Venous and arterial coronary artery bypass grafts in a pharmacological perspective

Rinia-Feenstra, M.

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GENERAL DISCUSSION
In the present study several factors which may influence the functional status of venous and arterial coronary bypass grafts were investigated, and a first step towards the improvement of the currently applied harvesting procedure was made. Perioperative factors that might change functional characteristics of the vascular wall such as the pre-existent condition of congestive heart failure (CHF), the exposure to (cardioplegic) solutions, and to surgical manipulation were investigated. Furthermore, the optimal preservation medium for SV, and the role in preservation of certain components of the solutions were determined. Finally, to improve the harvesting procedure the effect of calcium antagonists as potential spasmolytic agents in SV and IMA, was evaluated. The functional, pharmacological methods applied to estimate the quality of the blood vessels may offer important additional information beyond morphological investigations, which can only demonstrate the characteristics and presence of structures, without giving a clue to their functional relevance in vivo.

The alterations in SV function induced by the condition of CHF were determined in two rabbit models, reflecting the most prominent causes of the disease in patients subjected to CABG. SV obtained from rabbits exposed to volume-, and pressure-overload displayed an increase in contractile responses to α-adrenergic stimulation, whereas the dilatory reaction such as endothelium-, and β-adrenoceptor-mediated relaxations was diminished. Furthermore, the sensitivity to angiotensin II was reduced in these preparations. The exposure to elevated plasma levels of neurotransmitters and hormones, secondary to the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system in CHF, might play a causative role concerning these alterations. However, no functional changes were observed in SV from rabbit subjected to myocardial infarction. The explanation for this discrepancy might be the different pathophysiological mechanisms as well as the different degrees of heart failure between the two models.

Concerning the preservation of functional properties, University of Wisconsin solution, the gold standard in solid organ preservation, proved an excellent storage medium for human and rabbit SV, and rat aorta, respectively, for a period up to 48 hours. The effect of exposure to (cardioplegic) solutions and the role of chloride, as a component of these solutions were investigated in isolated rabbit lateral SV and rat aorta preparations. Contrary to our expectations the exposure to St. Thomas’ cardioplegic solution and heparinised Ringer’s lactate, as performed during CABG, did not influence SV function, even if the exposure time was prolonged to 48 hours. The high concentrations of potassium and chloride apparently did not play a major role in SV function preservation. However, the exposure to saline, whether phosphate-buffered or not, induced functional deterioration of SV and aorta, respectively, after 24 hours. In the
latter preparation high chloride concentrations induced a decline of function, as proved by the absence of this phenomenon when the chloride in the solution had been replaced by gluconate. The underlying mechanisms of chloride’s injurious effect, the absence of this effect after preservation of SV in cardioplegic solution, and eventual beneficial effects of gluconate itself deserve further investigation.

The application of minimally invasive venectomy techniques to reduce postoperative wound complications and the knowledge that surgical manipulation influences graft performance, prompted us to investigate the functional status of the SV dissected by these new procedures. Human SV preparations obtained after endoscope-assisted (Vasoview)-venectomy, and mediastinoscope-assisted venectomy were compared to conventional dissected preparations with respect to depolarisation-, and \( \alpha \)-adrenergic-induced contractions as well as to endothelium-dependent, and \( \beta \)-independent vasodilation, respectively. The endothelium-dependent relaxation induced by acetylcholine in these preparations was minimal, however, and all functional parameters assessed proved not to be influenced by the harvesting method applied.

It becomes more and more apparent that spasm of SV during its removal and the high-pressure distension required to overcome spasm are detrimental to SV graft performance, in vivo. Therefore, pharmacological intervention with a spasmolytic agent might be of great benefit. In addition, the currently applied pharmacological prevention of arterial graft spasm can be improved, since the agents applied may have some disadvantageous effects on vascular wall function or hemodynamics. Accordingly, calcium antagonists as potential spasmolytic agents were investigated in human SV and IMA preparations. In a comparative study on verapamil and mibefradil, it was demonstrated that in human SV their mechanism of dilation is explained by a blockade of L-type calcium channels. Under the conditions of potassium-induced depolarisation and noradrenaline-evoked contractions an effect on T-type calcium channels or potassium channels could not be demonstrated in human SV. In the subsequent experiments, lacidipine, a calcium antagonist with a long duration of action, was investigated with respect to its action after a relatively short incubation of the preparations, and the duration of this spasmolytic action in isolated human SV and IMA. In both preparations lacidipine caused a sufficient and strong spasmolytic effect immediately after incubation at receptor-dependent, and \( \beta \)-independent contractions, which was maintained for more than 24 hours. The long duration of action can be explained by the lipophilicity of the compound, although we observed that the duration of action of papaverine, which is more lipophilic than nifedipine, proved shorter. Therefore, other chemical properties of the compound play a role as well. Whether this
potential peroperative treatment of grafts to prevent spasm can be applied clinically requires further investigation.

In conclusion, the condition of congestive heart failure results in the combination of increased contractile and reduced dilatory responses of SV, and it is therefore an additive point of concern in the perioperative management of patients with this pre-existent disease subjected to CABG. The exposure to the currently applied solutions to store and rinse the SV during CABG do not influence its functional status, and they are therefore unlikely to play a pivotal role in the high incidence of failure of venous grafts. Human SV can be stored for 48 hours for reoperation, transplantation surgery or pharmacological study purposes, in University of Wisconsin solution of 4°C without a loss of functional characteristics. The surgical manipulation of the SV during its dissection and anastomosis clearly impairs endothelial-dependent relaxation. However, the new minimally invasive harvesting methods do not injure the vessel wall in a different manner than the classical techniques, and they can therefore be applied taking into account their advantages with respect to postoperative wound complications. The spasm of SV and IMA can be adequately prevented directly and for a longer period of time after the single incubation of the isolated vessels with lacidipine, a lipophilic, long-acting calcium antagonist.