Inspiration -sleep- rest and nuclear medicine

To the Editor: With great interest I have read the article under the title "Inspiration during the sleep stages without and after preceding exercise, as a factor supporting circulation of blood and the "resting procedure" by Grammaticos P, Daskalopoulou E, Grammaticou-Zilidou E, Kallistratos E, Daskalopoulos E. I think after testing this on a greater number of subjects it may be of major impact in sleep research in general. I would be especially interested if you wrote some words on the essential impact of this work in Nuclear Medicine in terms of routine protocols in brain and cardiac imaging.

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Authors' reply:

In reply to the letter of Professor Andreas Otte published in this issue, we would like to mention that it is important for nuclear medicine physicians to know whether patients undergoing heart or brain tests are at a stage of rest or fatigue. It was first Dr Johannes van Isselt from Utrecht who underlined to us the relevance of knowing whether patients tested for heart and/or brain investigations were at rest. In the N Engl J Med, Abidov A, Rozanski A, Hachamovitch R, et al, state that dyspnea is a predictor of an adverse outcome in patients with known or suspected coronary artery disease who are undergoing stress testing [1]. Sleep deprivation and fatigue may have a negative impact on brain function and on cognitive tasks [2-3]. During fatigue the coronary blood flow may increase from 5% to 25% per minute of the ejected blood volume. Somatic fatigue is strongly related to a myocardial infarction risk and to coronary heart disease [4]. Fatigue may be due to disturbed or insufficient sleep but also to cancer, chronic diseases and many other physical and mental disorders. Our paper to which Professor Otte refers (Hell J Nucl Med 2005; 8: 113-116) aims at finding signs that will describe the state of rest after sleep [5,6]. These signs may confirm that patients are at rest when examined for brain or heart studies. In this paper of ours, normal sleep was associated with increased duration of inspiration, as compared to the duration of inspiration during daytime. We also noticed that the periods of "arousal" may be considered as part of the usual sleeping time regarding respiration and ECG findings. In that study we have also noticed that in young subjects limited exercise before sleep was not sufficient to modify normal sleep pattern and sleep parameters.

We should avoid testing patients at fatigue who may collapse during a stress myocardial blood flow study [1]. The same is true for patients tested for cerebral regional blood flow because in that case, cerebral blood flow will differ significantly from normal.

Finally, we may suggest that before the above cardiac or brain tests, patients should complete a questionnaire referring to: heart rate, respiration rate, the duration of inspiration and the duration of sleep and emotional stress that may have been experienced by the patients prior to the test. Nuclear medicine physicians may consider postponing cardiac or brain tests on the grounds that such a test at a fatigue stage may be dangerous for the patient or may yield biased results.
The study of respiration may be very important not only for evaluating resting procedure, but also for investigating the mechanism through which respiration supports cardiac function at sleep and during daytime. This is a large field of investigation.

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About mentioning quality of preparation and quality control of radiopharmaceuticals used in nuclear medicine procedures

To the Editor: We have noticed that articles published in the Hellenic Journal of Nuclear Medicine as well as in most other nuclear medicine journals [1-6], using radiopharmaceuticals (rph) do not refer to whether the rph used were prepared according to the international principles of selection and quality control. It is our opinion that if rph are not properly prepared, the results of the whole study may be at stake and also allergic, toxic or inflammatory side effects may arise. In this letter we intend to generally describe the important procedures for the preparation, selection and quality control of the rph, quality criteria such as sterility, radionuclidic purity, radiochemical and chemical purity of the rph.

Diagnostic rph are used at very low concentrations between 10^{-6} and 10^{-8} M, and are not expected to have any pharmacological effect [6]. The specifications and quality control for most of the currently used rph have been described in the European Pharmacopoeia [5] with which the Hellenic Pharmacopoeia complies. The radionuclides used for rph are produced in a number of ways: as byproducts of fission, by means of neutron activation, by cyclotrons, and by generators. These methods may also produce radionuclides that have undesirable properties. Approximately 80% of all nuclear medicine procedures performed worldwide, use rph labeled with ^{99m}Tc [6-8]. Apart from ^{99m}Tc, a series of cyclotron-produced radionuclides, such as ^{201}Tl, ^{67}Ga, ^{111}In, ^{123}I or nuclear reactor-produced radionuclides (^{131}I) meet widespread application in visualization procedures, while several other radionuclides, such as ^{131}I, ^{90}Y, ^{89}Sr, ^{153}Sm and ^{186}Re / ^{188}Re, are used for therapeutic purposes [8].

