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

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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.

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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