There is increasing evidence that the angiogenic cytokine vascular endothelial growth factor (VEGF) plays an important cytoprotective role in the vascular endothelium, according to Drs Ian Zachary, professor of vascular cell biology and John Martin, British Heart Foundation professor of cardiovascular science and director of the Centre for Cardiovascular Biology and Medicine, University College, London. "Cancer patients treated with the inhibitory VEGF antibody, bevacizumab, have an increased risk of myocardial infarction, supporting a physiologically important protective role of VEGF in the adult human vasculature." VEGF-induced production of prostacyclin and other prostanoids mediated by cyclooxygenase (COX)-2 is implicated in mediating vascular protective effects of VEGF in vivo.

The COX-2 inhibitor rofecoxib was recently withdrawn as a treatment for rheumatoid arthritis because it increases the risk of myocardial infarction. Drs Zachary and Martin propose, "The similar cardiovascular side-effects of bevacizumab and rofecoxib may inhibit a key role that vascular endothelial growth factor plays in the vascular endothelium.

The side effects of drugs have always been a major concern to clinicians. Currently, there is great public interest in rofecoxib, a drug that was developed at enormous expense. “The collapse of rofecoxib is all the more worrying,” say Drs Zachary and Martin, “since the biology and pathology of common cardiovascular diseases have been intensively investigated over several decades. However, either our understanding of the causes of cardiovascular disease has not been deep enough or the relationship between the needs of industry and the mechanical sciences has not been close enough.”

VEGF is an essential angiogenic factor in development that also plays a central role in the neovascularisation that underlies the pathogenesis of diverse chronic diseases, such as cancer, rheumatoid arthritis, and eye disorders. Recognition of the clinical importance of inhibiting VEGF has led to the development of the first treatment specifically targeted against VEGF-driven angiogenesis. Bevacizumab is an inhibitory antibody directed against VEGF that is now available for patients with metastatic colorectal carcinoma in combination with more conventional chemotherapeutic drugs.

Cardiovascular diseases are the striking exception to the widely accepted view that too much VEGF is probably a bad thing to have in the adult state. A myocardial infarction (MI) is usually caused by the thrombotic occlusion of a coronary artery, resulting in a sudden restriction of the blood supply to the heart, frequently resulting in death. A consequence of MI is often myocardial ischaemia. “Hence,” say Dr Zachary and Martin, “a key therapeutic goal has been to use angiogenic cytokines such as VEGF to stimulate collateral blood vessel formation in the ischaemic heart.” This approach is called therapeutic angiogenesis.

VEGF is also a potentially powerful way of inhibiting restenotic intimal thickening after balloon catheter angioplasty or stenting through its ability to accelerate endothelial regeneration. However, though the use of VEGF in patients has an excellent safety profile, the data from clinical trials of VEGF for ischaemic heart disease have so far been inconclusive.

Drs Zachary and Martin suggest, “VEGF therapy for cardiovascular disease might also be effective through the stimulation of vascular protective effects on the endothelium, particularly production of nitric oxide (NO) and prostacyclin (PGI₂).” This in turn could protect arteries by inhibiting...
and excessive vascular smooth muscle cell proliferation.6-11 “This is a protective role in adult arteries,” explains Dr Martin, “distinct from VEGF-induced angiogenesis in foetal development or cancer.” He refers to the ability of VEGF to inhibit thrombus formation after balloon catheter injury and stent placement in rabbits19 and in pig grafts. “This ability, shown in our unpublished data, is probably explained as a consequence of the synergistic inhibition of platelet aggregation by NO and PGI2,” he says. Drs Zachary and Martin argue that this property of VEGF could potentially prevent the arterial occlusion by thrombus formation that leads to MI and thrombotic stroke.

While it is accepted that VEGF is essential for embryonic development, one of the current gaps in our knowledge is whether VEGF continues to be physiologically important during adult life. “It is highly likely that this is true in special contexts such as pregnancy and wound healing, because these processes involve angiogenesis. But do endogenous circulating levels of VEGF have a constitutive protective role in the adult vasculature?” asks Dr Zachary. Support for this idea has come from the finding that a proportion of patients treated with bevacizumab are at greater risk of developing thromboembolic disease, including cerebrovascular events, myocardial infarction and deep vein thrombosis.12

The side effects reported in these patients were surprising, partly because it had been assumed that the only significant VEGF production in adults was associated with neovascular diseases such as cancer. “However,” Dr Zachary says, “if it is supposed that there is a low constitutive level of systemic or locally produced VEGF that performs essential maintenance functions in the vasculature, then the thromboembolic events associated with bevacizumab can be understood as a consequence of inhibiting not only the angiogenic effects of VEGF produced by tumours, but also the physiological arterioprotective actions of VEGF.”

