CHRONIC LOW DOSE RADIATION

Why induced reactive oxygen species have a role in cardiovascular diseases?
Dr. A. BEHAR, on behalf of IPPNW FRENCH AFFILIATE
IN MEMORIAM

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The best specialist in low doses
Low dose ionizing radiation exposure and cardiovascular disease mortality. Study based on Canadian national dose registry (NDR) of radiation workers

Jan M ZIELINSKI et al
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Excess Relative Risk (ERR), Excess Absolute Risk (EAR), and Attributable Risk (AR) in the NDR cohort (1951–1995)

<table>
<thead>
<tr>
<th>SEX</th>
<th>ERR/Sv</th>
<th>EAR.Sv/10 000 PY</th>
<th>AR(0.01 Gy) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1.22 (0.47, 2.10)</td>
<td>37.6 (15.0, 62.5)</td>
<td>8.84 (3.65, 14.2)</td>
</tr>
<tr>
<td>Females</td>
<td>7.37 (0.95, 18.1)</td>
<td>59.1 (8.33, 129.2)</td>
<td>24.5 (4.08, 43.7)</td>
</tr>
<tr>
<td>Both</td>
<td>1.35 (0.59, 2.24)</td>
<td>37.5 (17.0, 60.1)</td>
<td>9.46 (4.42, 14.7)</td>
</tr>
</tbody>
</table>

- **ERR/Sv**, excess relative risk per Sievert, adjusted for sex, age, job type, calendar year and time since first exposure. **CI**, confidence interval, ex: (0.47,2,10)

- **EAR/Sv/10,000PY**, excess attributable risk per Sievert per 10 000 person-years of follow-up.

- **AR**, attributable risk, percentage for a dose of 0.01 Gy.

- Excess risk of cardiovascular diseases below 4 Gy
- $\text{ERR/Sv}= 0.17 \ (0.08,0.26)$ for heart disease
- $\text{ERR/Sv}= 0.12 \ (0.02,0.22)$ for stroke
- UNSCEAR (2007) and CIPR 103 were in agreement with these data (but don’t change theirs negative opinions)
Prevalence Survey in French nuclear testing veterans (2000 cases)

- It was only a prevalence enquiry and not an epidemiologic study like LSS
- The veteran mean age during nuclear testing was: $22.5 \pm 4$ years
- The veteran mean age at the moment of this survey was: $51.6 \pm 10.3$ years
2. - Pathologies recensées

- Pathologies non cancéreuses 82.0%
- Pathologies cancéreuses 34.7%
- En bonne santé 12.6%
Diseases numbers

Non cancer diseases

- cardio-vasculaires : 38%
- digestives : 30%
- osteo-musculaires : 26%
- dermatologiques : 24%
- cerveau : 22%
- problèmes dentaires : 17%
- broncho-pulmonaires : 15%
- chute cheveux : 14%
- ophtalmologiques : 14%
- diabète NID : 12%
- stérilité & procréation difficile : 10%
- fatigue chronique : 9%
The **ONLY** radioprotection in SAHARA nuclear test area
DISCUSSION 1

• Prevalence in veteran French study was slightly but significantly higher than population (38% vs 29.1%)

• The same for LSS study versus Canadian study: ERR/Sv 0.17 for LLS, 1.35 for NDR

• Why there is a difference between studies: is it the question of CHRONIC EXPOSURE like in Chernobyl area?
WHY?

- Y.I. Bandazhevsky’s proposals: (in:”radio caesium and heart”, 2001). Cs 137 as a potassium like, was up taking by myocyte, in consequence were there a radioactive direct effect in mitochondria and loss of ATP activity? **OBJECTION:**
  - 1- No cardiomyopathy in excess
  - 2- Vascular diseases in excess (coronary heart disease, hypertension, stroke…)
  - 3- In fact, it was a long term effect in cardiovascular system after irradiation, (as radio-induced cancers) and with stochastic consequences and not direct effects.
THE CHALLENGE

- What kind of ionising radiation effects could explain this epidemiologic impact in CVD?
- Why heart, macro and microcirculation were the target?
- Why there was a long term effect?
- Why radio induction was different in short exposure versus chronic radioactive exposure?
- Why second risk factors were crucial?
MY HYPOTHESIS

• The radiation effect in this issue is free radical production: as reactive oxygen species, in blood circulation
• The main target is vascular endothelium and at least, stress oxidative protection loss
• Chronic endothelium dysfunction is not enough to explain CVD, a second factor is needed
• This mechanism is biologic and not physics
IONIZING RADIATION AND ROS

- ROS are formed by interaction with biological molecules.
- ROS attacked molecules lost its electron and began a chain reaction, and specifically:
  - NADPH oxidase in neutrophile leukocytes became active which converted molecular oxygen to the super oxide anion
  - Radiation-induced oxidative stress both in micro and macro vascular endothelial cells, might serve to drive the progression of radio-induced late effects (ROBBINS, 2004)
Experimental study is difficult with radionuclide. Only external irradiation is available.

Menandez (2009), Soucy (2007), Collins-underwood (2008) demonstrated that oxidative stress induced by external radiation had a direct action on NO production (protective against oxidative stress), in the delayed phase of radiation.

This effect was also present after low dose exposure.
DISCUSSION 2

• We have enough evidences about ROS produced by external ionizing radiation, oxidative stress and endothelial dysfunction, but human radioactive exposure is different.

• Tribble (1999) demonstrated a crucial role of a second factor (high fat diet) in mice model for endothelial dysfunction.

• Mechanism of “long term effect after exposure” is unclear.

• A model of chronic oxidative stress with a second factor is needed.
MY ANIMAL MODEL

• ROBBINS (2004) demonstrated that chronic oxidative stress in Diabetes or radiation late effects was similar

• LYENGAR (1990) and BHAUMIK (1995) demonstrated a generation of free radicals during cold injury and warming up.

• In diabetic rats with chronic oxidative stress we had experimented cooling and warming up effect as second factor.
Figure 1: COOLING AND WARMING UP TECHNIC
Figure 2: Spectrometric detector for albumin retention during experimentation
OXYDATIVE STRESS LEVEL IN RATS

W= Wistar non diabetic rats as control out of any cooling
Gko and GK1= diabetic rats out of cooling between 4 and 5 month age
GK2= diabetic rats after 6 cooling/warming up
EXCESS ALBUMIN FILTRATION IN DIABETIC RATS (endothelial barrier marker)

GK1= Diabetic rats after only one cooling/warming up
GK2= Diabetic rats after 6 cooling/warming up (marker was in favour of micro angiopathy)
All experimental results might support these mechanisms:

- Radiation → free radicals → oxidative stress → endothelial dysfunction → cardiovascular disease (higher prevalence).

Low dose radiation exposure had effects long after exposure, and chronic exposure (like Chernobyl population or nuclear workers) had much more CVD risks than single exposure (like LSS study).

CVD prevalence is higher and earlier if a second factor did exist, like: lipid dysfunction, metabolic diseases, etc...

The second factor had a role not in addition but in promotion way as lung radiation exposure and smoking in excess on cancer.

More research is needed, but not on a pretext for delayed decisions by WHO, ICRP, UNSCEAR out of victims’ favour.
CONCLUSION

• ROS production, oxidative stress and endothelial dysfunction could be a good explanation for CVD in excess after radiation exposure

• We need a medical (biological) change for radioprotection, and less physical commitment for exposed population. (risk groups and not unique mean dose for a population)

• We need justice for Chernobyl population, nuclear workers and nuclear testing veterans and the end of official denied about radio induced CVD.
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