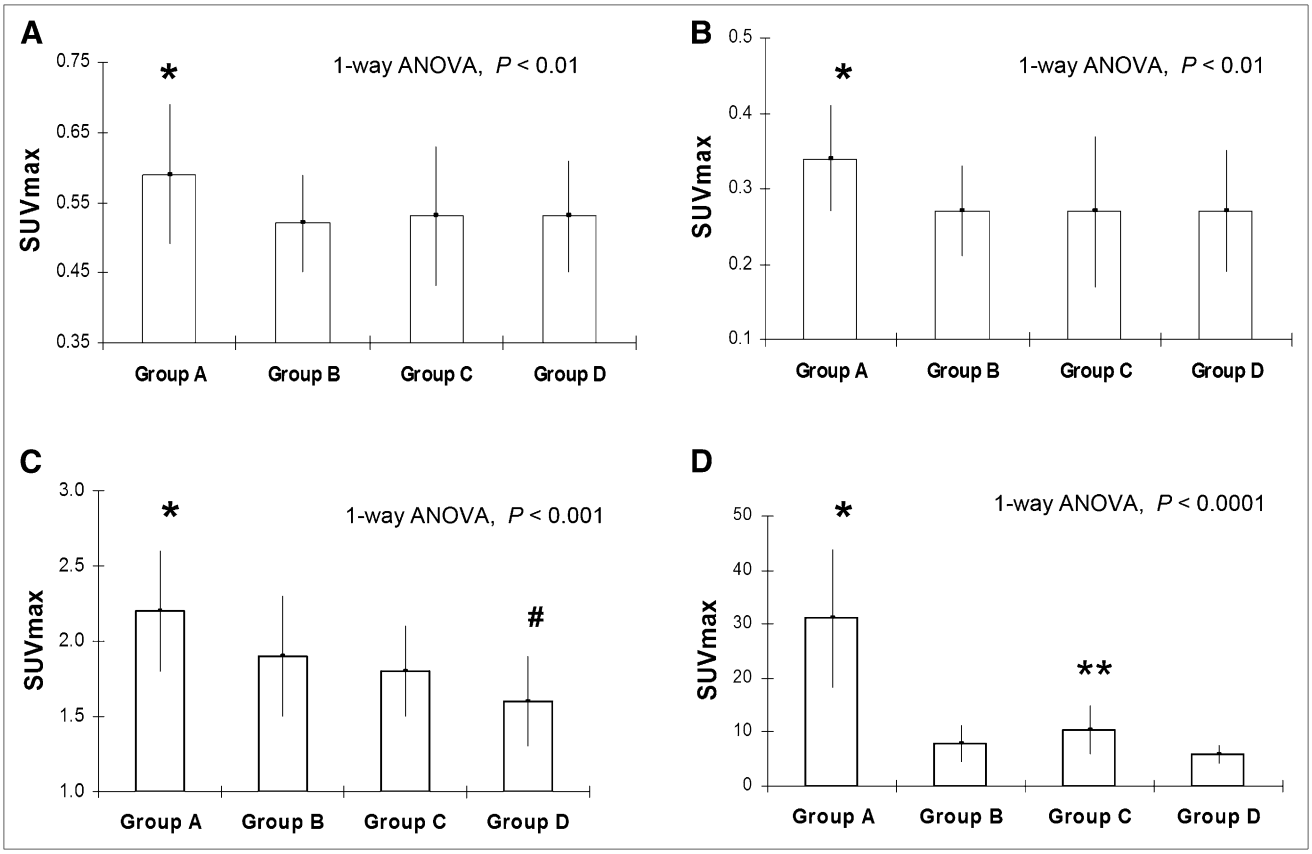

FIGURE 3. Distribution of SUVmax calculated in muscle (A), adipose tissue (B), kidney (C), and bladder (D) for the 4 groups. Newman–Keuls test: *$P < 0.05$, group A vs. groups B–D. #$P < 0.05$, group D vs. groups B and C. **$P < 0.05$, group C vs. groups B and D.

staff to ensure an effective result: this point is confirmed by the insufficient volume of water consumed by many subjects in group A (free oral hydration) with respect to those in group C (controlled oral hydration). On the other hand, parenteral hydration is a more efficacious procedure that ensures administration of the correct volume, obviating patient compliance. Moreover, the positioning of a small catheter in an antecubital vein allows for a simple way to administer a diuretic and is also functional for the ^{18}F-FDG injection.

