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)

SEX	ERR/Sv	EAR.Sv/10 000 PY	AR(0,01 Gy) %
Males	1.22 (0.47, 2.10)	37.6 (15.0, 62.5)	8.84 (3.65, 14.2)
Females	7.37 (0.95, 18.1)	59.1 (8.33, 129.2)	24.5 (4.08, 43.7)
Both	1.35 (0.59, 2.24)	37.5 (17.0, 60.1)	9.46 (4.42, 14.7)

- **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.

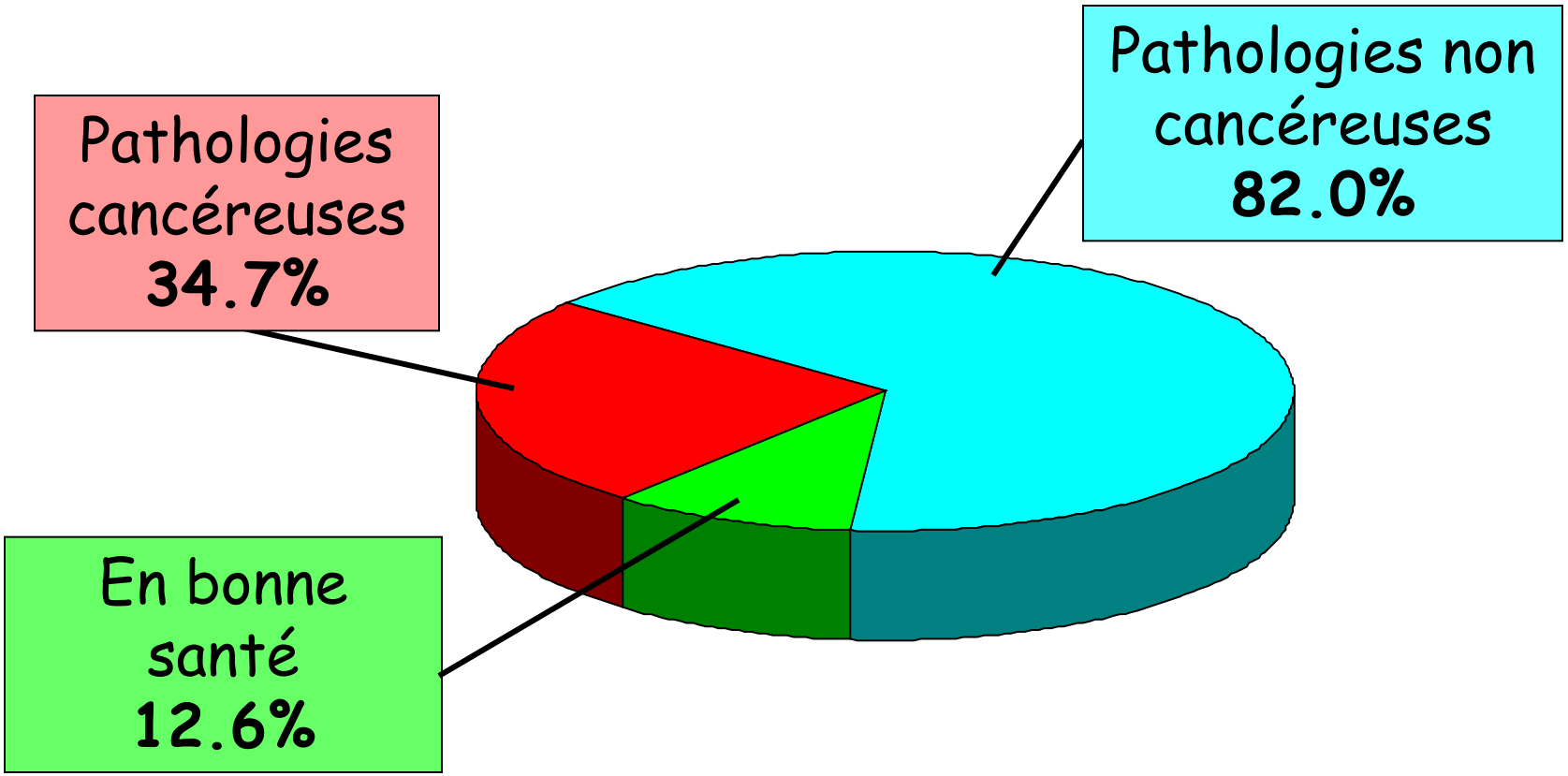
Life Span Study of atomic bomb survivors. PRESTON DL (2003)

