Should caution be exercised with regard to the use of cardiac magnetic resonance?

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Researchers at the GIGA-Cardiovascular Sciences laboratory of the University of Liege are advising caution with regard to repeated use of cardiac magnetic resonance, a commonly-used radiological examination. They showed that this examination induced signals that mimic DNA double-strand breaks in T lymphocytes, but that this effect, which is slight and temporary, disappears after one year. However, they still need to demonstrate the presence of such DNA double-strand breaks. If their results are confirmed, they will suggest a prudent approach to the use of this technology.

In the area of medical imaging technology. Cardiac Magnetic Resonance (cardiac MRI) is a radiological examination that is increasingly used for diagnosing and monitoring heart conditions. "This technology makes possible not only to study the structure of the heart but also to provide information on heart function and eventual disease, it is a very particular examination in extremely high definition. In comparison with chest radiography, scanners or scintigraphy, it has the advantage of being a non-ionizing technique", explains Professor Patrizio Lancellotti, a cardiologist and director of GIGA-cardiovascular (ULg).

In use for about twenty years, CMR has always been considered to be a harmless examination due to the fact that it does not emit ionizing radiation. However, some years ago, \textit{in vivo} and studies showed that there were possible alterations to cellular DNA and, particularly, to T lymphocytes. He continues, "As a cardiologist, I considered that it was essential to verify, support and complete these studies because this technique is more
and more being used. This is a very important issue because if the results of the study are wrong it means that
the technology is so harmless that it can be used a lot more in view of the fact that it provides very interesting
information”.

The GIGA-cardiovascular team, headed by Professor Lancellotti, Dr. Cécile Oury, biologist and researcher
at the FNRS, and Dr. Alain Nchimi, radiologist, evaluated the early and late biological response of blood cells
to CMR. (1)

These scientists enrolled 20 healthy males, with an average age of 20 who were asked not to practice intense
sports activities and from whom they took blood samples before and after (1-2 hours, 2 days, 1 month and 1
year) a CMR examination. The number of blood cells (lymphocytes, monocytes, neutrophils, platelets...) and
their activation status, as well as apoptosis were measured. They used a marker, a variant of phosphorylated
histone, gamma-H2AX, considered to be the best marker of DNA damage induced by ionizing radiation: an
increase in the levels of gamma-H2AX in circulating T lymphocytes, for example, very accurately reflects the
induction of DNA double-strand breaks by ionizing radiation.

The double-strand breaks signals return to baseline levels after one year

So what were the results? Professor Lancellotti and his colleagues were able to observe a slight but significant
increase in the level of gamma-H2AX after 2 days and 1 month post-CMR. This DNA damage did not, however,
induce the apoptosis of the T lymphocytes and activation of the T lymphocytes was not observed.

“We analysed the different sub-populations of lymphocytes: none of them was more marked than another.
But the T lymphocytes are the most important in this case because these are the longest-lasting blood cells.
Therefore if DNA damage accumulates in these T lymphocytes, that can have a real impact in the long term.
This is why we have advised caution if the examinations are to be repeated several times in the same month”,
comments Cécile Oury

This raises the question as to whether the observed effect is based on the dosage used. "There is probably
a connection between the energy absorbed by the patient”, replies Professor Lancellotti. "We showed that
there is a linear relationship between the energy absorbed or delivered to the patient and the persistence of
a high level of gamma-H2AX measured in the circulating T lymphocytes one month after the exam. It must
be understood that if longer-lasting examinations are conducted, this could have an impact on the energy
produced, released and then absorbed, theoretically leading to more lesions”.

"This depends not only on the timescale involved, but also on the type of sequence (2) or excitation. The
correlation observed between the quantity of energy and the lesions observed after one month exist, but a
greater number of subjects would be required in order for us to be absolutely certain", adds Alain Nchimi.

Other observed phenomena also interest Patrizio Lancellotti: "We noticed that the examination induced
temporary inflammation, characterised by a small decrease in the number of natural killer lymphocytes and
an activation of neutrophils and monocytes. The positive aspect in all this is that there was no activation of
platelets and therefore no prothrombotic (favouring thrombosis) phenomenon linked to the examination”.

