Association of plasma FAS-APO1 concentrations with left ventricular mass index in Black African hypertensive patients

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Background: Systemic hypertension induces pressure overload of the left ventricle and is the commonest cause worldwide for heart failure. Changes that occur in the myocardium in pressure overload states are difficult to measure directly. Fas-Apo1 is a marker of apoptosis. We investigated the relationship between plasma concentrations of Fas-Apo1 and left ventricular mass index (LVMI) in patients of African ancestry with moderate to severe hypertension.

Methods: 148 Black African patients with moderate to severe hypertension (age=53±10yrs, 56% females) and 31 normotensive controls without left ventricular hypertrophy (LVH), (age=42.6 ±8.9 years, 51.6% females) were studied. Treated patients had a two-week wash-out period before measurements. LVMI was calculated using echocardiography by the formula of Devereaux. Plasma Fas-Apo1 was measured using an isotopic quantitative immunoassay. Values are expressed as mean + SD or median (range) for Fas-Apo1 and comparisons made using a t test. Correlation between LVMI and Fas-Apo1 was performed using the Spearman test.

Results: LVMI in the control group was 87+18 and in the hypertensives 127+43g/m2 ($p<0.001$). Median Fas-Apo1 (pg/ml) was higher in the hypertensive group than controls (23.5[6.75-94] vs. 17[8.3-52.4], $p<0.003$). There was a significant correlation between LVMI and Fas-Apo1 ($r=0.2$, $p<0.02$).

Conclusion: (1) Fas-Apo1 is elevated in Black hypertensive patients with increased left ventricular mass index providing evidence for excessive apoptosis. (2) These results suggest that the processes of LVH and apoptosis occur concurrently in patients with hypertension and support the role for apoptosis in the transition from hypertension to heart failure.

How common is asymptomatic coronary atherosclerosis in Black patients with systemic hypertension? An analysis using myocardial perfusion imaging

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Background: Hypertension is an important risk factor for the development of atherosclerotic coronary artery disease, especially in Western populations where it clusters with other risk factors including dyslipidemia, obesity and impaired glucose tolerance. The prevalence of asymptomatic coronary artery disease in Black hypertensives is unknown.

Aim: We therefore sought to evaluate the prevalence of coronary artery disease in a group of asymptomatic Black hypertensive patients using myocardial perfusion imaging.

Methods: Gated myocardial perfusion imaging using Sestamibi was performed in 50 Black patients (23 females, 46%) with hypertension and no symptoms or prior history of coronary disease using either exercise or Persantin induced stress. All studies were reviewed by a single experienced nuclear physician blinded to all clinical data. Information on fixed defects indicating myocardial infarction (MI), reversible defects indicating myocardial ischemia, rest and stressed induced ejection fraction (EF) and wall thickness was obtained. Data are presented as mean ± standard deviation.

Results: Office BP was 162 (±26) /105(±16) mm of Hg, and ambulatory blood pressure monitor (ABPM) 24 hours was 164 (±15) /103(±8) mm of Hg. Total cholesterol (Tc) levels were 5.0(±), low density lipoprotein (LDL) cholesterol levels were 3.0(±1). Mean high density lipoprotein (HDL) levels were 1.0. 10% (n=5) of patients were diabetic and 30% (n=15) were smokers.

Myocardial perfusion imaging showed evidence of previous infarction in 6% (n=3) of patients, reversible ischemia in 6% (n=3) of patients and the combined endpoint (infarction or ischemia) in 12% (n=6). Mean left ventricular ejection fraction at rest was 51% and 50% during stress. Wall thickness (LVH) was 44% (n=22).

Conclusion: Asymptomatic coronary artery disease appears to be not infrequent in Black patients with systemic hypertension, contrary to common perception. These findings have important implications for the diagnosis and management of coronary atherosclerosis in Black patients with systemic hypertension.

Progression from hypertension to heart failure is associated with incremental rise in NT-pro-BNP

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Objective: To determine the relationship between progressive left ventricular (LV) remodelling in patients with moderate to severe hypertension (HT) and plasma NT-pro-BNP.

Design and Methods: A single-centre study of 176 Black African patients (53% female, age = 53.1±10.1 years) with moderate-to-severe HT was performed. Using echocardiography, patients were grouped as follows: (1) HT with no LV remodelling (2) HT with left ventricular hypertrophy (LVH) but normal systolic function (3) HT with systolic LV impairment. All measurements were made using standard American Society of Echocardiography definitions. Low ejection fraction (EF) was defined as < 50% using the Simpsons method, LVH as LV mass index > 120g/m² in males and > 100g/m² in females. HT was defined as systolic or diastolic daytime ambulatory BP (ABPM) > 140mmHg or 95mmHg respectively. Plasma NT-pro-BNP was measured using immunoassay. 33 normotensive age and sex matched patients were used as controls. Values are expressed as mean + SD for all variables except BNP (median and range) and comparisons made using ANOVA.

Results: There were 65, 85 and 26 patients in the 3 groups respectively. 24Hr ABPM in the control and 3 groups were 119±10/73±8, 156±12/99±7, 165±18/103±10 and 163±16/103±10mmHg respectively ($p<0.005$ for controls vs. all and <0.05 for (1) vs. (2) and (3). EF was significantly lower in group (3) vs. the others: 62±9% (controls), 66±10 (1), 62±7 (2) and 38±8% (3). There was a significant and graded rise in BNP (ng/l) from controls to group (3): C 57 (84-351), (1) 65 (13-652), (2) 108 (12-7825), (3) 246 (6-10277), $P < 0.0001$ for all comparisons.

Conclusions: (1) There is a significant and progressive rise in NT-pro-BNP concentrations across the entire spectrum from HT with no remodelling to end stage heart failure. (2) These data support the concept of progressive adverse remodelling of the LV in the pathogenesis of hypertensive heart disease.

Transcriptional Regulation of Cardiac Acetyl-Coenzyme A Carboxylase Gene by Nuclear Respiratory Factor-1

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Introduction: Nuclear respiratory factor-1 (NRF-1) is a pivotal transcriptional modulator controlling the expression of nuclear genes encoding mitochondrial proteins. Activation of 5'-AMP-activated protein kinase (AMPK) has been associated with enhanced NRF-1 gene promoter binding activity. Furthermore, NRF-1 has been linked with increased gene expression of carnitine palmitoyltransferase-1 (CPT-1), the rate-limiting mitochondrial fatty acid transfer enzyme. Upstream, the cardiac-enriched isoform of acetyl-CoA carboxylase (ACCβ) synthesises malonyl-CoA, a potent inhibitor of CPT-1 and fatty acid β-oxidation. Since ACCβ induction elevates malonyl-CoA levels, we hypothesised that NRF-1 inhibits ACCβ expression via AMPK activation to eventually increase cardiac fatty acid β-oxidation.

Methods: A 1,317 bp human ACCβ promoter-luciferase construct (pPIIβ-1317-Luc) was transiently transfected into rat neonatal cardiomyocytes ± the following expression constructs: NRF-1, dominant negative NRF-1 (dnNRF-1), and upstream stimulatory factor 1 (USF1) - a transactivator of the human ACCβ gene promoter. To activate AMPK, the transfected cardiomyocytes were treated with AICAR for 24 hours. In addition, the effect of NRF-1 on endogenous USF1 transcriptional activity was investigated by transfecting the cardiomyocytes with a luciferase construct containing multiple USF1-specific enhancer elements.

Results: NRF-1 overexpression reduced ACCβ gene promoter activity by 56±88% ($p<0.001$), an effect reversed by cotransfection with the dnNRF-1 construct. Addition of AICAR dose-dependently decreased ACCβ gene promoter activity ($p<0.05$). However, NRF-1 attenuation of ACCβ gene promoter activity was not altered by AICAR treatment. NRF-1 blunted the USF1-dependent upregulation of ACCβ gene promoter activity by 58±7.5% ($p<0.001$). This effect was abolished with the dnNRF-1 construct. NRF-1 reduced endogenous USF1 transcriptional activity by 55±6.2% ($p<0.001$). Cotransfection with the dnNRF1 construct abrogated this effect. Moreover, the NRF-1-dependent decrease of endogenous USF1 transcriptional activity was independent of AMPK activation with AICAR.

Conclusion: Our data reveal a unique, inhibitory role for NRF-1 in the transcriptional regulation of human ACCβ gene in the mammalian heart, independent of AMPK activation.

Fifteen years of Transcatheter Closure of patent ductus arteriosus in children at Chris Hani Baragwanath Hospital

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Introduction: Patent ductus arteriosus (PDA) is a common congenital heart lesion with isolated PDAs accounting for between 6-11% of all congenital heart defects. PDAs are relatively easy to diagnose, and as new devices become available, the majority can be safely and effectively closed without surgery, preventing not only the complications of the PDA itself but also the morbidity associated with surgery. There are, however, few reports of transcatheter closure of PDAs in the Southern African setting.

Methods: A retrospective analysis was performed on all children who underwent a transcatheter PDA closure at the Chris Hani Baragwanath Hospital, Soweto between 01/01/1993 and 30/06/2008 (15 years). Data such as patient demographics, device used, outcome and complications of procedure, hemodynamic data and ductal anatomy was sourced from patient files and the Pediatric Cardiac computerized database.

Results: Two-thirds of the 138 patients were female (66.0%; 91/138). The median age was 1.8 years (interquartile range = 1.1-4.6 years) and 10.4% (14/135) were older than 8 years. The COOK Flipper coil was used throughout the study period in a total of 76 children. Amplatzer PDA devices became available in 2003 and have become the more commonly used device, accounting for 91% (42/51) of PDAs closed since 2006. Over time the proportion of patients requiring both surgery and transcatheter procedures has decreased: 23% from 1993-2002 (11/47); 5% from 2003-2005 (2/37); and 2% from 2006 onwards (1/51; P=0.001). The waiting time for percutaneous PDA closure has also decreased in the last 2 years. The time from diagnosis to procedure decreased from a median of 15.9 weeks to 6.3 weeks (P=0.15), since 2006.

Conclusion: The trend in transcatheter closure of PDAs at Chris Hani Baragwanath Hospital has changed over the study period with the introduction of newer devices. In addition, the need for surgery to treat failed procedures has become less with the introduction of the Amplatzer device, which seems to offer a more effective closure of the PDA.

An unusual case of intrapericardial rhabdomyoma presenting in the neonatal period

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A 2.8 kg term newborn presented with severe respiratory distress requiring intubation and ventilation soon after birth. An antenatal ultrasound diagnosis of pericardial effusion and "mass close to the heart" had been made.

Marked cardiomegaly was present on chest X-ray. An echocardiogram demonstrated a large homogenous intrapericardial mass adjacent to the left ventricle with a significant pericardial effusion. No features suggesting tamponade were present.

A CT angiogram was performed and confirmed the echocardiographic findings.

ECG was abnormal with wide QRS complexes, ST segment depression and t-wave inversion in the inferolateral leads.

The patient was taken to theatre where the pericardial fluid was evacuated. The mass was inspected and was found to be solid, adherent to the myocardium and unresectable. A biopsy was performed before returning the patient to the intensive care unit. This confirmed the diagnosis of rhabdomyoma.

There was no family history of tuberous sclerosis and no features of this condition were present in the patient.

The child made a complete recovery and was discharged home a week later. A small pericardial effusion remained and did not progress. Follow-up over a ten-month period was uneventful with no change in the tumour size and no symptoms.

Intrapericardial tumours are rare, with teratomas being most frequently described in the neonatal period. While rhabdomyomas are the most frequently found cardiac tumours in the pediatric population and can be found anywhere in the heart, intrapericardial rhabdomyomas are rarely described.

The pediatric patient in an adult ICU

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Introduction: An audit by Bhagwanjee & Scribante (2007) on critical care resources in South Africa revealed that there were very few beds dedicated to pediatric and neonatal ICU patients (19.6%) for both public and private sectors. Only 3.8% of nurses were trained as neonatal ICU nurses. Therefore most pediatric patients were found in adult ICUs nursed by adult ICU trained nurses.

Bias towards adult care in ICU: While children may experience similar health problems to adults they are assessed and managed differently. Most health care facilities are built around the needs of adults and lack staff trained specifically for pediatric care, pediatric care protocols, and pediatric safeguards. Indeed literature shows that the potential for adverse drugs effects within the pediatric inpatient population is about three times as high as among hospitalized adults. Hence health care providers are urged to pay special attention relating to the pediatric population, especially in ICU, where the treatment modalities are multiple and/or clustered.

Challenges with Pediatric patients in ICU: The temptation may be to regard children as "small adults", yet children differ anatomically, physiologically, psychologically and emotionally. Most laboratory values, medications, blood product dosages and methods of administration and other therapeutic modalities differ from those used with adults. Their immune system is not fully developed, yet ICU stay is associated with reduced immune system of patients, even in adults, due to multiple invasive procedures, delayed enteral feeding and indigenous organisms in ICU. Developing hepatic and renal functions may not tolerate the multiple drugs in ICU. Children cannot understand their circumstances nor can they express experience of pain. Therefore someone must be able to recognize subtle changes in these children. Could this be a vigilant ICU nurse, or the parent for that matter? The aim of this presentation is to discuss strategies to reduce error with pediatric patients in ICU.

Conclusion: Evidence on outcomes of pediatric care in adult ICU versus dedicated pediatric ICU should be pursued. A dedicated pediatric ICU course should be implemented, thanks to the new approved qualifications by SANC.

Sarcomeric modifiers of hypertrophy in hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is an autosomal dominantly inherited cardiac disorder characterized by myocyte disarray, fibrosis, an increased risk of sudden cardiac death (SCD) and left ventricular hypertrophy (LVH). HCM thus serves as a model for the investigation of LVH, a symptom that is the strongest predictor of morbidity and mortality after age itself. Interestingly, the degree and pattern of LVH in HCM patients shows a large degree of variation even in patients with the same HCM-causing mutation.

Candidate modifiers include genes encoding proteins involved in contractility of the cardiac sarcomere, as well as sarcomere-associated metabolic enzymes involved with control of energy homeostasis. Due to its role in cellular energetics, muscle-type kinase (MM-CK), a member of the creatine kinase (CK) isoenzyme family, is considered a probable candidate modifier. MM-CK interacts with the M-band of the sarcomere and there it functions as ATP-regenerator. This study investigated four single nucleotide polymorphisms (SNPs) in the creatine kinase, muscle (CKM) gene. A total of 227 individuals, belonging to 22 HCM families with known founder HCM-causing mutations, were genotyped.

Three of the CKM gene SNPs investigated indicated association with a hypertrophic trait, independent of blood pressure. The data suggests that CKM plays a role in augmenting the extent of hypertrophy in HCM. The research thus offers insight into the factors that modify hypertrophy and highlights the potential for future therapeutic intervention studies.

Long QT syndrome type 1 (LQT1): Neural control of heart rate is a modifier of risk

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Introduction: Some long QT syndrome (LQTS) patients experience life-threatening attacks of cardiac arrhythmias, whereas others remain asymptomatic throughout life. This clinical heterogeneity is currently unexplained. We previously showed on ECGs obtained under a variety of conditions from persons afflicted with LQT1 that relatively low heart rates equated with lower risk of attacks. The aim of this study was to test the hypothesis that differences in autonomic responses might modify clinical severity LQT1 patients with a KCNQ1 mutation A341V with reduced I(Ks). The main arrhythmia trigger in LQT1 is sympathetic activation.

Methods: Mutation carriers (MCs) were stratified into those who had major cardiac events (symptomatic) and an asymptomatic group. The groups were compared with respect to resting heart rate (HR) and to baroreflex sensitivity (BRS) on and off beta-adrenergic blockers (BB).

