Targeting the vessel wall in cardiovascular prevention

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Summary and perspectives
SUMMARY

In chapter 8, we showed that there is an association between MPO levels and risk of CAD in a normal, apparently healthy population. However, measurement of MPO does not add substantially to current risk estimates. Next, we showed that MPO levels are not associated with IMT progression in FH patients (chapter 9). In chapter 10-11, we concluded that, although MPO levels are slightly higher in diabetic patients, they do not predict the presence of myocardial perfusion defects. Finally, in chapter 12, we show that exercise related increases in MPO levels reflect the extent of exercise levels, rather than that of myocardial ischemia.

PERSPECTIVES

The CardioMPO™ assay enables large clinical studies

The assay to determine MPO levels in peripheral blood was developed by Stanley Hazen and coworkers at the Cleveland Clinic after a journey, which is in some degrees similar to the glycocalyx story. After initial in vitro studies showing that MPO damages LDL- and HDL-cholesterol particles, the method to determine MPO levels in human blood was radically improved, just like we are improving our methods. Subsequent clinical studies using the new assay showed that MPO is a powerful prognostic determinant of myocardial infarction in patients suffering acute coronary syndromes. Ironically, like our study in chapter 7, the first mouse study had puzzling results. It showed that knocking out MPO increased atherosclerosis progression (1). The natural lack of expression of MPO in mouse atherosclerotic tissue may explain this unexpected outcome. Later studies, in which human MPO was knocked in specifically in macrophages, did show that MPO is harmful (2). Now, the assay is commercially available enabling large studies in different populations.

Myeloperoxidase is mainly a predictor of cardiovascular disease in the emergency room setting

In general, in our studies the relation between MPO levels and (markers of) cardiovascular disease risk is much weaker than in previous studies in an acute setting or even absent. In line, it was recently reported that plasma MPO levels are not elevated in patients with stable coronary artery disease (3). These results suggest that acute CVD specifically is characterized by systemic MPO release and that use of MPO as a biomarker in risk assessment in primary prevention and in a non-acute setting is limited. Of note, we could also not confirm previous studies which showed a difference in MPO levels between patients with and without history of CAD or heart failure (4-6). Future studies should corroborate whether MPO levels indeed can or can not differentiate between cardiac and non-cardiac origins of acute chest pain and identify patients with heart failure. Moreover, it would be interesting to see whether MPO
levels can provide a clinically useful indication of HDL-cholesterol quality, as MPO activity can damage this lipoprotein and hamper reverse cholesterol transport (7). As systemic MPO levels in an acute setting are likely to reflect neutrophil activity, it would be useful to determine whether the widely available white blood cell count renders similar information in a cheaper fashion (8). Finally, future development in molecular MRI imaging, visualizing MPO activity in the vessel wall, may help to detect unstable plaque (9).

Myeloperoxidase may play a role in the pathogenesis of atherosclerosis

Chapter 8 illustrates the limited discriminative ability of traditional risk scores, such as the Framingham risk score (area under the curve of the Receiver Operator Curve: 0.59). However, addition of MPO did not substantially improve risk stratification. Sole reliance on these statistics to judge whether new risk determinants offer additional value in risk estimation is incorrect (10), as they may still improve risk stratification, particularly in subgroups. Besides that, it does not assess their potential to reclassify individuals into risk categories that are associated with different treatment strategies. Moreover, even if new risk determinants do not improve risk stratification, studying their role may increase understanding of pathophysiology. Our results show that high MPO levels precede the clinical manifestation of CVD by years and support a role in disease progression.

Myeloperoxidase inhibition may be an attractive target to prevent cardiovascular disease

There are several mechanisms via which MPO could enhance atherogenesis. As discussed, these include conveying oxidative damage to LDL- and HDL-cholesterol as well as reducing NO availability. The findings that MPO may enhance atherosclerosis in many stages of the process have raised interests in the development of therapeutic strategies to inhibit MPO activity. A few hurdles need to be overcome, however. Past trials aimed at counteracting free radical damage were largely unsuccessful (11). Various combinations of antioxidants did not confer benefit. It is unclear whether these antioxidants are able to neutralize the effects of MPO, specifically within the vessel wall. Secondly, a likely side effect of MPO inhibition is an increased risk of infections, as is observed in patients with profound MPO deficiency (12). Therefore, careful dosing is warranted to maintain MPO levels in the functional range for host defense. Another solution might be to only target extracellular MPO and not MPO stored in granules of leukocytes or MPO active in killing microorganisms in the phagolysosome. These strategies are only in early stages of development and await extensive testing in randomized clinical trials (13).

Besides individually targeted therapy, population based therapy may be a different, effective approach

Unlike statin therapy, MPO inhibition probably has a limited therapeutic range because of its influence on the immune system. Only lowering consistently high levels within the normal
range or specifically treating patients with distinct MPO polymorphisms (14) may be beneficial, whereas lowering low to normal levels may be dangerous. This would require stringent patient selection and individually targeted therapy with regular laboratory control. Another, intrinsically different approach is not to identify and target specific, high risk patients, but to target the entire population. This approach is propagated by Ward et al. in the form of a so-called polypill (15). This pill consist of a combination of low dose, off-patent drugs (statin, beta blocker, ACE inhibitor, aspirin and folic acid) that lower cardiovascular risk. It is to be taken by everybody over 55 years old regardless of cardiovascular risk. Wald et al. estimated that this would reduce CVD by more than 80%. Although the concept can be criticized for undertreating high risk patients, medicalizing healthy individuals, overestimating compliance and inducing side effects, the idea to intervene early on a population level is not illogical. On the one hand, studies in patients with lifelong high (FH) or low cholesterol levels (PCSK9 mutants) (16) show the impact of life long exposition to this risk factor and suggest a benefit of early intervention. On the other hand, small changes within the normal range of risk factors such as blood pressure and cholesterol already affect risk (17, 18) and could have huge impact, when reached population wide. Studies in India testing this concept are underway.

REFERENCES