Abstract 138 Table 1

Main indication for surgery	Number of patients
Symptomatic severe aortic regurgitation (AR)	13
Asymptomatic severe AR with moderate LV function or LVIDd>7 cm	4
Thoracic aortic aneurysm	7
Severe left main stem disease with grade 3 AR and small aortic annulus	1
Severe subaortic stenosis (P max 100 mm Hg) with grade 2 AR	1

There were 17 men and 9 women, with median age 58.5 years (22–76 years). The proctor assisted in 9 cases; otherwise all procedures were performed by both first authors operating together. Follow up was 100% complete.

Results In 5 cases, AV repair was not deemed feasible intraoperatively, and was not attempted. AV repair was attempted in 21 and successfully completed in 19 patients (*Repair Group*; Table 2), including 6 bicuspid and 13 tricuspid aortic valves. The remaining 7 patients underwent AVR ± root replacement (*Replacement Group*).

Abstract 138 Table 2

Operative procedure	Number of patients
Isolated AV repair (with annuloplasty in 7 cases)	9
Excision of papillary fibroelastoma, subaortic membrane excision, AV repair	1
AV repair with pericardial patch to left coronary cusp, CABG	1
AV repair, remodelling of the aortic root, (external annuloplasty in 7 cases)	8
AV repair, replacement of ascending aorta (MV and TV repair in 1 case)	2

There were no deaths and no strokes. 1 patient in *Repair Group* developed atrial flutter, treated successfully by catheter ablation. 1 patient with isolated bicuspid valve repair has recurrent asymptomatic grade 3 AR seven months postoperatively. 1 patient in *Replacement Group* (background of SLE) was diagnosed with mechanical prosthesis dysfunction, and underwent bioprosthetic redo AVR. The valve leaflet was blocked by pannus. Another patient from *Replacement Group*, who had poor LV preoperatively, underwent CRT implantation. 1 patient from *Repair Group* (5%) and 3 from *Replacement Group* (43%) group are in group NYHA 2; the others are asymptomatic and well. 7 patients in *Repair Group* (37%) and 1 in *Replacement Group* (14%) are not on any antiplatelet or anticoagulant medications. The median follow up in *Repair Group* was 16 months. The median AR grade was reduced from 3 to 1 ($p<0.01$ in Wilcoxon matched-pair singed-rank test). The freedom from AR grade 2 or more was 79%, and freedom from AR grade 3 or more 95%. In patients in whom the proctor directly assisted, the freedom from AR grade 2 or more was 100%. The difference in AR reduction between proctored and independent procedures was not statistically significant ($p=0.084$ in independent-samples Mann-Whitney U test).

Conclusion These results reflect our learning curve. We feel we have achieved acceptable early results independently after the initial, directly assisted, procedures. We still need further experience, and an on-going dialogue with the proctor about the decision-making in AV repair will assist our progress.

Basic Science

139 AN INVESTIGATION INTO THE SUBCELLULAR DISTRIBUTION OF TWO-PORE CHANNELS IN CARDIAC VENTRICULAR MYOCYTES IN LIGHT OF THEIR DIFFERING CONTRIBUTIONS TO BETA-ADRENERGIC SIGNALLING

