care systems. Thus we need to implement more stringent criteria for determining who receives cardiac catheterization and their priority for this procedure irrespective of which hospital they present to. Finally we do not have the evidence base for supporting an approach for ‘routine’ cardiac catheterization and further randomized studies would be helpful including careful health economic evaluation of these resource intensive treatments.

A. BAKHAI
D. PEREZ DE ARENAZA
M. FLATHER
Clinical Trials and Evaluation Unit,
Royal Brompton Hospital,
London, U.K.

References

European Heart Journal (2001) 22, 2051–2054

Hormone replacement therapy in women with angina with normal coronary arteriograms. Pathogenetic or symptomatic therapy?

See page 2116, doi:10.1053/euhj.2001.2631 for the article to which this Editorial refers

Although the majority of patients undergoing cardiac catheterization for the investigation of chest pain are men, those in whom normal coronary arteries are most frequently found are predominantly women of whom most are post-menopausal[1–3]. This observation, coupled with the evidence that oestrogens are vasoactive substances, a deficiency of which is associated with vasomotor instability and decreased arterial flow velocity, has led to the suggestion that oestrogens may play a central role in the pathogenesis of chest pain in post-menopausal patients with angina with normal coronary arteriograms[4–5]. This hypothesis is also supported by the symptomatic benefit derived from oestrogen replacement therapy in post-menopausal women with the syndrome and by the finding that hyperaemic vasodilator reserve, found to be impaired in women with angina with normal coronary arteriograms, is normalized by oestrogen replacement therapy[3,6].

A significant 50% reduction in the frequency of episodes of chest pain in post-menopausal women with angina with normal coronary arteriograms when treated with oestrogen replacement therapy has been reported[6]. However, this beneficial effect upon chest pain is not coupled with any significant improvement in exercise time or changes in any of the variables assessed by either exercise testing or ambulatory ECG monitoring and suggestive of myocardial ischaemia. This indicates a dissociation between the beneficial effect upon symptoms and the results of cardiovascular assessment and shows that although angina with normal coronary arteriograms is likely to be heterogeneous with multiple pathogenetic components, the
chest pain in these patients may not be related to myocardial ischaemia. As mentioned, many mechanisms may account for the presence of chest pain in patients with angina and normal coronary arteriograms. Why oestrogen deficiency may trigger chest pain and changes on the electrocardiogram compatible with a diagnosis of myocardial ischaemia is still a matter of speculation\[7\]. Oestradiol 17\(\beta\) is vasoactive, and may modulate the release of catecholamines, endothelium-derived relaxing factor and have calcium antagonistic properties\[8\]. Oestradiol 17\(\beta\) has been shown to modulate acetylcholine-induced response in monkey and human coronary arteries, to block potential sensitive calcium channels in vascular smooth muscle, and to inhibit adrenaline release during hot flushes\[9,10\]. Oestradiol 17\(\beta\) improves exercise-induced myocardial ischaemia in patients with proven coronary artery disease\[11\]. Oestrogens could therefore mask a potential for angina with normal coronary arteriograms until the menopause because of their vasodilator properties. At the menopause, hormone deficiency may reveal the syndrome. The symptomatic benefits of oestradiol 17\(\beta\) in angina with normal coronary arteriograms may relate to analgesic action via other, as yet poorly understood, mechanisms. Alternatively, there may be central effects on psychological instability. The effects of oestradiol 17\(\beta\) in menopausal patients with angina with normal coronary arteriograms may be multifactorial, and may include an important improvement in the wellbeing of patients which may increase the threshold to the perception of pain.

Evidence of myocardial ischaemia, as detected by methods other than exercise electrocardiography, has been reported only in a limited proportion of patients with angina and normal coronary arteriograms\[11–15\]. Episodes of chest pain do not necessarily correlate with lactate production, or other signs of ischaemia such as increased diastolic pulmonary artery pressure\[11–13\] or regional ventricular hypokinesis\[11,12\]. These lines of evidence, together with the repetitive and long-lasting nature of the chest pain in patients with angina with normal coronary arteriograms\[16\] suggest that although the chest pain in angina with normal coronary arteriograms may be associated with abnormal coronary vasodilator capacity, it may not be mediated primarily by myocardial ischaemia.

**Endothelial dysfunction in patients with angina and normal coronary arteriograms**

In the last decade increasing interest has focused on vascular endothelium because of its important effects on the local regulation of blood flow. The presence of impaired endothelial function in patients with angina and normal coronary arteriograms has been suggested by Motz et al\[17\] who evaluated changes in coronary flow in response to acetylcysteine and dipyridamole in 23 patients. They found an impaired blood flow response to acetylcysteine but not to dipyridamole in eight patients and an impaired response to both stressors in six other patients, and took this as an indication of a reduced endothelial function in patients with angina and normal coronary arteriograms. Lagerqvist et al\[18\] found no evidence to any consistent acetylcysteine-mediated defect of perfusion in 20 patients with angina and normal coronary arteriograms. Vrints et al\[19\] showed an impaired endothelium-dependent cholinergic coronary vasodilator effect in those patients with angina and normal coronary arteriograms and typical chest pain, but not in those with atypical chest pain. However, the definition of typical and atypical chest pain was subjective and the maximal doses of acetylcysteine used in this study were higher than in other studies (10\(^{-4}\) M). Quyyumi et al\[20\] found endothelial dysfunction in those patients with angina, normal coronary arteriograms and microvascular angina, but not in those without microvascular angina. Holdright et al\[21\] evaluated the coronary blood flow response to acetylcysteine and Substance P in patients with angina with normal coronary arteriograms and in normal controls and found no difference in the degree of blood flow increase between patients and controls.

