mt and WT littermates. Electrophysiological studies in Isolated Langendorff DSG2wt/mt and WT hearts showed comparable ventricular action potential duration and effective refractory periods. DSG2 mutation correlated with increased arrhythmia inducibility after endurance training. Ventricular arrhythmias were induced in 5 of 8 DSG2wt/mt, but in none of 7 WT hearts during right ventricular stimulation by a single extrastimulus (p=0.03). In conclusion, endurance training reveals an ARVC-like phenotype in otherwise healthy and morphologically inconspicuous DSG2wt/mt mice presenting right ventricular dilatation, decreased right ventricular contractility and increased inducibility of ventricular arrhythmias during right ventricular pacing.

Abstract 111 Table 1

Genotype	WT	DSG2 mt/wt
n (females/males)	8 (6/2)	9 (7/2)
HR (bpm)	424Â±6	435Â±7
RVlav d (mm^2)	3.67Â±0.20	4.29Â±0.28*
RVsav d (mm^2)	4.76Â±0.28	6.26Â±0.29*
RVsav s (mm^2)	2.10Â±0.26	3.50Â±0.25*
RV FAC (%)	55Â±4	44Â±3*
Age (weeks)	21Â±0.2	21Â±0.2
Weight (g)	24.3Â±0.7	25.5Â±1.6

112 LOCATION OF SUBSIDIARY ATRIAL PACEMAKERS FOLLOWING ABLATION OF THE SINUS NODE IN THE GOAT

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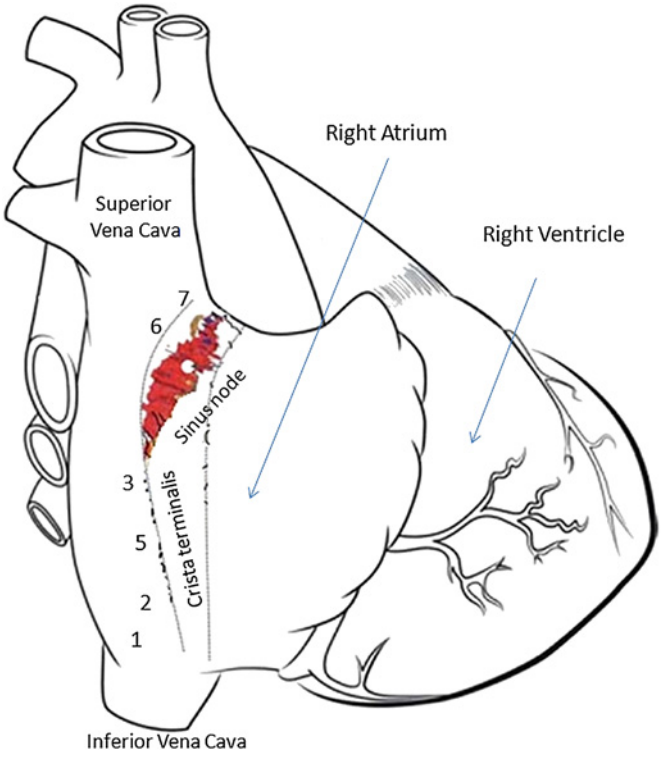
Introduction The development of sinus node dysfunction in patients may be accompanied by the emergence of subsidiary atrial pacemakers (SAPs) and/or junctional escape rhythms. It has been postulated that biological modification of SAPs may provide a potential alternative to implantation of artificial pacemakers for the treatment of sinus node disease ("biological pacemakers"). We investigated the structural and functional characteristics of SAPs in a chronic goat model.

Methods Adult female goats (n=7) underwent epicardial radiofrequency catheter ablation of the sinus node, via right thoracotomy. The endpoint for ablation was defined as a fall of heart rate by 50% accompanied by change in P wave morphology, or the emergence of a junctional rhythm. An epicardial pacing system was implanted for continuous monitoring. Single lead surface ECG, corrected sinus node/subsidiary atrial pacemaker recovery time (CSNRT, CART) and interrogation of the implanted pacemaker were performed at baseline and weekly for 4 weeks following recovery from anaesthetic. After 4 weeks epicardial mapping was performed and location of any SAPs determined.

