throughout the treatment period, then it can be expected to continue to do so. The ‘null result’ in HERS reveals, by contrast, a clear trend towards divergence ($P=0.009$ for decreasing acute ischaemic events over time on hormone replacement therapy), which could only predict further divergence had HERS been continued to its planned duration. HERS thus demonstrated an unlikely null result.

2. The study was prematurely discontinued. Indeed, if the study was conducted with a time schedule that is usual for these studies, the data and safety monitoring board should have had data from year 3 available. These data would clearly demonstrate no increased harm, and indeed a suggestion of an emerging benefit. When patients are recruited for clinical studies they are never assured that the treatment is more effective than the placebo. So the claim that ‘... conditional power estimates for primary CHD events were low and because of uncertainty about whether a sufficient proportion of women would consent to continue blinded treatment ...’ is not an obvious reason.

3. We noted that a significant proportion of cardiovascular events was due to venous thromboembolism, but in our editorial it was never stated that venous thromboembolism was considered a major cardiovascular end-point.

4. We are pleased to note that the authors now admit that the excess of CHD events in the intervention arm might have been due to a low event rate in the placebo group. Of importance, when they say that it is possible that the event rate in the placebo group was lower during year 1 because the women might have been healthier, they indirectly acknowledge an important confounding bias of the study, namely an imbalance between the two groups at baseline. Indeed if this was the case then the first year findings have no clinical relevance. A way to compensate for random fluctuations in events among placebo recipients was indicated in the HERS protocol. The analysis section urges bi-annual, rather than annual, efficacy analysis in order to increase woman-years per period and reduce random noise. If this is carried out, period one (yr 1+yr 2) harm is reduced to non-significance. A clearly significant within-treatment benefit is found for the HRT ($P=0.01$) arm. For period two there is a clear trend towards significant benefit compared with placebo.

5. Regarding the greater use of statins in the placebo group, the Cox regression analysis performed by the investigators does not address the question whether the new use of statins could have reduced the occurrence of cardiovascular events in those 1492 women not on statins at baseline (759 patients in the intervention group, 733 patients in the placebo group). The new use of statins led to a greater number of patients (6%) not on statins in the intervention group (623 compared to 572). According to the effect of statins in secondary prevention (35% reduction in cardiovascular events), the difference between the two groups in the number of patients not on statins at baseline who were then started on lipid lowering drugs after year 1 could have prevented more than 15 events in the placebo group. The beneficial effect of statins may have blunted the overall difference between groups.

We still believe that the position of the cardiological and Internal Medicine community, regarding the cardiovascular effect of ovarian hormones, is different in Europe from the US. We agree that conducted observational studies and clinical trials with surrogate end-points are not totally adequate to guide clinical decisions. However, a single large-scale randomized study is also insufficient to provide definite recommendations regarding clinical practice. This is specially true when considering the methodological concerns expressed in this letter and in our editorial. The need for further randomized study, particularly in Europe, is more urgent than ever.

G. ROSANO1
T. SIMON2
G. MERCURIO3
S. SANS4
K. SCHENCK-GUSTAFSSON5
J. C. STEVENSON6
E. SWAHN7
P. JAILLON8

1San Raffaele, Rome, Italy
2Faculté de Médecine Saint-Antoine Paris, France
3University of Cagliari, Italy
4Hospital Sant Pau, Barcelona, Spain
5Karolinska Institutet, Stockholm, Sweden
6Imperial College, London, U.K.
7University Hospital, Linköping, Sweden
8Faculté de Médecine Saint-Antoine Paris, France

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The abrupt no-flow: a no-reflow like phenomenon in hypertrophic cardiomyopathy

We congratulate the authors on their excellent article (Eekhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. Eur Heart J 2001; 729–739). They emphasize the underestimated clinical problem of the no-reflow phenomenon complicating percutaneous coronary interventions and discuss the complex mechanisms (predominantly intense microvascular constriction), assessment techniques (angiographic no-reflow, intracardiac Doppler registration or tissue no-reflow documented by contrast echocardiography), problems of therapeutic options and the potential of harmful outcome (incidence of no-reflow 0.6–7.7%, in-hospital death and myocardial infarction 15% and 31%).

The article addresses predominantly the no-reflow complication in patients with coronary heart disease after temporary coronary occlusion. Regarding other myocardial disorders the authors refer to a case with hypertrophic obstructive cardiomyopathy (HOCM). An angiographic no-reflow pattern and systolic retrograde flow in the first septal branch following alcohol septal ablation therapy, a new treatment option and an alternative to surgical treatment are shown to demonstrate the value of intracoronary Doppler registration for the assessment of coronary no-reflow.

In this context, we should like to offer a more detailed comment on the no-reflow phenomenon in hypertrophic cardiomyopathies, which perhaps should be called ‘abrupt no-flow’ or ‘no-reflow like’ phenomenon. It may occur in patients with and without preceding intervention. It was also observed in non-cardiomyopathic patients after routinely performed diagnostic coronary angiography11–14.

