New Drug Therapies Reduce Bleeding in Cardiac Surgery

Ph.D. Doctoral Dissertation

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Introduction

Coronary artery bypass grafting (CABG) is the most common surgical procedure performed on the heart. Around 1 million are conducted worldwide each year, and 3-5000 operations are conducted yearly in Hungary in the seven centres. Cardiac surgery with concomitant cardiopulmonary bypass (CPB) can profoundly alter haemostasis, predisposing patients to major haemorrhagic complications and possibly early bypass conduit-related thrombotic events as well.

Excessive post-operative bleeding during cardiac surgery occurs in 3.6% of patients undergoing CABG and increases to 11% in those requiring more complex operations. Five to seven percent of patients lose more than 2 litres of blood within the first 24 hours after surgery, between 1% and 5% require re-operation for bleeding. Re-operation for bleeding increases hospital mortality 3 to 4 fold, substantially increases post-operative hospital stay and has a sizeable effect on health care costs. Even without the requirement for re-operation, blood loss frequently leads to transfusion of allogenic blood products, which exposes patients to the risk of transfusion-related adverse effects, including allergic reactions, transfusion errors and blood-borne infections (particularly HIV and hepatitis). Nevertheless, re-exploration is a strong risk factor associated with increased operative mortality and morbidity, including sepsis, renal failure, respiratory failure and arrhythmias.

Concerns about transfusion safety, blood product shortages and increasing blood bank costs have generated an increasing interest in adopting risk-limiting strategies for post-operative bleeding.

To the present time we have had the following anti-fibrinolytic drugs to reduce post operative blood loss during cardiac operations: aprotinin, ε-aminocaproic acid, tranexamic acid. Until 2007, aprotinin was the most frequently used to prevent bleeding and reduce the need for blood transfusion. It is a non-specific serin protease inhibitor produced from bovine lung tissue, inhibits plasmin, trypsin, chymotrypsin, tissue plasminogen activator, kallikrein and thrombin, and decreases multiple markers of inflammation and complement activation following CPB. Aprotinin has antifibrinolytic and platelet preserving activity, and reduces blood loss in various cardiac operation, including coronary artery bypass grafting, cardiac reoperations, CABG on aspirin-treated cases and in orthopedic operations or organ transplantation. As aprotinin is in widespread clinical use, the possibility of an allergic reaction must be considered whenever this drug is used. The anaphylactic potential of aprotinin has been a major concern, the overall risk of anaphylactoid reactions to aprotinin is

estimated to be 0,5% and in re-exposed patients is higher, approximately 2,8%. The vascular effect of aprotinin is only partially clarified. Many authors showed, that aprotinin causes graft occlusion, especially vein graft occlusion. However, no clinical association could be identified between aprotinin use and graft occlusion in another study. Subsequent to a publication in 2007 on this subject, aprotinin was withdraw from distribution because the investigation demonstrated a higher incidence of myocardial infarction in patients treated with aprotinin in comparison to those treated using tranexamic acid.

Because of its withdrawal, in combined, high risk cardiac and orthopaedic procedures it is very difficult to reduce post-operative bleeding to an acceptable level. We must find a new drug with an equivalent effect to aprotinin but with anti-thrombotic properties, which effectively reduces post-operative blood loss, but also decreases the risk of graft occlusion after CABG.

Aims of the work

Recombinant aprotinin was newly developed to prevent these allergic reactions and infectious diseases.

The early aims of our study were the investigation of:

- the efficacy of recombinant aprotinin on blood loss in comparison to bovine aprotinin in a canine model of extracorporeal circulation.
- the effect of recombinant aprotinin on endothelium-dependent and -independent vasorelaxation of coronary arteries.

Consequent to the withdrawal of aprotinin from the market, a new, efficient drug needed to be developed to decrease post-operative bleeding. Over the past few years, our group has been involved in the development of novel, synthetic, small molecule serine-protease inhibitors such as CU-2010 (very short half-life: 17minutes) and CU-2020 (longer half-life: 45 minutes). As we previously described, the potential advantage of these new drugs includes the elimination of allergic and infectious risk. The other beneficial effect of the new class of serine-protease inhibitors is the reduction of thrombo-embolic risk due to improved

anti-fibrinolytic and anti-coagulatory profile (inhibitory potential of fXa and fXIa up to 100,000 times more than aprotinin).

The aims of the later studies were the investigation of:

- the efficacy of the new synthetic serine-protease inhibitors on blood loss in comparison with bovine aprotinin in a canine model of extracorporeal circulation both with and without aortic cross-clamping
- the effectiveness of CU-2010 and CU-2020 *in vitro* and *in vivo* on endothelium-dependent and – independent vasorelaxation
- the ability of CU-2010 to improve the recovery of myocardial contractility function after cardioplegic arrest and reperfusion

Methods

Experimental models

Investigation of recombinant aprotinin on CPB in a canine model

24 dogs underwent CPB without aortic cross-clamping and cardioplegia. Normothermic CPB was performed for 90 minutes and then the animals were monitored for 2 hours. Dogs were divided into three groups in a blinded fashion: control animals (n=8) received placebo, aprotinin treatment groups received bovine (n=8) or recombinant aprotinin (n=8) according to Hammersmith method. Coagulation parameters and blood loss was measured regularly at different time points. Endothelium-dependent and -independent vasorelaxation were investigated in isolated left anterior descendent coronary arterial rings by using acetylcholine (ACh) and bradykinin (BK) or sodium nitroprusside (SNP) and adenosine (ADO), respectively.