Results Epicardial mapping preablation confirmed sinus rhythm in all goats and guided attempts at ablation. The predefined acute endpoint of ablation was achieved in six goats. In five goats the ablated surface area was no greater than a 1×2 cm, occupying the cranial half of the intercaval region near the crista terminalis, but was more extensive in two goats (including the animal with failed acute endpoint). Despite profound postablation bradycardia, no animal required pacing for more than the first 24 h post-ablation. Follow-up monitoring revealed an abnormal CART (>500 ms) in three goats, and the P wave morphology remained different from the preablation state in five goats, consistent with a non-sinus rhythm. Repeat epicardial mapping 4 weeks post-procedure revealed stable SAPs located in the caudal half of the intercaval region (low right atrium) in four goats. In two animals there was evidence of recovery of sinus node function and in a further goat the SAP was located within the interatrial septum or left atrium.

Conclusion Destruction of the sinus node in this experimental model resulted in the generation of chronic SAP activity in all animals. In the majority of cases SAPs were located in the low right atrial free wall (Abstract 112 figure 1) and constitute a promising stable target for electrophysiological modification in a whole animal model of sinus node disease.



Abstract 112 Figure 1 Schematic diagram of location of subsidiary atrial pacemakers. Each number represent the location of SAP of an individual goat (1—7). Animal number 4 not displayed due to inaccessible SAP location.

113 BLOOD THROMBOGENICITY IS INVERSELY RELATED TO CORONARY LESION SEVERITY IN PATIENTS WITH NON ST-ELEVATION ACUTE CORONARY SYNDROME AND TYPE 2 DIABETES MELLITUS

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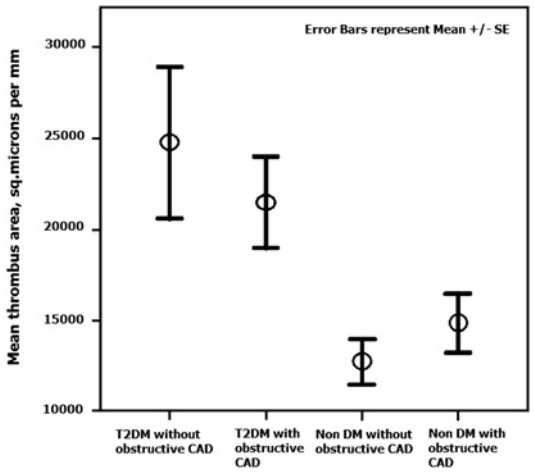
In patients with type 2 diabetes mellitus (T2DM), non-ST elevation—acute coronary syndrome (NSTE-ACS) occurs frequently secondary to non-obstructive coronary lesions than those without T2DM. Pathophysiological events leading to acute myocardial infarction in these individuals remain largely unknown, and subsequently demonstrate a poorer prognosis than those without T2DM.

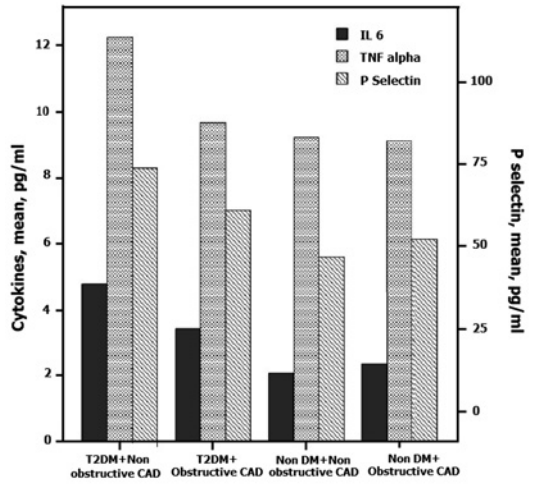
Methods We evaluated blood thrombogenicity (BT) in 80 patients with and without T2DM 7—10 days after troponin positive NSTE-ACS. In accordance to AHA/ESC recommendations all patients received secondary prevention therapy including aspirin and clopidogrel (300 mg loading and 75 mg maintenance doses respectively). Coronary artery disease (CAD) was quantified by coronary



Abstract 113 Figure 1 Oneway ANOVA showed significant difference bettween the groups, F=5.26, p=0.002. df (3.76). Post hoc compansion with Bonferroni test showed that BT was significantly higher in T2DM with non-obstructive CAD compared to the other three groups p<0.05.

angiography through an independent investigator blinded to clinical and laboratory data. Lesions were classified as either obstructive (plaque >75% of the luminal diameter) or non-obstructive (plaque 25%–75% of luminal diameter). We excluded those with minor plaques (<25% of the luminal diameter) and systemic inflammation (eg, sepsis). The subjects were divided: (i) T2DM and obstructive CAD (n=26), (ii) T2DM and non-obstructive CAD (n=14), (iii) non-diabetic and obstructive CAD (n=30) and (iv) non-diabetic and non-obstructive CAD (n=10). BT was measured by the ex-vivo Badimon chamber as total thrombus area. Cytokines and platelet activation markers were measured.