Results: In 56 MCs, mean HR was lower among asymptomatic patients ($p < 0.05$). Among MCs with a QT interval corrected for heart rate <500 ms, those in the lower HR tertile were less likely to have suffered prior cardiac events (odds ratio [OR] 0.19, 95% confidence interval [CI] 0.04 to 0.79, $p < 0.02$). The BRS was lower among asymptomatic than symptomatic MCs (11.8 +/- 3.5 ms/mm Hg vs. 20.1 +/- 10.9 ms/mm Hg, $p < 0.05$). A BRS in the lower tertile was associated with a lower probability of being symptomatic (OR 0.13, 95% CI 0.02 to 0.96, $p < 0.05$). A similar trend was observed during evaluation on BB. The MCs in the lower tertile for both HR and BRS were less frequently symptomatic than MCs with different patterns (20% vs. 76%, $p < 0.05$).

Conclusions: Lower resting HR and "relatively low" BRS, a "blunted" BRS, are protective factors in KCNQ1-A341V carriers. This runs counter to findings in post MI subjects where an increased BRS was associated with less risk of sudden cardiac death. A plausible underlying mechanism is that blunted autonomic responses prevent rapid HR changes which could be arrhythmogenic when I(Ks) current is reduced. These findings help understanding of the phenotypic heterogeneity in LQTS and identify a physiological risk modifier. Different arrhythmogenic substrates in LQT1 vs. that in a post myocardial infarction phenotype react differently to autonomic influences.

Risk factor profiles in South African patients with hypertrophic cardiomyopathy caused by distinct founder mutations

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Introduction: Implantable cardioverter defibrillators are increasingly used to prevent sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) patients deemed to be at high risk. Risk stratification assesses a number of factors, including a family history of SCDs, unexplained syncope, non-sustained ventricular tachycardia on Holter ECG, maximal left ventricular wall thickness (mLVWT) >30mm and abnormal blood pressure response during exercise testing. Early genetic studies also suggested that correlations exist between mutations and survival. The aim of this study was to compare risk factor profiles between three South African HCM founder mutation groups, to assess whether genotype correlated with the clinical risk profile.

Methods: Twenty-one South African families in which one of three HCM founder mutations segregated participated in this study. Thirty R92WTNNT2, 24 R403WMYH7, and 27 A797TMYH7 HCM mutation-bearing individuals as well as 67 of their non-carrier relatives were investigated with 2D and M-mode echocardiography and exercised under a modified Bruce protocol. Patient and family histories were obtained.

Results: Significantly more R92WTNNT2 individuals failed to increase systolic blood pressure by more than 20mmHg than did individuals from either the control or other mutation groups (p=0.015). R92WTNNT2 individuals also demonstrated more syncope (p=0.007) than did the control or other mutation groups. On the other hand, significantly more A797TMYH7 individuals demonstrated overt hypertrophy (mLVWT>30mm). Most SCDs occurred in R92WTNNT2 families, while A797TMYH7 families suffered more SCDs than R403WMYH7 families.

Conclusion: Consistency between clinical risk factor profiles and genotype underlying SCD could not be detected.

Slower heart rates associated with lower risk of serious arrhythmic attacks in Long QT syndrome type 1 (LQT1)

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Introduction: In the congenital long-QT syndrome (LQTS), there can be a marked heterogeneity for risk of attacks, namely syncope, cardiac arrest, or LQTS-related sudden cardiac death (SCD). Founder effects, by which many individuals share a mutation identical by descent, represent a tool to further understand the underlying mechanisms as, the mutation being the major cause, questions can be asked about what other factors influence risk of attacks. We are investigating one such founder effect, originating in South Africa in approximately AD 1700 and segregating the same KCNQ1 mutation (A341V). We investigated the hypothesis that heart rate may predict risk of attacks.

Methods: Heart rate (HR) was compared between asymptomatic and symptomatic subjects. Persons were only regarded as asymptomatic if they were older than 15 years and had no attacks. The group was also stratified into those with a QTc either below or above 500ms, as QTc ≥ 500ms has been associated with a greatly increased risk of attacks. Heart rate was obtained from ECGs collected at a variety of localities by different medical personnel.

Results: Of 166 mutation carriers (MCs) ECGs were available for age ≥15 in 86 cases (64 symptomatic; 22 asymptomatic) in absence of beta blocker therapy. MCs had a wide range of QTc values (406 to 676 ms), and 12% of individuals had a normal QTc (≤440 ms). A QTc >500 ms was associated with increased risk for cardiac events (OR_4.22; 95% CI, 1.12 to 15.80; P≤0.033). Nineteen of the 22 asymptomatic individuals clustered below 500ms. Furthermore, stratifying by heart rate 16 asymptomatic individuals clustered in the quadrant defined by QTc <500ms and <73 beats per minute. MCs with a heart rate <73 bpm were at significantly lower risk (OR=0.23; 95% CI, 0.06 to 0.86; P≤0.035).

Conclusion: The availability of an extended kindred with a common mutation allowed us to identify heart rate, an autonomic marker, as a novel risk factor.

Unusual Clinical Severity of Congenital Long-QT Syndrome (LQTS) associated with the KCNQ1 A341V mutation

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Introduction: The lifetime risk of attacks, namely syncope, cardiac arrest, or LQTS-related sudden cardiac death (SCD) is approximately 30% and age at first attack, circumstances precipitating attacks and severity of disease may further be influenced by the gene involved. In long QT syndrome type 1 (LQT1) caused by mutations in the KCNQ1 gene, risk can also be influenced by the mutation and the position of the mutation within the gene and whether the mutation has a dose effect or a dominant negative effect. Our aim was to compare the clinical pattern of persons with this mutation to other LQT1 mutations in the KCNQ1 gene and to explain our finding by cellular electrophysiological studies.

Methods: We genotyped 320 subjects [166 mutation carriers (MC), 154 non mutation carriers (NMC)]. The pattern of attacks was compared to the NMCs and to information on LQT1 individuals in an international database. Mutant KCNQ1 plasmids constructs were made with three mutations (A341V, G314S and 543 del/ins) and were expressed in a Chinese hamster ovary cell line (CHO). Whole-cell currents (IKs) were measured by the patch-clamp technique.

Results: A341V MCs are more symptomatic by age 40 years (79% versus 30%) and become symptomatic earlier (7.4 versus 13.9 years, both $P<0.001$) compared to the international LQT1 database. None of the control NMCs had attacks. In functional studies of KCNQ1-A341V the magnitude of IKs in the CHO cells co-expressing KCNQ1-A341V were reduced by approximately 50%. By comparison, co-expression of a recessive LQTS mutant (543-del/ins) had no effect on IKs amplitude, whereas a strong dominant LQTS mutation (G314S) suppressed current by approximately 70% at positive voltages. These results demonstrate that KCNQ1-A341V exerts dominant suppression of IKs to an extent slightly less than a strong dominant mutation but behaves in a manner distinct from a pure loss-of-function allele as previously suggested.

Conclusions: KCNQ1-A341V is associated with unusually severe phenotype than that reported for large databases of LQT1 patients. This may be partially explained by it having a dominant negative effect and not a dose effect as had been previously reported. Studies subsequent to this in LQT1 individuals from other ethnic backgrounds have confirmed the severity to be intrinsic to the mutation and unlikely due to something specific in our population.

Dilatable pulmonary artery banding in infants with low birthweight or complex congenital heart disease allows avoidance or postponement of subsequent surgery

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Objectives: Banding of the pulmonary artery remains good early palliation in low-weight or complex congenital heart disease neonates. A fixed band needs to be removed surgically when the patient outgrows his pulmonary blood flow. We evaluated the efficiency and safety of dilatable bands in order to avoid or postpone further surgery.

Methods: 2 types of "handmade" bands were evaluated:

Group I: isolated pulmonary trunk: non-resorbable nylon 2 mm cord around PA, ends sewn together with polypropylene 6.0; ends of nylon cord folded back and fixed with 3 vascular staples - this design allows a "dilatable" restriction;

Group II: branch pulmonary artery during hybrid procedure (stent duct & bilateral banding): open ring of 3.0 – 4.0 mm Gore-Tex re-closed with one 7.0 polypropylene stitch - this design allows a "breakable" band.

Balloon dilatation was done with high-pressure non-compliant balloons, starting with a small diameter and increasing until desired result was achieved.

Patients & Results: Balloon angioplasty was performed in 19 patients (median birth weight 2.9 kg range: 1.25 – 4.5):
Group I palliation: 5 patients: large VSD or complex CHD requiring additional surgery. Progressive dilation after 22 (3-59) weeks allowed postponement of surgery.
Group I relief: 8 patients: large VSD ± coarctation. Spontaneous restriction of VSD occurred in 6 patients, band became redundant and was blown away after median of 39 (7-91) weeks. There was a decrease in median pulmonary artery gradient from 90 mm Hg to 38 mm Hg ($p<0.0001$).
Group II palliation: 4 pts: hybrid procedure. In 1 pt (BW 1.6 kg) dilation after 8.7 weeks with 3.5 mm balloon resulted in high flow, requiring rebanding; in 3 other patients balloon dilation with a balloon ratio of 1-1.3 after 10-19 weeks gave a 6,5% increase in saturations and allowed postponement of stage II Norwood.
Group II relief: 1 pt: hybrid procedure for critical AS and borderline LV; proceeded to successful percutaneous biventricular repair with closure of duct and balloon dilatation(8mm) with relief of bands as final procedure.
Conclusions: A dilatable band is an attractive alternative in well selected patients. The "dilatable" design with staples allows for predictable progressive dilation from early on. In this series the "breakable" designs resulted in unrestrictive flow when dilated < 9 weeks; after 10 weeks sufficient restriction persisted.

Hybrid Approach as Bridge to Biventricular Repair in a Neonate with Critical Aortic Stenosis and Borderline Left Ventricle

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Introduction: Critical neonatal aortic stenosis remains a difficult condition to manage. Small left ventricular size, poor left ventricular function and the presence of endocardial fibro-elastosis are all associated with higher morbidity and mortality.
Methods: A 4.2kg newborn of a mother with poorly controlled insulin-dependent diabetes mellitus presented with poor circulation and critical aortic stenosis. Initial balloon dilatation was successful, but the infant tolerated biventricular circulation poorly due to small left ventricular volume and the development of significant pulmonary hypertension. Our clinical impression was that the strategy at that stage would lead to irreversible pulmonary hypertension and a single ventricle hybrid approach was decided upon. This strategy would buy some time and allow the left ventricle potential to grow.
Report: At day 25 the infant was taken to the catheterization laboratory where a Rashkind was performed and the duct stented. This was followed by the placement of 4mm dilatable Goretex bands on the left and right pulmonary arteries. At 8 months of age, test occlusion of the ductus and interatrial septum indicated that biventricular repair was possible. The bands were progressively dilated to 8mm and the ductus closed with a 4/6 Amplatzer ductal occluder and an 8mm Amplatzer vascular occlusion device. At three years of age he is doing well with a biventricular circulation and small residual interatrial shunt.
Conclusion: This case highlights the fact that the hybrid procedure may be considered in neonates with borderline left hearts as a bridge to possible biventricular repair allowing the clinician several months to make a decision for single of biventricular repair. It also demonstrates that biventricular repair may be achieved by percutaneous intervention, avoiding further surgery.

Perforations of the Aortic sinuses by the Atriasept percutaneous atrial septal defect occluder

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Introduction: Percutaneous atrial septal defect closure (ASD) has become a routine procedure. The Atriasept device is a double disc device with nitinol struts. Initial studies showed good closure rates with no significant complications.

Methods: Case report of 2 asymptomatic patients: 14-year-old female presenting with second ASD for closure and 10-year-old male with suspicious transthoracic echocardiogram.

Report: Transesophageal echocardiography indicated protrusion of a left-sided strut into right and non-coronary sinuses of the aorta respectively. Real-time fluoroscopy clearly showed out-of-phase movement of one arm of the device. Angiographic views in orthogonal planes also showed fracture and absence of the circumferential wire. The device was removed in patient 1.

Conclusion: Serious complications occur in 0.1-0.3% of all percutaneous ASD closure devices. Patients in whom Atriasept devices have been used to close secundum ASDs should be closely monitored for fracture of the outer ring associated with perforation of adjacent cardiac structures. Diagnosis requires TEE and/or fluoroscopy.

Premature fetal closure of the arterial duct: clinical presentations and outcome

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Introduction: Intra-uterine dysfunction of the ductus arteriosus occurs, but the incidence and clinical consequences are poorly understood. This study was set to investigate the echocardiographic abnormalities and outcomes of this phenomenon.

Patients and methods: Retrospective analysis of fetal (n = 602) and neonatal echocardiographic databases (n = 1477) between 1998 and 2007. Clinical and imaging studies were reviewed for pathology due to or associated with premature closure of the duct.

Results: Twelve cases were identified. Eight (1.3%) were diagnosed prenatally at a median gestational age of 29.0 weeks (range: 20.0 – 37.5 w). Four neonates (0.3%) were also included: all presented at birth with significant cyanosis and absence of the arterial duct. Echocardiographic features were: right ventricular hypertrophy (n = 12), more than usual tricuspid regurgitation (n = 12) and pulmonary regurgitation (n = 11), and right atrial dilation (n = 8). Other notable findings were pulmonary artery dilation in 42%, dysplastic pulmonary valve in 25% and hydrops in 8%. Premature delivery was advised for 5 patients. Neonatal therapy consisted of observation and oxygen administration in 7, ventilation with pulmonary vasodilators in 5, of which one required extracorporeal membrane oxygenation (ECMO). Respiratory failure with severe pulmonary hypertension was the cause of death in 3 neonates. During follow-up two children required additional right heart procedures and one developed a non-compaction cardiomyopathy at the age of 4 years.

Conclusion: The incidence of ductal dysfunction may be grossly underestimated. Fetal premature closure of the arterial duct causes stress at different fetal ages and many different levels of the right heart and pulmonary circulation, resulting in a wide range of secondary pathology. Clinical outcomes range from antenatal hydrops and right heart damage to lethal respiratory insufficiency. Premature delivery may be indicated in selected patients.

Transapical left ventricular access for difficult-to-reach interventional targets in the left heart

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Objective: Interventional targets may be virtually "excluded" due to vascular access problems or surgical procedures such as prosthetic valves or Fontan circuits. This study reviews our experience using transapical left ventricular puncture to gain direct access to the systemic ventricle.
Patients: Patient 1 (74y, 2 previous sternotomies) and patient 2 (66y, 5 previous sternotomies) with prosthetic valves presented with a paravalvular mitral valve leak. Patient 3 (6.3y, 2 previous sternotomies) with a Fontan circuit for double inlet left ventricle, had significant residual leak after 2 previous surgical attempts of patch closure of a severely regurgitant right atrioventricular valve. Patient 4 (10mo) with tachycardia-induced cardiomyopathy had failed standard ablation of the posteroseptal region of the mitral valve with persistent life-threatening episodes of ventricular tachycardia.
Methods: Procedures were performed under general anesthesia. The apex was identified and punctured during short period of expiratory apnea to avoid lung puncture. Entry site was via the skin in three patients and in one a mini-thoracotomy was used. Sheaths were then placed (6Fr) using standard Seldinger technique, followed by the procedure as required. Direct surgical closure of the puncture site was done in 3 patients and in patient 3, a percutaneous vascular occlusion device (Prostar XL device, Perclose Europe, Berkshire, UK) was used.
Results: Easy and immediate access was obtained in all patients. The paravalvular leaks were crossed within seconds and closed with a 4mm and 8mm Amplatzer occluder (AGA Medical Corporation, Plymouth, MN, USA), respectively. In patient 3 the valve was crossed using a stiff end-hole instrument (Brokenbrough) and a 12mm Amplatzer device was placed. Patient 4 was successfully ablated using 7 Fr irrigated catheter endo- and epicardially. In one patient the coronary artery was punctured and in one a hemothorax developed.
Conclusion: Direct left ventricular puncture offers a very useful alternative access site in selected patients to reach "inaccessible" targets for certain percutaneous interventions in patients where standard approaches may be impossible or difficult. Complications occur, but are usually minor and can be minimized by careful attention to technique.