Not as harmless as previously thought

These results lead to the conclusion that this examination is perhaps not so risk-free as generally thought: "In
our work, we showed that in half of the subjects, there was an increase in these alterations and which was
more marked after one month of follow up. On the other hand, the reassuring thing is that, after one year,
there was a complete normalization. It is clear that there is a phenomenon and that it needs to be confirmed”,
considering the cardiologist.
He adds, "The question we are asking, is whether the patient is more likely to develop DNA lesions linked
to magnetic resonance, which, in this case, was conducted without injection of gadolinium. Use of the
latter provides a better visualisation of cardiac structure, but it is also potentially toxic and could therefore
accentuate the deleterious phenomena observed. This is really something new because most of the data
previously obtained in vivo involved an injection of gadolinium: in this case, you cannot distinguish between
the examination itself and the contrast agent used”.
Some other questions raised by this study are: will the modifications reoccur if the examination is repeated
and what are the consequences of these modifications in the short and long term? “The most important thing
from my point of view”, points out Patrizio Lancellotti, “is to know what will happen if we conduct several
examinations. Let’s imagine that I do a chest scan, a CMR and a PET scan in order to establish a diagnosis:
what impact will this have on lymphocyte DNA? What has been recommended - and is in fact more of a
suggestion - is to at least avoid conducting several CMR examinations, perhaps within the same month, on
individuals that are considered healthy as we do not yet know the consequences of this”.
This warning is all the more valid if contrast agents are used. “Prudence and similar restrictions
already apply to examinations which use X-rays and nuclear imaging”, warn the GIGA researchers.
Furthermore, what worries them, independently of the results, is the fact that the study involved young men whereas the mechanisms for DNA repair are less efficient in elderly...

**How can the current doubt be confirmed?**

The work of the team from GIGA therefore does not stop here. The risk needs to be confirmed and clarified by means of in vitro and in vivo tests on animals (mice). For the in vitro section, they plan to conduct several tests directly on human blood in order to observe the effect of this non-ionizing radiation on lymphocytes. "By keeping these lymphocytes in culture for several days after exposure to a magnetic field, we will be able to study the DNA repair mechanisms and to see whether or not DNA double-strand breaks are indeed induced
by the magnetic field in question”, explains Cécile Oury, who speaks very highly of the working environment offered by GIGA and the University Hospital of Liege: "The environment is ideal, it makes this study possible thanks to direct collaboration between cardiologists, radiologists and biologists (molecular and cellular)".

In order to determine the effect of the contrast agent, the researchers consider that it will be necessary to use real patients. "It is no longer legitimate to repeat a study in healthy subjects but rather we could look at subjects who are due to undergo an examination in the context of screening, for example", considers Patrizio Lancellotti. "It would also be necessary to establish whether it is something that only applies to heart examinations or whether it could also apply to brain or osteoarticular examinations, which is a very big question". More generally, it would be important to demonstrate the impact of non-ionizing radiation on health. We already know that this can cause nausea and dizziness. "Warnings have been issued against intensive use of this non-ionizing radiation for the wider public and workers who are exposed to it", says Alain Nchimi. "On one hand, a formal link between the exposure to non-ionizing radiation and clinical effects such as cancer or other pathologies has not been proved yet. On the other hand, as with every theory, there is a counter opinion which states that this non-ionizing radiation is protective (of DNA, as far as external attacks are concerned)".

Controversial results

This study, which proves for the first time that there is a causal link between an increase and persistence of gamma-H2AX and CMR, was published in a journal of the American Heart Association, Circulation
Cardiovascular Imaging. While some individuals such as the editor of the publication, and Philip Kaufmann describe these results as remarkable, others are more critical. Nevertheless, if there is a problem, it must be demonstrated and the medical community must be warned. For example, it would be inadmissible not to speak of the effects of ionizing radiation on cells when these have already been well-established. In order to reduce these effects, doses are adapted accordingly, exposure times are reduced, etc. Perhaps the same thing could apply to CMR where specific sensitivity markers should be used...

The head of GIGA-cardiovascular acknowledges that there is a certain ambivalence: "We were not seeking to cause controversy. We are all confronted by the clinic of everyday life and we do not want to send out a message that is too strong without being sure whether or not there is a risk".

"We are not saying we are sure that there are problems", insists Alain Nchimi, "we are saying that we have observed a certain number of troubling facts and that we are not alone in this. Before us, several studies observed the same facts, including in laboratory tests. Those studies, with one exception, have not resonated with the medical community and it is worrying that manufacturers have not reacted to these results. It is important to elicit a response from manufacturers and other scientists who wish to investigate the question in order to establish whether radiofrequencies generally, are having an effect".

"Currently, manufacturers are not arguing against the studies published on the subject", adds Alain Nchimi: "Their argument - which is a valid one - is that the anomalies that can be observed after examination by means of non-ionizing radiation are physiological in nature (caused by intense physical activity, for example), and can exist in any individual subjected to the same type of radiation. Statistically, this may be true but more research is needed on the subject". There is enough material here to inspire several research projects which will make it possible to conduct these examinations in total safety...

1 Biological Effects of Cardiac Magnetic Resonance on Human Blood Cells, Circ Cardiovascular Imaging 2015; 8:e003697

2. An MRI sequence includes all the parameters which define magnetic field pulses and the characteristics of measurements made by magnetic resonance imaging.