Results All baseline cardiovascular risk factors were similar between groups (p>0.05). BT was higher in T2DM than in those without (22 481±12 336 vs 14 650±8074, p=0.024). When stratified according to CAD status, BT was highest in those with T2DM and non-obstructive CAD (p=0.002, ANOVA F=5.26) (Abstract 113 figure 1). Inflammatory cytokines TNF α (p=0.018, ANOVA F=3.15) and interleukin 6 (p=0.031, ANOVA F=5.0) and platelet activation as measured by P selectin were highest in this group. (p=0.022, ANOVA F=3.422) (Abstract 113 figure 2). Interleukin 1, interferon γ and soluble CD40 ligand levels were similar between the groups.



Abstract 113 Figure 2 Patients are grouped according to their diabetic status and coronary lesion characteristics. One way ANOVA for IL-6 F=5.006,p=0.03, TNF α F=3.153, p=0.03, P-selectin F=3.44, p=0.02, post hoc tests including Bonferroni showed t p<0.05 for multiple comparisions between T2DM+Non obstructive CAD group and the rest.

Conclusion Patients with T2DM and non-obstructive CAD had highest BT and markers of platelet activation and inflammation. These findings suggest biochemical changes also play a significant role in evolution of NSTE-ACS in T2DM. A causal link, if confirmed by large-scale studies may offer us an opportunity to identify therapeutic targets like individualised anti thrombotic therapy and anti inflammatory therapy in this high risk population.

114 WHOLE GENOME SEQUENCING TO IDENTIFY GENETIC VARIANTS UNDERLYING CARDIOVASCULAR DISEASE AMONG INDIAN ASIANS

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Introduction Indian Asians have a twofold higher risk of cardiovascular disease compared to Europeans which is not explained by conventional cardiovascular risk factors or known genetic variants. The genetic architecture of Indian Asians has not previously been described. We hypothesised that whole genome sequencing of Indian Asians may identify both common and rare variants specific to this population that contribute to their increased cardiovascular disease risk.

Methods We carried out whole genome sequencing (mean depth 28.4×) in eight men of Indian Asian origin participating in the London Life Sciences Population (LOLIPOP) study. Sequencing was carried out using paired end and mate pair libraries on an Illumina GA2 machine. Read alignment was done by BWA, and variants called using GATK and SAMtools. Sensitivity for single nucleotide polymorphism (SNP) detection was assessed by comparison to whole genome data.

Results We identified 6 602 840 autosomal variants, 436 823 of which are novel SNPs. Of these, 50 585 appear to be common (present at least twice, corresponding to minor allele frequency >10%). We found 21 659 autosomal SNPs that were expected to affect protein coding, of which 2174 are novel. Among the coding SNPs identified, 145 are in genes linked to human diseases, such as obesity (FTO, UCP1), diabetes mellitus (CDKAL1, GCGR, HNF1B), lipid metabolism (APOB), hypertension (NOS2), and renal disease (NPHP4, PKD1). We also found 65 613 novel autosomal indels of which 35 097 are present at least twice, and 2301 novel deletions >100 bp. We show that >50% of the novel genetic variants are not in high LD (r2¡Ý0.8) with tag SNPs and hence not captured on available high-density microarrays.

Conclusions We identify more than 500 000 genetic variants not previously reported in 1000 genomes or dbSNP, and likely to be Indian Asian specific. The novel variants identified here are strong candidates for genetic factors underlying the increased risk of diabetes and cardiovascular disease among Indian Asians.

115 UNIQUE CHARACTERISTICS OF CD14++CD16+ MONOCYTES IN PATIENTS WITH ACUTE HEART FAILURE AND IMPLICATIONS FOR CLINICAL OUTCOME

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Background Monocytes play important roles in inflammation, angiogenesis and tissue repair and may contribute to the