Variants in renin and renin-binding protein genes modify cardiac hypertrophy in hypertrophic cardiomyopathy patients, independent of blood pressure

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Hypertrophic cardiomyopathy (HCM), an inherited primary cardiac disorder mostly caused by defective sarcomeric proteins, is considered a model for studying left ventricular hypertrophy (LVH) in the absence of increased external loading conditions. The disease manifests extreme variability in the degree and pattern of LVH, even in HCM patients with the same causal mutation. The clinical phenotype of HCM can therefore be viewed as a product of the effect of sarcomere dysfunction and of additional genetic modifiers. Components of the renin-angiotensin-aldosterone system (RAAS) are plausible candidate modifiers because of their effect on blood pressure and their direct hypertrophic effect on cardiomyocytes. Although much attention has been paid to the role of ACE in LVH, the renin section of the RAAS pathway has not previously been investigated in HCM.
Here we investigated four Single Nucleotide Polymorphisms (SNPs) in the renin (REN) and three in the renin-binding protein (RENBP) genes for association with cardiac hypertrophy traits, in 353 individuals comprised of genetically and echocardiographically affected and unaffected family members, belonging to 22 HCM families with HCM founder mutations.
We found evidence for association of all three SNPs in RENBP and three of four SNPs in REN with one or more hypertrophic traits, including echocardiographically determined left ventricular mass and other wall-thickness measurements, independent of blood pressure and other known hypertrophy covariates ($p<0.05$).
We demonstrate for the first time that variations in the REN and RENBP genes play a role in modulating hypertrophy in HCM, independent of blood pressure. Both these genes are plausible modifiers for hypertrophy due to their functions within the RAAS: renin is a rate-limiting component of the RAAS as it controls the initial conversion of angiotensinogen to angiotensin I, while renin-binding protein inhibits renin activity. The identification of such modifiers for HCM may offer novel targets for anti-hypertrophic therapy.

Left Ventricular Dysfunction following Balloon Angioplasty for Pulmonary Valve Stenosis in a 12-year-old Child

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Introduction: We present an unusual case of a child who underwent balloon angioplasty of severe pulmonary stenosis complicated by pulmonary regurgitation which was followed by the development of left ventricular systolic dysfunction.

Case Report: This 12-year-old boy presented with normal left ventricular function, symptomatic severe valvar pulmonary stenosis with a peak-to-peak gradient of 134 mmHg and mild pulmonary regurgitation. He underwent a balloon angioplasty procedure with a balloon measuring 102% of the pulmonary valve diameter. An echocardiogram the following day showed the patient to have left ventricular dysfunction with an ejection fraction of 39%, complete relief of the pulmonary stenosis (peak-to-peak gradient 10mmHg), but with severe pulmonary regurgitation and volume overload of the right ventricle. The left ventricular dysfunction resolved over the next 12 months on oral digoxin and afterload reduction. He remains with moderate pulmonary regurgitation.

Discussion: The interdependence of the two ventricles in terms of the "Bernheim" and the "reversed Bernheim" effects is well described. A pressure overloaded as well as a volume overloaded right ventricle can result in both an underfilled left ventricle and a dysfunctional left ventricle. The coexistence of left ventricular systolic dysfunction and a volume overloaded right ventricle such as occurs in atrial septal defects, severe tricuspid regurgitation and Ebsteins's anomaly has been reported.

Conclusion: The mechanism for the left ventricular systolic dysfunction associated with volume overload such as occurred in our patient is not clear but may be as a consequence of acutely impaired septal-free wall shortening due to end-diastolic leftward ventricular displacement by the overloaded right ventricle.

A child with restrictive-constrictive disease: the diagnostic conundrum continues

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The combination of constrictive pericarditis and restrictive cardiomyopathy in the same patient is relatively rare, with few reports in the literature. This case report deals with such an example and lends itself to a greater appreciation of the pathophysiological mechanisms and diagnostic features operating between the two processes.

An 11-year-old girl with a background of fully treated pulmonary tuberculosis 8 years previously presented with features of acute rheumatic fever, severe mitral regurgitation and biventricular failure as well as a moderate pericardial effusion (PE). Over the course of 4 months, despite full therapy including cover for TB and corticosteroids, she manifested signs of a mixed restrictive cardiomyopathy-constrictive pericarditis with a refractory PE requiring three separate procedures for drainage - two surgical (with pericardial windows) and one percutaneous. Pericardial fluid chemistry, microbiology and cytology as well as histology of pericardial tissue were negative or non-specific on all occasions.

Cardiac catheterization was performed to obtain endomyocardial biopsies (also non-specific) and to further delineate the pathophysiology and hemodynamics as there were persistent features of a restrictive cardiomyopathy. This confirmed a mixed restrictive-constrictive picture. Due to the constrictive element she underwent a pericardial stripping procedure and direct right atrial biopsy which surprisingly showed endocardial fibroelastosis. Subsequently her PE resolved but she was left with residual severe mitral regurgitation and will likely require a repair or replacement in the near future. The etiology of her disease remains undefined.

We review the pathophysiology and diagnosis of restrictive versus constrictive disease and emphasize the importance of distinguishing between the two due to their significantly different management implications.

Diagnosis, treatment and outcome of acute heart failure in sub-Saharan Africa – preliminary results of the THESUS-HF project

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There is a general lack of data on etiology, treatment and outcome of acute heart failure in sub-Saharan Africa. The sub-Saharan Africa Survey of Heart Failure –THESUS-HF, is a simple registry of patients consecutively admitted to 8 university hospital centers in 5 sub-Saharan countries with Acute Heart Failure.

Patients were submitted to a base line and 7th day clinical and biochemistry evaluation and a bidimensional echocardiogram. Patients were followed for 6 months. The results of the first 80 patients are presented.

These 80 patients, 50% males and 98,8% blacks with a mean age of 51.2±17.9 years, had a previous history of hypertension on 40(50%), diabetes mellitus on 5(6.2%), ischemic heart disease on 4(5%), HIV on 7(8.9%). Mean length of hospitalization was 9.1 ± 6.0 days, 4(5%) patients died and 5 were readmitted in the first 60 days after admission. Serum sodium was 136.5 and 136.2 mmol/L, serum creatinine was 1.61 and 1.29 mg/dL and systolic blood pressure was 131.5 and 118.9 mmHg respectively on admission and on the seventh day. Mean ejection fraction evaluated by echocardiogram was 37.9%±16.6, mean left atrial area was 44.35±11.87 cm^2 and mean thickness of the inter-ventricular septum was 10.59 ± 2.90 mm. 64(80%) patients had systolic and 35(44%) had diastolic dysfunction. Hypertension was the main diagnostic in 32(40%), primary dilated cardiomyopathy on 17(21%), rheumatic heart disease on 8(10%), peripartum cardiomyopathy and acute pericarditis on 7(9%) patients each and ischemic heart disease in 5(6%) patients. On discharge day ACE inhibitors were prescribed to 82%, loop diuretics to 79%, betablockers to 43%, hidralazine to 1.3% and nitrates to 2.5% of the patients.

In conclusion, acute heart failure in sub-Saharan Africa appears at an earlier age and has hypertension as major risk factor and main diagnosis. Ischemic heart disease is still very uncommon.

Barth syndrome: how to (easily) find a needle in a haystack

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In early August 2008, a 2-year-old boy presented to the Red Cross Children's hospital in congestive cardiac failure due to severe dilated cardiomyopathy. His ejection fraction was less than 20%, with a small area of left ventricular noncompaction, and it was noted that he had failure to thrive, with skeletal muscle wasting. He was admitted to the intensive care unit, requiring ventilation and inotropic support to bring his heart failure under control. As part of the routine diagnostic workup for cardiomyopathy at Red Cross Hospital, an organic aciduria screen revealed evidence for excretion of 3-methylglutaconic acid and 3-methylglutaric acid. This clinical spectrum suggested a diagnosis of Barth syndrome.

Barth syndrome (BTHS; MIM302060) is an X-linked disorder manifesting with dilated cardiomyopathy, skeletal myopathy or weakness, failure to thrive and, occasionally, neutropenia and organic aciduria. At present this severely debilitating disorder is very rare (approximately 120 affected boys known internationally), but since the diverse phenotypic manifestations, other than the cardiomyopathy, are easily overlooked, it is probable that the disease remains under-diagnosed. As yet, only 2 South African boys, who are cousins, have been genetically confirmed to have Barth syndrome (De Decker and Harrisberg, SAHA Congress 2006). Acute and chronic cardiomyopathy are common presentations in pediatric cardiac practice, but a definitive etiological diagnosis is rarely reached. It has been shown that a confirmed diagnosis of BTHS increases the chances of survival to adulthood significantly, since management can be focused on the unique manifestations of the syndrome.

To detect BTHS, screening tests such as 3-methylglutaconic aciduria or demonstrating cyclical neutropenia have proven to be unreliable and nonspecific, and until recently, the diagnosis of BTHS has depended on the detection of a disease-causing mutation in the tafazzin gene - an arduous undertaking in South African patients. However, earlier this year a simple blood spot screening test was published (Kulik, W et al. 2008. Clinical Chemistry 54: 1) which has proven to be 100% sensitive and specific for BTHS. The test assays the ratio between monolysocardiolipin (MLCL) and cardiolipin (CL) in a 5mm drop of dried blood on filter paper (e.g. Guthrie cards). In collaboration with the Dutch team which has developed this screening test, we should now able to offer the test in South Africa.

The bloodspot test will be described, and we hope to be able to present the result of our patient's bloodspot MLCL/CL ratio at the time of the SAHA congress in November 2008.

The incidence of the 22q11.2 deletion syndrome in children referred to the cardiology service at the Red Cross Children's Hospital, Cape Town, South Africa: a prospective study

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Introduction: Previous estimates of the prevalence of the 22q11.2 deletion syndrome in a pediatric cardiac clinic population in South Africa (SAHA congress 2006) were based on a retrospective review of our experience with these patients at the Red Cross Children's Hospital, Cape Town. This prevalence, presumably based on the ability of clinicians to recognise the syndrome from clinical indices, had increased in 2006 to a peak of 1.8% of the new patients seen at this centre. This correlated well with a rate of 2% approximated from published 22q11.2 deletion syndrome prevalence rates and the known population birth incidence of congenital heart disease. However, since the syndrome exhibits marked phenotypic variability, we were concerned that the diagnosis may be missed in patients in whom the facial features were less recognisable. A confirmed diagnosis is essential for the optimum clinical management of these patients, as well as the genetic counselling of their parents.

Aims: (1) To determine the exact incidence of the 22q11.2 deletion syndrome in a cohort of patients with congenital heart disease presenting to a tertiary cardiology referral centre. (2) To assess the utility of an international scoring system for the clinical recognition of the 22q11.2 deletion syndrome in patients with congenital heart disease.

Methods: All "new patients" with a significant congenital cardiac lesion presenting to the cardiology service at the Red Cross Children's Hospital were assessed for recruitment to the study. The following categories of patients were excluded: (1) Neonates with an isolated patent ductus arteriosus. (2) Any child with an identifiable cardiogenetic syndrome other than the 22q11.2 deletion syndrome.

Parents of these patients were approached by a genetic counsellor for inclusion of their child into the study. Once consent was obtained, all children were tested for the 22q11.2 deletion by the standard TUPLE1 fluorescent-in-situ-hybridization (FISH) probe.

All children were assigned a clinical "O score" at presentation, derived from Oskarsdöttir et al. (2005). This was based on the presence of 8 phenotypic hallmarks and used to estimate the indication for TUPLE1 FISH testing. A score of 2 or more suggests the need for FISH testing.

Results: The study is an ongoing prospective investigation, and the current figures, given here, will be revised and re-presented at the congress. Since March 2008, to date 88 patients have been recruited and FISH tested; of these, 69 (78.4%) FISH tests have been reported, and 4 (5.8%) have been found to carry the deletion. The mean O score of these 4 positive patients on presentation was only 2.5 (range 2-3).

Conclusions: Preliminary results of this study suggest that the 22q11.2 deletion is more than twice as common in a referred cardiac population than previously anticipated. Clinical suspicion must remain high to ensure that the diagnosis is not missed in these patients. The utility of a phenotypic scoring system in our patient population is unconvincing and requires review.

The financial impact of surgical site infection reduction by using integuseal, a microbial sealant

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Introduction: Surgical site infection (SSI) remains a substantial cause of morbidity, which increases costs after cardiac surgery due to adequate treatment and prolonged hopitalization. This study was performed to evaluate the impact of a new microbial sealant on SSI as well as the resulting financial impact.

Methods: Between January 2006 and July 2008, 580 patients underwent cardiac surgery by a single surgeon at our institution. Patients were divided into two groups. The control group (n=280) received standard institutional preoperative preparation starting from January 2006 till February 2007. The InteguSeal group (n=300) received additionally to the standard institutional preparation this microbial sealant starting from February 2007 till July 2008. Pre- and peri-operative characteristics were evaluated for both groups including the SSI risk scores of Fowler. End-point of this study was freedom of superficial or deep SSI and the secondary costs resulting from SSI.

Results: Follow-up was complete. Comparing pre- and peri-operative characteristics of both groups, a significantly higher rate of carotid artery disease ($p<0.004$), diabetics ($p<0.011$), congestive heart failure ($p<0.009$), previous cardiac surgery ($p<0.001$) and bilateral internal mammary arteries ($p<0.002$) were seen at the InteguSeal group. A significantly higher rate of hyperlipidemia ($p<0.045$) however was seen at the control group. The preoperative risk score of the control and the InteguSeal group were respectively 10.6 ±4.7 and 11.0±4.5 ($p=0.293$).

The clinical end-point showed a significant decrease of SSI in the InteguSeal group 2.4% (n=7) versus the control group 6.7% (n=19), ($p<0.011$). The reduction of secondary costs by using the microbial sealant showed a saving of 305.000 Euro on billing the insurances, calculated by the Diagnosis Related Group (DRG) payment system.

Conclusions: InteguSeal not only reduces statistically significantly the risk for surgical site infection, but also decreases hospital costs. This has also a positive economical impact in patients undergoing cardiac surgery.

The effects of gender and obesity on myocardial tolerance to ischemia

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Introduction: The incidence of obesity in both men and women is increasing at an alarming rate throughout the world. Obesity, with its associated dyslipidemia, may lead to coronary artery disease and consequent myocardial ischemia. The effects of gender on myocardial tolerance to ischemia are of interest as it has been proposed that women are more resistant to ischemic damage than men. The effect of obesity on the apparent increased tolerance to ischemia in women is however unknown.

Aim: To determine whether female rats are more prone to obesity and how the obese female rats tolerate myocardial ischemia compared with age-matched obese male rats. We also wish to determine how circulating adiponectin, IL-6, estrogen, insulin, glucose and lipid levels were influenced by obesity in male and female rats.

Methods: Male and female Wistar rats were fed a high caloric diet (HCD) or a control diet for 18 weeks. Rats were fasted for 10 hours, anesthetized and blood was collected for biochemical analyses. In a separate series of animals, HCD and control diet fed rats underwent 45 minutes in vivo coronary artery ligation followed by 2 hours reperfusion. Hearts were stained with TTC and infarct size was determined.

Results: Both male (29±1.33g vs. 19±0.96, $p<0.001$) and female (21±1.18g vs. 10±1.25g, $p<0.001$) rats fed the HCD had elevated visceral fat content compared to control littermates. The HOMA index was increased in HCD fed male rats versus their control littermates (33.58±16.97 vs. 13.95±3.037, $p<0.01$) but not in the females (2.98±0.71 vs. 2.986±0.60). Male HCD fed rats had larger infarct sizes (43.2±19.3% vs. 24.4±7.8.6%, $p<0.05$) and females unchanged infarct sizes (31.8±4.3% vs. 23.9±3.26% $p>0.05$) compared with their control littermates.

Conclusions: Despite the increased body weight and visceral fat content in HCD fed female rats, they did not develop insulin resistance and were less prone to ischemic/reperfusion injury than their male counterparts.

Grown up congenital heart disease as done by one surgeon in Sudan

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Objectives and methodology: Grown up congenital heart (GUCH) disease has emerged as a new discipline in cardiac surgery. In the developed world it is predominantly patients who have had cardiac surgery for congenital heart disease in their childhood in the past and are now presenting in adulthood with related diseases. In developing countries it mainly manifests as patients with congenital heart disease who present for the first time in late life.

