**Introduction**

Despite the rigid regulatory framework, advances in preclinical modelling and the emergence of in silico technologies, approximately 25% of human pharmaceuticals fail in late stage development or are withdrawn from the market due to effects on the heart and vasculature. Using fresh, functional cardiac tissues we attempt to bridge the gap between the currently utilised, yet over replied upon, cell-based assays, animal models and the clinical situation.

**Methods**

**Tissue:** Whole human hearts unsuitable for transplant were ethically obtained from Biopta’s tissue network. Upon receipt at the laboratory, tissue was dissected into the preparations outlined below. The function of each tissue preparation was assessed using known standards prior to assessing drug responses. **Coronary Artery Myography:** Small (<500 µm) and large (500-1000 µm) coronary arteries were dissected from the surface of the heart. Using wire myography, isometric forces were recorded from each isolated artery. Responses to sumatriptan, tegaserod and mephedrone were assessed.

**Ventricular Muscle Contractility:** Trabeculae of endocardial muscle were isolated from the left ventricles and suspended in large organ baths. Electrical field stimulation (‘EFS’) was applied and the changes in force of contraction recorded. Alterations in ventricular contractility can place a huge strain on the circulatory system and may be most detrimental in those with pre-existing CV disease. Drug effects were assessed at 1 Hz (60 bpm) stimulation frequency. In addition, the arrhythmogenic capabilities of tegaserod and cisapride were assessed by increasing the frequency of stimulation from 1 Hz up to 8 Hz with the threshold for anomalies noted.

**Results**

Sumatriptan, tegaserod and mephedrone were all shown to cause a constriction in coronary arteries although in the case of mephedrone this was not at therapeutically relevant concentrations (Figure 1).

Initial experiments (n = 2) demonstrated that tegaserod produced a concentration-dependent inhibitory effect on EFS-induced contractions of isolated human ventricular muscle (Figure 2).

Preliminary data indicates that it is possible to assess the arrhythmogenic potential of compounds in human ventricular muscle trabeculae. Tegaserod was not shown to lower the arrhythmogenic threshold which is in line with the effects observed in the clinic. Cisapride was shown to induce anomalies at a lower threshold than vehicle although further experiments are required to confirm this finding (Figure 3).

**Conclusion**

The purpose of these investigations was to demonstrate the use of fresh, functional human cardiac tissue in the detection of adverse effects of human therapeutics. All the compounds used in the assays above (sumatriptan, tegaserod, mephedrone and cisapride) have been withdrawn from the market or have restricted use due to a variety of observed cardiac events. Sumatriptan (a 5-HT agonist) was licensed for use in migraine. Serious cardiac events following use of the drug include fatal coronary artery vasospasm, myocardial infarction and myocardial ischemia. The data above demonstrates that sumatriptan causes a concentration-dependent constriction of large coronary arteries in line with the clinical effects. In addition, specific side effects of tegaserod, mephedrone and cisapride were all detected in the above assays.

The data presented above show that fresh functional human tissue can be used to assess the cardiac safety of human pharmaceuticals. Responses of novel compounds can be investigated for various parameters including ischemia, force of contraction, rate of contraction/relaxation and arrhythmogenic potential complementing the existing battery of tests already performed.