Dr Martin points out, “A similar problem to that observed in trials of bevacizumab has come to light in patients using rofecoxib. COX-2 is responsible for one of the key, rate-limiting steps in the biosynthesis of prostanoids, and plays a particularly crucial role in the endothelial production of PGI2.” The VIGOR (Vioxx and Gastrointestinal Outcomes) clinical trial found a significant 4-fold increased risk of MI in those taking rofecoxib compared to those taking naproxen, a nonselective, nonsteroidal anti-inflammatory drug.13

“The most likely explanation for the cardiovascular effects of rofecoxib,” he considers, “is that because endothelial PGI2 synthesis is largely dependent on COX-2, inhibition of this enzyme would reduce a powerful inhibitor of platelet aggregation and thrombosis, processes that play crucial roles in triggering acute coronary syndromes.” This interpretation is supported by the discovery that other COX-2–specific drugs such as celecoxib are also associated with increased risk of MI.15,16

The biological function of VEGF-induced PGI2 production remains to be fully elucidated, but the possibility that VEGF plays an important role in regulating PGI2 endothelial generation in the adult vasculature is supported by the fact that VEGF is able both to activate cytosolic phospholipase A2, which mediates release of arachidonic acid, the major precursor for prostanooid biosynthesis, and to induce COX-2 expression.9 Dr Zachary suggests, “Either circulating or locally produced VEGF may have a protective function in the vasculature, mediated via enhanced endothelial production of PGI2, possibly acting in concert with NO, which is also produced in response to VEGF and also has antiplatelet effects.” NO and PGI2 act synergistically, they point out, causing inhibition of platelet aggregation together at concentrations that elicit little effect when these vaso-active mediators are administered alone.17

Inhibition of either VEGF or COX-2–dependent PGI2 biosynthesis would consequently abolish a tonic protective pathway, thereby increasing the risk of thrombosis. “This is precisely what appears to happen in some patients treated with bevacizumab or rofecoxib,” Dr Martin explains (see Figure). “The level of VEGF that would be most effective in maintaining such a protective effect is likely to be at the low end of the physiological range for this cytokine, because resting levels of circulating VEGF are low and because excessive VEGF production is frequently associated with neovascular disease.”

Bevacizumab and rofecoxib may impair the arterioprotective actions of VEGF thus: VEGF binds to its major endothelial receptor, KDR, triggering activation of endothelial nitric oxide synthase (eNOS) and COX-2, enzymes that mediate production of nitric oxide (NO) and prostacyclin (PGI2). NO and PGI2 are released by endothelial cells and act locally and synergistically to inhibit platelet aggregation and proliferation of vascular smooth muscle cells (VSMC), actions that are responsible for preventing thrombosis and arterial wall thickening. Bevacizumab and rofecoxib can block this arterioprotective pathway by inhibiting, respectively, VEGF itself or COX-2.

If their hypothesis is correct, say Drs Zachary and Martin, it may have important clinical implications. Perhaps the most heretical, given the orthodox view that VEGF is a pathogenic agent in many diseases, is that a modest increase in either the systemic or local tissue levels of VEGF may be a rational way of boosting the naturally protective mechanisms of the circulatory system.

While delivery of the natural cytokine is the simplest approach to pro-VEGF therapy, its efficacy and utility may
be limited by the short half-life of VEGF and the need for nonoral administration. “In the future,” Dr Zachary speculates, “development of small molecule agonists of the main signalling receptor for VEGF, kinase insert domain-containing receptor (KDR) or VEGF receptor-2, could provide an alternative approach to stimulating arterioprotection.” A protective role for VEGF also has implications for explaining individual differences in the development of certain illnesses.

“Thus,” Dr Martin concludes, “an underlying cause of a person’s susceptibility to cardiovascular or neurodegenerative diseases or to the adverse effects of treatment with drugs such as bevacizumab or rofecoxib may be variations in the constitutive level of VEGF.

“In addition to the amyotrophic lateral sclerosis study discussed above,” Dr Zachary adds, “there are other reports that common polymorphisms in the human VEGF promoter are associated with altered VEGF plasma levels and linked to risk of diseases, including diabetic microvascular complications and acute renal allograft rejection.1,3,9

“It is unknown whether specific VEGF promoter haplotypes are associated with an increased risk of coronary heart disease,” says Dr Zachary, “and this is something that needs to be addressed. If this were so, genetic screening might determine which patients might be more susceptible to cardiovascular side effects associated with VEGF or COX-2 inhibition.”

Further research is now vital to unambiguously demonstrate a protective role for VEGF in adults. This would then pave the way to making the effective utilisation of the protective functions of VEGF a major therapeutic goal.

