Venous and arterial coronary artery bypass grafts in a pharmacological perspective
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Chapter 1

The introduction offers an overview of the history of myocardial revascularisation in combination with pharmacology, the morphological, biophysical/-chemical, and pharmacological properties of saphenous vein (SV) and internal mammary artery (IMA), and finally the epidemiology and pathogenesis of graft failure after aortocoronary bypass grafting (CABG).

Coronary artery bypass graft failure is a growing dilemma in clinical practice since the number of patients subjected to CABG is still increasing. Ten years after CABG only 60% of the venous grafts are patent, and of these patent grafts another 50% display a significant degree of stenosis. The recurrence of clinical symptoms and the need for reintervention shows a similar pattern. Compared to venous grafts, arterial grafts perform better and exhibit patency rates of 90% after 10 years, or even longer periods of follow-up.

Three pathophysiological-linked processes form the basis of SV graft disease, which are thrombosis, intimal hyperplasia, and atherosclerosis. The IMA possesses a relative immunity against atherosclerosis. Specific intrinsic properties make the vein more vulnerable to graft failure. Other factors influencing venous graft performance can be divided into patient-related, vessel-related, and surgical procedure-related factors. A central role in the pathogenesis of graft failure plays the changes in endothelial, and probably, vascular smooth muscle cell function, due to the aforementioned factors. With the increasing knowledge of the underlying mechanism of graft failure more and more strategies are developed to improve clinical outcome after CABG. Most relevant are the stimulation of the use of arterial grafts, the postoperative risk factor management, and the reduction of vascular injury during the surgical procedure. Potential strategies counteracting specific pathogenic mechanisms, such as gene therapy, are under intensive investigation.
Chapter 2

A patient-related factor, the presence of congestive heart failure (CHF) was investigated with respect to alterations in saphenous vein function. In organ baths the contractile responses to cumulative concentrations of angiotensin II, adrenergic, and endothelium-dependent compounds were analysed in SV obtained from New Zealand White rabbits subjected to CHF and compared to those from control animals. Two models of CHF were applied and compared. In the volume-, and pressure-overload model (CHF-PO), CHF was assessed by destruction of the aortic valve and subsequent banding of the aorta. In the second, myocardial infarction model (CHF-MI), ligation of a coronary artery and the following myocardial infarction induced CHF. In the isolated SV obtained from CHF-PO rabbits the maximal effect evoked by the non-selective α-adrenoceptor agonist noradrenaline, and the α1-agonist methoxamine was enhanced, whereas that of the α2-agonist B-HT 933 was not. Angiotensin II provoked small contractions in endothelium-denuded preparations and showed a decrease in potency in CHF-PO preparations. Dilatory responses induced by the β-agonist isoproterenol and by the endothelium-dependent vasodilator methacholine were both reduced in SV obtained from CHF-PO animals. The aforementioned changes in responsiveness were absent in SV obtained from rabbits subjected to CHF due to myocardial infarction. These findings indicate that under the condition of CHF the SV displays a combination of increased contractile, and diminished dilatory responsiveness. The occurrence of changes in SV responsiveness is dependent on the underlying pathophysiological mechanism and/or the degree of CHF.