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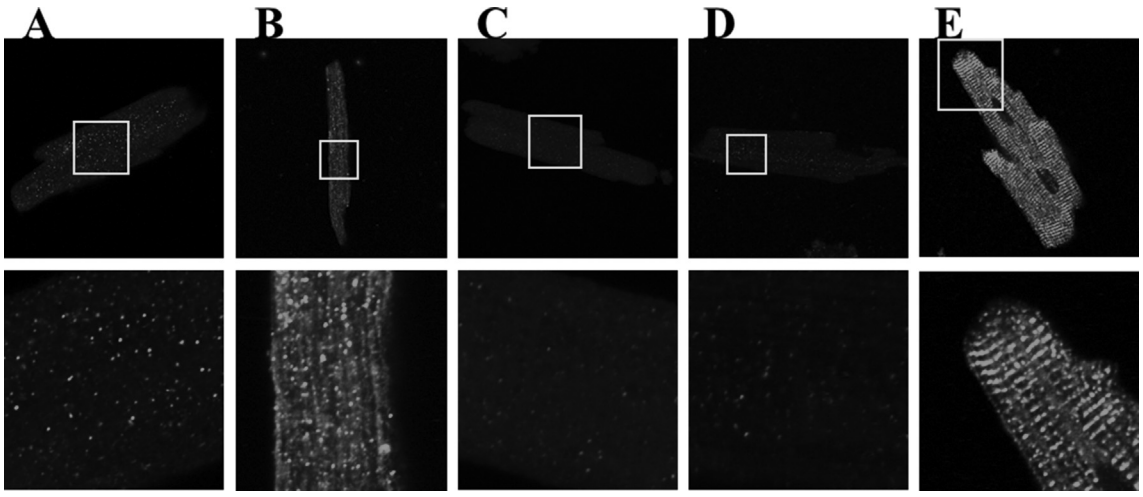
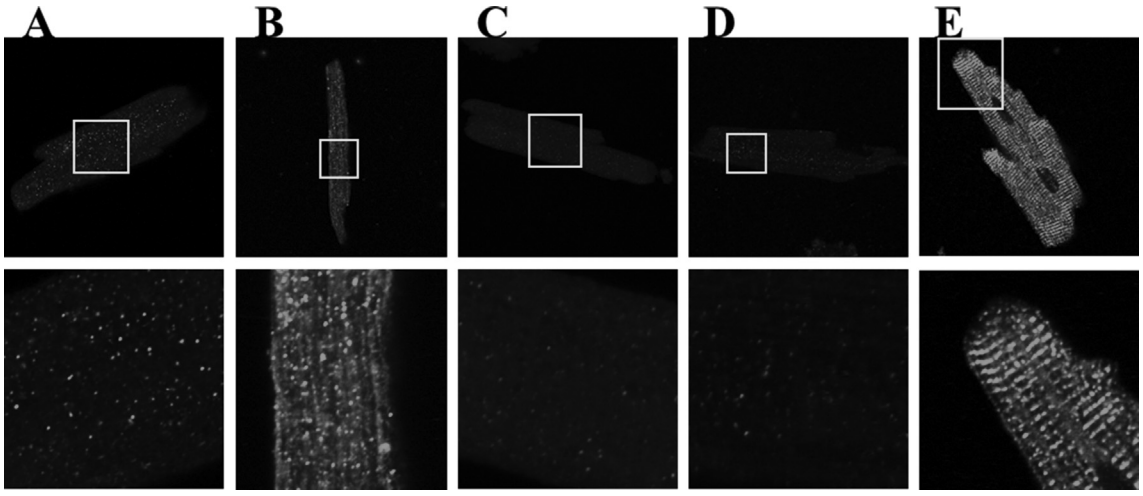
Introduction Nicotinic acid adenine dinucleotide phosphate (NAADP) is a calcium-mobilising messenger that acts via two-pore calcium channels (TPCs). NAADP releases calcium from a lysosome-related acidic compartment distinct from the endo-



Abstract 139 Figure 2 Representative images (immunocytochemistry) showing the subcellular distributions of: (A) TRP-ML1; (B) LAMP2; (C) TPC1; (D) TPC2; (E) RyR2.



Abstract 139 Figure 1 Effect of bafilomycin on the contractile response of cardiac ventricular myocytes to isoprenaline.

sarcoplasmic reticulum and has been identified as an important mediator of acute and chronic beta-adrenergic signalling in the heart. Genetic or pharmacological manipulation of NAADP signalling appears to be protective in pre-clinical models of cardiovascular diseases, such as ischaemia-reperfusion injury, arrhythmia and cardiac hypertrophy. Recent evidence has indicated that TPC2, rather than TPC1, mediates the effects of beta-adrenergic-evoked NAADP signalling, although whether this reflects differing subcellular distributions of TPC1 and TPC2 remains to be established.

