Vascular inflammation

I read with interest the recent article by Ramón Arroyo-Espliguero and Juan Kaski on the role of vascular inflammation as a possible mechanism underlying cardiac syndrome X.[1] The hypothesis that systemic or vascular inflammation is involved in endothelial dysfunction is attractive. If it is correct, a reduction in systemic plasma inflammatory markers should improve endothelial function and thereby normalize coronary flow in patients with cardiac syndrome X.[2]

Some cardiac drugs, such as statins, have a therapeutic anti-inflammatory effect. Statins have been shown to have a beneficial clinical effect in patients with cardiac syndrome X, which appears to have led some people to support the idea that inflammation is a likely cause for this condition.[2] On the other hand, statins can also increase the expression of endothelial nitric oxide synthase,[3] which produces endothelial nitric oxide. Nitric oxide has been recognized as an endothelial mediator that directly regulates vascular smooth-muscle tone. For example, it has been shown that intracoronary administration of the nitric oxide synthase inhibitor N^G-monomethyl-L-arginine reduces epicardial coronary artery diameter and blood flow.[4] Other drugs of clinical benefit in cardiac syndrome X, such as angiotensin-converting-enzyme inhibitors and estrogens, also reduce inflammation and increase the expression of endothelial nitric oxide synthase.[5] Therefore, before we assume that cardiac syndrome X results primarily from vascular inflammation, we should first consider further the role played by endothelial nitric oxide synthase.

Craig S. McLachlan
Department of Physiology
National University of Singapore
Singapore

REFERENCES

1. Arroyo-Espliguero R, Kaski JC. Microvascular dysfunction in cardiac syndrome X: the role of inflammation. *CMAJ* 2006;174:1833-4.
2. Li JJ, Li YS, Zhang Y, et al. Inflammation: a possible pathogenic link to cardiac syndrome X. *Med Hypotheses* 2006;66:87-91.
3. Landmesser U, Engberding N, Bahlmann FH, et al. Statin-induced improvement of endothelial progenitor cell mobilization, myocardial neovascularization, left ventricular function, and survival after experimental myocardial infarction requires endothelial nitric oxide synthase. *Circulation* 2004; 110:1933-9.
4. Kaufmann PA, Rimoldi O, Gnecchi-Ruscone T, et al. Systemic inhibition of nitric oxide synthase unmasks neural constraint of maximal myocardial blood flow in humans. *Circulation* 2004;110:1431-6.
5. Wang J, Tokoro T, Matsui K, et al. Pitavastatin at low dose activates endothelial nitric oxide synthase through PI3K-AKT pathway in endothelial cells. *Life Sci* 2005;76:2257-68.

DOI:10.1503/cmaj.1060177

Nitric oxide has beneficial effects that go beyond vasodilation. An article about the role of inflammation in cardiac syndrome X, such as the recent *CMAJ* Analysis piece by Ramón Arroyo-Espliguero and Juan Kaski,[1] should point out that nitric oxide has profound anti-inflammatory effects in endothelial cells.

In-vitro experiments with human aortic endothelial cells and in-vivo experiments with mice have shown that nitric oxide plays a key role in inhibiting the exocytosis of Weibel–Palade bodies, which are vascular mediators of inflammation, from endothelial cells. Patients in whom the synthesis of nitric oxide in endothelial cells is inadequate are at greater risk of vascular inflammation; this could be because of proinflammatory mechanisms such as leukocyte activation by Weibel–Palade bodies subsequent to decreased production of nitric oxide.[2] A delicious way to boost the formation of nitric oxide in endothelial cells is by enjoying dark chocolate.[3]

Ettore Corsi
Department of Biology
Concordia University
Montréal, Que.

REFERENCES

1. Arroyo-Espliguero R, Kaski JC. Microvascular dysfunction in cardiac syndrome X: the role of inflammation. *CMAJ* 2006;174:1833-4.
2. Matsushita K, Craig NM, Beatrice C, et al. Nitric oxide regulates exocytosis by S-nitrosylation of N-ethylmaleimide-sensitive factor. *Cell* 2003;115: 139-50.
3. Helmut S, Tankred S, Christian H, et al. Cocoa polyphenols and inflammatory mediators. *Am J Clin Nutr* 2005;81:304S-12S.

DOI:10.1503/cmaj.1060161

Nitrofurantoin and pregnancy

The recent *CMAJ* teaching case report by Aneez Mohamed and colleagues elegantly details an important complication of treatment with nitrofurantoin,[1] which might have occurred even if the patient had not been pregnant. However, the complication should have been avoided in this case, given that nitrofurantoin use is contraindicated in pregnant patients in whom labour is potentially imminent.

Nitrofurantoin is commonly used to treat urinary tract infections in pregnancy.[2] Animal model studies have not demonstrated an obvious problem with fetal exposure to this antibiotic.[3] The authors of a meta-analysis of studies in humans did not find evidence of harmful effects in pregnancy, but they were cautious about drawing conclusions because of the small amount of data available.[4]

Nitrofurantoin use in pregnancy continues to be of concern for several reasons. This antibiotic can affect glutathione reductase activity and hence can cause hemolytic anemia (analogous to the problems it causes in patients with glucose-6-phosphate

dehydrogenase deficiency). Newborns and fetuses are apparently susceptible to this effect on glutathione reductase activity and hemolytic crises have been documented in these patients.[5,6] Other evidence links craniosynostosis to fetal exposure to nitrofurantoin and drugs with similar chemical structures.[7,8]

The US Food and Drug Administration continues to list nitrofurantoin as a Category B drug (probably safe). The *Canadian Compendium of Pharmaceuticals and Specialties* (2007) continues to state that nitrofurantoin use is contraindicated in pregnancy when patients are close to delivery;[9] until further data are available, it would be prudent to follow this guideline.