Chapter 3

During CABG the SV is stored, distended, and rinsed with various solutions. To analyse the effect of exposure to these solutions rabbit isolated SV were exposed to St. Thomas' cardioplegic solution or heparinised Ringer's lactate for 1h, 24h, or 48h. Responses to cumulative concentrations of phenylephrine, sodium nitroprusside, and methacholine were quantified in a standard organ bath set-up, and compared to those of preparations stored in saline (NaCl 0.9%) (a poor preservation medium), or University of Wisconsin solution (the gold standard in solid organ preservation). After storage at 4°C in St. Thomas’ cardioplegic solution, heparinised Ringer’s lactate, or University of Wisconsin solution for a time period of 48 h all functional parameters assessed remained intact. However, after storage in saline the contractile response elicited by depolarisation due
to a high concentration potassium chloride solution (60 mM) (KCl) was reduced by 33% after 24h, and even 56% after 48h of storage, in contrast to the α₁-adrenoceptor-mediated responses, which remained unaffected. Furthermore, the maximal endothelium-dependent relaxation evoked by methacholine was reduced as well, and amounted to 73% after 24 h, and 64% after 48h of the initial value, respectively, whereas the dilation in response to the nitric oxide-donor sodium nitroprusside was unchanged. The sensitivity of the SV preparations to the agonists remained stable after storage in the different media under investigation, independently of the time interval examined. These findings are discussed with respect to the composition of the various solutions, and the discrepancy between receptor-dependent, and –independent contractile response changes after preservation. In conclusion, the exposure to St. Thomas’ cardioplegic solution and heparinised Ringer’s lactate did not change SV wall function, and those solutions turned out to be comparable preservatives of SV function as University of Wisconsin solution. Saline, however was detrimental to vascular wall quality. The injury induced by this solution demonstrated to be selective for depolarisation-induced contraction, and endothelium-dependent relaxation, and time-dependent.

Chapter 4

Since SV displayed a relative immunity against preservation, another model was searched for to investigate the role of the individual components of preservation media. Male Wistar rat isolated aorta displayed rapid function deterioration when stored in phosphate-buffered saline (PBS), and was considered as a suitable model to study preservation mechanisms in detail. The role of chloride in storage media on function preservation was investigated. PBS was compared to PBS in which the sodium chloride had been replaced by an equimolar amount of sodium gluconate (PBS-gluconate), with respect to their effects on functional responses to KCl-induced depolarisation, α₁-adrenoceptor stimulation by phenylephrine, relaxation in response to the NO-donor sodium nitroprusside and the endothelium-dependent vasodilator methacholine. The first results using this model demonstrate that rat aorta stored in PBS at 4°C displayed a deterioration of contractile function. By comparison KCl-induced responses were diminished by 58%, which was more progressive than the phenylephrine-induced responses (38%) in the same period of 24h. After 48h the phenylephrine-induced responses amounted to 29% of the initial value and therefore the vasodilatatory responses to sodium nitroprusside and
methacholine could not be obtained in the PBS-preserved group of preservations. Further investigations with other precontractile stimuli are ongoing. Preparations preserved in PBS-gluconate exhibited a similar reduction in contractile response to phenylephrine. However, surprisingly, the response to depolarisation as well as to phenylephrine recovered completely after another 24h storage. The dilatory responses to sodium nitroprusside and methacholine remained intact in contrast to those responses in preparations preserved in PBS, which displayed a trend towards reduction. These preliminary data indicate that a high chloride concentration in preservation solutions might impair rat aorta mechanical functions. Again deterioration after preservation was different for receptor-dependent, and -independent contractions, and preservation in gluconate impaired contractile function transiently. The explanation for these observations requires further investigation.

Chapter 5

The application of minimally invasive venectomy techniques to reduce postoperative wound complications, and the knowledge that surgical manipulation influences graft performance, made it seem of interest to investigate the functional properties of the SV dissected by these new procedures. SV remnants obtained from patients subjected to CABG with conventional, mediastinoscope-assisted, or endoscope-assisted venectomy. After 24-48h of preservation in University of Wisconsin solution (UW), ring preparations were mounted in 8 ml organ baths, and concentration-response relationships were constructed for phenylephrine, sodium nitroprusside, and acetylcholine. SV reactivity remained intact after preservation in UW. Isolated human SV displayed a maximal contraction between 27-42 mN after exposure to KCl (123.8 mM). For the vein preparations harvested by means of the three venectomy methods, no differences were demonstrated for responses evoked by depolarisation, α1-adrenoceptor stimulation, or NO-donation. The maximal endothelium-dependent dilatory response to acetylcholine of precontracted vein rings varied between 5-12%, independently of the surgical technique applied.