Investigation of CU-2010 and CU-2020 on non-ischemic CPB in a canine model

37 dogs underwent CPB without aortic cross-clamping and cardioplegia. Normothermic CPB was performed for 90 minutes and then the animals were monitored for 2 hours. Dogs were divided into five groups: control (n=5), aprotinin (n=8; Hammersmith scheme, i.e. i.v. bolus/into the prime/continuous infusion), CU-2010 (I. scheme: n=8, 1,6 mg/kg Hammersmith scheme) CU-2010 (II. scheme: n=8, 1,6 mg/kg continuous infusion) and CU-2020 (n=8, 8,9 mg/kg, Hammersmith scheme). Endpoints were blood loss during the first

two hours after protamine, activated clotting time (ACT), activated partial thromboplastin time (aPTT), and prothrombin time (PT). At the end of the experiments coronary rings were removed for in vitro testing of relaxation responses to ACh and SNP.

Investigation of CU-2010 on an ischemic CPB in a canine model

36 dogs were divided into six groups: control, aprotinin (n=8; Hammersmith scheme), and CU-2010 (0.5; 0.83; 1.25 and 1.66 mg/kg). All animals underwent 90-minute cardiopulmonary bypass with 60 minutes of hypothermic cardioplegic arrest. Endpoints were blood loss during the first two hours after application of protamin, as well as recovery of myocardial contractility (slope of the end-systolic pressure volume relationship, Ees), coronary blood flow and vascular reactivity.

Measurements of blood loss, biochemical parameters

Blood loss was measured by gauze bandages after weaning from CPB and 15 minutes after finishing of protamine at different time points (in 120., 160., 220. min. after initiation of CPB). Bandages were placed into the operating area (pericardial sack and surrounding tissues). Weight of gauze bandages was measured before and after cleaning the operating area. We calculated blood loss from difference of weight of gauze bandages. The same number of bandages (3 pieces at once) was removed in every ten minutes during the first 30 minutes of the observation period, and thereafter every 20 minutes in order to standardize the blood loss measurement protocol and to avoid overfilling of operation area with blood. Activated clotting time (ACT), prothrombin ratio (Quick), activated partial thromboplastin time (aPTT) were monitored before CPB and before application of heparin and study medication, at 45 and 90 minutes on CPB and after weaning from CPB at 105 and 220 mins from the time point of the initiation of CPB.

The influence on whole blood clotting was assayed with rotational thrombelastometry using ellagic acid (INTEM reagent) as activator of the intrinsic system or tissue factor (EXTEM reagent) as extrinsic coagulation activator. ROTEM® clotting time, (CT equal to reaction time) and maximum clot strength (MCF equal to maximum amplitude) were obtained as coagulation parameters. Fibrinolysis was determined by measuring loss of clot strength with time (LT, lysis time).

Haemodynamic measurements

Left and right ventricular systolic and diastolic pressures and volumes were measured by a combined 2F Millar pressure-volume conductance catheter, which was inserted via the apex. The femoral artery was cannulated for recording mean arterial pressure (MAP). Heart rate (HR), left ventricular systolic pressure (LVSP), maximum and minimum pressure development (+dP/dt, -dP/dt), end-diastolic pressure (LVEDP) were monitored continuously. Vena cava occlusions were performed to obtain a series of loops for calculation of the slope (Ees) and intercept (V0) of the left and right ventricular end-systolic pressure-volume relationships. In addition, the slope of the left ventricular end-systolic pressure-volume relationship (ESPVR) and preload recruitable stroke work (PRSW) were calculated as load-independent indices of myocardial contractility.

Coronary vascular function – in vitro

Endothelium-dependent and –independent vasorelaxation was investigated in isolated coronary arterial rings of the dogs. After the end of the experiments the coronary arteries (LAD) were excised and placed in cold (+4 ºC) Krebs-Henseleit solution. The coronary arteries were prepared and cleaned from periadventitial fat and surrounding connective tissue and cut transversely into 4-mm width rings using an operation microscope. Isolated coronary rings were mounted on stainless steel hooks in individual organ baths, containing 25 ml of Krebs-Henseleit solution at 37 ºC and aerated with 95% O_2 and 5% CO_2. Special attention was paid during the preparation to avoid damaging the endothelium.

The coronary rings were placed under a resting tension of 3.5 g and equilibrated for 60 minutes. During this period, tension was periodically adjusted to the desired level and the Krebs-Henseleit solution was changed every 30 minutes. Potassium chloride (KCl) was used in these experiments to prepare vessels for stable contractions and reproducible dose-response curves to other vasoactive agents. Coronary rings were contracted with KCl (80 mM) and rinsed after the contraction until resting tension was again obtained. Thromboxane A_2-receptor agonist U46619 ($5x10^{-7}$ M) was used to precontract the rings until a stable plateau was reached, and relaxation responses were examined by adding cumulative concentrations of endothelium-dependent dilator acetylcholine (ACh, 10^{-9}-10^{-4} M) and bradykinin (BK, 10^{-10}-10^{-4} M), as well as the endothelium-independent dilator sodium nitroprusside (SNP, 10^{-10}-10^{-5}

M) and adenosine (ADO, 10^{-6}-10^{-3} M). Contractile responses are expressed as grams of tension, relaxation is expressed as percent of contraction induced by U46619.

Coronary vascular function – in vivo

Coronary blood flow was measured by an ultrasonic flow meter placed on the left anterior descendent coronary artery. Coronary vascular resistance was calculated as the difference between mean aortic pressure and central venous pressure divided by coronary blood flow. Coronary endothelium-dependent vasodilatation was assessed after intracoronary administration of a single bolus of acetylcholine (ACh, 10^{-7} M) and endothelium-independent vasodilatation after nitroglicerol (NTG, 10^{-4} M). The vasoresponse was expressed as percent change of baseline coronary vascular resistance.