The results of this study demonstrate that effective hydration decreases the ^{18}F-FDG background activity: group A, which received a smaller volume of liquids, had a soft-tissue SUVmax higher than that of the other groups. A similar trend, although not statistically significant, was found for blood-pool activity in the aorta and left cardiac cavity.

The comparable SUVmax shown for muscle and fat in groups B–D suggests that the 250 mL of saline solution could be a volume sufficient to guarantee significant effects. The same results also indicate that oral hydration, under strict control of the volume of liquids taken, may provide efficacy comparable to the parenteral strategy. Moreover, the data of group D demonstrate that, compared with hydration starting just after tracer administration, hydration starting after a 30-min delay did not significantly modify the ^{18}F-FDG distribution in blood pool, muscular tissue, or adipose tissue, suggesting that the timing of hydration is not crucial to its efficacy.

In our population, the final blood-pool activity did not seem to be significantly affected by hydration level. The interpretation of this point is more difficult, because the residual ^{18}F-FDG concentration in the blood pool is the result of different mechanisms of uptake and excretion, including not only the physiologic activity of the normal soft tissues and the kidneys but also the size of the tumor mass and the metabolic rate of the neoplastic cells. Nevertheless, our data seem to indicate that in conditions of poor hydration, the increased extraction from the soft tissues compensates for the reduced excretion by the kidneys (*24*).

The adjunctive use of furosemide does not affect tracer distribution in the blood pool and soft tissues: our results indirectly confirm, in the clinical setting, the previously published data in animal and human experimental models (*8,24*) that diuretics accelerate ^{18}F-FDG excretion but do not change the total amount of eliminated tracer. On the other hand, the reduced urinary flow caused by insufficient hydration increased the SUVmax in the kidneys and bladder of group A. Obviously, the injection of diuretics significantly affected ^{18}F-FDG activity in the urinary tract: in particular, the later injection of furosemide in group D brought about the lowest renal ^{18}F-FDG concentration. In contrast, the only hydration without diuretic caused a slightly increased bladder activity in group C in comparison with groups B and D. The use of diuretic appeared well tolerated by the patients and, also when injected late, did not generate urinary urgency requiring interruption of the PET acquisition.

Our experience was better than that recently published by Nijjar et al. (*12*), who found that the acquisition had to be interrupted for 4% of patients after infusion of 500 mL of saline solution and 20 mg or more of furosemide administered late, 45 min after ^{18}F-FDG injection. Nevertheless, the reported bladder SUVmax is comparable to that found in our study either with late (group D) or early (group B) parenteral hydration, suggesting that the high dosages of diuretics do not improve residual bladder activity but increase the risk of urinary discomfort or urgency, particularly when administered near the beginning of the imaging acquisition and in association with a high volume of liquids.

To avoid unnecessary administration of diuretics and the risk of urinary discomfort during the scan, some authors recently tested a different approach, in which the injection of furosemide during the PET acquisition was planned only if requested by the physician after evaluation of the abdominopelvic imaging (*11*). Although effective, this procedure is time consuming, requiring a second abdominopelvic scan, which may generate some troubles in departments with a high workload and a strictly scheduled diagnostic activity. For this reason, this protocol is not common in clinical routine and we have chosen not to consider it in our study.

CONCLUSION

Controlled hydration with the administration of a significant volume of liquid (≥250 mL) reduces background activity in the muscular and adipose tissue, with the potential benefit of increasing the tumor-to-background contrast. The infusion of saline solution is preferable to oral hydration by guaranteeing more efficacious and standardized results, avoiding the need for strict monitoring of the procedure by the nursing staff. Furosemide does not affect the distribution of ^{18}F-FDG in soft tissues but reduces residual activity in the excretory system, particularly if the furosemide is injected late and with sufficient hydration. Therefore, our experience demonstrated that the use of a hydration-optimized protocol may significantly improve the quality of the PET/CT scan. Among the different procedures tested, the best practical solution may be intravenous injection of 10 mg of furosemide and parenteral infusion of 250 mL of saline solution starting 30 min after tracer injection.

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