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Is poloxamer truly effective in dystrophic cardiomyopathy of mdx-mice?

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1 INTRODUCTION

SIR – We wish to comment on a Letter by Soichiro Yasuda and colleagues „ Dystrophic heart failure blocked by membrane sealant poloxamer“ (Nature, 436:1025-1029;2005M).

How can control (C57BL) and mdx-mice be compared if they differed considerably at baseline concerning end-systolic volume, end-diastolic volume, end-systolic pressure, stroke volume, and dP/dtmin?

Left ventricular (LV) end-systolic diameter, LV end-diastolic diameter, and LV-mass increase and fractional shortening decreases with age and by age 42w all mdx-mice have dilated cardiomyopathy. It is not mentioned if all of the investigated mice had the same age.

Also gender of the investigated mdx-mice is not given. Gender might be relevant since sex-associated changes in response to calcium were reported in mdx-mice.

Different parts of the myocardium are differentially affected by the dystrophic process and myocardial fibrosis in mdx-mice. It is not mentioned from which part of the heart cardiomyocytes were taken. Were they taken from the left or right atrium or ventricle? Was the location of biopsy the same in control and mdx-mice?

Mdx-mice develop progressive LV dilatation and by age 42 weeks all have dilated cardiomyopathy. How to explain that in the present study end-diastolic-volume was smaller in mdx-mice compared to control mice and that there was diastolic instead of systolic dysfunction? Did any of the mdx-mice develop dilated cardiomyopathy or restrictive haemodynamics?

Mdx-mice develop ECG abnormalities, like tachycardia, similar to those in DMD. Were ECGs registered during the experiments and did the frequency of ECG abnormalities differ between P188-treated and untreated mdx-mice? Why did P188 not affect the heart rate? How to explain heart rates of 582-600bpm in anaesthetised control and mdx-mice whereas previous studies reported heart rates of 350-380bpm in anaesthetised C57BL mice?

How to explain that P188 only increases LV end-diastolic volume without affecting LV end-diastolic pressure? If P188 actually improves the diastolic function, expressed as dP/dtmin, a decrease in LV end-diastolic pressure would be expected.

Since the end-diastolic-pressure did not differ between control and mdx-mice at baseline, the latter do not seem to have diastolic dysfunction. Increase in end-diastolic pressure after P188 indicates ineffectiveness of the agent concerning diastolic function.

Why was dobutamine chosen as a cardiac stressor, since isoproterenol or aortic constriction have been acknowledged as appropriate cardiac stressors in mdx-mice? The study referenced for giving dobutamine actually used aortic constriction and isoproterenol, but not dobutamine. How can one be sure that myocardial P188 concentrations were high enough after local or intravenous application to be effective?

Differed hearts morphologically or functionally between control and mdx-mice? What were the pathoanatomic and histological findings in hearts of P188-treated and untreated mdx-mice? Did they differ from control mice? Was there a difference in the amount of damaged cardiomyocytes and fibrosis? Were there any cases with LV hypertrabeculation/noncompaction? Why was no echocardiography or cardiac MRI carried out to monitor the therapeutic effect of P188?

The presented data do not justify to claiming a therapeutic effect of P188 for mdx cardiomyopathy because the study groups were unequal, cardiac changes after treatment were equivocal, and because of various other methodological uncertainties.

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