In this paper we look at GUCH patients as operated on by one adult cardiac surgeon in Sudan Heart Center (SHC).

Data from the operating room database and the patient files was used to fill a questionnaire which was then analyzed using SSP.

Results: From 01/02/2000 till 31/08/2007 in SHC one surgeon did 880 operations (670 open heart and 210 closed heart and others). Out of the 670 open heart 47 (7%) were GUCH cases.

The 47 GUCH cases age ranged from 16 to 80 and were 55% female. 25 (53%) of them were atrial septal defects. The others were subaortic membranes(8), Tetralogy of Fallots(4), partial atrioventricular defects(3), pulmonary stenosis(2) and one each was ventricular septal defect, ruptured coronary sinus, patent ductus arteriosus, supraaortic stenosis and complete atrioventricular canal defect. Their presentation will be detailed.

There were 4 (8.5%) early and 2 (4.3%) late mortalities in this group.

Conclusion: GUCH forms a part of the practice of any cardiac surgeon in the developing world and needs a concerted effort by the health authorities to curtail it.

Off-pump repair of anomalous right coronary artery arising from main pulmonary artery

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Introduction: Major coronary artery anomalies are being increasingly recognized with advances in diagnostic imaging. Unlike the more common anomalous origin of the left coronary artery from the pulmonary artery, anomalous right coronary artery from the main pulmonary artery (ARCAPA) is a rare and often an incidental finding.

Method/Result: One such case in a 25-year-old HIV positive woman presenting with an incidental finding of a heart murmur during pregnancy is presented. The bizarre and non-specific symptomatology, and the challenges of pre-operative diagnosis is highlighted.

Surgery was by off-pump separation of the anomalous coronary artery from the pulmonary artery and direct re-implantation onto the ascending aorta. The post operative course was uneventful.

Conclusion: A high index of suspicion in the presence of unexplained heart murmur and echocardiography by an experienced cardiologist establishes the diagnosis, which is confirmed by selective coronary angiography.

Off-pump repair is feasible and the result usually good.

The Psychologial Aspects following Myocardial Infarction

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Following a myocardial infarction, a patient and the family may experience a range of physical and psychological impairments. The most significant psychological morbidities for the patients are anxiety and depression. Anxiety after acute myocardial infarction is also associated with an increased risk of in-hospital complications such as lethal arrhythmias, ongoing myocardial ischemia and reinfarction. It is highly probable that the potential for post myocardial infarction related psychological distress continues as the transition to discharge home poses new problems. These can range from confusion, fear of dying, reduced quality of life and cognitive dysfunction. The process of adaptation and recovery is a struggle for the patient and family as both parties grapple with regaining control of their life situation.

Women appear to be at a higher risk for negative emotions than do men following a myocardial infarction. Studies have reported that women have anxiety levels higher than those of psychiatric patients. On the other end of the spectrum, some research has reported that men had a positive outlook following a myocardial infarction. The patients felt that that they had control over their health by altering and changing their lifestyle.

Irrespective of the research findings, almost all patients experience psychosocial problems within the first 6 months following discharge from hospital and this should be addressed in the discharge planning of such patients. Education of cardiac patients is not optimal and should be addressed in nursing curricula.

There is potential for nursing research in the South African context looking at the psychosocial aspects following a myocardial infarction. Is it the problems that these patients experience that lead to a need for information, or does the need for such information lead to problems?

A review of the practice of a staged approach for biventricular repair in Red Cross Children's Hospital over the past 6 years: Is the placement of a pulmonary artery band safer in perceived high risk cases?

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Introduction: Patients who are generally in a poor condition due to a cardiac defect that causes a large left to right shunt may be regarded as a high risk for cardiopulmonary bypass and definitive repair of their defect. In the belief that their surgical risk may be lowered and their condition optimized by reducing their lung blood flow, a pulmonary artery band (PAB) may be applied in the first instance. We tested this hypothesis by a review of our institutional experience with this approach over a six-year period.

Materials and Methods: This is a retrospective review of all patients that received a pulmonary artery band at Red Cross Children's Hospital during the period 1 January 2002 to 31 December 2007. Patients who underwent a pulmonary artery band with the aim to later achieve a biventricular repair were analyzed further. If the PAB was applied with a view to a univentricular repair, they were excluded. A standardized data collection sheet was used to retrieve relevant information.

Results: Of the 187 files that were reviewed retrospectively 144 had a PAB with a view to later achieving a biventricular repair, while 30 were excluded due to planned univentricular repair and 13 files were lost. The overall mortality for the 144 patients who underwent a PAB with the view to achieving biventricular repair was 24% (N = 35). Of the total number of deaths, 8% (N = 12) occurred in hospital, whilst 16% (N = 23) occurred after hospital discharge whilst awaiting definitive repair. In these cases the cause of death was not established. The PAB had to be revised in 5% (N = 7). Growth was assessed by a comparison of pre- and post-PAB weights and this information was available for 119 patients. Of these 52% (62/119) either did not increase in weight or lost weight. The mean weight at PA banding was 5.34 ± 2.94kg (range, 1.8 to 25kg). The mean time interval between PA banding and definitive repair was recorded as 21.79 ± 13.34 months. Interval hospital admissions were recorded in 83 (57.64%) patients between PAB and either definitive surgery or to date. The mean number of interval hospital admissions is 1.5 ± 1.98, the majority being due to respiratory tract infections. The mean ICU stay at PAB was 6.76 ± 14.91 days with a mean hospital stay of 21.10 ± 34.36 days.

At termination of the study 63 (64%) have not had definitive correction.

Conclusion: Despite an acceptable in-hospital mortality, the practice of deferring biventricular repair by the application of a pulmonary artery band carries such a high total mortality that consideration should be given to early definitive repair.

Early and intermediate results of replacing the mitral valve only by one surgeon in Sudan

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Mitral valve disease is the most common problem faced by cardiac surgeons in many developing countries. In this study we looked into the early, intermediate and late results of replacing the mitral valve only by one surgeon in one institute (Sudan Heart Center-SHC) since its inauguration in 01/02/2000 to 01/05/2007.

171 patients (53.2% female) were enrolled in the study with ages ranging from 9 to 80 years (mean age 33.94 and 59% of them within their second to third decades).

Dyspnea was the most common presentation in nearly all the patients, followed by palpitations (79.1%), followed by cough (47.4%) and then orthopnea and atrial fibrillation (34.5% each).

Almost half the patients were in Grade III of the New York Heart Association grading for dyspnea, one-third in Grade II and the remainder were distributed equally between Grades I and IV.

55% of the patients were mitral stenosis, 21.6% mitral regurgitation and 23.4% had both stenosis and regurgitation.

Deaths in the first 24 hours were 2.3%, in the first four weeks were 12.3% and late deaths after four weeks were 12.3%. 58.4% of all the alive patients had post-operative complications.

Mortality was found to be statistically higher in middle-aged patients and among females. Late presentation with severe symptoms, small mitral valve area and post-operative cardiac arrhythmia had a strong correlation with mortality.

Severer preoperative symptoms also correlate positively with increased risk of post-operative complications.

In conclusion, in the developing world we expect the situation to be the same as ours where more work needs to be done in the primary and secondary health arenas to allow patients to come to cardiac surgeons earlier to have a better outcome.

The identification of proteins which interact with KvLQT1: an experimental method for discovering novel candidate modifier genes

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Introduction: The Long QT Syndrome (LQTS) is a monogenic, inherited arrhythmic disorder displaying considerable clinical and genetic heterogeneity. We have used the unique resource of the South African LQTS founder families (Brink et al. Circulation. 2005; 112:2602-2610.) to investigate the role of ion channel encoding genes as candidate modifiers of this phenotype. However, we hypothesized that ion channels themselves may not be the only elements responsible for variability of the repolarization phenotype; proteins that modulate the function of ion channels may also play a role.

Methods: The yeast two-hybrid (Y2H) technique was employed as a method to identify interactors of the KCNQ1 encoded potassium channel protein, KvLQT1, to identify novel candidate genes. The cDNA encoding the C-terminal cytoplasmic region of KvLQT1 was cloned into a Y2H bait vector, which was subsequently used to screen a yeast cardiac cDNA library. Putative interactors were identified by increasingly stringent nutritional selection and specificity of interactions assessed by heterologous bait matings. Interactor clone sequences were identified by BLAST-comparisons against publicly available databases.

Results: Of the seven interactors of the carboxyl-terminal of KvLQT1 identified in this manner, two (PRKAR1A and SYNE1) were considered putative physiological interactors based on the plausibility of the interactions as assessed in silico. The interaction of KvLQT1 with PRKAR1A may indicate direct docking of PKA via its regulatory subunit to its phosphorylation target, KvLQT1, while the interaction of KvLQT1 with SYNE1 may reflect processes involved in transport and cellular membrane localization of KvLQT1.

Conclusion: As the South African LQTS founder families carry an A341V mutation in the KvLQT1 protein, these KvLQT1-interactors are plausible candidate modifier genes of the repolarization phenotype caused by the A341V mutation.

A first-in-man trial to determine the clinical safety of the Stellium drug-eluting stent in humans

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Introduction: Clinical research has shown that non-coated bare metal stents (BMS) are associated with a significant but variable risk of restenosis and repeat percutaneous coronary intervention (PCI). The development of drug-eluting stents (DES) has led to reduced restenosis, but has also led to concerns of late and very late thrombosis, potentially caused by suppression of stent coverage from the drug or long-term inflammation from durable polymers. The Stellium DES contains a Paclitaxel and PolyLactic-Glycolic Acid (PLGA) polymer coating. Even though Paclitaxel has demonstrated a profound ability to attenuate in-stent neointimal proliferation, the potency of the drug suggests there is a narrow window of dose and release rate in which the balance between safety and efficacy is achieved. This balance was explored in pre-clinical animal studies, which led to the development of the very low Paclitaxel dose of the Stellium (Jabara R et al. J Invasive Cardiol. 2006; 18:383-90). The PLGA coating is fully erodible, which avoids long-term drug leaching and healing inhibition. The Stellium 1 study is a small single-arm non-controlled experience, with the aim of establishing first-in-man levels of clinical safety and efficacy.

Background studies:

In-vitro studies: Drug and polymer load was determined by Gravimetric analysis and High Performance Liquid Chromatography (HPLC) respectively. In-vitro elution rates for PLGA and Paclitaxel were determined by in-vitro elution studies by DISA Vascular.

Pre-Clinical Data: A series of 28-day and 90-day porcine coronary implant studies were conducted by the American Cardiovascular Research Institute (Atlanta, USA).

Methods: The trial has enrolled 37 patients who met all the required inclusion and exclusion criteria, from 7 hospital sites from around South Africa. Clinical follow-ups to be performed at 1, 6, 12 and 24 months. Telephonic follow-ups at months 2, 3, 5 and 9. The primary end point of the study is 6 months Major Adverse Coronary Events (MACE). Secondary endpoints are 1 and 2-year MACE and 6-month binary restenosis. A subset of 20 patients are to have angiographic follow-up and Optical Coherence Tomography (OCT) at 6 months. The purpose of the OCT is to determine the degree of stent coverage and apposition.

Results: Results for all 37 patients to 6 months will be presented.

A Case of Esophagopericardial Fistula

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Introduction: We report a case of suppurative pericarditis as a result of an esophagopericardial fistula following recent upper gastrointestinal endoscopy.

Case Report: A 38-year-old man presented to our emergency unit with acute severe restrosternal chest pain of 2 hours duration which was constant, non-radiating and associated with sweating and breathlessness.

The patient was an institutionalized schizophrenic with a history of gastro-esophageal reflux disease (GORD) with a previous esophageal stricture dilated 3 months earlier. On the day before presentation he had undergone gastroscopy during which he forcefully pulled out the endoscope at mid-esophageal level. A barium swallow post endoscopy was normal.

He was afebrile, with a tachycardia of 109 beats per min and a blood pressure of 108/89 mmHg. The rest of his examination including cardiac evaluation was normal. Initial ECG revealed a sinus tachycardia and subtle saddle shaped ST elevation in V3 to V6. Chest radiograph (CXR) was unremarkable and a troponin level was <0.03ng/ml. Analgesia was given and he was observed overnight.

The following morning he developed severe pain and was found to be cold and clammy with a thready pulse, unrecordable blood pressure and distended neck veins. Widespread marked saddle shaped ST elevation was present on ECG and repeat CXR revealed an enlarged cardiac silhouette.

Echocardiography confirmed a pericardial effusion with echo bright densities within the pericardial space. Pericardial aspiration yielded 70 millilitres of frank pus. Surgical drainage was performed and a pericardial drain was left in situ. Pericardial biopsy performed at surgery revealed acute suppurative inflammation with food particles.

Antibiotic therapy and pericardial drainage was continued for 14 days. A repeat barium swallow and computerized tomography (CT) scan of the chest revealed no esophageal fistula. He was finally discharged 24 days after initial presentation. He remained well at follow-up 2 weeks post discharge.

Discussion: This is a rare but serious complication of esophageal intubation which may be easily missed and is associated with a high mortality if treatment is delayed. This case emphasizes the importance of being well acquainted with the potential complications of invasive procedures. A high index of suspicion is imperative and if a patient presents with symptoms after an invasive procedure it should be assumed to be due to a complication of the procedure. Our case is consistent with the reported barium swallow sensitivity of 69–80% for the detection of esophagopericardial fistula.

Diagnostic Utility of Myocardial Biopsy in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): Preliminary Observations from the ARVC Registry of South Africa

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Introduction: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive, genetically determined disorder of the right ventricular myocardium that results in ventricular arrhythmia, heart failure, and sudden death. Diagnosis is established by a combination of major and/or minor criteria. Tissue characterization by myocardial biopsy is one of the major diagnostic criteria. We sought to evaluate the utility of myocardial biopsy and histology in the assessment of patients with suspected ARVC.

Methods: The ARVC registry of South Africa is organized under the auspices of the Cardiac Arrhythmia Society of South Africa (CASSA) and is based at the Cardiac Clinic, Groote Schuur Hospital (GSH), Cape Town. The registry has been enrolling patients with suspected ARVC referred from attending physicians since January 2004. We determined the number of probands who underwent myocardial biopsies or histological examination and whether these had contributed to confirming the diagnosis of ARVC.

Results: As of August 2008, the registry has enrolled 80 cases of ARVC of whom 70 are probands. Twenty-five of the 70 patients (36%) had a total of 30 biopsies or histological examinations with tissue obtained by percutaneous endomyocardial biopsy (EMB) in 23, at post mortem examination (PM) in 3, from explanted hearts (EPH) at the time of transplantation in 3 and 1 surgical biopsy during right ventricular disconnection surgery. The EMB were done in patients with suspected ARVC at only 2 centres: GSH and Wentworth hospital. There were no complications.

Histological examination was diagnostic of ARVC in 22 of 30 (73%). Of the 23 EMB 15 (65%) were diagnostic. The sensitivity, positive and negative predictive value of EMB was 69%, 100% and 0% respectively. All of the examinations from PM and EPH were diagnostic for ARVC and additionally showed left ventricular involvement in 3 of 3 PM and 2 of 3 EPH. Inflammation was present in 6 of 30 (20%). A diagnostic biopsy result was pivotal in establishing the diagnosis in 7 of 25 (28%) patients.

Interpretation: To the best of our knowledge, this is the largest series of myocardial biopsies performed in patients with suspected ARVC in Africa. The high diagnostic rate of 73% is in keeping with previously published series. A myocardial biopsy remains critical in the establishment of the diagnosis of ARVC in a significant proportion of patients. It is also essential in subsequent screening of family members as it forms the basis of criteria for familial ARVC diagnosis. Despite endomyocardial biopsies being invasive with the potential for serious complications, at the two centres involved in the registry the procedure proved to be safe and cost-effective.