Statistics

All values were expressed as mean ± standar error of the mean (SEM) or standard deviation (SD). Individual means between the groups were compared by one-way analysis of variance followed by an unpaired t-test with Bonferroni correction for multiple comparisons and the post-hoc Scheffe´s test. A probability value less than 0.05 was considered statistically significant.

Results

Recombinant aprotinin in a canine model of CPB without aortic cross-clamping

Blood loss after CPB

Post-operative blood loss during the first two hours after injection of protamin was significantly reduced in the aprotinin-treated groups (recombinant aprotinin and bovine-derived aprotinin) in comparison to control ($p<0.05$), while there was no difference between the two treatment groups (Fig. 1.).

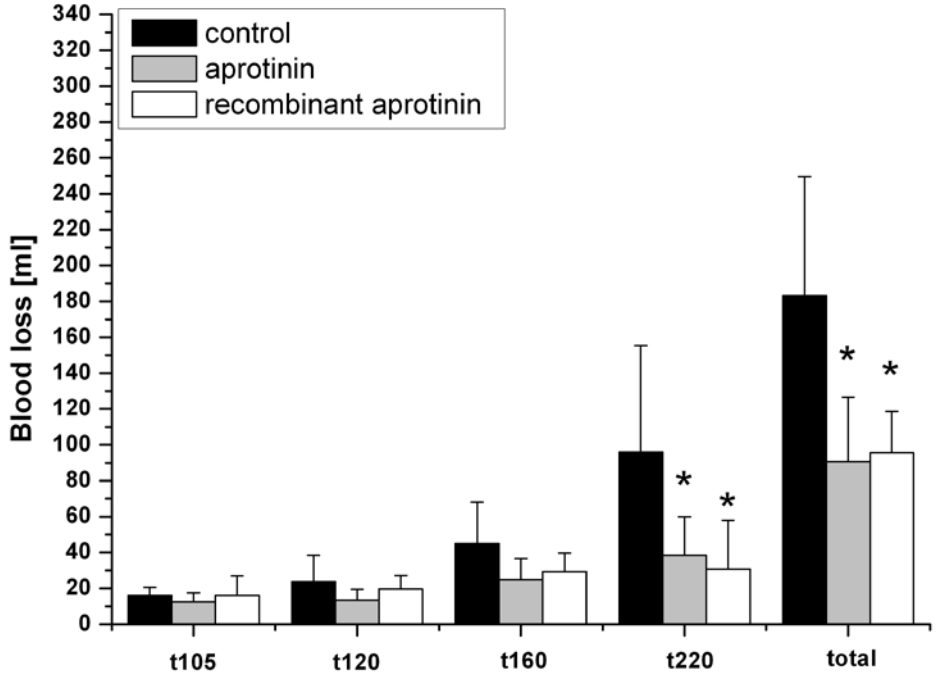

Figure 1.: Post-operative blood loss after cardiopulmonary bypass shown as cumulative data. All values are given as mean ± standard deviation (SD). *****$p<0.05$ vs. control at a given time point.

Blood coagulation parameters

There was no significant difference between all three groups regarding Quick, aPTT and ACT (Fig. 2.) at any time points. As expected, aPTT and ACT increased significantly in all groups after heparinisation and remained elevated during CPB. After protaminisation ACT and aPTT returned to baseline levels. The Quick values decreased significantly during CPB and remained at this level until the end of the observation period.