In the literature, endothelial-dependent vasodilation or pharmacological interventions using the cold pressure test are implemented to measure no-reflow aspects in hypertrophic cardiomyopathies1,2. Regarding clinical observations after percutaneous catheter treatment using transcoronary ablation of septal hypertrophy (TASH) the first 2-year
vasively. Severe angiographically patients with HOCM, 182 with trophic cardiomyopathies (373 to medical treatment. In the ··

tions were observed in three patients ·

coronary artery, apparently due to ··

contrast medium was injected into the left coronary artery. ··

Within seconds abrupt no-flow like complica-

tions in 0-4%[3]. Kim and co-workers report an incidence of 10% (2 out of 20 patients). However the ethanol dose was high (8 ml)[4].

Our observations of patients with hypertrophic cardiomyopathies are based on the prospective registration of complications, including no-flow, since 1991, when we initiated the development of a new catheter-based treatment of HOCM[5–6].

Since 1991, 555 patients with hypertrophic cardiomyopathies (373 patients with HOCM, 182 with HNCM) have been investigated invasively. Severe angiographically documented no-flow like complications were observed in three patients (0-5%) and a minor form in another three patients (0-5%). All patients suffered from severe HOCM, refractory to medical treatment. In the first patient (32-year-old male) out of three with severe no-flow like/abrupt no-flow complications after uncomplicated routine right coronary artery angiography, contrast medium was injected into the left coronary artery. Within seconds abrupt no-flow developed. It began in the periphery of a large diagonal branch with subsequent spastic involvement of the left anterior descending coronary artery (LAD). Finally, the contrast medium completely failed to clear from the left coronary artery, apparently due to extreme diffuse microvascular constriction. Severe cardiogenic shock developed. The occlusion was refractory to all intracoronary interventions including verapamil, nitroglycerin and abeximab injections, and PTCA manoeuvres. We decided to perform an ‘emergency TASH’. We were able to inject 3 ml of ethanol into the first septal branch of the LAD, followed by total abolition of extreme intraventricular obstruction, and subsequently partial, then transiently even complete, coronary artery reopening was seen. In the catheterization laboratory a stable circulation was restored. There was no evidence of a systemic allergic reaction in terms of urticaria or bronchospasm. At discharge from hospital the patient was in a good condition. However, a distinct left ventricular anterior wall motion disorder was found at echocardiography.

The remaining two patients, showing the same complication, died because of irreversible cardiogenic shock. Both of them developed complete no-flow of all large branches of the total left coronary artery. In one of them with labile, severe intraventricular obstruction (female, 68 years old), for technical reasons (resuscitation) an emergency TASH procedure could not be performed. Thus in this patient, alcohol was not injected. The other patient (male, 59 years old), developed the phenomenon some minutes after a TASH procedure had been performed (1.6 ml of ethanol).

In other three patients minor, temporary angiographic abrupt no-flow after TASH was observed, starting in the circumflex coronary artery in one of them. On discharge from hospital, no, or only a moderate, left ventricular contraction disorder was seen on the echocardiogram.

A most striking aspect of all the abrupt no-flow patients was an extremely anxious, stressed personality, which might have exacerbated a vasospastic reaction. The 59-year-old patient, who died recently, suffered from both pronounced anxiety neurosis and severe sleep deficit because of sleep anxiety.

Thus, severe or minor no-flow like phenomenon, observed in our institution during the last 10 years in 555 patients with hypertrophic cardiomyopathies, is relatively rare. However, as in patients with coronary heart disease, this is a potentially lethal event and exclusively occurred in the obstructive type of hypertrophic cardiomyopathy. It was seen both after contrast injection without any catheter interventional procedure and after therapeutic intervention. The total number of invasive procedures in our patients (TASH, diagnostic control examinations, re-TASH, transient septal branch occlusion) amounts to 580, the total incidence of no-flow (mild and serious forms) to 1-03%.

In HOCM patients, the no-flow induced a fall in blood pressure and the subsequent, specific potential of an extreme increase in intraventricular obstruction may have led to a more serious outcome. Careful analysis of all cases with abrupt, transient or permanent no-flow was performed. They turned out to be independent of a history of allergy and of the type of contrast medium used (ionic or anionic). The only striking, common link remained an extremely anxious, stressed personality.

As a consequence, in such patients prophylactic deep intravenous sedation and anxiolyis during the diagnostic and/or therapeutic session is performed using an intravenous infusion of midazolam.

No-flow in hypertrophic cardiomyopathy might be related to the fact that the disease should be regarded not only as a hypertrophic disorder but also as a systemic disease entity in terms of vascular autonomic dysfunction[6–8]. One may speculate that the apparent concentration of no-flow in patients with the obstructive form of hypertrophic cardiomyopathies is related to differences of vasomotion in patients with HOCM and HNCM[9–13], possibly due to a different molecular genetic or morphological[10] basis.

H. KUHN
F. GIETZEN
C. LEUNER
The Bielefeld Klinikum, Department of Internal Medicine Cardiology, Bielefeld, Germany

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