Surgery for for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): The ARVC Registry of South Africa Experience

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Introduction: ARVC is a progressive cardiomyopathy affecting mainly the right ventricle associated with life threatening ventricular tachycardia (VT). Treatment is palliative and aimed at the prevention of VT and sudden death. Surgery has been advocated as a potential therapeutic option in selected patients. We sought to evaluate the use of surgery as a therapeutic option and its outcome in a group of patients enrolled in the ARVC registry of South Africa.

Results: 80 patients with confirmed ARVC have been enrolled to date. 9 surgical procedures were performed in 7 of 80 (9%) patients: 4 orthotopic heart transplantation (OHT), 4 right ventricular disconnection (RVD) procedures and 1 Glenn shunt.

Three total and one partial RVD were performed. The median age of surgical patients was 44 years (range: 20-53) and 3 were males. The indication for surgery was VT refractory to medical therapy. Left ventricular (LV) ejection fraction was normal pre-surgery in all. All patients had intra operative electrophysiological studies and VT was not inducible post RVD in all. Permanent pacemakers were inserted in two of three patients who had total RVD.

With a follow-up of 17 years, only 1 patient (partial RVD) remains alive. Three (all with total RVD) have died: on day 1 post surgery from low output cardiac failure, at 6 weeks from progressive LV failure and at 9 years (8 days post OHT) after a period of progressive RV dysfunction.

All total RVD patients had atrial fibrillation, which developed post surgery in 2. There was no VT recurrence post surgery in any patients.

The median age of the 4 patients who underwent OHT was 38 (range: 16-62) and 3 were males. VT was the presenting symptom in 3 of 4 and effort intolerance in another. Two OHT patients were siblings who were transplanted within one year of one another. Two patients had previous surgical interventions for ARVC; Glenn shunt and total RVD at six and nine years prior to OHT respectively. Follow-up ranged from eight days to 3 years. One death occurred at 8 days post OHT in the patient who had a previous total RVD.

Discussion: Total RVD has been shown to result in progressive RV dilatation and RV failure. Our experience supports this finding. The poor outcomes coupled with the availability of effective alternative therapies such as implantable cardioverter defibrillators and radiofrequency ablation have resulted in RVD becoming near obsolete in the treatment of ARVC. OHT is the only effective treatment for patients with severe heart failure despite optimal medical therapy, and results are favourable.

The Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Registry of South Africa: An Update on a Work in Progress

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Introduction: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive, genetically determined disorder of the right ventricular myocardium that results in ventricular arrhythmia, heart failure, and sudden death. Despite a low estimated prevalence of 1:2,500 to 1:5,000, it is a major cause of sudden cardiac death in the young, especially athletes. Much of our understanding of ARVC emanates from international registries. To this end the ARVC Registry of South Africa has been established to define the epidemiology, pathogenesis, prognosis and treatment in the South African context.

Design: The ARVC Registry of South Africa is organized under the auspices of the Cardiac Arrhythmia Society of South Africa (CASSA) and is based at the Cardiac Clinic, Groote Schuur Hospital, Cape Town. The registry has been enrolling patients with suspected ARVC referred from attending physicians since January 2004. Affected patients and their families are invited to partake in the registry and consent is obtained for genetic studies. The registry has six major missions: DNA/Tissue bank, Epidemiology, Risks Assessment and Evaluation of Therapy, Imaging, Pathological Diagnosis and Diagnostic Validation.

Results: To date 80 confirmed cases of ARVC have been enrolled of which 54/80 (68%) were males. The median age at diagnosis was 27.5 years (range 11-74); 23/80 (29%) were ≤20 years at diagnosis. 48/80 (60%) had either a family member with confirmed ARVC or a history of sudden cardiac death (SCD) or sudden unexplained death. Left ventricular involvement was present in 35/80 (44%), 4 of whom had heart transplants with another awaiting transplantation. Implantable cardioverter defibrillators were implanted in 30/80 (38%). 40/80 (50%) participated in some form of organized sport. 4/80 (5%) were survivors of resuscitated SCD which occurred whilst participating in sporting activity. Follow-up data are available for 66/80 (83%) of whom 14/66 (21%) had died. Genetic screening of the plakophilin-2 gene, the commonest genetic cause of ARVC, has revealed disease-causing mutations in 3/25 (12%) of the probands; one genetic mutation is novel to the South African cohort.

Discussion: This project represents the largest collection of ARVC patients from the African continent. The results confirm that it is a potentially deadly disease affecting predominantly young males. Despite its short existence and minimal financial support the registry compares well with international registries with respect to recruitment, data collection and novel findings. Physicians and cardiologists are strongly encouraged to refer suspected cases of ARVC for enrollment in the ARVC Registry of SA.

Race and gender representation of hypertrophic cardiomyopathy or long QT syndrome cases in a South African research setting

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Introduction: We researched hypertrophic cardiomyopathy (HCM) and long QT syndrome (LQTS) as models for studying the pathophysiology of arrhythmias and hypertrophy, and in the process we have had the opportunity to compare local disease profiles with global patterns.

Methods: We trawled our database entries over the past 20 years to identify all cases of heart muscle and arrhythmic disease. Among these, we separated the index cases from the rest of their family members, segregating for the relevant heart disease, so that numbers were not biased by family size, and analysed the race and gender composition of the HCM and LQTS sectors.

Results: The majority of HCM index cases (n = 90, 51.1% of HCM index cases) were of mixed ancestry (MA), with white Caucasian ancestry following closely behind with 74 cases (42.0%); only a few black African (n = 9, 5.1%) or Indian/Asian (n = 3, 1.7%) cases were seen or referred. The LQTS index cases were almost exclusively white Caucasian (n = 36, 88% of LQTS index cases), with four cases (9.8%) of MA, one (2.4%) of Indian/Asian and none of black African descent. These race demographics did not fit the national demographics for South Africa as a whole. In contrast, in both groups, gender biases (slightly more male than female HCM cases, and a 0.4 ratio of males to females in LQTS) previously reported elsewhere appeared to be replicated in our database.

Conclusion: Genetic bias is an unlikely explanation for the skewed demographics in our database; a more likely explanation relates to various missed opportunities to diagnose, missed diagnoses and misdiagnoses, as well as the real population drainage of our main referral centre in the context of a differentiated healthcare system.

A prospective study of children with sensorineural deafness with a view to identify Jervell and Lange-Nielsen syndrome

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Introduction: Jervell and Lange-Nielsen (J-LN) syndrome is a rare autosomal recessive variant of the Long QT syndrome (LQTS) characterized by co-existing prolongation of the QT interval on an electrocardiogram (ECG), and profound congenital sensorineural deafness. Affected patients are prone to syncopal episodes and life threatening arrhythmias, typically polymorphic ventricular tachycardia. J-LN is the most severe variant of LQTS. Despite the fact the J-LN and the most prevalent form of LQTS in South Africa share the KCNQ1 mutation, J-LN syndrome has never been described in South Africa.

Our hypothesis is that J-LN syndrome has been overlooked in South Africa.

Based on current international studies we anticipated the incidence of J-LN syndrome to be 1-2 per 100 deaf children, and hope to identify 2 to 5 cases of J-LN syndrome amongst the approximately 300 pupils at the De La Bat and Nuwe Hoop schools in Worcester.

Furthermore, we hypothesize that the LQTS has been overlooked in black South Africans.

Methods: 198 children with sensorineural deafness were studied with 12 lead ECGs and the QTc interval measured. In a second step children with QTc interval in excess of 430ms were further evaluated by means of a follow-up ECG and a bedside step exercise test.

Results: QTc intervals of more than 430ms were found in 17 out of 198 patients. Out of this group, 4 children had a persistently prolonged QTc on second ECG.

None of these 4 children had prolongation of the QTc interval during exercise on a bedside bench and none demonstrated electrocardiographic findings of T wave configuration changes, repolarization abnormalities or arrhythmias characteristic of J-LN syndrome.

None of the patients fulfilled the definitive diagnostic criteria for the diagnosis of LQTS according to the original Schwartz criteria, but 6 were assessed to be at intermediate probability of LQTS and 11 at low probability of LQTS based on the revised criteria.

We have failed to identify any children with the J-LN syndrome in this study. Our work has again not been able to show significant QTc prolongation in the black population group.

Conclusion: This is the first study of this kind in South Africa. This prospective trial raises a number of questions about the incidence of J-LN syndrome in South Africa. We aim to address not only this but also the fact that the Long QT syndrome has not been diagnosed in a black African population.

Use of tenecteplase for thrombolysis of occluded right modified Blalock Taussig shunt

E. Hoosen, N.J. Buckles and A. Nzimela

A number of strategies have been described for the management of occluded modified Blalock Taussig shunts. These include reoperation, balloon dilatation or stenting, and thrombolytic therapy. We describe our experience with shunt thrombolysis using tenecteplase.

A four-year-old male presented for the first time deeply desaturated. A diagnosis of Tricuspid atresia with pulmonary atresia was made. Pulmonary arteries were not identified adequately on echocardiography, and cardiac catheterization demonstrated small disconnected pulmonary arteries. A palliative right modified Blalock Taussig shunt was performed with a good initial result. However, within four to six hours post shunt desaturation recurred, with no shunt flow demonstrated on echocardiogram. Heparin infusion was commenced but was discontinued when bleeding within the pleural space was noted. The following morning the patient was returned to the cardiac catheterization laboratory and a blocked shunt confirmed. Balloon angioplasty of the shunt was considered, however it proved impossible to stabilize a wire within the shunt. An end hole catheter was therefore secured with the tip in the shunt and the patient was returned to the intensive care. A bolus dose of 50 units of tenecteplase was administered followed by an infusion of 10 units hourly and the patient closely monitored for bleeding. The infusion was stopped when blood was noted in the pleural drain an hour later. Within three to four hours following the infusion an improvement in saturations occurred. Patency of the shunt was confirmed on echocardiogram and subsequently on CT angiography.

Tenecteplase is a newer modified form of recombinant tissue plasminogen activator with a longer half life than alteplase. Direct administration of the agent into the shunt at low doses minimizes the risk of systemic effects, however, doses used are still arbitrary and the optimal dose for such applications is unknown.

The effect of inhibition of the angII receptor on insulin signalling and nitric oxide production in the insulin resistant rat heart

B. Huisamen, S. Pêrel, S. Friedrich, H. Strijdom and A. Lochner

Physiological concentrations of nitric oxide (NO) play an important role in maintaining normal vascular function. That NO synthase (NOS) activity and the production of NO may be chronically impaired in insulin resistance (IR), is indirectly supported by the observation that exogenous insulin therapy improves endothelial function in such patients. Insulin stimulates production of NO in endothelial cells and cardiomyocytes by activating insulin receptor substrate-1, phosphatidylinositol-3-kinase (PI-3-K), protein kinase B (PKB/Akt) and eNOS.

AngII plays a pivotal role in the development of atherosclerosis and hypertention. AngII type 1 (AT1) receptor-evoked oxidative stress has been implicated in the inactivation of NO, leading to impaired endothelium-dependent vasodilatation. Blocking the actions of AngII with an AT1 receptor antagonist (Losartan), has beneficial effects in patients with IR or type 2 diabetes mellitus.

We therefore investigated whether (1) elevated AngII influenced myocardial IR, insulin signalling and NO production in a rat model of diet-induced obesity (DIO) and (2) Losartan can alleviate this.

Hyperphagia-induced obese, insulin resistant rats (DIO=diet supplemented with sucrose and condensed milk for 16 weeks) were compared to age-matched controls. Half the animals were treated with 10mg/kg Losartan for 1 week. Afterwards, isolated hearts were perfused with or without 0.03 uIU/mL insulin. Fasting blood glucose, insulin (RIA), and body weight were recorded. Western Blotting and flow cytometric methods were utilized to determine protein expression, phosphorylation and NO production respectively. Stats: 2-way ANOVA followed by the Bonferroni post-test ($P<0.05$ as significant).

Hearts from DIO rats were insulin resistant (higher SerP IRS-1, lower insulin-stimulated phosphorylation of both PKB/Akt and eNOS, lower NO production). Losartan restored the impaired NO production and eNOS expression and unmasked that AngII signalling modulates myocardial PKB/Akt and eNOS expression. We conclude that elevated AngII signalling leads to inhibition of NO production in insulin resistance that can be improved by AT1 antagonism.

Diavite™ is cardioprotective in rat models of insulin resistance

B. Huisamen, C. Hill and A. Lochner

Obesity and its associated complications, the metabolic syndrome, hypertension, diabetes and cardiovascular disease, are escalating world wide. In some of our population groups, the incidence of obesity is currently 60%. In recognition of this, untested remedies advertised as anti-diabetic agents are flooding the market. One such remedy is Diavite™ whose producers are seeking MCC registration for their product and therefore require scientific validation of its effects. We utilized rat models to investigate this.

Two models were used: (1) Hyperphagia-induced obese, insulin resistant rats (DIO=diet supplemented with sucrose and condensed milk for 16 weeks) were compared to age-matched controls, and (2) 40% animal fat was added to the DIO to also create hypertension (DIO + BP). Oral Diavite™ treatment was introduced after 8 weeks on diet.

Trunk blood was collected in a fasting state for determination of blood glucose and insulin levels. Cardiomyocytes were prepared by standard collagenase perfusion digestion and glucose uptake measured via accumulation of [3H] 2-deoxyglucose. Isolated hearts were perfused (Krebs-Henseleit buffer, 10mM glucose) and subjected to 35 min regional ischemia by tying of the left anterior descending artery, followed by 120 min reperfusion to determine infarct size (conventional TTC staining methods).

Treatment was cardioprotective as evidenced by smaller infarct size in hearts from both control and DIO animals ($P<0.05$, 2way ANOVA). In cardiomyocytes from DIO animals, Diavite™ treatment improved insulin stimulated glucose uptake vs. controls ($P<0.05$, 2way ANOVA). In DIO + BP animals, Diavite™ (1) when given from day one, prevented the rise in BP or (2) corrected elevated BP if commenced after the rise in BP. No detrimental effects in both the rat models or in a toxicity study in non-human primates were detected.

We conclude that Diavite™ has insulin sensitizing, anti-hypertensive and cardioprotective effects.

Myocardial bridging shown by CT angiography

Daniel Jodocy

Objective: To assess the relationship between left anterior descending (LAD) coronary artery myocardial bridging detected by 64-slice computed tomography (CT) and clinical findings.

Methods: 221 consecutive patients were examined with coronary 64-slice CT angiography. 21 patients with coronary stenosis >50% were excluded. The length, depth, and luminal narrowing of LAD myocardial bridges during systole and diastole were measured. CT findings were compared with the treadmill ECG stress test, and clinical symptoms.

Results: Myocardial bridges of the LAD were found in 23% of patients (51/221) (length, 14.9mm±6.5; depth, 2.6mm±1.6). A significant difference was noted between the LAD luminal diameter before the intramyocardial course and intramyocardially, for both diastole and systole ($p<0.001$); with a higher diameter reduction of 27% for end-systole compared to end-diastole with 15% ($p=0.006$). Systolic LAD intramyocardial luminal narrowing >50% was found in 3/25 (8%). 30/51 (59%) of bridges were "deep" (>2mm myocardial depth), 21/51 (41%) were "superficial". The prevalence of a positive ECG stress test for the anterior myocardial region was significantly higher in patients with LAD myocardial bridges (34/50; 68%) compared to those without (28/144; 19.4%)($p<0.001$). There was no difference between "superficial" and "deep" LAD myocardial bridges in regard to a positive treadmill ECG stress test. Typical angina was rare with 6%.

Conclusion: LAD myocardial bridges are common findings and can explain a positive exercise ECG stress test for anterior myocardial ischemia. Intramyocardial LAD segments show mild-to-moderate luminal narrowing at rest, which is higher during end-systolic phase.