- Excess risk of cardiovascular diseases below 4 Gy
- ERR/Sv= 0.17 (0.08,0.26) for heart disease
- 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 ± 4 years
- The veteran mean age at the moment of this survey was: 51.6 ± 10.3 years

2. - Pathologies recensées



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'** 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.

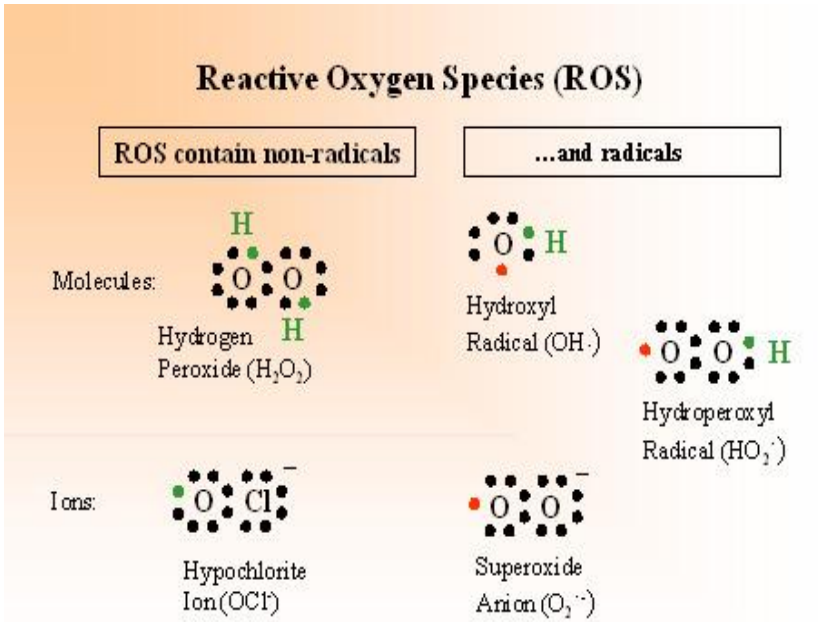
THE CHALLENGE

- 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

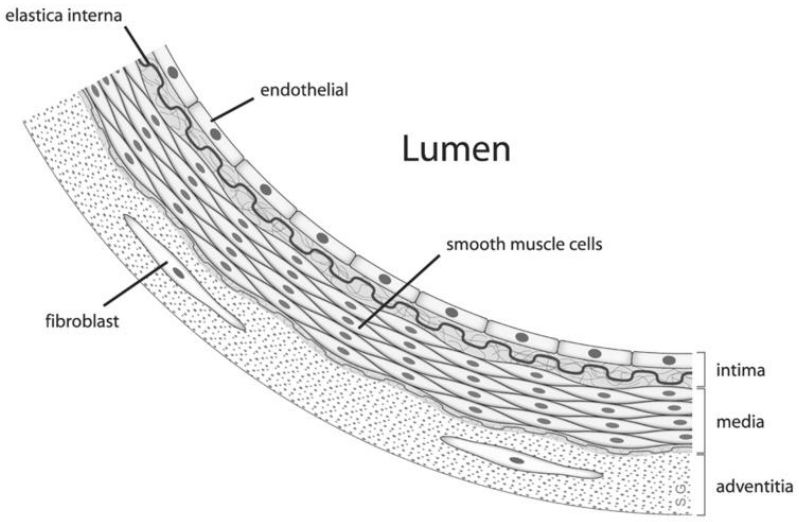
- The radiation effect in this issue is free radical production : as reactive oxygen species, in blood circulation
- The main target is ***vascular endothelium*** and at least, stress oxidative protection loss
- Chronic endothelium dysfunction is not enough to explain CVD, a second factor is needed
- 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)

