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Letters to the Editor

Red cell volume measurement: using technetium as a replacement for chromium

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We read with a great interest the technical note written by Ainslie-McLaren *et al*. [1] about the red cell volume measurement using indium as a replacement to chromium. We encountered the same issue regarding the GE Healthcare facility's closure which manufactured ^{51}Cr-EDTA and $^{51}CrO_4Na$. Like the authors, we had to replace the ^{51}Cr-EDTA with ^{99m}Tc-DTPA for the glomerular filtration rate studies. However, unlike the authors, we did not use ^{111}In for the labelling of undamaged red blood cells to assess the red cell volume in patients. We labelled erythrocytes with ^{99m}Tc following the recommendations of the EANM [2]. The authors argue that the ^{99m}Tc-erythrocytes label is less stable over time than ^{111}In label and prevents its use in patients with splenomegaly due to the 1-h injection delay. Indeed, their study shows that ^{111}In-tropolonate is perfectly retained into the red blood cells and fits well with the literature [3]. After a technique optimization, they can assess the blood volume directly and we congratulate their pharmacist for providing them the sterile tropolone solution for the chelation of ^{111}In.

The remaining question is why we (and others) use ^{99m}Tc-erythrocytes to evaluate the red cell volume without any problem? In our nuclear medicine department, all patients (about 40 per year) with splenomegaly or various haematologic diseases are submitted to our erythrocyte labelling process, and no relevant pitfalls about ^{99m}Tc elution from erythrocytes was detected. We are committed to giving the best results to patients and clinicians and this study has been questioning us.

We regret that this study does not compare ^{99m}Tc-erythrocyte label with ^{111}In-erythrocyte label. We therefore read the literature references provided by the authors where the labelling instability had been described. The papers from Radia *et al*. [4] and Peters *et al*. [5] refer to a unique work from Jones and Mollison [6]. At the time, the labelling kits (with pyrophosphate or citrate) were difficult to access and quite expensive and the aim of their study was to design a method without labelling kits. They found an elution of the technetium from the erythrocytes at about 8% after 1 hour of incubation at 37°C. Previously to this work, Schmidt *et al*. [7] found the elution of technetium from the erythrocytes was in the same order of magnitude (7.6% per hour) with a similar procedure without using any weak chelator.

But, when stannous weak chelators are used like pyrophosphate (PYP Technescan); it is observed that the stannous pyrophosphate can cross over the erythrocyte's membrane easily and cause more avid binding on the haemoglobin's globin chain. The work of Holt *et al*. [8] showed the absence of significant technetium elution from erythrocyte during the first hour when using a stannous pyrophosphate. Indeed, we experimentally found in our nuclear medicine department a weak or nonsignificant technetium elution (*<2%*) from erythrocytes after a 1-h delay when replacing chromium by technetium and using a stannous pyrophosphate. The EANM guidelines report that the 'In vitro labelling gives by far the highest labelling efficiency and, over time, the most stable labelling. Measurement of erythrocyte volume by in vitro labelled RBCs with ^{99m}Tc gives values similar to labelling with the gold standard ^{51}Cr' [2].

Moreover, the short half-life of ^{99m}Tc makes it possible to ensure counting on the whole blood sampling. We then wait for a radioactive decay (about 3 days) to count ^{125}I. No additional procedure is needed in the counting window.

To conclude, until proven otherwise, we will continue to label red blood cells by ^{99m}Tc as a replacement for ^{51}Cr [9]. We think this method is simple and robust. This does not detract from the quality of the work on ^{111}In erythrocyte labelling with tropolone.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Bronchopulmonary MDR protein expression may protect against COVID-19 infection

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Whether or not otherwise healthy cigarette smokers are less likely to become infected with coronavirus disease (COVID-19) is controversial. The findings in several studies that have reported a lower prevalence of smoking in hospitalised patients compared with the general population [1–4] have been criticised on the grounds that hospitalised patients tend to be older and that older patients tend not to smoke. However, at least one study controlled for age and gender [4]. That smokers, once hospitalised, have a poorer outcome than nonsmokers [5] is not surprising, but what is not clear is the proportion of smokers in subjects undergoing 'test and trace' who test positive for COVID-19 but who are not necessarily symptomatic. In a recent scientific brief, the WHO reported that no such studies have yet been undertaken [5]. However, from the perspective of protection from infection in the first place, these subjects, rather than smoking patients hospitalized and with poor outcomes, form the most important group.

We speculate that otherwise healthy smokers may be protected from COVID-19 infection as the result of upregulation of bronchopulmonary expression of ABC cassette transporter (multi-drug resistance) proteins. These membrane-linked proteins, the best known of which is P-glycoprotein (P-gp), have been likened to rotating doors that inhibit the entrance of or extrude a wide range of foreign substances from cells. In general, they furnish parts of the body that interface with the outside world, such as bronchopulmonary, gastrointestinal and renal tubular epithelia, and bile canaliculi, 'pumping' towards the exterior. They are also present in blood–brain barrier, protecting the brain.

In previous work using dynamic gamma camera scintigraphy, we measured the disappearance rate from the lungs of Tc-99m-labelled methoxyisobutyl-isonitrile (MIBI), administered as an inhaled radioaerosol. This compound, widely used in nuclear medicine, especially for myocardial perfusion imaging, is an multi-drug resistance (MDR) substrate. Interestingly, healthy cigarette smokers showed a striking reduction in clearance rate compared with nonsmokers, the opposite to the clearance rates of Tc-99m-diethylenetriaminepentaacetic acid. Cigarette smoke is full of xenobiotics, raising the strong possibility that bronchopulmonary MDR proteins are upregulated by cigarette smoke and suggesting that the rate of clearance of the tracer across the pulmonary blood-gas barrier could be a quantitative marker of bronchopulmonary MDR protein expression [6], especially P-gp. We subsequently showed, however, that the Tc-99m-MIBI clearance rate strongly correlated with the pulmonary immunohistological expression of MRP1, rather than P-gp, and that expression was increased in smokers [7].

The question, therefore, arises as to whether such upregulation could hinder the cellular entry of viruses. It has been shown that P-gp in T-lymphocytes is capable of extruding hydrophobic peptides essential for the fusion of HIV-1 [8]. Other than HIV-1, however, it is difficult to find publications in the literature relating MDR to the infectivity of viruses.

If the above speculation turns out to be correct, then the administration of ingredients of cigarette smoke, such as nicotine which has been suggested as the mediator of protection in smokers [1], are likely to be ineffective in showing protection if administered via routes other than inhalation. Starting to smoke would potentially be harmful as substrates are initially MDR blockers, with upregulation following later.

Caveats to the above speculation are that in nonsmokers, we found first, no difference in clearance rate between men and women, and second, a trend for clearance to be delayed, rather than accelerated, in older subjects [9]. However, as implied in the WHO scientific brief alluded to above, the known poorer clinical outcome in the elderly and in males is a separate statistic from infection rate itself.

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Conflicts of interest

There are no conflicts of interest.