Ascertaining low-dose radiation impact on the heart

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We are all exposed to radiations. Such exposure can be harmless at very low doses but damage our health above certain thresholds. But what happens in between is more difficult to predict. The PROCARDIO project is casting light on part of this mystery, with a focus on radiation-induced heart disease.

We might not always realise it, but our body is constantly subjected to radiations. Part of this consists of what is commonly called 'background exposure'. Over their lifetime, Europeans are exposed to an average 2 400 ÂµSv (microsievert) every year. About 80?% of these radiations are natural, and have a very limited impact on our health. Others, like those emitted by cell phones, have been debated for years as intensive use is suspected to increase cancer risk.

Other non-natural sources of radiations include work in nuclear power plants, medical imaging and radiation therapy technologies. Although essential to diagnosis and treatment, the likes of X-rays and CT scans have to be used parsimoniously. Every time a patient's body is scanned for a fracture or tumour or - in the case of cancer treatment - is subjected to radiations, there can be varying levels of impact on our health.

But what exactly do we know about such impacts? Experts agree that the actual radiation risk to different parts of the body varies. Radiations at high doses are known to cause cancer, however research around 'Radiation-induced heart disease' (RIHD) has recently been gaining

momentum.

The EU-funded PROCARDIO (Cardiovascular risk from exposure to low-dose and low-dose-rate ionising radiation) project, which involved partners from Europe, the United States and Japan, will be capital in this quest for understanding radiation impact on the human heart. It is also very unique since, unlike previous research, it involves researchers who decided to look into the impact of low-dose exposure while challenging preconceptions and casting new light on contradictory findings.

Prof. Mike Atkinson, Director at the Institute of Radiation Biology in Germany and coordinator of PROCARDIO, told us about his team's findings so far.

What are the main objectives of the project?

Prof. Mike Atkinson: PROCARDIO was designed to address a very specific problem in radiation protection. We know that high doses of radiation, typically those received in cancer treatment or from atomic bomb detonations, damage the human heart. Our concern is that much lower doses, those typically received in the nuclear workplace or from diagnostic medical imaging such as CT scanning, may also be damaging to the heart. If this were true, we would need to amend clinical practice and workplace dose limits to afford adequate protection.

Unfortunately, the epidemiological evidence of an effect on the heart at these low doses offers contradictory findings. A major reason for the lack of consensus lies in the way in which effects at low doses are predicted. This is based on the extrapolation of evidence collected at high doses where the effects are easy to identify. Whilst it may be true that the effects decrease in a linear fashion with decreasing doses, it may equally be true that there is a threshold below which no damage may be expected, or even that lower doses may be more damaging than

predicted by a linear dose response. Only by understanding the biological mechanisms of radiation action on the heart can we construct the correct dose response relationship needed to extrapolate effects down to low doses.

What is new or innovative about the project's approach?

Our understanding of cardiovascular effects of radiation is very much coloured by the experience of observations made at very high, almost lethal doses. Here, tissue damage and cell death predominate, leading to heart failure due to destruction of vital functions or massive inflammatory responses to the damage.

In PROCARDIO we have thrown away these preconceptions and started from a blank sheet of paper, making no assumptions about the mechanisms operating at low doses. We have formulated a number of new hypotheses to explain the radiation effects at low doses, low-dose rates (acute versus chronic exposures), the effects of different radiation qualities (e.g. photons vs. heavy ions) and the cell types directly and indirectly involved in the response to radiation insults. At the same time, we joined forces with a large EU-funded epidemiological study on the survivors of childhood cancer. This allowed us to gather new epidemiological data on the long-term effects of cancer radiotherapy and to use these data to test our hypotheses.

What were the main difficulties you faced and how did you resolve them?

The diversity of activities meant that we had to assemble a highly interdisciplinary research team, many of whom had no prior experience of cardiovascular research. This was resolved by recruiting an

international scientific advisory board led by one of the chief cardiologists in the United States. A second major difficulty was the lack of experimental facilities for the study of chronic effects of radiation. Here, we formed a strategic alliance with the Institute of Environmental Sciences, Rokkasho, Japan in one of the first joint Europe-Japan collaborations in radiation research. Our project plan included a sister project (CEREBRAD) to study the risks stemming from radiation exposure to the brain. Combining two large projects was a daunting task, but we have worked very hard to maintain and grow the links between the two projects, including running joint scientific sessions, organising common training and education activities, and sharing technology and results. We are all very proud that the two projects have grown closer together, with a lot of unexpected cross-fertilisation arising.

Are you satisfied with the project outcomes so far?

Although it is rather early to consider the overall project outcomes, we have already made a number of exciting scientific breakthroughs thanks to PROCARDIO. These have changed the way that the cardiovascular effects of radiation are viewed. For example, we show that two distinct types of cell are affected by low doses of radiation, the vascular endothelial cell (a blood vessel lining cell) and the cardiomyocyte (contractile heart muscle cell). Another immediate impact of the work is that we identified the role of the mitochondria (energy-producing sub cellular structure) as the major site of damage. Our biomathematical activities have produced a whole series of mathematical models that will be used to test the shape of the dose response curve when our epidemiological efforts are finished.

What are the next steps for the project itself and after it ends?

National funding is already being awarded to consortium members to continue the work started under PROCARDIO. We have already begun to reformulate new hypotheses to replace those that were disproved by the research work, thus driving our understanding of radiation effects forwards.

When and how do you expect patients to start benefiting from your research?

Already we can see the impact of our work, as stakeholders and medical practitioners have been specifically targeted to make them aware of the potential long-term health risks of even low doses of radiation exposure to the heart. This new awareness of the risks to the heart is being seen in therapy planning and in imaging activities, where the heart is now spared from exposure as much as possible. We are seeing a shift in perception in the radiological protection community as well, where the heart is no longer considered a radiation-resistant organ, adequately protected by legislation designed to protect against cancer.

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