Summary

In this Ph.D. thesis, following aims were addressed: 1/ early detection of anthracycline cardiotoxicity on the experimental rabbit model using echocardiographically examined diastolic function and biomarker troponin T, 2/ changes in concentrations of selected metals in the left ventricular myocardium of animals with experimentally induced anthracycline cardiotoxicity and dexrazoxan afforded cardioprotection, 3/ safety and possible toxicity of repeated administration of novel aroylhydrazone chelators – pyridoxal 2-chlorobenzoyl hydrazone (o-108) and salicylaldehyde isonicotinoyl hydrazone (SIH), 4/ pharmacokinetics of both iron chelators after single dose i.v. administration to rabbits 5/ potentially cardioprotective effects of o-108 and SIH on the model of daunorubicin-induced chronic cardiotoxicity in rabbits including the dose response relationships.

It was revealed that Doppler evaluation of the left ventricular filling is technically demanding with respect to the relatively high heart rate which is physiological in rabbits. High quality evaluation of all standard parameters was feasible only in the combined anaesthesia containing xylazin. In contrast to more sensitive examination of the left ventricular diastolic function performed via catheterisation measurement this echocardiographic approach was unable to identify diastolic dysfunction induced by daunorubicin. This fact might be related to the heamodynamic effects of xylazin. Unlike complicated echographic examination, cardiac troponin T was shown as useful and sensitive biomarker of chronic anthracycline cardiotoxicity. Significant elevation of troponin T was determined even before the middle of the study, i.e., at the low cumulative dose of daunorubicin (200 mg/m^2) and concentrations were progressively increasing until the end of the experiment.

Furthermore, it was revealed that anthracycline cardiotoxicity is associated with significant changes in concentration of selected metals in the left ventricular myocardium. One of the most significant findings was the increase in myocardial calcium concentrations. This was the only finding which significantly correlated with the left ventricular dysfunction. Model cardioprotectant dexrazoxane was able not only to prevent the premature mortality and systolic dysfunction but also changes in metal concentrations in the left ventricle. Repeated administration of neither daunorubicin nor its combination with dexrazoxane had no impact on myocardial total iron levels.

Repeated administration of novel iron chelators (o-108 and SIH) was not associated with the significant organ toxicity or changes in functional cardiovascular parameters. No signs of sideropenia, anaemia or blood count changes were observed. The changes in biochemical parameters were mostly mild, without dose-response relationship which corresponded with the absence of distinct changes in morphology of studied organs (e.g., liver, kidney). In the group with the highest dose of o-108, the increased concentrations of troponin T were determined, however, no functional or morphological correlate was found.

Pilot study of pharmacokinetics of aroylhydrazone iron chelators after i.v. single dose administration in rabbits revealed quite rapid distribution as well as elimination of both chelators under study. In the equimolar dose, maximum concentrations of the chelator were more than four times higher in the o-108, whereas volume of distribution of this chelator was in the same ratio lower than in SIH. In both chelators, relatively short biological half-life of elimination was observed. More detailed study of pharmacokinetics

and reason of their short biological half-lives as well as the possibility to optimize them through targeted modification of the chemical structure deserve more sensitive analytical methods and further study.

In the final part of this thesis it was revealed that both chelators o-108 and SIH are able to completely prevent the premature mortality and significantly mitigated left ventricular dysfunction induced by daunorubicin. Both chelators also decreased the progression and intensity of morphological signs of daunorubicin cardiotoxicity as well as plasma troponin T raise. However, using 2,5-fold higher dose, an unknown toxicity (unrelated to the myocardial damage) appeared. Surprisingly, in the surviving animals no cardioprotection was observed. Analogically, in the case of SIH, which was administered i.v. (in contrast to o-108), no cardioprotective effects were detectable in the highest studied dose. Both chelators, irrespectively to their chemical structures or routes of administration, were able to afford significant cardioprotection against chronic anthracycline cardiotoxicity. Nevertheless, unusual dose-dependence and mechanisms involved in this observation merit further study.