Ethanolamine is a downstream metabolic product of sphingosine-1-phosphate that can confer cytoprotection

R.F. Kelly, L.H. Opie and S. Lecour

Introduction: Ethanolamine (Etn) is a biogenic amine found in wine and many other food products. It is also a downstream metabolite of sphingosine-1-phosphate (S1P: a major component of HDL) and its formation requires the activation of fatty acid amide hydrolase (FAAH) and/or S1P lyase. S1P is known to protect the heart against ischemia but its mechanisms remain unknown. Therefore, we suggest that Etn can confer cytoprotection against ischemia and that S1P protects the heart via Etn.

Methods: L cell fibroblasts were pretreated for 30 min with 100nM S1P (S1P group) or varying amounts of Etn (0.1μM, 0.3μM, 1μM, 5μM, 10μM). Thereafter, cells underwent 30 min of drug-free incubation followed by 8.5h of simulated ischemia (Esumi buffer, pH 6.4, 1% O2). In another set of experiments, the inhibitors of fatty acid amide hydrolase (URB; 1μM) and/or S1P lyase (2 deoxypyridoxine (DP); 500μM) were added together with S1P. Cell viability was evaluated at the end of simulated ischemia by trypan blue exclusion.

Results: Pre-treatment with Etn at concentration of 0.3μM, 1μM, and 5μM increased cell survival after simulated ischemia [Etn (0.3μM) 65±9%, Etn (1μM) 63±5%, Etn (5μM) 66±5%, $p<0.01$ vs. control 36±4%] whereas protection was lost at higher concentrations [Etn (10μM) 46±6%, ns vs control]. Similarly, S1P pretreatment also induced cytoprotection [48±4%, $p<0.01$ vs. control 25±4%]. Although each inhibitor alone did not significantly reduce this protection [URB (31±10%) or DP (40±6%)] the protective effect was abolished in the presence of URB and DP together (21±5%, $p<0.05$ vs. S1P).

Conclusion: Our findings demonstrate that ethanolamine can confer cytoprotection against ischemia. Moreover, our data strongly suggest that S1P-induced cytoprotection is mediated by production of ethanolamine via both S1P lyase and FAAH. These enzymes seem to counterbalance each other to maximize production of ethanolamine. This novel mechanism may lead to innovative therapeutic approaches.

Myocardial preconditioning with Sphingosine-1-Phosphate, a major component of HDL, protects against ischemia via STAT-3 activation

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Introduction: Sphingosine-1-phosphate (S1P) is a sphingolipid that can mimic ischemic preconditioning. To investigate this protective mechanism, we hypothesised that S1P protects the heart via activation of the prosurvival factor, Signal Transducer and Activator of Transcription-3 (STAT-3).
Methods: Isolated rat hearts were exposed to 30min regional ischemia (I) and 2h reperfusion (R). 3 groups were studied: Control (CTL), S1P (10nM for 7min prior to I/R followed by 10min washout prior to I/R) and S1P+AG490, a STAT-3 inhibitor (100nM, co-administered with S1P). Similarly, isolated hearts from wildtype or cardiac specific STAT-3 knockout mice were pretreated with S1P prior to 35min global ischemia and 45min of reperfusion. At the end of each experiment, infarct size was assessed by TTC staining. Additionally, cultured fibroblasts were subjected to 7h simulated ischemia and were preconditioned with either 100nM S1P or 1μM SEW2871 (a S1P receptor type 1 specific agonist). At the end of the protocol, cell survival was measured by trypan blue staining and data were normalized to ischemic control.
Results: Measurement of infarct size demonstrated a dramatic reduction of infarct/area at risk (I/AAR) ratio in S1P-treated rat hearts (6±2% for S1P vs. 22±2% for CTL, $p<0.05$, n=6). Perfusion of AG 490 with S1P reduced the cardioprotective effect of S1P (I/AAR ratio: 17±3%, n=4). Similarly, S1P reduced the infarct size in wildtype mice (12.8±1.2 vs. 32.7±2.8% for CTL, $p<0.05$) but failed to protect the heart in knockout mice (34.5±4.1 vs. 29.3±2.6% for CTL, ns). Interestingly, pre-treatment with SEW2871 in fibroblasts increased cell survival to a similar extent to S1P (Control; 30%, S1P; 56±5%, SEW2871; 55±5%, $p<0.05$ vs. control).
Conclusion: Our data strongly supports a role for STAT-3 signalling in S1P-mediated cardioprotection and suggests that this protective effect is mediated, at least in part, via the activation of the S1P receptor type 1.

The GAP junction protein, connexin 40 interacts with mucolipin

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Connexins (Cx) are major proteins of gap junctions, dynamic pores mediating the relay of ions and metabolites between cells. Cxs 40, 43 and 45 are the predominant cardiac isoforms and their distinct distribution raises questions about their functional differences. Their cytoplasmic (C)-terminal domains are involved in protein-protein interactions. Disruption of Cx40 expression in transgenic mice results in conduction disturbances. We hypothesised that delineation of the protein ligands of the C-terminus of Cx40 would help elucidate its functional roles and shed light on the processes underlying human conduction disease.
Yeast-two-hybrid methodology was used to discover putative Cx40 ligands. Five plausible ligands were identified: beta-actin (ACTB), mucolipin1 (MCOLN1), NADH dehydrogenase, 6, (NDUFA6), prosaposin (PSAP) and filamin A (FLNA). In order to verify Y2H results, mammalian two-hybrid (M2H) was used. The M2H analysis confirmed the interaction of Cx40 with MCOLN1, a member of the superfamily of transient receptor potential (TRP) Ca2+ channels. This interaction was further verified using three-dimensional co-localization in HEK293 and H9C2 cells.
Identification of novel connexin interacting proteins may shed some light on the independent role each connexon plays in the formation of gap junctions and could contribute to our understanding of cardiac conduction disturbances.

History of Cardio-Pulmonary Bypass

Andre Kopper

Looking at history, there has been interest in the heart dating back to 2000 BC, with Egyptians seeing it as a symbol of goodness, Romans discovering the beating of the heart on the battlefield, and William Harvey describing circulation, etc. in the 1600s.

- Doctors in middle ages burned at the stake for their medical beliefs by Protestant religious groups, further medical discoveries, etc. Servatus said heart and lungs connected but was scorned by religious groups
- 1816 French physician Rene Leannex developed stethoscope
- 1885 Development of first HLM without interrupted bloodflow
- 1912 First diagnosis of heart attack
- First heart/lung machine prototype pioneered by Gibbon, 1952 engineers involvement, first surgery experience, live donor circulation from parent to child support, overview of successes and failures
- Initial tests on cats "fairly" successful, but not adequate on dogs and humans
- Equipment used and prepared in the late 50s and early 60s and looking at current designs
- Concluding with slides of current clinical use and where "we" came from

TNFα signalling – a critical role in ischemic postconditioning?

Lydia Lacerda

Introduction: Ischemic pre- and post-conditioning (IPC, IPostC) are two protective phenomena that activate intrinsic signaling cascades in the heart. Tumor necrosis factor alpha (TNFα) is known to be a mediator in IPC but its role in IPostC is unknown. We hypothesized that endogenous TNFα is a key protective mediator in IPostC and that exogenous TNFα can mimic IPostC.

Methods: Isolated ischemic/reperfused hearts from the wild type mouse (WT) and 3 transgenic mouse models from the same background (TNF knockout, TNFReceptor1 knockout or TNFReceptor2 knockout) were postconditioned by either ischemic episodes or TNFα (0.5 µg/L). Infarct size (IS) was evaluated at the end of reperfusion by triphenyltetrazolium chloride staining.

Results: IPostC reduced IS in WT and TNFR1-/- hearts by 33% ($p<0.001$) and 27% ($p<0.001$) respectively, whereas the TNF-/- and TNFR2-/- hearts could not be postconditioned. These data were confirmed in WT mice by using specific TNFR1 and TNFR2 antibodies. Postconditioning with TNFα (TPostC) reduced IS by 37% ($p<0.001$) in WT hearts only. Administration of wortmannin, an inhibitor of the Akt pathway, during the postconditioning stimulus did not abolish the infarct-sparing effects of TPostC, while AG 490, an inhibitor of signal transducer and activator of transcription-3 (STAT-3) abolished the protective effect of TNFα.

Conclusion: We report for the first time, to our knowledge, that exogenous TNFα, given at the onset of reperfusion, can confer protection against reperfusion-injury. Furthermore, we describe an alternative and Akt-independent pathway in ischemic postconditioning that requires activation of STAT-3 after the binding of TNFα to its receptor 2.

Percutaneous balloon mitral valvuloplasty (PBMV) in pregnancy at Tygerberg Hospital, Cape Town, South Africa – a ten-year retrospective audit

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Severe mitral stenosis is poorly tolerated in pregnancy and often requires intervention. Percutaneous balloon mitral valvotomy (PBMV) is an effective intervention. Limited data is available for PBMV during pregnancy in the South African population. This study aimed to determine if the outcome of our pregnant patients requiring PBMV mirrors the experience recorded in other populations and to determine if the pregnant patient undergoing PBMV experiences adverse outcomes not seen in non-pregnant patients.

Methods: Patients (141) undergoing PBMV were identified from the cardiac cathlab database at Tygerberg Hospital (January 1997 to December 2006). Twenty-nine pregnant patients (mean age 32 years) who underwent PBMV for severe mitral stenosis during pregnancy (mean gestational age 24 weeks) and a control group of 29 non-pregnant women of childbearing age were included. Data was obtained from patient folders, catheterization laboratory and echocardiogram laboratory records.

Results: The procedure was successful in 97% in the pregnant group and 100% in the control group. A significant improvement in mitral valve area (1.05 ± 0.20 cm^2 to 1.73 ± 0.35 cm^2 [$p<0.001$]), reduction in mean transmitral gradient (14.4 ± 8.3mmHg to 6.6 ± 3.4mmHg [$p<0.001$]) and NYHA Class (2.9 ± 0.99 to 1.2 ± 0.43) was noted in the pregnant group. The outcomes were mirrored in the control group. There were no maternal deaths. Complications included TIAs (6%), atrial fibrillation (6%), anaphylaxis (3%), and mitral regurgitation (17%). Favourable outcomes were maintained at follow-up (mean 2.78 ± 2.71 years).

Conclusion: PBMV is safe and efficient during pregnancy. Procedural success is equivalent to non-pregnant patients with sustained benefit. The hypercoagulable state of pregnancy must be taken into consideration when selecting patients suitable for PBMV in pregnancy. An abbreviated period of anticoagulation to allow for non-surgical intervention in the pregnant patient is not recommended.

Rooting out the active cardioprotective components in red wine

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Introduction: Many epidemiological, clinical and basic studies have demonstrated the cardioprotective effect of moderate red wine consumption. The alcoholic content and polyphenols/flavonoids in red wine are thought to contribute to this protection. Here, we compared the cardioprotective properties of a French red wine (Cabernet Sauvignon, 12% alcohol by volume) with the same wine that was subjected to the lirisation® process for partial removal of the alcohol content (Lir, 6%) without any alteration to the other components of the original wine. We also explored the cardioprotective effects of alcohol, resveratrol or ethanolamine on their own, given at a similar concentration as found in the wine

Methods: The drinking water of male Wistar rats used for controls was supplemented by red wine (12%), Lir (6%), alcohol (6%), resveratrol (7mg/l) or ethanolamine (0.33µM). After 10 days of treatment, hearts were isolated on a Langendorff system and subjected to 30min global ischemia followed by 30min of reperfusion (I/R).

Results: Control hearts subjected to I/R presented a rate pressure product (RPP expressed as a percentage of baseline value) of 20.5±4.5%. Pretreatment with wine or Lir improved the rate pressure product to 40±6% and 43±6%, respectively ($p<0.05$ vs. control). Neither resveratrol nor alcohol 6% on their own improved the function of the heart while ethanolamine was protective (RPP: 33.9±6.7% $p<0.05$ vs. control).

Conclusion: Our results suggest that the biogenic amine ethanolamine rather than resveratrol or the alcohol content in the wine contribute to the cardioprotective effect of moderate red wine consumption.

Obesity as a Predictor of Myocardial Ischemia in Patients Referred for Myocardial Perfusion imaging

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Introduction: Obesity is an independent risk factor for coronary artery disease and premature death. We evaluated whether obesity is independently associated with myocardial ischemia in patients referred for myocardial perfusion imaging (MPI).

Methods: The relationship between obesity and the presence of myocardial ischemia was assessed in 315 patients referred for MPI, 192 of whom (age = 58.9±11.4, female gender = 35 [28%]) were without known coronary artery disease (CAD) and were referred for diagnostic purposes (group 1) and the remaining (group 2) of whom (age = 58.8±10.1, female gender = 118 [61%]) were known to have CAD, but required an evaluation to determine whether persistent myocardial ischemia was present. In the analysis, adjustments were made for age, gender, and the presence of hypertension, diabetes mellitus (DM), smoking, elevated cholesterol concentrations, and angina pectoris (AP).

Results: No differences were noted between groups 1 and 2 in age, or the frequency of patients with either DM (group 1 = 54 pts [28%], group 2 = 35 pts [29%]), or obesity (group 1 = 158 pts (82%), group 2 = 93 pts (76%]). However, the groups differed in the proportion of patients who were female ($p < 0.0001$), who had hypertension (group 1 = 170 pts [89%], group 2 = 79 pts [64%], $p < 0.0001$), who were regular smokers (group 1 = 18 pts [9%], group 2 = 26 pts [21%], $p = 0.0044$) and in cholesterol concentrations (group 1 = 65 pts [34%], group 2 = 74 pts [60%], $p < 0.0001$). In the patients without established CAD, (group 1) AP (OR = 2.51, CI 95% = 1.08 -5.81, $p = 0.032$) and male gender (OR = 3.69, CI 95% = 1.57 – 8.67, $p = 0.0027$) were predictors of myocardial ischemia on MPI. In patients with known CAD, obesity (OR = 2.81, CI 95% = 1.13 – 6.97, $p = 0.026$), but not AP was the only independent predictor of myocardial ischemia.

Conclusion: The presence of obesity in patients with established CAD may be a useful predictor of persistent myocardial ischemia independent of the presence of AP.

Blood Pressure Changes During Antihypertensive Therapy are More Closely Associated with Reductions in Left Ventricular Wall Thickness Than Mass Index

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Introduction: Regression of left ventricular (LV) hypertrophy during antihypertensive therapy independently predicts a reduced cardiovascular risk. However, as changes in blood pressure (BP) with therapy are poorly correlated with changes in LV mass (LVM); we hypothesized that changes in LV wall thickness may be a better predictor of antihypertensive effects on LV size.

Methods: In the Chris Hani Baragwanath Hypertension Study, a single-centre, randomized, open-label study exploring the impact of antihypertensive therapy on LV changes, we evaluated the relationship between changes in ambulatory BP and either LVM index or wall thickness in 173 hypertensive patients of African descent (age=50.9±9.9 years, 132 females) with a mean daytime diastolic BP ranging from 90-114 mm Hg off-treatment over a 4-month treatment period. Antihypertensive therapy was added to achieve a target daytime diastolic BP below 90 mm Hg. Statistical analysis was performed with SAS 9.1 package. Repeated measurement ANOVA and Multiple Regression analysis were used, with a significance of 0.05.

Results: After 4 months antihypertensive therapy, LVM index decreased from 118±34 g/m2 at baseline to 101±25 g/m2, ($p<0.0001$), mean wall thickness from 1.18±0.20cm to 1.09±0.15 cm ($p<0.0001$) and relative wall thickness (RWT) from 0.50±0.12 0.48±0.11 ($p<0.01$). Although 24-hour BP was not associated with LVM index, 24-hour systolic BP was associated with in-treatment LV mean wall thickness ($p=0.007$) and LV relative wall thickness ($p=0.001$).

Conclusions: Changes in LV mean and relative wall thickness may be a better index of the beneficial effects of antihypertensive therapy on the heart than changes in LVM index in groups of African descent.

Thoracic surgery in Central South Africa

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Objectives: To perform a situational analysis of thoracic surgery in Central SA, based on the hypothesis of a significant performance gap between actual clinical activity and the burden of disease in the community.