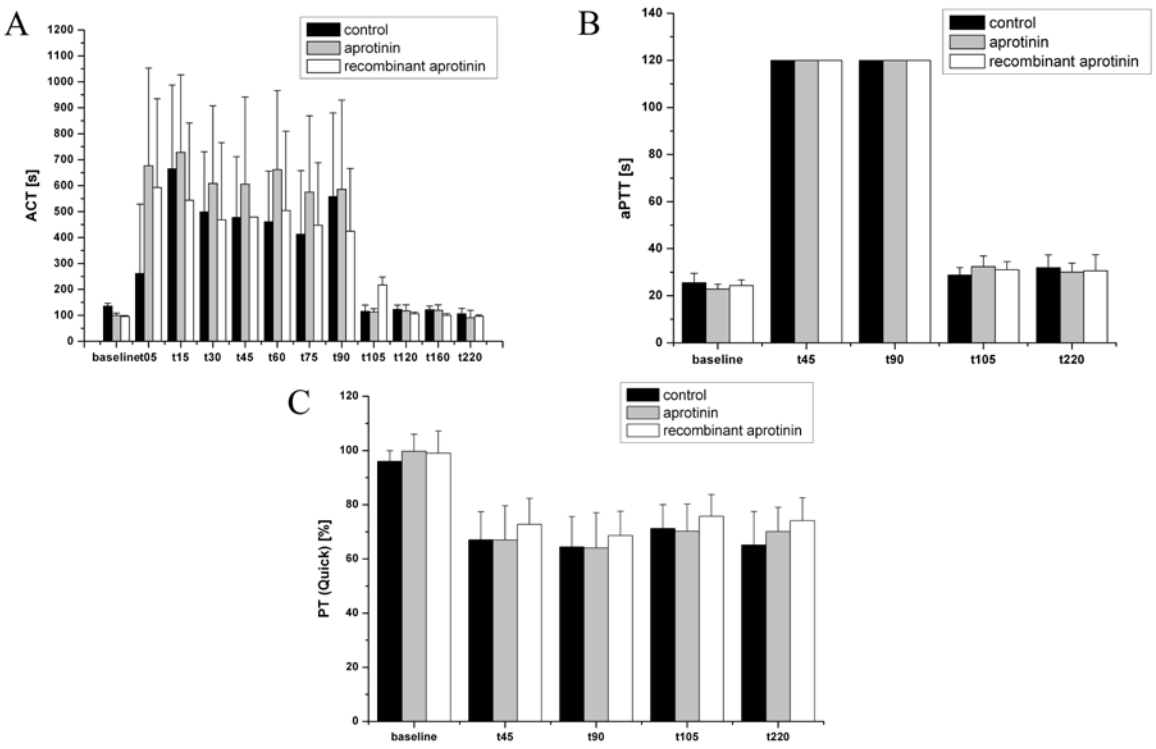

Figure 2.: Blood coagulation parameters during the first two hours after cardiopulmonary bypass. A: activated clotting time (ACT), B: activated partial thromboplastin time (aPTT), C: normalized prothrombin time (Quick). All values are given as mean ± SD.

Coronary vascular function

The endothelium-dependent vasorelaxation of the precontracted coronary arterial rings to ACh was unaffected by aprotinin treatment, but there was a tendency towards impaired relaxation to the endothelium-dependent vasodilator bradykinin (BK) in the concentration range from $5x10^{-9}$M to $5x10^{-7}$M in both aprotinin treatment groups, however, this did not reach statistical significance. The receptor- and cAMP-mediated, mainly endothelium-independent vasorelaxation to adenosine (ADO) was significantly increased in both of the aprotinin treatment groups when compared with controls. In contrast, application of aprotinin did not affect the endothelium- and receptor-independent cGMP-mediated vasorelaxation to SNP (Fig. 3.).

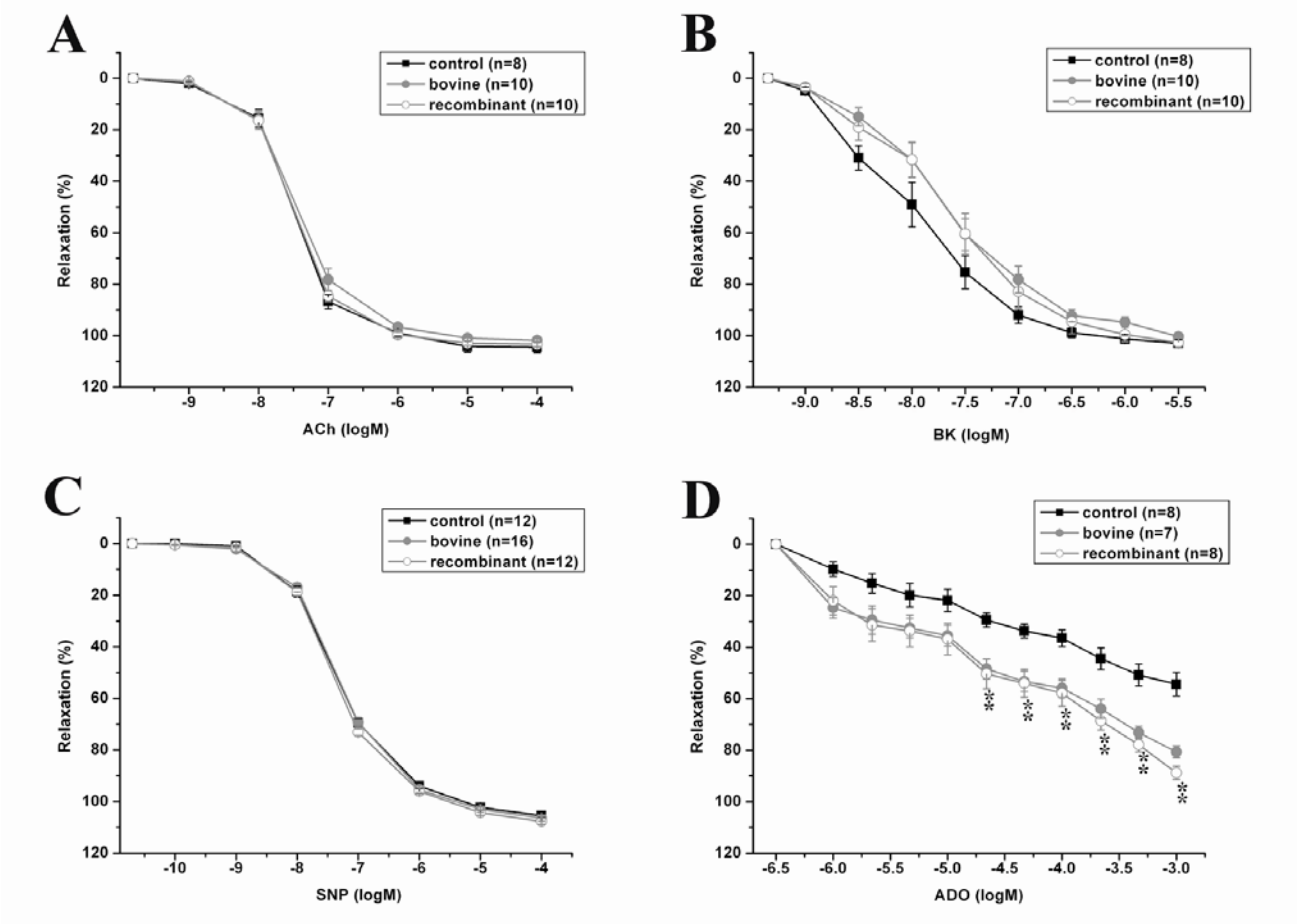

Figure 3.: Endothelium-dependent and –independent vasorelaxation of coronary arterial rings induced by (A) acetylcholine (ACh), (B) bradykinin (BK), (C) sodium nitroprusside (SNP), (D) adenosine (ADO) in the different groups (n=number of arterial rings). Values are mean ± SEM. *****p<0.05 vs. control at a given time point.