IONIZING RADIATION AND ENDOTHELIAL DYSFUNCTION



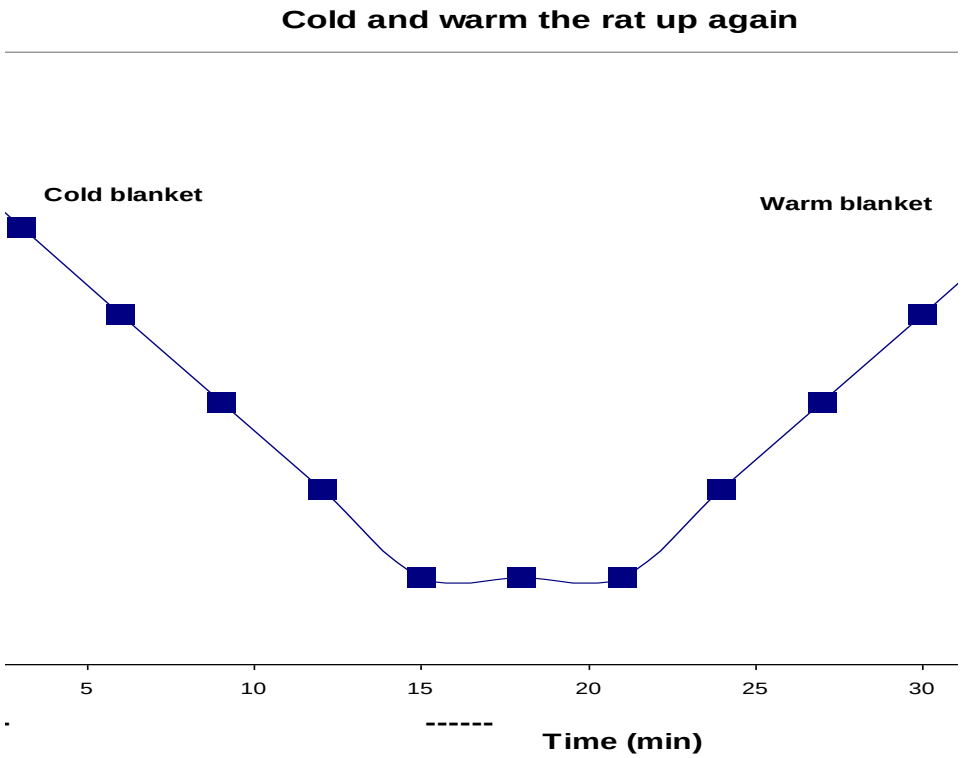
- Experimental study is difficult with radionuclide. Only external irradiation is available.
- Menandez (2009),Soucy (2007), Collins-underwood (2008) demonstrated that oxidative stress induced by external radiation had a direct action on NO production (protective against oxidative stress), in the delayed 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.*