Nevio Cimolai
Department of Pathology and Laboratory Medicine
Children's and Women's Health Centre of British Columbia
Vancouver, BC
Tomas Cimolai
Faculty of Science
University of Alberta
Edmonton, Alta.

REFERENCES

1. Mohamed A, Dresser GK, Mehta S. Acute respiratory failure during pregnancy: a case of nitrofurantoin-induced pneumonitis. *CMAJ* 2007;176(3):319-20.
2. Le J, Briggs GG, McKeown A, et al. Urinary tract infections during pregnancy. *Ann Pharmacother* 2004;38:1692-701.
3. Prytherch JP, Sutton ML, Denine EP. General reproduction, perinatal-postnatal, and teratology studies of nitrofurantoin macrocrystals in rats and rabbits. *J Toxicol Environ Health* 1984;13:811-23.
4. Ben David S, Einarson T, Ben David Y, et al. The safety of nitrofurantoin during the first trimester of pregnancy: meta-analysis. *Fundam Clin Pharmacol* 1995;9:503-7.
5. Gait JE. Hemolytic reactions to nitrofurantoin in patients with glucose-6-phosphate dehydrogenase deficiency: theory and practice. *DICP* 1990;24:1210-3.
6. Bruel H, Guillemant V, Saladin-Thiron C, et al. Anémie hémolytique chez un nouveau-né après prise maternelle de nitrofuratoïne en fin de grossesse. *Arch Pediatr* 2000;7:745-7.
7. Kallen B, Robert-Gnansia E. Maternal drug use, fertility problems, and infant craniostenosis. *Cleft Palate Craniofac J* 2005; 42:589-93.
8. Gardner JS, Guyard-Boileau B, Alderman BW, et al. Maternal exposure to prescription and non-prescription pharmaceuticals or drugs of abuse and risk of craniosynostosis. *Int J Epidemiol* 1998;27:64-7.
9. Canadian Pharmacists Association. *Canadian compendium of pharmaceuticals and specialties. The Canadian drug reference for health professionals.* 42nd ed. Ottawa (ON): The Association; 2007.

DOI:10.1503/cmaj.1070028

Physicians' participation in research

I (the first author) am currently working with the Motherisk program at the Hospital for Sick Children, where I am helping with a research project that involves contacting family physicians' offices, describing a survey to the nurse or office manager and inquiring if the physician would be interested in completing a 5-minute questionnaire. I have been very surprised by the number of physicians who report that they do not participate in research. In Canadian medical schools, we are taught that physicians are expected to practise evidence-based medicine, which is based on research findings. Clinicians should play a pivotal role in research, because they require the results of these studies to optimally treat their patients.

The role of the physician is a demanding one, with many time constraints. It would be unreasonable to expect physicians to participate in every survey that crosses their desk, but we feel that they should at least consider the research proposals that are presented to them, rather than becoming irritated and immediately discarding them. Perhaps the exposure of medical students to role models and the way research is presented within the medical school curriculum should be evaluated to ensure that graduating physicians are open to participating in research.

Shauna Tsuchiya
Second-year medical student
University of Toronto
Adrienne Einarson
Assistant Director
Motherisk
The Hospital for Sick Children
Toronto, Ont.

DOI:10.1503/cmaj.1070030

Maintaining ethical standards in chart audits

My physician recently told me that he had audited the charts of his patients with diabetes. I casually asked who had done the audit for him. He replied, "My daughter." My heart dropped; his daughter is a student nurse in the program in which I teach.

In a later conversation I asked if all identifying information had been removed before the audit took place. It soon became clear that the physician's daughter had had full access to my medical file.

I feel that during the conduct of this audit there was a failure to adhere to several ethical standards. First, patient privacy and confidentiality were violated. Second, informed consent was not obtained, as required by the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*.[1] Third, the CMA Code of Ethics was breached, particularly some of the guidelines itemized in the sections entitled "Fundamental Responsibilities" and "Responsibilities to the Patient."[2] In addition, student nurses need to be aware that they must adhere to the Canadian Nurses Association's Code of Ethics[3] under all circumstances, regardless of whether or not a physician has asked them to do something.

I am writing this letter not to complain, but to ask physicians to stop and think about the methods they are using to evaluate their practices. I urge the colleges of physicians to review protocols for chart audits to ensure that patient confidentiality is safeguarded and to give serious consideration to insisting that written informed consent be obtained before any information collected during such audits is disclosed to third parties. I appreciate my own physician's professionalism in listening to my concerns.

Registered nurse

REFERENCES

1. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada. *Tri-Council policy statement: ethical conduct for research involving humans. 1998 (with 2000, 2002 and 2005 amendments).* Available: pre.ethics.gc.ca/english/policystatement/policystatement.cfm (accessed 2007 May 11).
2. Canadian Medical Association. *Code of Ethics.* Ottawa: The Association; 2004. Available: www.cma.ca/index.cfm/ci_id/2419/la_id/1.htm (accessed 2007 May 11).
3. Canadian Association of Nurses. *Code of ethics*