7.2. CU-2010 and CU-2020 in a canine model of CPB without aortic cross-clamping

Blood loss

Post-operative blood loss during the first two hours after the injection of protamine was significantly reduced in the aprotinin as well as CU-2010 and CU-2020 treated groups in comparison to the control (P<0.05), while there was no difference between the four treatment groups (Figure 4.).

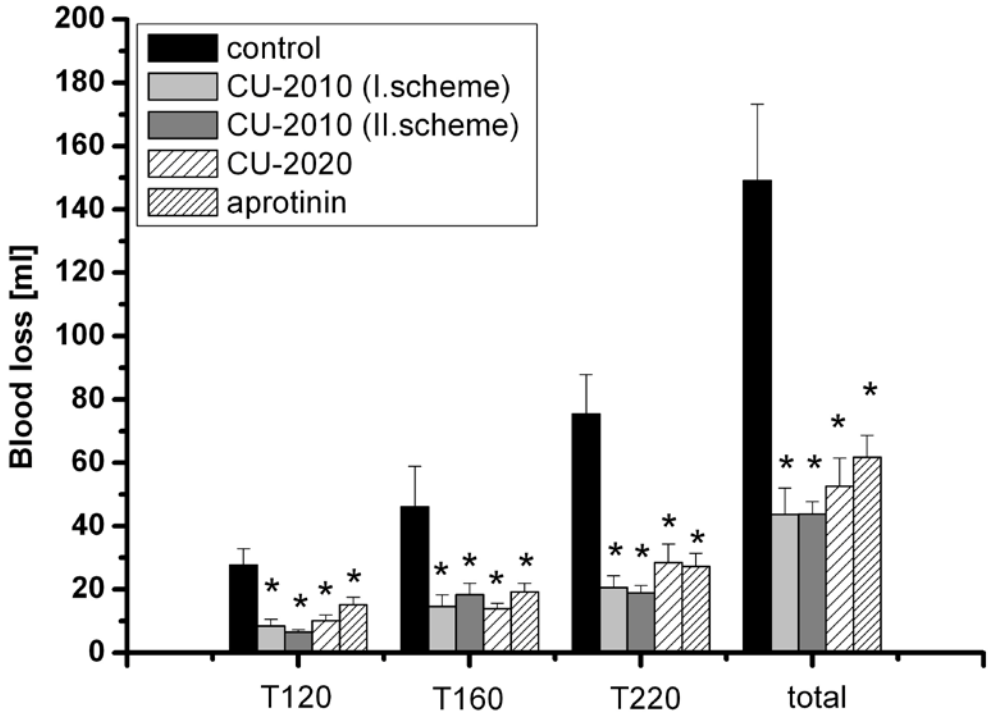

Figure 4.: Blood loss after weaning from CPB and protamine. Time points indicated the time from the initiation of CPB which corresponds 20 (T120), 60 (T160), and 120 (T220) minutes after protamine, respectively. All values are mean ± SEM, *p<0.05 vs. control.

Blood coagulation parameters

As expected, aPTT and ACT increased significantly in all groups after heparinisation and remained elevated during CPB (Figure 5.). After protamineisation ACT returned to baseline levels. Quick values decreased significantly during CPB and remained at this level until the end of the observation period. As shown in Figure 5., treatment with CU-2010 (II. scheme) and CU-2020 significantly elongated PTT after CPB at 105 and 220 minutes. There was also a tendency towards prolonged ACT values without reaching the level of significance.

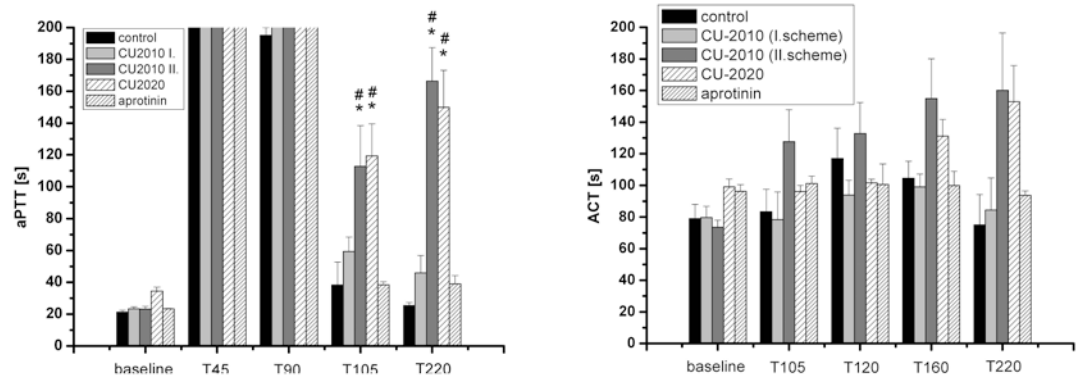

Figure 5. Blood coagulation parameters during the first two hours after cardiopulmonary bypass. A: activated clotting time (ACT), B: activated partial thromboplastin time (aPTT). All values are given as mean ± SEM.

Coronary vascular function

The endothelium-dependent, receptor-mediated vasorelaxation of the precontracted coronary arterial rings to ACh was unaffected by each treatment scheme with both synthetic aprotinin analogues (Figure 6.). Application of the synthetic aprotinin analogues did not affect the endothelium and receptor-independent cGMP-mediated vasorelaxation to SNP (data not shown).

