The cardiac effects of ace-inhibitors

Tio, Rene Anton

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1990

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
SUMMARY

This thesis describes experimental data on bradykinin and its relation with the effects of angiotensin converting enzyme inhibitors. The angiotensin converting enzyme not only activates angiotensin, a potent pressor substance, but also inactivates bradykinin, one of the most potent depressor substances known. Although it has been known since 1970 that the angiotensin-converting enzyme both activates angiotensin and inactivates bradykinin, the role of bradykinin has always been controversial. In this thesis first the historical perspective was given, explaining why we were interested in bradykinin in the first place (chapter 1). In chapter 2 the controversy between bradykinin and angiotensin was outlined. Angiotensin was presented as a substance primarily aimed at preservation of the perfusion pressure in the kidney and hence at kidney function. Bradykinin on the other hand was presented as a substance aimed predominantly at preservation of the cardiac function, especially at the local, tissue level.

The following chapter (3) dealt with the effects of bradykinin and ACE inhibitors on ischemia and reperfusion of the myocardium. It was shown that bradykinin is present in the effluent of isolated rat hearts; during ischemia and reperfusion bradykinin production is elevated. Our own data, in appendix D, show that especially during reperfusion bradykinin efflux was elevated and that captopril treatment enhanced this phenomenon. Our results corroborate those found in vitro and in vivo by other authors: during ischemia and reperfusion in dogs and man, bradykinin concentrations were elevated. Furthermore, it was shown in isolated rat hearts that bradykinin has beneficial effects on the post-ischemic, reperfused myocardium. Although bradykinin in the closed chest pig model of ischemia and reperfusion, which we use, did not reduce catecholamine or purine efflux from the heart, nor the increase in oxygen requirement, it did reduce the enzymatic infarct size, as was presented in appendix J. The in vitro effects of bradykinin, could be enhanced by ACE inhibitors. Furthermore, it was described that ACE inhibitors themselves, also have beneficial effects in ischemia and reperfusion. These effects could in part be related to bradykinin, and were probably the result of inhibition of the local converting enzyme in the heart. In our pig model early reperfusion is beneficial in itself as was shown in appendix H, but a considerable improvement was found after oral pretreatment with zofenopril. In appendix I, the data found after zofenopril pretreatment showed that not only neurohumoral deterioration in the acute phase was reduced, but also that electrophysiologic stability after two weeks was increased. Therapy with converting enzyme inhibitors post myocardial infarction results in a modulation of the so-called...
remodeling process. Remodeling is the process which after myocardial infarction results in a dilatation of the left ventricle and hence a reduced left ventricular function. Finally, the first study on therapy with an ACE inhibitor during early reperfusion in patients with a myocardial infarction, receiving concomitant thrombolytic (reperfusion) therapy was discussed. From these results it can be concluded that ACE inhibitors have beneficial effects on ischemia followed by reperfusion in man.