In conclusion, the surgical technique is most likely to influence endothelial function of SV. However, the minimally invasive techniques for the dissection of the SV, developed to improve clinical outcome at the site of expantation, did not affect the vascular reactivity in a different manner than the conventional method.
Chapter 6

In order to study the properties necessary to prevent spasm of SV of calcium antagonist, the effect of verapamil and mibefradil was compared in isolated human SV, obtained from patients subjected to CABG. In a standard organ bath set-up the effect of the two calcium antagonists on vasoconstriction induced by KCl and noradrenaline was studied. Furthermore, the role of potassium channels in the spasmolytic effect of mibefradil was explored. Verapamil appeared to be 2.5-fold more potent, and 1.3-fold more effective than mibefradil in inhibiting depolarisation-induced contractions. Both calcium antagonists did not block the KCl-induced responses completely, which might be due to the use of incubation rather than addition after precontraction of the calcium antagonists, for studying the effect. Both calcium antagonists reduced noradrenaline-evoked contractions with equal potency and efficacy. Verapamil inhibited contractions provoked by depolarisation more effectively than those induced by noradrenaline. The effect of mibefradil at α-adrenergic receptor-induced contractions demonstrated to be independent of KATP, or KCa-channel-blockade by glibenclamide and charybdotoxin, respectively.

Apparently, both calcium antagonist inhibit receptor-dependent and, -independent contractions in human SV. Under the conditions investigated this effect is expected to be predominantly the result of L-type calcium channel blockade and α-adrenoceptor antagonism. A relevant role for an effect of the compounds on the T-type calcium-, or potassium channels could not be demonstrated.

Chapter 7

Per-, and postoperative graft spasm can cause morbidity and mortality after myocardial revascularisation. In the present study we investigated whether exposure to a high concentration of lipophilic calcium antagonist of isolated internal mammary artery (IMA) or saphenous vein (SV) during a limited period prior to the anastomotic use can prevent graft spasm for a longer period of time. Human IMA and SV remnants obtained from patients after CABG, were mounted in a standard organ bath setup, after preservation in UW for maximal 2 days. After 30 minutes of incubation with solutions of equal concentrations (0.1 mM) lacidipine, nifedipine, or papaverine the vessels were continuously superfused (rate 2 ml.min⁻¹) with drug-free buffer for 24 hours. During the protocol, contractions evoked by a high KCl-solution (60 mM), or by the α₁-adrenoceptor agonist phenylephrine (0.3 mM) were repeated, every half hour.
Basal contractile responses were stronger in SV than in IMA. The duration of action of lacidipine exceeded the protocol (> 24 hours) independent of the vasoconstrictor stimulus and preparation, whereas the effect of nifedipine was abolished after 8.5 and 4.5 hours, and that of papaverine after 1 and 1.5 hours of superfusion in IMA and SV preparations, respectively. Immediately after incubation, the inhibition of KCl-provoked responses by lacidipine was equal to that produced by nifedipine and papaverine in IMA preparations (65.4 ± 11.1%, 79.9 ± 4.4% and 90.4 ± 4.4% of the initial KCl-induced response, for lacidipine, nifedipine and papaverine respectively), although less in SV preparations (38.7 ± 2.1%, 78.4 ± 3.3%, 94.6 ± 1.3% of the initial KCl-induced response, respectively). The maximal effect of lacidipine, reached after 1.5 hour in IMA and 3.5 hours in SV, was identical in IMA (85 - 90%), although less pronounced in SV (76.6 ± 3.1%) when compared to nifedipine (79.4 ± 3.5%) and papaverine (94.6 ± 1.3%). Furthermore the maximal effect of lacidipine was stronger in IMA than SV, and greater on KCl-, than on Phe-induced responses. These results imply that incubation of SV and IMA with a solution containing a high concentration lacidipine can prevent contractions evoked by depolarisation and α1-adrenoceptor activation, immediately after 30 minutes, and that this effect is maintained for a period as long as 24 hours. The spasmolytic effect of lacidipine depends on the preparation and contractile stimulus studied. The comparison with nifedipine indicates that the long action of lacidipine is most likely to be caused by its lipophilic character.