Administration of non suitable diagnostic or therapeutic rph to the patients could induce abnormal biodistribution and could interfere with diagnostic interpretation and/or treatment effectiveness [9]. Moreover, absorbed radiation dose may be unnecessarily increased, while suboptimal images lead to repetition of the diagnostic procedure. Therefore,

quality control testing of rph should be routinely performed before use to ensure compliance with various purity standards such as total radioactivity, radionuclidic purity, chemical and radiochemical purity, pharmaceutical purity, and biological purity.

All principal investigators who formulate drugs outside institutional pharmacies must pass these audits before they can obtain a rph investigation permit. The audit team meets with the candidate to describe to him his duties and check his professional knowledge. An expert in the preparation of radioactive drugs, a radiopharmacist or/and radiopharmacologist also participate. Problems that have been identified by audits include lack of sterility and pyrogenicity testing, formulations that are open to the laboratory environment, failure to use pharmaceutical-grade chemicals, inadequate quality control methods or records, inadequate training of the person preparing the drug and improper unit dose preparation [7].

Special conditions for production of radioactive drugs are [1-4]: Hot Laboratories with easy to clean surfaces, manipulators, air-conditioned and air filtering systems, remote control apparatus and vacuum transport of liquid media. Disinfection, cleaning, sterilization and aseptic work are parameters to be assessed in every product prior to release [5]. Also, total radioactivity and radioactive concentration should be measured. Radiochromatography will be used to identify and quantify radiochemical impurities before administration to patients. Electrophoresis, gel filtration, high performance liquid chromatography (HPLC) and solvent extraction are also used [10,11]. Finally, gross particulate contamination should be eliminated.

For sterility and bacterial endotoxin testing, a minimum of three random samples drawn on the same day are required [4-8]. The presence of Gram negative bacterial endotoxins is the most common source of pyrogenic contamination and is detected by specific tests like The Limulus (horseshoe crab) or the Amoebocyte Lysate (LAL) test.

Quality control parameters for ^{99m}Tc are the following [12-14]: a) Each ^{99m}Tc- solution obtained from the generator will be tested for possible ^{99}Mo contamination. The maximum allowable ^{99}Mo contamination should not be more than 5.5 kBq (0.15 μCi) of ^{99}Mo per 37 MBq (1 mCi) of ^{99m}Tc at the time of administration to the patient. Any preparation of ^{99m}Tc rph with unacceptable ^{99}Mo level should be immediately discarded. b) Due to its short, about 6 hours half-life, synthesis of the rph has to be completed within approximately 30 min. c) The yield of the rph must be greater than 90% since the injection of a mixture of different ^{99m}Tc-containing species will decrease organ specificity, and needlessly increase radiation dose to the patients.

Some important quality control parameters for ^{99m}Tc labelled kits are as follows [1,2,4,5]: a) Radiochemical purity (RCP) testing of products prepared from licensed labelling kits should preferably be performed on every new batch. When a new kit is prepared or a kit that has failed before to pass the RCP test, subsequent preparations should be tested for RCP prior to patient application. b) Measurements of pH using narrow range pH paper must be performed on ^{99m}Tc generator eluates.

A wide number of new diagnostic and therapeutic radiopharmaceuticals have been developed during recent years. For the first time the revision of the "Guidelines for Radiation Protection in Medicine" defines extensive quality control procedures for rph before patient administration [14]. It is hoped that high standard rph preparation will be maintained nationwide. We suggest, as mentioned above, that researchers and practicing physicians should check quality control before using rph in vivo. Perhaps the Editors of Medical Journals should also ask the authors of the papers they publish, to provide assurance that the rph they have used meet proper quality control.

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