The fourth chapter dealt with bradykinin and the coronary circulation. It was shown that bradykinin as well as ACE inhibitors increased coronary flow in vitro in the isolated rat heart. First experimental data in the isolated rat heart, focused on the effects on the coronary flow were shown. Our data showed that bradykinin increases coronary flow by stimulating bradykinin-2 receptors and that bradykinin-1 receptors counteract this effect (Appendix A). Experimental evidence, found in vitro, led to the conclusion that ACE inhibitors differ remarkably in their bradykinin dependency. This was shown by our data in appendix B: using a selective bradykinin-2 receptor antagonist we were able to antagonise the vasodilating effects of bradykinin and enalaprilat almost completely. The vasodilating effect of zofenoprilat was only partly antagonized, whereas the vasodilating effects of captopril and its inactive stereoisomer SR-captopril were not affected at all. Using indomethacin the possible involvement of prostaglandins was investigated (appendix C). It was shown that bradykinin was able to stimulate prostacyclin production but only in high concentrations; enalaprilat, captopril, zofenoprilat, or SR-captopril were inactive in this respect. Inhibition of this prostacyclin production did not reduce bradykinins vasodilating capacity in the isolated rat heart. Neither was the vasodilation of enalaprilat, captopril, zofenoprilat or SR-captopril affected by indomethacin. The bradykinin induced release of the endothelium derived relaxing factor (EDRF) probably is a major mechanism involved in this vasodilation. Apart from differences in bradykinin dependency, ACE inhibitors also differ in their effects that are unrelated to inhibition of the converting enzyme. The potent endogenous vasodilator EDRF, which has been shown to be nitric oxide (NO), requires sulfhydryl groups to become active. From this point of view, it is interesting that the sulfhydryl group containing ACE inhibitors, captopril and zofenopril, were found to be more potent coronary vasodilators in the isolated rat heart than the ACE inhibitors lacking such group. In vivo experiments regarding the bradykinin dependency of ACE inhibitors were conducted in rats. These data were presented in appendix E showing that the blood pressure lowering effect of enalaprilat was to a greater extent bradykinin dependent than that of zofenoprilat. In appendix Four data on bradykinin dependency of enalaprilat and zofenoprilat on their regional hemodynamic effects were presented. From these data it could be concluded that in many organs both enalaprilat and
zofenoprilat reduce vascular resistance via a bradykinin dependent mechanism, albeit the latter to a lesser extent. This may be an indication that the sulfhydryl group is responsible for direct vasodilating effects in vivo. Finally, a clinical study could be conducted. In this study we did not just investigate the effects of ACE inhibitors on coronary flow or resistance, but we were interested in the effects on coronary vasoconstriction induced by sympathetic activation. We found that in patients with coronary lesions that activation of the sympathetic nervous system, as is achieved with the cold pressor test and even more with the so-called diving test, causes an increase in coronary vascular resistance. This increase in coronary resistance could be reduced with captopril. It was argued that the underlying mechanism may of course be on the one hand, the well known diminished noradrenergic facilitation due to lower angiotensin II concentrations, but on the other hand the role of bradykinin in noradrenergic transmission may be considered as well.

In chapter 5 some wider thoughts were given to evolving clinical indications and possible future developments. The place of ACE inhibitors in the therapy of ischemic heart disease seems promising. Firstly, therapy with an ACE inhibitor during the acute phase of early reperfusion after an infarction has been shown to have beneficial effects in many experimental models. In patients the first results on ACE inhibitor therapy during reperfusion, i.e. during thrombolytic therapy, showed similar results. Of course, these effects have to be confirmed by larger studies first, before this therapy is used on a wider scale. Secondly, the prevention of deterioration of the left ventricular function with ACE inhibitors is an important therapeutic tool against developing heart failure in patients after a myocardial infarction. Finally, the use of ACE inhibitors in anginal patients opens two new perspectives. The first is related to the presence of a sulfhydryl group; it has been shown in vitro that captopril can reverse nitrate tolerance, and the first clinical data are promising. The second is related to the interaction of ACE inhibitors with the sympathetic nervous system. It was shown that captopril reduces the noradrenergic transmission in the coronary arteries of patients with angina pectoris. It may be concluded that the mechanism of action of converting enzyme inhibitors on the coronary flow as well as on ischemia and reperfusion is multifactorial. Apart from lower angiotensin II concentrations, converting enzyme inhibition results in higher bradykinin concentrations. Both factors may contribute independently to the improvement of a variety of conditions, that have myocardial ischemia as a common denominator. To the activity of both, additional phenomena (less noradrenaline release, prostacyclin or EDRF stimulation, concomitant presence of a sulfhydryl group; Figure 7) may contribute. In this thesis, the role of the second, hitherto rather neglected factor, i.e. bradykinin is presented more in detail, with special reference to its
Figure 7: The cardiovascular actions of the converting enzyme and its peptides. An ACE-inhibitor can reduce angiotensin II formation and increase bradykinin concentrations. Some ACE-inhibitors can exert an additional effect through a sulfhydryl group. SH = sulfhydryl group; EDRF = endothelium derived relaxing factor; PG = prostaglandins.