


Over-training syndrome as a model of a coronary inflammation process?

As scientists in sports medicine we were very interested in the excellent review of Woods et al[11], the papers of Erikssen et al[12] and Mendall et al[13] as well as the corresponding editorials dealing with the role of inflammation in coronary heart disease. Comparable results with regard to erythrocyte sedimentation rate have also been recently reported by Sharma and colleagues in patients who were treated with ACE-inhibitors[14]. On the other hand, inflammatory parameters could not predict the outcome of cerebrovascular disease, which supports the specific role of the heart or its vessels in this respect[15]. However, the stress protein HSP70 is increased in patients with occlusive arterial disease and may be a more suited parameter for peripheral vascular disease[16].

Physical training leads to plenty of neurohumoral and immunological changes including increased phagocytosis, inflammatory reactions, decrease of NK cells, and increase of TNFalpha, IL-6, IL-10 or IL-1ra (IL-1 receptor antagonist) in plasma[17]. The IgA of nasal mucosa decreases and antigen presentation to macrophages is reduced[18]. The overall impression is that the immune system shows some kind of depression after intensive physical exercise. In case of over-training, leptin and inhibit B are reduced and may be of diagnostic value[19]. Some therapeutic interventions in the acute phase of the over-training syndrome are carbohydrates, glutamin or vitamins, although definite recommendations cannot be made.

Obviously, the neurohumoral and immunological changes which are discussed by the authors as prognostic factors in patients with coronary heart disease are markedly similar to those parameters used in sports medicine as a diagnostic tool in the over-training syndrome, which occurs in normally well trained athletes with a great deal of compensation capability. If the physician in charge of the athlete does not react adequately, a decrease in performance in the consequence and somatic sequelae cannot be excluded, if the athlete does not discontinue over-training. We therefore ask the question, is over-training in well compensated athletes comparable to inflammation processes in coronary heart patients with lack of compensation? Encouraged by the excellent papers presented we have begun to compare data of both entities. Possibly the over-training syndrome may be a model which will help in our understanding of the long-term prognostic factors of coronary heart disease.

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References


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Effects of oral sotalol administration before electrical cardioversion of persistent atrial fibrillation

I read with attention the article by Frick et al[10], that compared, in a randomized controlled trial, the effect of magnesium alone or as an adjuvant to sotalol in the cardioversion of atrial fibrillation and subsequent maintenance of sinus rhythm. I observed that their data can help to elucidate some clinical situations in which the efficacy of oral sotalol has not yet been demonstrated. One is its ability in the pharmacological conversion of atrial fibrillation and another is its effect on the success of electrical cardioversion.

Sotalol has been largely used for the maintenance of sinus rhythm in patients with atrial fibrillation[12,3–5]. However, the scientific documentation in support of an effect on cardioversion to sinus rhythm is weak. While several studies failed to demonstrate efficacy with sotalol[3,6–11], only one randomized controlled study reported a higher cardioversion rate with intravenous sotalol when compared to digoxin[12]. The difference between sotalol’s ability in the maintenance of sinus rhythm and the absence of efficacy in cardioversion to sinus rhythm has been attributed to ‘reverse rate dependence’[13].

Some studies have demonstrated that a previous administration of
sotalol decreases the atrial defibrillation threshold\footnote{Hohnloser SH, van de Loo A, Matthiesen T, et al. Efficacy and safety of sotalol in digitalized patients with chronic atrial fibrillation. Am J Cardiol 1991; 68: 1227–30.} and prevents early recurrences of atrial fibrillation after successful electrical cardioversion\footnote{Frick M, Darpö B, Östergren J, Rosenqvist M. The effect of oral magnesium, alone or as adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation. Eur Heart J 2000; 21: 1177–85.} However, to my knowledge, there is no randomized controlled trial examining the clinical impact of these effects. Other antiarrhythmic drugs, such as propafenone, amiodarone and ibutilide, were recently examined and showed that they increase the efficacy of direct current shock or, at least, prevent early recurrences of atrial fibrillation\footnote{Frick M, Darpö B, Östergren J, Rosenqvist M. The effect of oral magnesium, alone or as adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation. Eur Heart J 2000; 21: 1177–85.} The excellent article of Frick et al\footnote{Frick M, Darpö B, Östergren J, Rosenqvist M. The effect of oral magnesium, alone or as adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation. Eur Heart J 2000; 21: 1177–85.} was comprised of two parts: (1) a magnesium study that scheduled 170 patients for their first electrical cardioversion and (2) a sotalol and magnesium study that scheduled 131 patients, with recurrence of persistent atrial fibrillation after previous cardioversion, for treatment with sotalol. Both randomly assigned patients to therapy with oral magnesium or placebo with the aim of identifying a possible role of magnesium in the cardioversion and recurrence rates of atrial fibrillation; no role was proved. Comparing the group of patients who received oral sotalol before the electrical cardioversion with the group of patients who did not, it was possible to observe that oral sotalol has some efficacy in the conversion of persistent atrial fibrillation to sinus rhythm (26% vs 0% in the control group, P<0.001). Table 1. Furthermore, the strategy of starting the drug before electrical cardioversion resulted in an increased conversion rate (87% vs 77% in the control group, P=0.03). However, excluding cases that previously converted to sinus rhythm, it was not possible to demonstrate that sotalol increases the efficacy of direct current shock (82% vs 77% of the control group, P=ns).

The groups treated with sotalol or not had the same inclusion and exclusion criteria, except for the presence of previous episodes of atrial fibrillation in patients treated with sotalol. Thus, the worst presentation of arrhythmia occurred in the sotalol group, strengthening its efficacy.