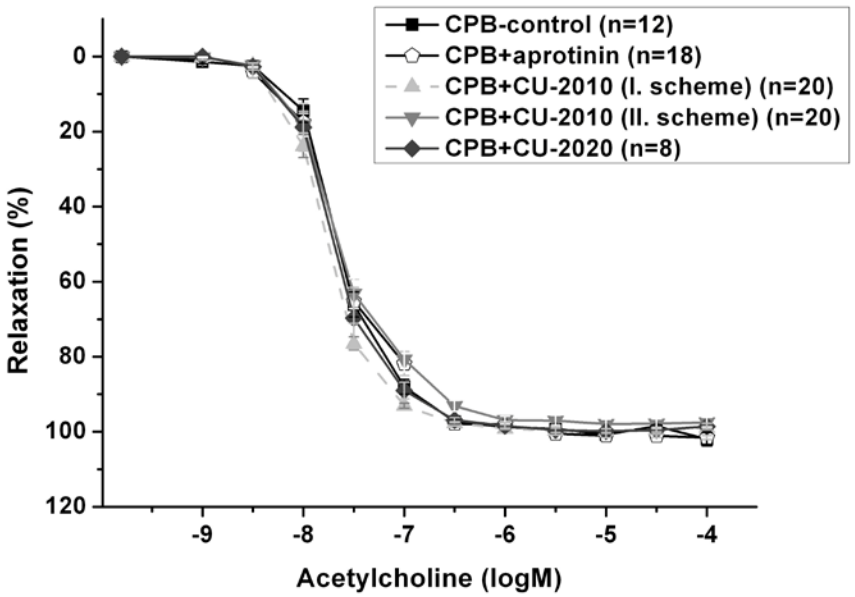

Figure 6. Endothelium dependent relaxation after application of acetylcholine (ACh). All values are mean ± SEM.

CU-2010 in a canine model of CPB with cardioplegic arrest

Blood loss

Post-operative blood loss during the first two hours after injection of protamine was significantly reduced in the aprotinin-treated group in comparison to the control ($P<0.05$). The application of CU-2010 resulted in a significant, dose-dependent reduction of post-operative blood loss (Figure 7.).

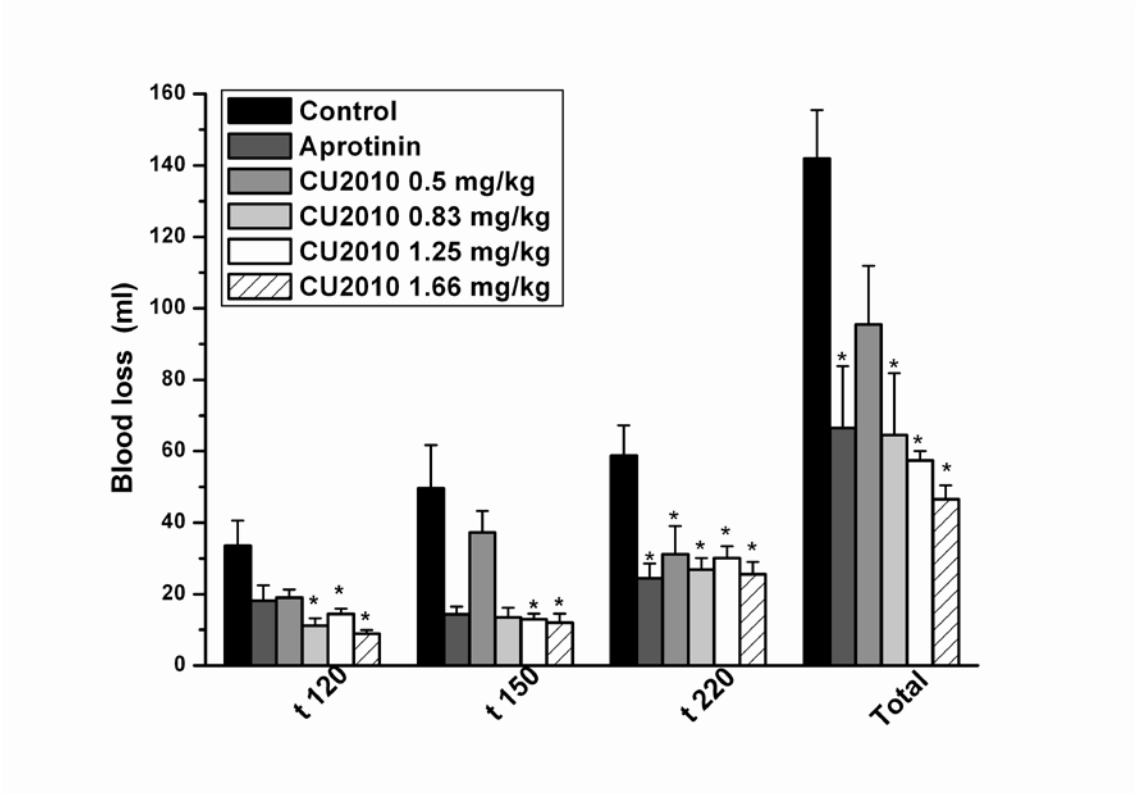

Figure 7.: Blood loss after weaning from cardiopulmonary bypass and protamine. Time points indicated the time from the initiation of CPB which corresponds 20 (T120), 50 (T150), and 120 (T220) minutes after protamine, respectively. All values are mean±SEM, *$p<0.05$ vs. control.