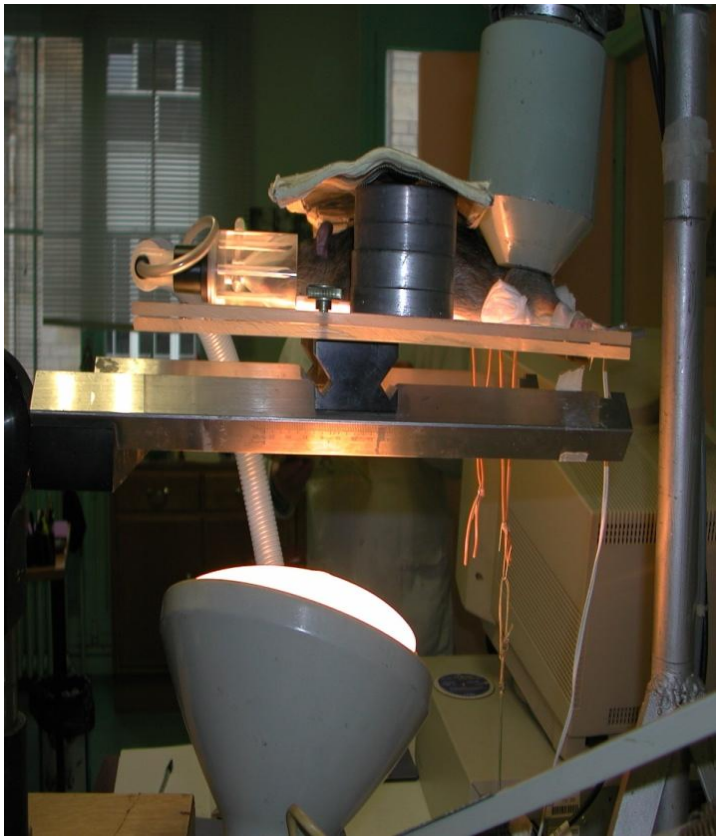
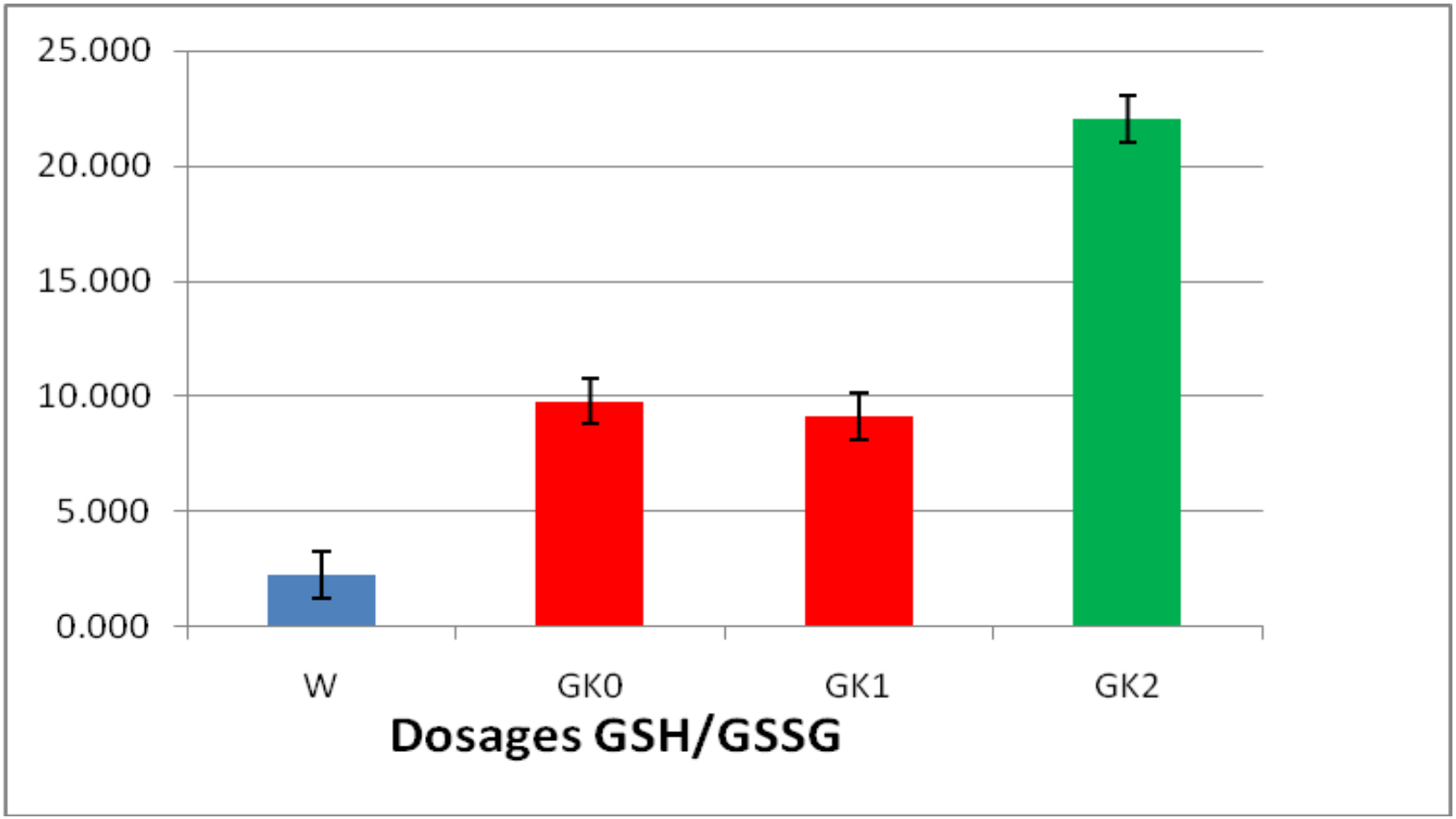