Method: Mixed methods research techniques were applied. Quantitative and qualitative data was obtained in interviews with heads of departments in cardiothoracic surgery in SA universities, all cardiothoracic surgeons in Central SA and the heads of department of internal medicine, surgery, trauma and pediatrics in the regional hospitals of Central SA. Billing data was obtained for a wide spectrum of thoracic operations from Medscheme and Discovery. An extensive literature survey included burden of disease data in 5 pathologies, namely Inflammatory pleuropulmonary disease, TB, Lung cancer, Esophageal cancer and Thoracic Trauma as well as a systematic review of the SA thoracic literature over 50 years. The contribution of the research was evaluated using the Oxford Centre for Evidence-based Medicine levels of evidence.

Results: All respondents agreed that thoracic surgery in Central SA had serious problems and required urgent, corrective action. The table below illustrates the current number of operations performed for lung and esophagus cancer in Central SA compared to the estimated burden of disease requirement.

Summary of reported and expected lung and esophageal resections for SA and Central SA

	Lung cancer	Esophagus cancer
Age standardized Incidence rate	15.2 / 100 000	12.6 / 100 000
Expected annual Incidence based on ASIR - SA (population 47m)	7144	5922
Expected annual incidence based on ASIR - Central SA (population 4.2m)	638	523
Annual reported mortality in SA	7173	5803
Annual reported mortality in Central SA	369	258
Estimated no. of operations required per annum SA	717 - 714	580 - 592
Estimated No. operations required per annum Central SA	36 - 64	52
Operations actually recorded SA universities	Estimated to be < 50	26
Operations actually recorded in Central SA university	4	3

Conclusion: The mixed methods research technique established the facts in thoracic surgery in the region and proved that a clinically relevant performance gap exists between the actual service provision and the burden of disease in the community. In response to the situational analysis and prioritization of needs and constraints, a strategic clinical model is under construction using various project management and systems theory principles.

Cell death in ischemic injury – a dynamic response concept

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Three main morphologies of cell death have been described: Type I, better known as apoptotic cell death, which is characterized by cell shrinkage and chromatin condensation, Type II, or cell death with autophagy, presents a morphology with intracellular accumulation of autophagic vacuoles and Type III, better known as necrosis, is characterized by cellular swelling and rapid loss in cellular membrane integrity. However, recent literature strongly argues against rigid classifications in the context of cell death mechanisms. Therefore, we aim not only to dissect out the molecular overlap between these death types but also to place them into clear context of the cellular metabolic condition and its environment, in order to interpret manifesting morphological features.

Due to its clinical relevance, we are using a model of simulated ischemia (SI), and hypothesize that cell death is a dynamic response scheme, that provides cellular adaptability to a given stressful condition, ensures highest likelihood for cell survival but can extend into the process of dying and cell death. We employed the rodent derived cardiac myoblast cell line H9C2, grown in Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), and incubated under 5% CO_2 conditions. Cells were submitted to a protocol of 2, 4 and 8 hours of SI followed by 1 hour reperfusion respectively. To modulate ATP availability, the metabolic inhibitors 2-deoxy-glucose, sodium dithionate and a combination thereof are employed. We evaluated the contribution of each cell death mode using a combination of viability and ATP assays. Molecular markers for each cell death process such as LC3, bcl-2 and HMGB-1 were evaluated using 3-dimensional fluorescence and live cell-imaging techniques as well as western blot analysis and flow cytometry.

Our results strongly indicate a differential induction of cell death, which is dependent on the duration of the ischemic insult and the metabolic state of the cell. The inhibition of glycolysis leads to the induction of autophagy and apoptosis, whereas the inhibition of mitochondrial respiration induces primarily necrotic cell death. We furthermore showed that a combination of viability techniques is crucial to determine truthfully the cell death process and its endpoint.

Insulin paradoxically protects the rat heart during low flow ischemia via cAMP, but not PI3K, while blunting pathological signals from the b-AR and PKA

John Lopes, Amanda Genis, Amanda Lochner and Barbara Huisamen

Background: Insulin protects the heart against ischemia/reperfusion injury by increasing in glucose metabolism and pro-survival signaling, attributed to the activation of PI3K during both ischemia and reperfusion. In contrast, increased adenylyl cyclase (AC) activation by the β-adrenergic receptor (β-AR), followed by phosphodiesterase inhibition, leads to cAMP accumulation during ischemia that promotes cardiac damage through cAMP activated protein kinase (PKA). The relationship between protection by insulin and damage via β-AR signaling is however poorly understood.

Aim: To investigate the role of the β-AR, adenylyl cyclase (AC) and PKA signaling in rat hearts protected by insulin during LFI.

Experiments: Isolated male Wistar rat hearts were perfused with and without insulin (0.3 mIU/ml) during 30 min stabilization, followed by 30-45 min low-flow ischemia [LFI] (0.2 ml/min) and 30 min reperfusion. We blocked the β-AR (5μM propranolol), AC (10 μM MDL-12,330A), PKA (16 μM Rp-8-CPT-cAMPS) and PI3K (100 nM Wortmannin) respectively throughout LFI. Time to onset of contracture (TOIC), total tissue cAMP levels and PKA-mediated PLN phosphorylation on Ser-16 were measured during LFI.

Results: Insulin delayed the TOIC and reduced the severity of contracture during LFI, while reducing hypercontracture and improving functional recovery during reperfusion, indicating cardioprotection. MDL-12,330A prevented cAMP accumulation during LFI and abolished the delay in TOIC, showing that insulin-mediated protection is cAMP-dependent. Propranolol and Rp-8-CPT-cAMPS, respectively delayed TOIC in non-insulin perfused hearts, but did not enhance protection by insulin. These results suggest the harmful effects of the β-AR and PKA might be opposed by insulin. Indeed, both insulin and Rp-8-CPT-cAMPS inhibited PKA-mediated phosphorylation of PLN on Ser-16. Interestingly, PI3K inhibition did not alter cAMP accumulation and failed to abolish protection by insulin.

Conclusion: We found that PI3K does not play a role in protection by insulin during LFI, which is in contrast to its role in reperfusion. Instead, we propose that insulin protects the rat heart during LFI in a cAMP-dependent manner, while inhibiting detrimental signals from the β-AR through cAMP/PKA, implying a possible role for insulin in compartmentalization of cAMP.

Atrial Fibrillation Substrate Modification Ablation with a Novel Combined Mapping and Ablation Catheter

F. Lorgat

RF Ablation of Atrial Fibrillation is now an established procedure. The demand for AF ablation is escalating rapidly. Existing techniques utilize point by point mapping with cooled Ablation catheters delivering 30 watts of RF energy. The procedure is time consuming, expensive, and has a significant risk factor profile.

We describe here our experience with a novel RF Ablation system (Ablation Frontiers) which uses a Pulmonary Vein Ablation Catheter (PVAC), Multi Array Septal Catheter (MASC) and Multi Array Ablation Catheter (MAAC) capable of simultaneously mapping and ablating from the same bipoles. The system uses low power (max 10 watts) phased array combined bipolar and unipolar ablation, the ratio of which can be adjusted depending on the depth of lesion required.

Seven patients were included in this pilot study. Five had paroxysmal AF and two persistent AF. Successful Pulmonary Vein Isolation (PVI) was achieved in all veins in all 7 patients. PV isolation was validated using pacing techniques. Sinus rhythm was restored in all patients at the end of the procedure. No significant complications were encountered. Mean procedure time was approximately 2 hours per patient.

We have demonstrated this new ablation system to be efficient at PVI despite low power delivery. This would suggest that the system is inherently safer than existing techniques and shows huge potential to reduce procedure times and cost.

Successful RV Lead Extraction with the Novel Evolution Cutting Device

F. Lorgat

Pacemaker lead extraction is challenging. Fibrous adhesions form along the length of the lead and can make extraction with conventional techniques impossible. Technologies have been developed using either Laser or RF energy. These are expensive and require significant hardware. We describe here successful lead extraction with the Evolution Cutting Device (a disposable hand held and manually powered rotatory cutting device).

A 71-year-old retired Orthopedic Professor had AV Ablation and DDD Pacemaker Implant in 1994 for intractable Atrial Fibrillation. In October 1997 he developed Ca Lung and underwent lobectomy. The post operative course was complicated by septic shock. He developed inflammation over the PPM site. Incision and drainage was performed. MRSA was cultured. Peroxide washes were performed and the leads were capped and buried. A new device was placed on the opposite side. Dual antibiotic therapy with Zyvoxid and Rifampicin was commenced. Despite continuous antibiotic therapy the infection recurred and formal lead extraction was undertaken. The atrial lead was removed using conventional traction and counter-traction with a Locking Stylet and Byrd dilator. The RV lead was resistant however due to adhesions in the SVC. The RV lead was capped and buried. Antibiotic treatment was continued as above. A few months later the infection recurred. Incision and drainage was once again performed. The Evolution Cutting Device was employed and the RV lead was dissected free and removed. Extensive fibrous adhesions were encountered with the cutting device. There was rapid clinical improvement and normalization of CRP. MRSA was cultured from the tip of the RV lead.

This is the first use of the Evolution Cutting Device in Africa. It is a valuable addition to our existing lead extraction tools. It requires no power and no additional hardware or capital expenditure and has a minimal learning curve.

EPAC (exchange protein directly activated by cyclic amp) mediated cardioprotection via ERK

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Many effects of cAMP, previously attributed to protein kinase A, may depend on activation of a novel cAMP receptor protein, the guanine nucleotide exchange factor, Epac. The aim was to establish the significance of Epac in the cardioprotection of ischemic (IPC) or beta-adrenergic (BPC) preconditioning.

Isolated rat hearts were perfused with an Epac agonist 8-CPT-2'-O-Me-cAMP (5 min CPT, 2 µM) or subjected to IPC (5 min global ischemia) or BPC (5 min isoproterenol, ISO, 10-7M), followed by 5 min reperfusion, before 35min regional ischemia and 30 min reperfusion. Non-preconditioned hearts (nPC) were subjected to sustained ischemia and reperfusion only. Hearts were freeze-clamped and activation of p38MAPK, CREB, ERK and PKB were evaluated by Western blot. Rap-1 activity was used as indicator of Epac activation. Infarct size (I/S) was determined using TTC staining and expressed as % of area at risk.

Rap-1, as well as CREB and ERK, were activated by CPT, IPC and BPC but not p38 or PKB. Co-perfusion of ISO with the PKA inhibitor H89 (10 µM) further increased Rap-1 activity. Activation of Rap-1 during sustained ischemia by both IPC and BPC was associated with a reduction in I/S (12.8±2 and 14.0±1, respectively vs. 44.6±3 nPC, $p<0.001$). Although 5 min perfusion with CPT did not reduce I/S (54.5±6 vs. nPC, ns), pretreatment with CPT directly before sustained ischemia significantly reduced I/S (14.9±3 vs. nPC, $p<0.001$). This Epac-mediated protection by CPT could be abolished by the ERK inhibitor, PD98059 (10 µM) (36.9±5 vs. CPT, $p<0.001$).

Thus, Epac is rapidly activated by CPT, IPC and BPC and is enhanced by simultaneous PKA inhibition. The latter suggests an alternative beta-adrenergic signaling pathway. Although activation of Epac did not trigger preconditioning protection, it may mediate protection during sustained ischemia via ERK. This is the first demonstration of a role for Epac in cardioprotection.

Fenofibrate prevents cardiac pump dysfunction in isoproterenol model of cardiac hypertrophy

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Background: Heart failure has been associated with metabolic remodeling and impaired mitochondrial function. We have previously shown that long-term administration of isoproterenol (ISO) results in cardiac pump dysfunction in rats. Whether ISO-induced cardiac structural and functional changes are accompanied by metabolic remodeling is still unknown. The aim of our study was therefore to determine (1) the role of peroxisome proliferator-activated receptor alpha (PPARα), a key regulator of fatty acid oxidation (FAO) and nuclear respiratory factor 1 (NRF-1), a modulator of respiratory enzymes, in the ISO model of heart failure and (2) whether fenofibrate can prevent ISO-induced pump dysfunction.

Methods: Control rats received no treatment, Feno group received fenofibrate (100 mg/kg/day, gelatine cubes), ISO group received isoproterenol (0.04 mg/kg/day, subcutaneously) and ISO+Feno group received both fenofibrate and isoproterenol, as previously mentioned. All rats had daily access to food and clean water.

Results: Endocardial fractional shortening (FSend), a measure of cardiac pump function, was determined using echocardiography. ISO-treated rats showed a marked reduction in pump function (Control 54.2±1.2% vs. ISO 46.2±2.9%, $p<0.05$). Interestingly, fenofibrate treatment prevented ISO-induced pump dysfunction (ISO+Feno 55.1±3.0%, $p<0.05$ vs. ISO group), n = 7-8. Previous studies have associated myocardial dysfunction with impaired mitochondrial function. To investigate whether PPARα and NRF1 are associated with ISO-induced pump dysfunction, relative mRNA expressions were measured using real-time polymerase chain reaction and GAPDH as a standard. Our preliminary data reveals a downregulation of both PPARα (Control: 1.46±0.21 vs. ISO: 0.71±0.08) and NRF1 (Control: 1.52±0.45 vs. 0.89±0.30) in ISO-treated group whereas fenofibrate treatment prevents downregulation of these transcription factors (PPARα: ISO+Feno: 2.83±1.70 and NRF1: 1.61±0.36) (n = 4-6).

Conclusion: Our data suggest that ISO-induced cardiac pump dysfunction may be associated with downregulation of PPARα and NRF-1. Interestingly, fenofibrate may prevent cardiac pump dysfunction via regulation of fatty-acid oxidation and mitochondrial respiration.

Prevalence of Plakophilin 2 gene (PKP-2) Mutations in South African patients with Arrhythmogenic Right Ventricular Cardiomyopathy: Preliminary Results of the ARVC Registry of South Africa

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Abstract: Genetic mutations in the plakophilin-2 (PKP2) gene cause 25-50% of cases of inherited arrhythmogenic right ventricular cardiomyopathy (ARVC). The aim of this study was to determine the prevalence of PKP2 gene mutations in ARVC patients who are enrolled in the ARVC Registry of South Africa.

Twenty-five DNA samples from ARVC patients were screened for variants in the PKP2 gene using the denaturing high-performance liquid chromatography and sequencing. Population frequencies of novel PKP2 variants were determined in control individuals by SNaPshot and restriction enzyme digestions.

We found six polymorphisms (five novel) and three disease-causing mutations in our ARVC cohort. The mutations were (1) a C1132T transition in exon 4 (2) a reported insertion/deletion in exon11 (2197-2202delCACACCinsG) and (3) a reported intronic splice-site mutation in intron 11 (IVS2146-1G-C). The C1132T mutation results in a novel premature stop codon (Q378X) in two affected brothers in family1. The insertion/deletion mutation causes a premature truncation of PKP2 and was found in two affected siblings of family19. The intronic slice-site mutation is known to acitivate crytptic slice acceptor sites in either intron 12 or exon 13 and was found in an isolated proband. A novel fourth variant, the C1162T (R388W), occurred in three ARVC probands with the same genetic background. This variant was not found in >400 control chromosomes but was found in the unaffected mother of family19. The two affected siblings in family19 co-inherited the rare C1162T variant and the insertion/deletion mutation. The severe phenotype observed in these children suggests a disease-modifying effect for this novel variant.

In our cohort, we have found the prevalence rate of PKP2 gene mutations to be 12%, which is much lower than the reported global frequencies. Additionally, we postulate that the C1162T variant may have a functional effect on PKP2 that confers a gene-dose effect on the phenotype. We also postulate that this variant, which occurred in probands with the same genetic background, may represent a founder effect.

Assessing Rheumatic Mitral Stenosis (MS) with the Proximal Isovelocity Surface Area (PISA) method in a Broad MS Population

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Objectives: To evaluate the PISA technique as an accurate load independent method of assessing MS. The standard methods used to assess mitral valve area include pressure half-time (PHT) and 2-dimentional (2D) planimetry, both of which have limitations. PHT is significantly affected by loading conditions and ventricular properties whereas 2-D planimetry relies heavily on image quality and is technically demanding. The PISA method uses the hemodynamic principle of flow acceleration as fluid approaches a restrictive orifice. It has been validated in the assessment of mitral regurgitation (MR), where it has proven resistant to changes in loading conditions. Limited data is available for MS.