Blood coagulation parameters

As expected, aPTT and ACT increased significantly in all groups after administering heparin and remained elevated during CPB. After administering protamine, the ACT and aPTT returned to baseline levels in the control and aprotinin groups, but remained elevated (ACT only slightly, aPTT remarkably) in the CU-2010 treatment groups (Figure 8.).The PT values increased slightly during CPB and remained at this level until the end of the observation period in all groups (Figure 8.).

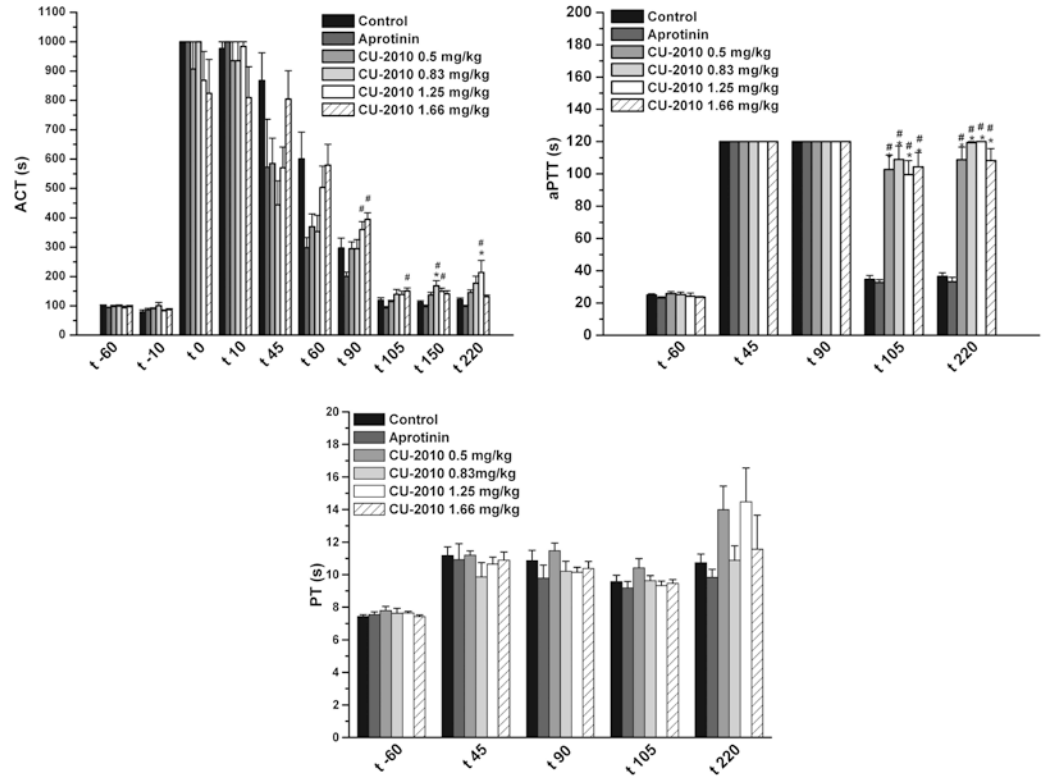

Figure 8.: Activated clotting time (ACT), activated partial thromboplastin time (aPTT), prothrombin time (PT). Time points indicated the time from the initiation of CPB (t0). All values are mean±SEM. *p<0.05 vs. control, # p<0.05 vs. aprotinin

At the end of the observation period, CT (both EXTEM and ITEM) was prolonged in the CU-2010 groups in comparison to the vehicle and the aprotinin groups. EXTEM MCF showed a significant decrease after CPB but did not differ between the groups at baseline and at the end of the observation period. If ITEM reagents were used, similar data could be obtained except that no significant decrease could be observed in the aprotinin group in comparison to the baseline and the MCF was significantly lower in comparison to aprotinin treatment group in the CU-2010 1.25 mg/kg group. However, in all groups except the aprotinin group, ITEM MCF still did not reach its maximum in one or more individuals within the measurement time and therefore the values are somewhat underestimated. LT (EXTEM) reached the designated end-point (reduction of the amplitude to 10% MCF) in neither the CU-2010 nor the aprotinin groups, but only in the control group.

Haemodynamic parameters

MAP and dP/dt min decreased in all groups. dP/dt max and CBP showed a significant decrease in the control group after CPB ($p<0.05$), while they remained unchanged in the treatment groups. After CPB, both left ventricular ESPVR and PRSW decreased significantly in the control and the aprotinin group, which could be partially and possibly totally preserved by the application of CU-2010. Due to the physiological variations of the absolute values of ESPVR and PRSW a comparison between the groups was somewhat difficult therefore percentage recovery values were calculated (Figure 9.). CU-2010 in higher doses significantly improved the percentage recovery in comparison to the controls (and in case of PRSW in comparison to the aprotinin group as well).