Methods Single ventricular cells were isolated enzymatically from guinea pig hearts and superfused with physiological saline solution (36°C). Cells were field-stimulated (3 ms pulse duration) to fire action potentials. Cell shortening was measured with an edge-detection system. To confirm the involvement of a lysosome-related acidic compartment in beta-adrenergic signalling, the effect of isoprenaline (a beta-adrenoceptor agonist) on cell contraction was investigated in the presence and absence of bafilomycin (a vacuolar H^+-ATPase inhibitor that depletes acidic calcium stores). Data are presented as mean±SEM; comparisons were made using one-way ANOVA. In additional experiments, standard immunocytochemical techniques were employed to investigate the cellular distributions of TPC1, TPC2, transient receptor potential channel mucolipin-1 (TRP-ML1), lysosome-associated membrane protein-2 (LAMP2) and ryanodine receptor-2 (RyR2). Immunofluorescence was visualised using a Zeiss LSM 510 confocal microscope.

Results Isoprenaline (3 nM, 3 min) increased myocyte contraction (relative to control) by 86±9% (n=8) in the absence of bafilomycin, 62±13% (n=6) in the presence of 100 nM bafilomycin, and 44±12% (n=8) in the presence of 300 nM bafilomycin (Figure 1). The effect of bafilomycin tended closely toward statistical significance ($p<0.06$, one-way ANOVA). TPC1 and TPC2 displayed qualitatively similar patterns of punctate intracellular labelling. This punctate pattern resembled that for the lysosomal markers TRP-ML1 and LAMP2. In contrast, RyR2 labelling showed a striated appearance, consistent with the known organisation of the sarcoplasmic reticulum in cardiac myocytes (Figure 2).

Conclusions/implications This is the first direct immunocytochemical evidence in cardiac cells describing the localisation of TPC1 and TPC2. The subcellular distribution of TPC1 and TPC2 does not appear to explain their differing contributions to beta-adrenergic signalling. Our data are also consistent with a role for lysosomal calcium stores in the inotropic effect of beta-adrenoceptor agonists.

140 HETEROZYGOUS DELETION OF PMCA1 MIGHT SERVE A PROTECTIVE ROLE IN THE HEART FOLLOWING MYOCARDIAL INFARCTION

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Introduction Coronary artery disease (CAD) and its main consequence-myocardial infarction (MI) are the UK's biggest killers. Most of these deaths occur either acutely post-MI or chronically as a result of pathological cardiac remodelling eventually leading to heart failure. Recent genome-wide association studies (GWAS) elucidated a potential link between the PMCA1 gene, *atp2b1*, and these diseases.

Objective PMCA1 has been shown to associate with many of the key features predisposing to the development of heart failure. Given the GWAS findings this study aims to investigate the potential role of PMCA1 in the post-MI remodelling process.

Methods Moderate and severe MI via permanent ligation of the LAD coronary artery, alongside a sham procedure was induced in either wild type or mice expressing a heterozygous mutation of the PMCA1 gene ($PMCA1^{Ht}$). Occurrence of ischemia was confirmed by evaluation of plasma levels of cardiac troponin I (cTnI) and histologically. Post-surgery the animals were kept for either 1 or 4 weeks. Electrocardiography (ECG) and echocardiography were performed *in vivo* to assess cardiac function. To further characterise the cardiac response *in vitro*, histological analysis was performed at both time points.

Results 24 hours post LAD coronary artery ligation a significant increase in the plasma cTnI levels was recorded in both WT and $PMCA1^{Ht}$ mice. However, overall survival 4 weeks post-surgery was significantly lower in WT-MI mice when compared to $PMCA1^{Ht}$-MI mice and both WT and $PMCA1^{Ht}$ sham control groups. In addition, a significant difference in