invaginations (NI), increased numbers of mitochondria (M), and loss of register between the sarcomeres (LR) (Figs 4, 5).

**Discussion**

Liao et al. stated that clinical heart failure in animals has been achieved experimentally with relative ease but that it has been more difficult to produce a model that mimics closely the various aspects of the human condition. The effect of toxic plants on ruminants has been intensively investigated and the models are well established. The electron micrographs clearly showed that the myocardium was affected by our experimental toxin, some sections showing varying degrees of decay from relatively normal looking areas to others with extensive damage. The degeneration of the myosin filaments was more pronounced than that of the actin filaments. Compared to sections made from the untreated group, the increased number of mitochondria was very obvious. Many abnormal mitochondria were also observed.

The cardiodynamic parameters of the treated rats all differed significantly from those measured in the control rats. The significant drop in $\frac{dP}{dt_{max}}$ suggested a marked decrease in the contractility, which together with the decrease in LVSP implied that these hearts were less efficient in generating a normal contractile force. The increased LVEDP further implied depressed cardiac pumping ability, suggesting backward failure of the left ventricle of the treated group. The increases in the LVEDP of the treated group are typical of heart failure. We do, however, acknowledge the controversy regarding the reliability of $\frac{dP}{dt_{max}}$ as an index of contractility when the loading conditions of the heart are altered. In our treated group, therefore, loading conditions favoured a slight overestimation of contractility. The electron micrographs suggest also that other factors than the loading conditions could have contributed to the decreased $\frac{dP}{dt_{max}}$ values. The reduced number of myofilaments was clear and would have adversely affected the performance of the hearts.

The significant decrease in the HR of the treated group was somewhat unexpected when the contractile force of the left ventricle was obviously compromised. A decrease in heart rate was also seen in the ruminant model, although the rate increased during the terminal stages of the disease. In this study the compensatory increase in heart rate typical of the final stages of heart failure was not observed because the animals were killed before this stage was reached. A direct effect of the extract on the nodal cells should not be disregarded. This might be linked to a disturbance in Ca$^{2+}$ handling by the damaged myocardium, because enhanced activity of the Ca$^{2+}$/Na$^{+}$ exchange system in the failing heart prolongs the cardiac muscle action potential, leading to reduced heart rate.

A reduced uptake of Ca$^{2+}$ by the sarcoplasmic reticulum is a characteristic of both the human condition and the ruminant model for heart failure. As we did not directly measure Ca$^{2+}$ movements, the only means of deducing Ca$^{2+}$-behaviour was indirectly by considering the isovolumic relaxation rate ($T$), which gives an indication of Ca$^{2+}$ sequestration. $T$ was significantly increased in the treated group suggesting a prolonged relaxation rate, which in turn implies that Ca$^{2+}$ uptake by the sarcoplasmic reticulum of the rat was also compromised.

The reserve capacities of the heart are taxed during physical exercise. For the purpose of evaluating the possible effect of the plant extract on cardiac reserves, we employed a method of non-exercise stress by administering adrenoreceptor agonists. The use of this procedure in animal models for comparison or extrapolation to humans should, however, be done with circumspection, because there is considerable variation in receptor distribution and density between species. It is nevertheless a valuable tool in the evaluation of myocardial performance in the same species.

In humans, heart failure is characterized by hypotension, elevated sympathetic nervous activation and down regulation of $\beta_1$-receptors. Down regulation has been observed in some rat models of heart failure and hypertension. This aspect...
still has to be investigated for this model and should therefore be considered as a possibility until proved otherwise. Administration of a β₁-receptor agonist to evaluate myocardial performance could therefore be compromised by a decrease in the number of available β₁-receptors. The aim of this study was to evaluate whether the extract compromised heart function. Any significant underperformance in the treated group in response to Dobutrex implies altered function. In all of the parameters that were measured the treated group did indeed respond significantly differently to the challenges of the adrenoreceptor agonists compared to the control group.

The two main cardiac reserves, heart rate and stroke volume (SV), can both increase by approximately two and a half times in humans and larger animals, such as dogs, should the need arise. However, with the relatively high resting HR of rats, it is unlikely that the same increase in HR will be observed, since such a high rate would severely compromise filling time. The HR response of our treated group implied a reduction in HR capacity when the hearts were taxed (Fig. 3). As mentioned above, a possible contributor to the stroke volume of the heart. It can be assumed that contractility be compromised, the SV will be attenuated. It should also be noted that apart from the lower responses to receptor stimulation, there was also a large difference between the resting values of the two groups of animals as shown in Table 1.

Finally, reduced performance of the hearts of the animals receiving the extract is illustrated by cardiac work. The significant differences coupled with the lower systemic blood pressures suggest that the normal functioning of the heart was severely compromised in the experimental rats. The heart to body weight ratios of the two groups did not differ significantly, although the hearts of the treated group increased slightly in weight. In the ruminant model the hearts of treated animals were significantly heavier but this was due to fluid accumulation and not hypertrophy.

This study demonstrated considerable evidence for diminished cardiac function in rats that received a subcutaneous administration of an extract made from Pavetta harborii. Further studies need to be done on rats to determine whether this would progress to a congestive failure phase as is seen in ruminants.

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