The data on endothelial function in patients with angina and normal coronary arteriograms are in keeping with the heterogeneity of this group of patients. Therefore, abnormal endothelial function may be responsible for the reduced blood flow response and symptoms in some patients with angina and normal coronary arteriograms but this is not a feature common to all patients.

**The present study**

In the present study, Sitges et al\[22\] evaluated the effect of hormone replacement therapy on brachial endothelial function in women with angina and normal coronary arteriograms. As mentioned, impaired coronary endothelial dysfunction is not a common feature of patients with angina with normal coronary arteriograms, while an impaired peripheral endothelial function is commonly found in women after the menopause. Because of the small sample size of patients undergoing evaluation of coronary endothelial function and because the study of coronary endothelial function was performed only at baseline.

and not tested after pharmacological intervention, the conclusion of the present study should only be limited to the effect of hormone replacement therapy on peripheral endothelial function.

Several studies in healthy post-menopausal women and in women at increased cardiovascular risk have shown that oestrogen replacement therapy alone or in association with non-androgenic progestins such as medroxyprogesterone acetate improve coronary and peripheral endothelial function. Therefore it is possible that the beneficial effect seen in this study after administration of hormone replacement therapy is only related to the correction of menopausal endothelial dysfunction. Whether the improvement of endothelial function shown by Sitges et al. is of pathogenetic importance in patients with angina with normal coronary arteriograms and whether improvement of endothelial function correlates with symptomatic benefit in patients with angina with normal coronary arteriograms remains to be elucidated.

Although the study from Sitges et al. was not designed to look specifically at the effect of hormone replacement therapy upon chest pain, the authors found a trend towards an improvement in the number of episodes of chest pain during hormone replacement therapy and reported that a significant proportion of patients experienced improvement of symptoms with hormonal therapy. In a randomized placebo-controlled study, the introduction of norethisterone acetate to oestrogen replacement therapy resulted in a worsening of the number and severity of episodes of chest pain in post-menopausal women with angina and normal coronary arteriograms, to the point of patient withdrawal from the trial[6]. In the study from Sitges et al. the addition of medroxyprogesterone acetate did not reduce the beneficial effect of oestrogen replacement therapy on either symptoms or brachial endothelial function. This apparent discrepancy is most probably related to the different effect of the different progestins. Norethisterone acetate has been shown to reverse the beneficial vascular effects of oestrogens, while these effects are not blunted by medroxyprogesterone acetate.

In this study, the beneficial effect of oestrogens on endothelial function was observed despite the lack of an effect of oestrogens on plasma lipids. This is a well documented phenomenon, which suggests that the vascular effect of oestrogens are independent of the metabolic effect of the hormones. The lack of an effect of hormone replacement therapy on the lipoprotein profile shown in this study is dependent on the use of transdermal hormone replacement therapy. Several studies using transdermal hormone replacement therapy have failed to show a significant lipid lowering effect of hormone replacement therapy. It seems that the oral route of administration is needed in order for there to be a significant beneficial effect of hormone replacement therapy on plasma lipids.

In conclusion, the effects of hormone replacement therapy, as seen in the present study, are shared by all post-menopausal women and are not specific to patients with angina with normal coronary arteriograms. Until we have clear evidence of a direct relationship between the vascular effect of ovarian hormones on symptoms, hormone replacement therapy (as well as other therapies suggested for patients with angina with normal coronary arteriograms such as imipramine) must be seen as an analgesic rather than a pathogenetic therapy for such patients.

**G. M. C. ROSANO**

**M. FINI**

**G. MERCUCO**

1 Cardiovascular Research Unit, San Raffaele, Rome, Italy; 2 Department of Cardiology, University of Cagliari, Cagliari, Italy

**References**


The sirolimus coated stent: will the Achilles heel of interventional cardiology finally be cured?

See page 2125, doi:10.1053/euhj.2001.2892 for the article to which this Editorial refers

Restenosis has been identified as the Achilles heel of percutaneous revascularization. Stenting has been established as an effective procedure for reducing acute complications and long-term restenosis, using mechanical scaffolding principles to prevent recoil and negative arterial remodelling and to secure the largest possible lumen at the completion of the procedure. However, long-term success is still limited by in-stent restenosis due to neointimal proliferation in response to the arterial injury.

The search for effective prevention of in-stent restenosis started in the early days of stenting. Mechnical techniques such as atherectomy prior to stenting, optimal methods to monitor stent expansion etc. led to only limited success. Intracoronary radiation has been established as an effective method to prevent restenosis[11] yet it is limited by potential long-term sequelae such as edge restenosis and late thrombosis[2] and its very long follow-up effects are unknown. In addition, the combined use of radiation and stenting in de-novo and restenotic lesions may be associated with an increased risk of late thrombosis. Numerous pharmacological approaches to reduce restenosis have failed, possibly due to insufficient local drug concentrations, inadequate kinetics and other factors.

Local drug release at the site of vascular injury via a polymeric-coated stent is an elegant approach to achieve effective local concentration for a planned duration[3]. However, the safety and efficiency of such an approach critically depends on the delicate combination of the drug, the polymer and the kinetics of the release. Among multiple possible effective compounds, a number of stents coated with antiproliferative drugs are currently being investigated to assess their efficiency and safety in the prevention of restenosis. Among the agents studied in different stent models, those with the largest animal and clinical experience are paclitaxel, actinomycin D and sirolimus.

Sirolimus (rapamycin, Rapamune®), a macrocyclic lactone antibiotic produced by Streptomyces hygroscopicus, was originally developed as an anticandidal agent in 1975[4]. It is a unique compound with pharmacological activity targeted at various phases of the cell cycle. It has potent, immunosuppressant, and antitumour properties — inhibiting the translation of key mRNAs of proteins required for cell cycle progression from G1 to S phase. The Food and Drug Administration approved it for the prophylaxis of