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Application of intermittent negative upper airway pressure as a novel rat model for obstructive sleep apnea and atrial fibrillation
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Background: Obstructive sleep apnea (OSA) is associated with increased occurrence of atrial fibrillation (AF). Obstructive respiratory events lead to intermittent hypoxia (IH) and ineffective inspiration against the occluded upper airways result in intrathoracic pressure changes and increasing cardiac transmural pressure gradients. Animal models mimicking intrathoracic pressure changes on top of IH are not available.

Method: In spontaneously breathing sedated rats (2% isoflurane), IH (n=9) was applied by intermittent increase in the respiratory dead volume. Reproducible and standardized obstructive respiratory events were induced by defined intermittent negative upper airway pressure (INAP – inverse CPAP) applied via a customised mask which was connected to a negative pressure device (n=9). One minute of IH or INAP was followed by atrial pacing (LV) tissue was processed for histological and biochemical analyses.

Results: Blood pressure and end-diastolic left ventricular pressure were not affected by IH or INAP. Intermittent desaturation (< 77% O2) and post-apneic hyperventilation was comparable in INAP- and IH-rats, but INAP-rats showed significantly higher breathing efforts during apneas compared to IH-rats (IH: 3.44±0.13 vs. INAP: 4.47±0.14 mbar; p<0.01). LA interstitial fibrosis formation (LA: Ë 135% vs. CTR, p<0.01) and LA-myocyte diameters (LA: 107% vs. CTR) were increased in INAP-rats, but unchanged in IH-rats. This was associated with longer inducible AF durations in INAP-rats (p=0.02 vs. CTR; INAP: 11.65 seconds; CTR: 0.98 seconds) but not in IH-rats (p=0.31 vs. CTR; IH: 1.28 seconds).

Conclusion: Application of INAP in rats mimics important components of OSA beyond IH and allows the study of the progressive arrhythmogenic substrate in the atrium independent of the development of hypertension or overt diastolic dysfunction.

P799
The role of gap junctions in stretch-induced atrial fibrillation
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Aims: This study investigated the functional role of gap junctions in the setting of atrial fibrillation (AF) by analysing the effects of a gap junction enhancer and blocker on AF vulnerability and electrophysiological properties of isolated hearts.

Methods and results: AF model was constructed by the acute atrial stretch in the isolated rabbit heart was used. Sustained AF (SAF) was induced by a burst high-frequency stimulation of the Bachmann’s bundle. The effective refractory period (ERP) was measured. The total conduction time (TCT) and the pattern of conduction of the anterior surface of the left atrium were monitored by using an optical mapping system. The effect of enhancing gap junction function by 100-1000 nM norepinephrine (NEP) and block by 30 µM carbamol on these parameters was measured. SAF inducibility was increased with an elevation of intra-atrial pressure. Enhanced gap junction conductance induced by treatment with 100-1000 nM rotigaptide (ZP123) and block by 30 µM carbenoxolone reduced SAF inducibility, and the gap junction blocker carbenoxolone increased. In the absence of gap junction enhancer or blocker, normal conduction was observed at 0 cmH2O. When intra-atrial pressure was raised to 12 cmH2O, the conduction pattern was changed to a heterogeneous zig-zag pattern and TCT was prolonged. Conduction pattern was not affected by either agent. Rotigaptide shortened TCT, whereas carbenoxolone prolonged TCT. ERP was significantly shortened with an increase in intra-atrial pressure, but ERP was unaffected by either agent.

Conclusion: Modulations of gap junction conductance affected AF inducibility through their effects on atrial conduction, not by altering ERP.

P800
Number of CTG repeats in myotonic dystrophy: a new risk factor of ventricular tachycardia?
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Ventricular tachycardia (VT) and sudden death are common in myotonic dystrophy (MD). MD is the most frequent inherited neuromuscular disorder and is caused by an expanded cytosine– thymine–guanine (CTG) repeat on chromosome 19 (–38 repeats). A higher number of CTG repeats have been associated with more severe neuromuscular symptoms and progression but it is unknown if this could also be the case for patients presenting with VT.

Methods: All consecutive patients with MD admitted to our centre due to sustained monomorphic VT were studied. The number of CTG repeats was analysed by the Southern blot technique.

Results: 8 patients (7 male, 36.9±7.8 years) were included. All had monomorphic VT which was confirmed at electrophysiological evaluation and had a bundle-branch reentrant mechanism. All patients underwent wide-complex tachycardia followed by pacemaker implantation. The number of CTG repeats was 785±547 (range 1200-1600).

Conclusion: Patients with MD and sustained monomorphic VT often show a high number of CTG repeats. This may be considered a risk factor for development of ventricular arrhythmias.

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Arrhythmogenic mechanisms in ageing: insights from murine models of arrhythmia
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Cardiac ageing is attributable to a range of pathological conditions. The age-related progressive deteriorations in cellular and tissue function in the heart results in, among other changes, increased incidences of cardiac arrhythmias. Of these, atrial fibrillation (AF), is the commonest arrhythmia and is associated with substantial morbidity and mortality. Its overall adult prevalence is ~1–4% but this rises to >13% in those over age 80 y. Similarly, the incidence of ventricular arrhythmias potentially resulting in sudden cardiac death increases with age and with a higher prevalence in males than female. These incidences converge by the eighth decade of life. Ageing is itself accompanied by structural and biochemical changes that may independently increase arrhythmic risk. Here we will discuss experimental evidence bearing on pro-arrhythmic changes related to ageing in three distinct murine models of arrhythmia. These models include the Scn5a−/− mouse modelling Brugada Syndrome (BrS), the Scn5a−/−deltaKPQ mouse modelling Long QT Syndrome type 3 (LQTS3) and the PGCGBetar−/− mouse modelling metabolic syndrome. Interestingly, even though patients are born with such inherited genetic defects, the arrhythmic event tends to present much later in life. Our multiple studies converge in suggesting that ageing superimposes a complex multi-factorial arrhythmogenic pathway on the underlying genetic defect in each of the above conditions. This involve changes at the subcellular, cellular, tissue and systems level, manifesting as alterations in electrophysiological properties, gene expression profiles, membrane protein expression as well as microscopic structural changes. Thus, (1) our BrS murine model studies implicated a combination of age-related myocardial fibrosis and genetic changes in development of a pro-arrhythmic phenotype, which has been recapitulated in a recent clinical study, demonstrating the translatability of these murine models to the clinical setting. (2) Our LQTS3 murine model studies suggest the development of an overlap syn- drome with age, where depolarisation abnormalities are present in addition to the expected repolarisation defects. (3) Our PGC1beta studies demonstrate that at the systems level, ventricular activation was prolonged in these mice consistent with slowed action potential conduction and shorter repolarisation intervals. Intracellular atrial cardiomyocyte recordings at progressively incremented pacing rates demonstrated age-dependent atrial arrhythmic phenotypes attributable to compromised action potential conduction and repolarisation wavefronts. Overall these studies demonstrate a multi-factorial arrhythmogenic process with ageing that offers a potentially wide range of therapeutic targets. Further elucidating these complex interactions between ageing and arrhythmogenic tendencies will allow clinicians to manage the ageing population in a targeted manner.

P802
A novel scn5a loss-of-function mutation in a family with symptomatic brugada syndrome
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Introduction: Brugada syndrome is an inherited channelopathy associated with an increased risk of sudden cardiac death. The individual risk stratification remains challenging, and even the diagnosis may be controversial in some cases. Genetic