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**References**


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**Spotlight: Paul G. Hugenholtz, MD**

Dr Paul Hugenholtz restructured the European Society of Cardiology and is credited with providing the organisational basis for its massive success today. Robert Short, BSc, speaks to him about his endeavours.

Dr Paul Hugenholtz, emeritus professor of cardiology at the Erasmus Medical Center, Rotterdam, The Netherlands, became president of the European Society of Cardiology (ESC) in 1984 and remained in post for 4 years. However, he feels his most revolutionary work was done before those years in office. The ESC was actually founded in 1950, and Dr Hugenholtz says, “I did not create the ESC. I visualised what the component parts of today’s organisation would be and put them together.”

The ESC was once like a travel club of roughly 70 professors who made visits to each other across borders and met at the big conferences in the United States. In those days, “European cardiology” and its thought processes did not exist across countries. To change this, Dr Hugenholtz, together with Henri
Denolin, MD, a Belgian professor who was president of the ESC from 1976 to 1980, took a number of steps that he had originally prepared in his position as councillor of the ESC from 1976 to 1980.

The first step was the creation of a journal with the British cardiologists Peter Harris, MD, and, later, Desmond Julian, MD, to be the voice of the ESC. This became the *European Heart Journal* and was first published in 1980.

For the second step, Dr Hugenholtz focussed on making the congresses a true expression of European cardiology. Although a congress had been held every 4 years since 1952, the new aim was to establish a real European-wide congress at shorter intervals.

In 1972, Dr Hugenholtz was asked by the Dutch Society of Cardiology to prepare for a European congress in Amsterdam in 1976. This, he decided, should have a format that would break the ground for a future with regular annual conferences. It was to be the model for a true joint European congress. The success of the Amsterdam congress was unprecedented. It established the organisational confidence in the ESC that became the driving force for the now annual conferences. But institutions need time to change, and it was only in 1984 that the General Assembly of the ESC overwhelmingly voted to increase the frequency of the European Congress so that it became an annual event, starting with the Vienna meeting in 1988.

While he was a councillor of the ESC, and then secretary (from 1980 to 1984), Dr Hugenholtz took steps to create organisational structures within the ESC that could deliver a vibrant society and a strong scientific programme. He determined to weave the ESC into a tough fabric. Simply marrying up the national societies was not enough to make the ESC strong. National societies of that time tended to have small memberships. Dr Hugenholtz explains, “It was the era of the ‘town versus the gown.’ Societies were typically run by eminent, middle-aged academic professors who varied in their ability to interest young researchers and expand membership.”

He believes that the strength must come from involving young cardiologists across Europe. “An idea that we had, coming from my American experience, was to produce a mechanism to combine the research groups that I had met throughout Europe. These were young people with the same interests and disciplines. I thought of the idea of making working groups outside the national societies around specific topics, but across Europe.”

Initially, 15 working groups were created. These finally expanded to 27, and in the meantime, 7 of these formed 5 new associations. Dr Hugenholtz said, “You can look at the current national societies as vertical fibres and the working groups as horizontal fibres. That makes for a very strong design of fabric.” Dr Hugenholtz is convinced that this design was an essential part of the current success of the ESC.

The power of a working group to negate national idiosyncrasies became obvious quickly. Dr Hugenholtz gave a vivid example. “I still shudder that in early 1972 the Dutch cardiology establishment voted that echocardiography was a ‘nonissue’ for the congress programme, and withheld funds for its development. But within the working group it lived. The horizontal fibres conveyed the message.”

A key move made by Dr Hugenholtz was to make the ESC the organiser of its own congresses. It was obviously wasteful of experience to have different countries develop and host a programme for a “one-off” hosting of a congress. This step required the development of the ESC’s own offices, its own money, and a permanent staff.

That decision led to the first office in Nyon, Switzerland, in 1986. Plans were subsequently made by the late Attilio Reale, MD, president of the ESC from 1990 to 1991, to create the European Heart House in France. Dr Reale was succeeded by Michel Bertrand, MD, who was president of the ESC from 1991 to 1994, and it was he who laid the foundation stone in 1992. The Heart House, which is located in the technology park of Sophia Antipolis, was inaugurated in 1993. The ESC now employs some 100 staff who provide support to constituent bodies and generally administer activities related to the mission and strategies of the ESC.

Dr Hugenholtz reflected, “The ESC has perhaps in some ways outstripped my vision of it, thanks to the efforts of my colleagues, who shared my vision.” In September, the ESC hosted the World Congress of Cardiology in Barcelona, which was a joint venture with the World Heart Federation, and, Dr Hugenholtz commented, “Our president, Michal Tendera, MD, said at the opening ceremony that a total of 32,000 doctors, researchers, and healthcare workers had registered for the congress, ‘to see the best cardiology that the world has to show.’”

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