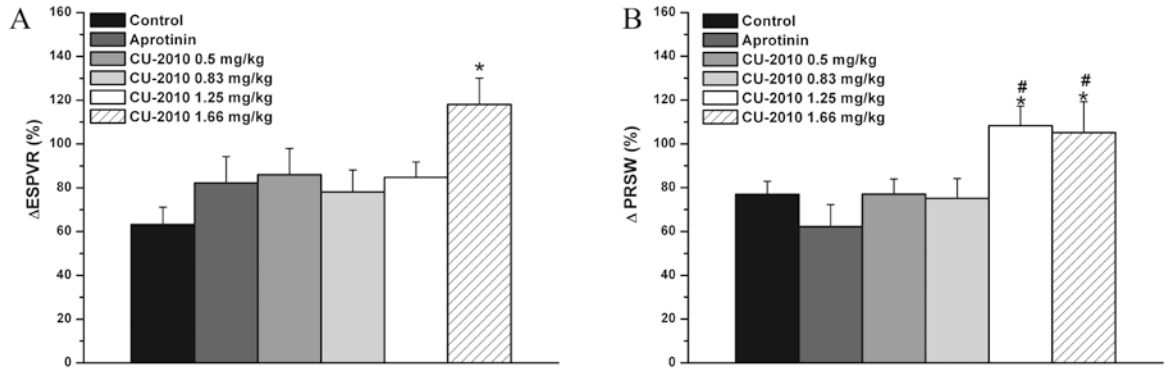

Figure 9. A: Percentage recovery of the load independent slope of the end-systolic pressure-volume relationship (ESPVR), B: Percentage recovery of the load independent preload recruitable stroke work (PRSW) two hours after weaning from cardiopulmonary bypass. All values are mean±SEM.*$p<0.05$ vs. control.

Coronary vascular function -*in vivo*

The vasodilatative response to ACh was similar in all groups before CPB. After CPB endothelial function (vasodilatative response to ACh) was significantly reduced in the control group, but this was abolished by aprotinin and all doses of CU-2010 (Figure 10.). The endothelium-independent vasodilatation after NTG did not differ between the groups and over time (Figure 10.).

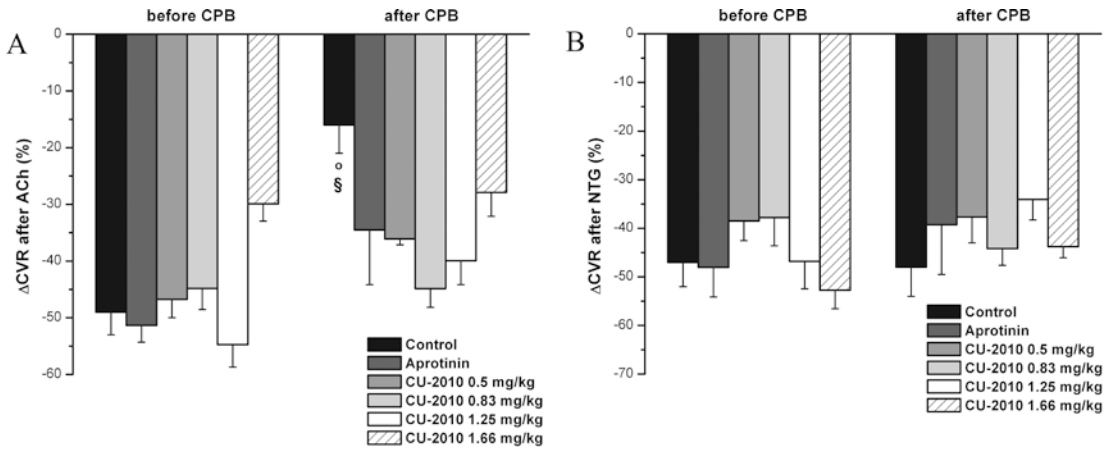

Figure 10. A: Endothelium dependent relaxation after application of acetylcholine (ACh). B: Endothelium independent relaxation after application of nitroglycerin (NTG). All values are mean±SEM. °:$p<0.05$ vs. baseline, §:$p<0.05$ vs. all other groups.

Conclusions

Cardiac surgery procedures with CPB can produce a certain amount of blood loss and in serious cases one of the most important tasks is to minimise post-operative bleeding. There are only a few anti-fibronilytic drugs available which have this effect (aprotinin, tranexamic acid, ε-aminocaproic acid). Bovine-derived aprotinin has been a widely accepted drug used for this purpose, however there have been several side effects including allergic reactions and infectious diseases. The withdrawal of aprotinin from the market created a major problem as there was no replacement available which gave the same benefits. A new group of serine-protease inhibitors based on aprotinin appeared to be a possible replacement.

In the initial study, we demonstrated that the effectiveness of recombinant aprotinin on blood loss and coagulation parameters were equivalent to those of bovine-derived aprotinin. Neither recombinant aprotinin nor bovine aprotinin impaired the endothelium-dependent vasodilatative function of coronary arteries. As recombinant aprotinin probably reduces the risk of allergic reaction and the transmission of animal disease, and bovine aprotinin was withdrawn (2007), it should be utilized clinically though further investigations would be needed.

The studies with novel low molecular weight serine-protease inhibitors CU-2010 and CU-2020 in a non-ischemic model of CPB, were shown to reduce blood loss in an equivalent manner to aprotinin and to have improved anti-coagulative properties (100,000-fold impact on fXa and fXIa in comparison with aprotinin). As these small synthetic molecules have

numerous advantages over aprotinin, we believe they may offer a true alternative in the “post-aprotinin” era.

In our final study, we demonstrated several beneficial effects of CU-2010 in an ischemic model of CPB:

1. CU-2010 dose-dependently reduces postoperative blood loss after CPB which is comparable to aprotinin
2. it has an improved antikoagulatory property (elongated aPTT, ACT) relative to aprotinin
3. at higher dosages, because of the anti-inflammatory effect it may improve left ventricular function recovery
4. CU-2010 improved coronary endothelial function and this improvement was comparable to aprotinin

We believe that this compound may provide an “all-in-one” solution, addressing major issues (such as bleeding, inflammation, cardioprotection) in cardiac surgery and therefore deserves further investigations for clinical application. However, learning a lesson from the current debates, several safety trials should be performed before moving into the clinical arena.

List of publications

Publications related to the dissertation:

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