and fits with our hypothesis of micro-thrombi on larger ASD devices resulting in the appearance of migraine. Indeed, even macro-thrombi seem not to be so uncommon after device closure.\(^3\) Nevertheless, we do agree that (paradoxical) micro-emboli are generally distributed randomly. However, regional differences in cerebral arterial reactivity might be present\(^6\) and explain why diffuse micro-emboli can cause repeated lateralized signs. In addition, it can be hypothesized that micro-emboli do not have to induce brain ischaemia to provoke a migraine attack, but only to modulate the neurovascular vaso-reactivity.

Finally, the appearance of migraine is strongly age dependent. Although it is purely hypothetical, it is possible that the interaction between trigger substances and the neurovascular excitability for these trigger substances changes over time. With device closure, we might influence this interaction. The fact that migraine appeared or disappeared almost immediately after ASD closure suggests a causative relationship. However, a larger study sample in a controlled prospective study design will be necessary to answer the remaining questions.

References


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Enhancement of perfusion reserve by cardiac resynchronization therapy

With great interest, we read the recent work by Lindner et al.,\(^1\) which investigated the effects of cardiac resynchronization therapy (CRT) on regional resting myocardial oxidative metabolism and perfusion. Even though the observed homogenizing effects of CRT on regional metabolism are not new and confirmed by previously reports,\(^2-3\) the studied patient population is by far the largest to date. Owing to the large sample size, subgroup analysis was feasible, which hinted at a more favourable effect of CRT in non-ischaemic patients than in ischaemic patients.

Among others, the authors conclude that "...studies have to clarify whether long-term CRT is able to improve perfusion and metabolism on a global level suggesting regression of cardiomyopathy." We would like to point out that our group has recently addressed this issue by demonstrating a (reversible) enhancement of global perfusion reserve during CRT.\(^4\) In line with the results of Lindner et al.,\(^1\) ischaemic heart failure patients tended to improve to a lesser extent than non-ischaemic patients, although the sample size in our study was too small to be able to perform a reliable subgroup analysis. Furthermore, the level of augmentation seemed to be related to the degree of reduction in wall stress, which in turn was related to the degree of reverse remodelling.

Impairment of perfusion reserve is a hallmark of both ischaemic and non-ischaemic cardiomyopathy and an independent prognostic marker for an unfavourable outcome.\(^4\) Regardless of its aetiology, impairment of perfusion reserve is believed to cause repetitive stunning (intermittent periods of ischaemia), leading to chronic reversible left ventricular dysfunction.\(^4,5\) In fact, signs of ischaemia have been observed in patients with idiopathic dilated cardiomyopathy, making the term 'non-ischaemic' cardiomyopathy a matter of debate.\(^5\)

Although the benefit of biventricular pacing is related to mechanical resynchronization of the interventricular septum and lateral free wall, it is likely that enhancement of perfusion reserve and its subsequent reduction of ischaemic episodes also play a role in the recovery of function associated with CRT. In our opinion, this demonstrates, at least in part, a true regression of cardiomyopathy.

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Enhancement of perfusion reserve by cardiac resynchronization therapy: reply

The letter from Dr Knaapen and co-workers raised an interesting and critical point about our conclusion that further studies have to clarify whether long-term cardiac resynchronization therapy (CRT) is able to improve myocardial perfusion and metabolism at a global level, suggesting a regression of cardiomyopathy. This conclusion was based on the observation that global resting MBF and MVO$_2$, which were reduced in our cardiomyopathy patients, did not change after 4 months of CRT.$^1$ As recently demonstrated, there is evidence that CRT is able to improve hyperaemic MBF (1.91 ± 1.03 at baseline vs. 2.66 ± 1.66 after 3 months of CRT vs. 1.92 ± 1.06 mL/min/g during CRT off), which may play a role in functional recovery by CRT due to a reduction in ischaemic episodes.$^2$

However, this observation was not confirmed by the study of Sundell et al.,$^3$ who reported no significant change in vasodilator MBF (1.8 ± 1.1 during CRT on vs. 1.6 ± 0.9 mL/min/g during CRT off) after 8 ± 5 months of CRT.

The point of discussion now is to define which criteria need to be applied before one can talk about a real regression of cardiomyopathy. It is beyond doubt that the benefit of CRT is related to an electromechanical resynchronization of the left ventricle, which induces, among other things, a reverse remodelling process and potential improvements in hyperaemic MBF. But as Knaapen et al.$^2$ also demonstrated, the effect on hyperaemic MBF vanishes as soon as CRT is interrupted. Therefore, we regard it as justified to state that the underlying cardiomyopathic process is not essentially suspended by CRT within a 3-4-month observation period. Nevertheless, the results of Knaapen et al.$^2$ indicate that CRT initiates mechanisms which could induce a real regression of cardiomyopathy over a long-term period.

Within this context, there is, in our opinion, a basic need to clarify the range of quantitative MBF and MVO$_2$ in advanced cardiomyopathy. As the current scientific literature indicates, there exists a wide range of data, based to some extent on different methodological approaches, to measure MBF and MVO$_2$.

References


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Recombinant streptokinase: evidences from clinical use

In the study of Hermentin et al.,$^1$ a significant discrepancy between claimed and measured streptokinase (SK) activity of various tested products was found in addition to other physicochemical differences. However, it is difficult to interpret the results as they analysed only one sample of most products, and in some cases even from only one batch. The authors also raise the matter of the relationship between their data and clinical performance, but this kind of statement should be backed up by evidence from clinical trials and pharmacovigilance studies.

In this respect, we wish to report that there is enough clinical experience with one of the recombinant SKs mentioned in the paper (Heberkinase). First, coronary patency (TIMI 2 and 3) was achieved in 14/20 (70%) acute myocardial infarction (AMI) patients after intracoronary administration of this product. Then clinical studies were performed in AMI patients treated with intravenous 1.5 × 10$^6$ IU of recombinant SK. A randomized trial in 224 patients$^2$ compared it to the same reference product used by Hermentin et al.$^1$ (natural SK: streptase). Similar results were obtained with respect to coronary patency, changes in haemostasis, and safety profile. Additionally, anti-SK antibody titres and their anti-SK neutralizing activities in serum were not only comparable between both groups, but also crossreacting, which shows that the small differences in structure do not seem to have clinical or immunological repercussions.$^3$ A national extension study in 2923 AMI patients from 52 hospitals throughout Cuba evaluated Heberkinase in clinical practice.$^4$ A 28.3% relative and 4% absolute lethality reduction was found when compared with a survey made before recombinant SK treatment was introduced. Intracranial haemorrhage was only reported in nine (0.3%) patients. Further use of this treatment in the country has been monitored by a pharmacovigilance system, where a similar post-marketing safety profile to those suggested in clinical trials was observed (manuscript in preparation). At present its pre-hospital use in Cuba is being extended as a national program to improve survival through a shorter symptom-needle period. A recent study with this recombinant SK in an albumin-free formulation suggested that its intravenous administration is a safe and appropriate therapy to get early (90 min) coronary patency in patients with AMI.$^5$ The product has been successfully used in other applications of thrombolysis such as heart valve prosthesis thrombosis.$^6$ Therefore, we can conclude that this product is clinically useful, which contrasts from what could be inferred from the report of Hermentin et al.$^1$