It must be clear that my considerations are limited because the trial was not designed to answer these questions. However, in the absence of any data favouring oral sotalol for pharmacological conversion or for a strategy including this therapy before electrical cardioversion, these observations suggest that oral sotalol may have some role before electrical cardioversion of persistent atrial fibrillation. Future randomized clinical trials should solve these important clinical topics.

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References

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\section*{Table 1 Success rate at pharmacological, direct current (DC) plus pharmacological and DC exclusively cardioversion}

<table>
<thead>
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<th>Sotalol</th>
<th>Control</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>SR with pharmacological cardioversion</td>
<td>34/131</td>
<td>0/70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SR after pharmacological plus DC cardioversion</td>
<td>114/131</td>
<td>131/170</td>
<td>0.03</td>
</tr>
<tr>
<td>SR after DC cardioversion exclusively</td>
<td>80/97</td>
<td>131/170</td>
<td>ns</td>
</tr>
</tbody>
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*Chi-square test; SR=sinus rhythm; ns=not significant.*

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Letters to the Editor


Cholesterol reduction, statins and the cytochrome P-450 system. No more recipes please

In their letter published in the Journal[1], Drs Cockcroft and Wilkinson highlighted an omission in the article by Horsmans[2] on the different potential of statins for drug–drug interactions, saying that his review focused only on the increased risk of adverse drug reactions (ADRs) deriving from pharmacokinetic interactions. In contrast, they assert that drug–drug interactions are not necessarily always deleterious.

Drs Cockcroft and Wilkinson quote a clinical trial in hypercholesterolaemic patients published by Yeo et al.[3] showing that an interaction between the calcium channel antagonist, diltiazem, and the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin, results in an enhanced cholesterol-lowering response to simvastatin (median decrease in serum cholesterol of 33%) as compared to a similar dose of simvastatin alone (median decrease of 25%).

Though the differences seen between the two groups may be partly explained by confounding factors in the study design, the postulation that the enhanced pharmacodynamic effect of simvastatin is due to its increased plasma concentrations as a result of a pharmacokinetic interaction with diltiazem is reasonable. Both drugs undergo hepatic phase I metabolism via the 3A4 isoenzyme family of the cytochrome P450 (CYP3A4). Moreover, diltiazem is also a relatively potent inhibitor of CYP3A4. Thus, an increase in plasma concentrations of simvastatin following co-administration of diltiazem is likely to occur[4]. The prolonged inhibitory effect on the hepatic HMGCoA reductase activity resulting from the increased systemic availability of the active drug and metabolite(s) returning to the liver may therefore translate into an enhanced cholesterol lowering effect.

In Drs Cockcroft and Wilkinson’s view, co-administration of cardioactive drugs, which may increase levels of statins mediated by inhibition of the CYP3A4, may allow for greater reduction in cholesterol at lower statin doses and without additional costs. Furthermore, they suggest that, for patients on statins metabolized by CYP3A4, a glass of grapefruit juice, a potent inhibitor of this CYP isoenzyme, at breakfast will lead to further reductions in cholesterol and CHD risk.

They recognize that the benefits of potentiating the pharmacodynamic effects of statins by co-administration of CYP3A4 inhibitors must be weighted against the potential for increased ADRs. Nevertheless, I believe that their conclusions are hazardous and may imply a misleading recommendation to the physicians.

Musculoskeletal toxicity, characterized by marked elevation of serum creatine kinase (CK) with or without diffuse myalgia, though rare following statin monotherapy, may become one of the most serious observed ADRs. It appears to occur more frequently when statins are co-administered with CYP3A4 inhibitors, suggesting that this adverse event has a pharmacokinetic basis. Intracellular alterations in the striated muscle cells, possibly involved in determining myotoxicity, have been found to be drug-concentration dependendent[5,6]. The risk of skeletal muscle ADRs may be even higher when increased concentrations of circulating active metabolites contribute to systemic HMGCoA reductase inhibitory activity, particularly for statins which inhibit cholesterol synthesis outside the liver, such as simvastatin[7].

Short-term co-administration of simvastatin with diltiazem was well tolerated in the 19 patients receiving this combination[9]. However, attention should be drawn to the fact that cholesterol-lowering drug therapy is given on a long-term basis. A patient may therefore be exposed to the risk of a drug–drug interaction several times during the treatment course because of the prescription of other commonly used drugs such as sotalol for suppression of recurrent symptomatic atrial fibrillation. Am J Cardiol 1993; 71: 558–63.


A reply

We agree with Dr H. H. Veloso that the efficacy of oral sotalol to convert atrial fibrillation to sinus rhythm deserves further investigation. The conversion rate with oral sotalol (26%) in our study is in accordance with some smaller studies[1–2]. The relatively modest conversion rate has to be judged in the context that all the patients in our study endured atrial fibrillation for more than 1 month. On the other hand, the duration of atrial fibrillation or the presence of an unknown duration of atrial fibrillation did not influence the pharmacological conversion rate. The efficacy of pharmacological conversion of oral sotalol seems to be comparable to the efficacy of oral amiodarone (23%)[3]. In clinical practice, it is important to achieve adequate anticoagulation therapy before initiating oral sotalol therapy.

As Dr Veloso mentioned, sotalol probably decreases the atrial fibrillation threshold. At present we are performing a prospective study in patients with persistent atrial fibrillation who have failed to convert at DC conversion. In these patients a second DC cardioversion is performed after a treatment period with oral sotalol.

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References

[1] Reimold SC, Cantillon CO, Friedman PL, Antman EM. Propafenone versus