Figure 1:COOLING AND WARMING UP TECHNIC

Figure 2: Spectrometric detector for albumin*retention during experimentation

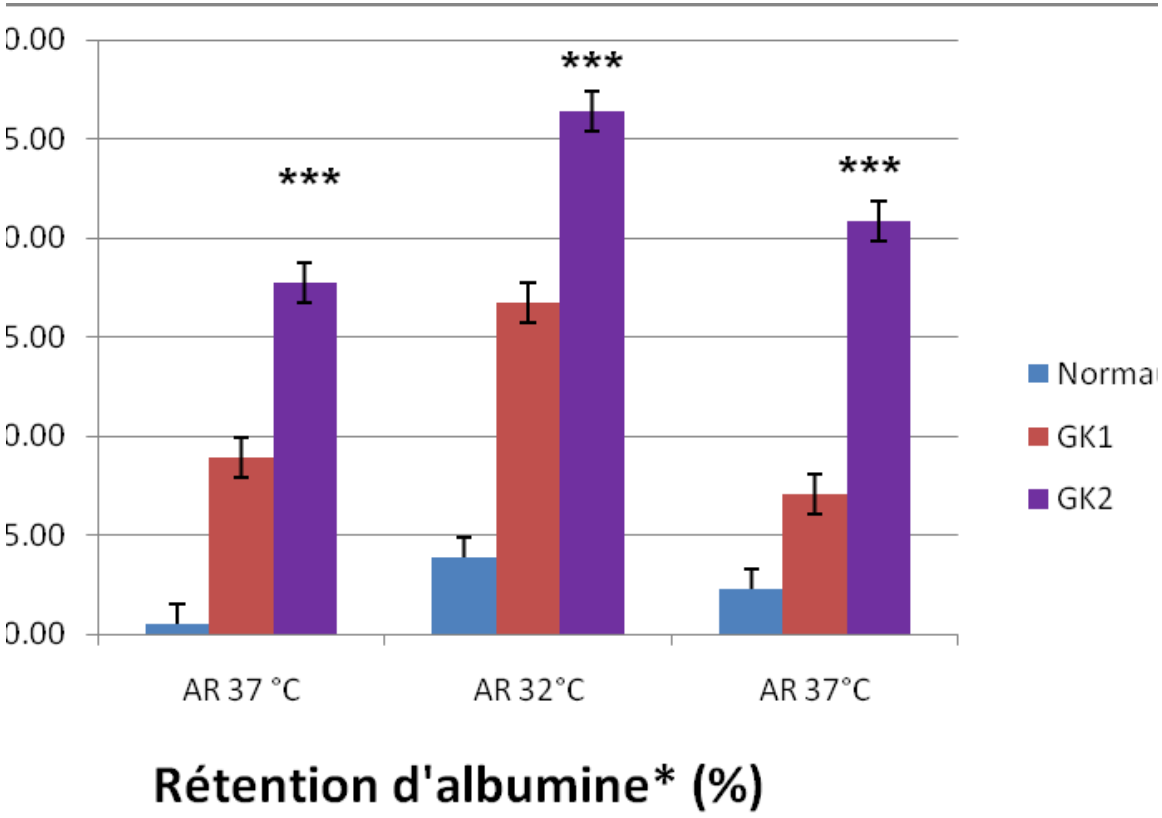


OXYDATIVE STRESS LEVEL IN RATS

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)

DISCUSSION 3

- 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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