Methods: Patients diagnosed with MS during the period 1/1/2007-1/6/2008 were included. Patients with mixed mitral valve disease, associated aortic valve disease and previous mitral valvuloplasty were also included. Transthoracic echocardiography was used to compare MVA measurement by the PHT and PISA methods against the 2-D planimetry as a gold standard.

Results: 8 patients were studied in this pilot phase. Mitral Valve Areas (MVA) varied from 1.1-1.8cm^2. Two patients had associated severe aortic stenosis (AS), 1 patient severe MR and 1 patient severely impaired left ventricular (LV) systolic function (ejection fraction = 25%). PHT and PISA correlated well with 2D planimetry in patients with isolated, pure MS and those with lesser degrees of associated valve dysfunction. Interestingly, both also correlated well in the cases of associated severe AS and severe MR with preserved LV systolic function. PHT however correlated poorly with 2D planimetry in the patient with poor LV systolic function and also less well in the case of severe AS and associated moderate LV impairment, whereas the PISA correlation remained excellent.

Conclusion: The PISA method shows promise as a robust method to assess MS severity in the range of mild to moderate MS and over a range of hemodynamic loading conditions. Further study over a larger MS severity range and in a larger patient cohort is needed to further investigate this promising technique.

Perfused hypoxic hearts overexpressing PKCepsilon have decreased cardiac function on exposure to fatty acid/glucose perfusate

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Cardiac-specific overexpression of constitutively active PKCε (aPKC) orchestrates cardioprotection at the mitochondrion. Further, aPKCε mouse hearts exposed to an acute or chronic oxidant stress are robustly cardioprotected. We have also reported that aPKCε hearts perfused in working mode with glucose only have increased glucose oxidation rates compared to WT littermate controls, which persists after chronic hypobaric hypoxia. Elevated glucose oxidation rates were accompanied by increased ATP synthesis and tissue glycogen, possibly contributing to maintained cardiac function. In light of persistently elevated glucose oxidation, we hypothesized that aPKCε hearts would not metabolize fatty acids as efficiently as glucose, and might have diminished cardiac function.

Method: Hearts from normoxic or hypobaric hypoxic aPKCε and WT mice were perfused for 40 mins in working heart mode with radiolabelled glucose/palmitate. Rates of glucose and palmitate oxidation were calculated per gram dry tissue weight. Cardiac function (HR, PSP, aortic flow, CO and cardiac work) was measured simultaneously.

Results: aPKCε mouse hearts oxidized more glucose than WT both at normoxia (0.051± 0.02 vs. 0.011±..004, *p<0.05) and after 14d hypobaric hypoxia (0.907±0.17 vs. 0.335± 0.11, *p<0.05). However, fatty acid oxidation rates were similar at baseline (0.198±.02 vs. 0.226±.02, p=n/s) and after 14d hypobaric hypoxia (0.196±.016 vs. 0.213±.014,p=n/s). Cardiac work was higher in normoxic (2.01±0.18 vs. 1.7±0.24, p<0.05) than hypoxic aPKCε mice (0.95± 0.21 vs. 1.25±0.2, *p<0.05). Percentage contribution to ATP production from fatty acid oxidation was calculated and aPKCε hearts showed reduced contribution from fatty acids (45.72±3.86 vs. 65.61±7.38, *p<0.05) as compared with concomitantly increased contribution from elevated glucose oxidation(54.3±3.86 vs. 34.4±7.38, *p<0.05).

Conclusion: (1) Presence of fatty acids disrupts PKCε cardioprotective signaling triggered by hypobaric hypoxia. (2) After hypoxia aPKCε persistently oxidise more glucose. (3) Increased glucose oxidation appears detrimental ⟶ reduced cardiac function in aPKCε mice, possibly glucotoxic.

Metformin mediated restoration of mitochondrial integrity is associated with improved cardiac contractility in isoproterenol-induced model of heart failure

P. Mgandela, T. Maswanganyi, R. Brooksbank, A.J. Woodiwiss, G.N. Norton and S. Makaula

Background: Diabetic cardiomyopathy is characterized by metabolic defects, mitochondrial dysfunction and a severe decline in myocardial performance. Metformin, a metabolic modulator, has been shown to improve metabolic profile and left ventricular dysfunction in diabetic rat hearts. Whether metformin can exert its beneficial effects on non-diabetic failing rat hearts has not been fully elucidated. The aim of this study was to investigate whether (1) isoproterenol induced model of heart failure is associated with loss of mitochondrial integrity, and (2) whether metformin ameliorates left ventricular dysfunction in non-diabetic failing hearts.

Methods: Rats were divided into 4 different groups, namely: the control rats received no treatment, ISO rats were injected with 0.04 mg/kg isoproterenol (ISO) daily for 4 months, metformin control (METF) received 300mg/kg metformin in drinking water and ISO+METF received isoproterenol and metformin daily for 4 months. To evaluate cardiac mitochondrial and myofibrillar morphological changes, muscle strips were fixed into 2.5% glutaraldehyde and processed for transmission electron microscopy (ETM). Changes in cardiac dimensions were determined using echocardiography.

Results: Employing ETM, we observed mitochondrial and myofibrillar derangements, reduced mitochondrial abundance and accumulation of fat droplets in ISO treated rats. However, metformin treatment reversed ISO-induced deleterious effects on mitochondria damage and reduced accumulation of fat droplets. Moreover, echocardiographic analysis of cardiac dimensions revealed significant increase in left ventricular end diastolic diameter (LVEDD) (11.9±0.4 mm, p<0.05), left ventricular end systolic diameter (LVESD) (4.90±0.40 mm, p<0.05) and reduction in endocardial fractional shortening (FSmid) (41.46±1.68 %, p<0.05) compared to controls. ISO+METF treated rats showed a significant reduction in LVESD (3.64±0.37 mm, p<0.05 vs. ISO) and improved FSmid (52.10±3.70%, p<0.05 vs. ISO) however moderate changes were observed in LVEDD (10.43±0.7 mm, NS vs. ISO).

Conclusion: We demonstrated that metformin induced restoration of mitochondrial integrity is associated with improved cardiac contractility in the isoproterenol-induced model of heart failure.

Transesophageal Echocardiography for the Prevention of Embolic Complication after Catheter Ablation for Atrial Fibrillation

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Introduction: Thrombo-embolic complications during left sided ablations range between 1.8-5%. Pre-procedural transesophageal echocardiography (TEE) has been used to exclude the presence of left atrial thrombi in order to minimize risk. This practice is empiric and it has not been evaluated in contemporary practice. The TEE is used either routinely or selectively as a pre-ablative strategy in patients electively undergoing catheter ablation for atrial fibrillation(AF). The primary aim of this study was to assess the impact of these strategies on thrombo-embolic events in a cross section of Canadian centres. A secondary objective was to determine the prevalence of left atrial (LA) thrombi identified on TEE in a contemporary patient population.

Methods: A multi-centre national survey evaluating the practice of 11 AF ablation centres across Canada.

Results: The survey covered procedures on 2 225 patients. There were 996 in a routine pre-procedure TEE strategy and 1 190 in a selected TTE strategy; 39 had no TEE strategy. 12 of 996 in the routine unselected cohort had thrombi identified (prevalence 1.2%). 200 TEEs were performed in the 1 190 selected cohort; 4 left atrial thrombi were observed (2.0%); there was no significant difference in prevalence of thrombus (p=0.34). A total of 11 embolic events occurred. There was no difference in event rate between the two strategies; (0.6% and 0.4%, p=0.054, in the unselected routine and selected strategies respectively). Events were unrelated to AF duration (persistent vs. paroxysmal, r=0.03, N=2225,p=0.9).

Conclusion: The selection criteria employed to perform TEEs did not increase the chance of identifying LA thrombi. The overall thromboembolic event rate was low (0.49%) and was not significantly different between the two TEE strategies.

Learning was fun for the first time in my life!

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#Lucile Packard Children's Hospital at Stanford Hospital (LPCH), USA

Introduction: Red Cross Children's Hospital and Lucile Packard Children's Hospital entered into a working relationship supported by the Heartlink initiative aimed at improving nursing care to children with cardiac defects and retaining staff with scarce skills [paediatric intensive care unit (PICU) staff]. The team from Lucile Packard Children's Hospital introduced the concept of a skills fair as a teaching method that they had successfully used to improve practice standards. This concept was introduced to the PICU team at Red Cross Children's Hospital in an attempt to promote a culture of life-long learning, promote team work and boost morale amongst staff in the PICU.

Methods: A training needs analysis was done amongst PICU staff. An 82% response rate was obtained.

An international, interdisciplinary focus group reviewed the results of the training needs analysis. Educational offerings were developed to address the nurses' needs, promote their confidence in practice, and optimize patient care delivery.

Nine skills were identified for improving PICU professional nursing staffs skills and included: line care, electrocardiogram tracings, managing central lines, defibrillation, hand washing, resuscitation, suctioning, bedside set-up and medication safety. The focus group brainstormed on creative methods to implement hands-on, practice-based education.

A carnival theme was selected and interactive games and simulation training were developed for each of the nine topics. Important skills fair components included: learner-centered approach; a fun, non-threatening environment; multi-modal, performance-based training; utilization of positive critique, and fostering development of critical thinking skills. Patricia Benner's Novice-to-Expert model was employed at all stations and teachings modified to suit the learner. When appropriate, practice protocols were reviewed to standardize patient care delivery. Equipment was demystified and offering positive critique challenged staff in a beneficial manner. Professional nurses' (PNs) confidence in care was assessed pre- and post-implementation of the skills fair.

Results: Forty-five (45) PICU PNs were working in the PICU at the time of the skills fair. Twenty-nine (PICU) PNs completed pre- and post-implementation questionnaires (64.5% of total number of PNs in PICU). Data demonstrated a modest increase in confidence and a considerable increase in knowledge after the event. All PNs enjoyed the fair, learned from it, and would recommend it to their peers. 82% preferred this method of teaching, 94.5% would attend again without pressure from their supervisor, and 98.6% asked for another skills fair. In addition to our data, there was overwhelming positive verbal feedback and on evaluation forms supporting our data.
Conclusions: Through use of innovative teaching strategies, learning can be fun, successfully increase PNs' confidence in their practice, and can help standardize patient care delivery.

Suppressing unfavorable biological response of vein grafts through external nitinol mesh

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Introduction: According to a WHO report of 2005, there were 17.5 million cardiovascular deaths accounting for 30% of the global deaths. Of these deaths at least 7.5 million was due to ischemic heart disease. It is predicted by the year 2010, cardiovascular diseases will be the leading cause of death in developing countries.
Coronary artery bypass surgery is a tried and tested modality of treatment for coronary artery disease and currently the most commonly used conduits are the internal thoracic artery combined with saphenous vein grafts. Unfortunately the vein grafts have a high attrition rate; about 1-2% per year in the first five years, increasing to 4% per year from year six to eleven postoperatively. Only approximately 60% of vein grafts remain patent eleven years postoperatively. The pathognomonic feature of vein graft disease is intimal hyperplasia leading to vein occlusion. In spite of this major drawback, vein grafts still serve as a very popular conduit in coronary surgery. Much emphasis has been placed on trying to prolong the life span of such grafts and in doing so, our aim in this study was to test the biological effect that an external saphenous vein support (eSVS) mesh had on intimal hyperplasia.
Methodology: Single aorto coronay grafts were performed in each of thirty-two chacma baboons. Coronary artery bypass grafting of the left anterior descending artery was done with the aid of cardio-pulmonary bypass and ischemic cardiac arrest using autologous saphenous veins. Sixteen baboons received this eSVS mesh while sixteen grafts were unmeshed; of which eight received external glue application while eight grafts were unglued.
In the baboons that survived until six months; their hearts were explanted and the grafts underwent angiographic, macro and microscopic evaluation.
Results: There were four premature deaths(12.5%). Fourteen of the sixteen(87.5%) meshed aortocoronary grafts were patent while in the non meshed group, six of the eight(75%) nonglued grafts and also six of the eight(75%) glued grafts were found to be patent. With regard to patency no statistical significance was observed between the meshed and non-meshed grafts.
Microscopic examination, however, revealed a statistically significant reduction ($p < 0,0001$) in intimal hyperplasia in the vein grafts with the eSVS mesh as compared to the non meshed group.
Conclusion: Our studies have proven a statistically significant reduction in intimal hyperplasia in vein grafts fitted with the eSVS mesh. This abodes well for the longevity of aorto-coronary vein grafts.

A giant rhabdomyoma in a neonate with tuberous sclerosis

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Introduction: Cardiac rhabdomyomas, while rare at all ages, are the most common primary cardiac tumors in infancy. They are common in patients with tuberous sclerosis but also occur as single lesions in non-tuberous sclerosis patients. The clinical course of a patient who presented with a giant right atrial and several smaller left ventricular rhabdomyoma and other features of tuberous sclerosis is described.

Case report: A 7-day-old female infant was referred for assessment of a bradycardia. The child was delivered at a peripheral hospital by caesarean section for fetal distress and bradycardia. An electrocardiogram (ECG) done post delivery showed a bizarre junctional rhythm and giant P waves. A surprise finding on echocardiography was a large mass filling the right atrium together with several smaller masses within the interventricular septum and left ventricle suspicious of intracardiac rhabdomyomas. The heart was otherwise normal. Dermatological findings and a CT scan of the brain and kidneys showed features consistent with tuberous sclerosis. The patient had a successful surgical resection of the giant right atrial mass which was confirmed to be a rhabdomyoma on histology. The patient had a successful post operative course with the post surgical ECG showing normal sinus rhythm. An echocardiogram done 3 months post presentation revealed spontaneous regression of the remaining rhabdomyomas within the left ventricle. The patient will be followed up by a multidisciplinary team with respect to the tuberous sclerosis.

Discussion: Rhabdomyomas are benign myocardial hamatomas that most often involve the left ventricle (80%) but can occur in any location in the heart including the atria. Large tumors occur most commonly in the ventricles. Since these tumors demonstrate benign pathological characteristics and tend to regress over time a conservative treatment approach is preferable. Complete regression has been described in as little as 3 weeks but can take as long as 4 years. Surgical resection may be indicated in symptomatic patients presenting with cardiac failure, symptoms associated with obstruction to blood flow or abnormalities of the conduction system, as demonstrated in the above patient. Untreated symptomatic rhabdomyomas are associated with a fatality rate of 53% in the first week of life and 78% by 1 year.

Pulmonary atresia with ventricular septal defect with main pulmonary blood supply from coronary artery fistula

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Patients with pulmonary atresia and ventricular septal defect (PA – VSD) present with severe cyanosis and hypoxemia in neonatal life. These patients often have severe abnormalities in the size and distribution of the pulmonary arterial tree and well-developed systemic collateral arteries which supply all or portions of lung parenchyma. Blood supply to the lungs is derived entirely from the systemic arterial circulation. These sources are the ducts arteriosus, systemic to pulmonary collateral arteries and occasionally a coronary artery and plexuses of bronchial or pleural arteries.

We present two cases of patients with PA – VSD with absent native pulmonary arteries whose main supply to the lungs is left coronary artery for one patient and right coronary artery for the other. Both patients were deeply cyanosed and hypoxemic. They were both investigated with use of echocardiography, cardiac catherization and angiography.

Plasma Arginine Concentrations are Related to Proline Concentrations in Black South African Subjects

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Introduction: The semi-essential amino acid arginine

- is synthesized by the kidney and is used in protein synthesis, including the cross-linking of collagen;
- is the precursor to the vasodilator nitric oxide, which is also a neurotransmitter and is essential in the defense against infectious diseases (e.g. malaria);
- plays a significant role in burn victims (in nitrogen metabolism) although its benefit in wound healing per se is less clear;
- inhibits platelet aggregation and decreases PAI-I and fibrinogen concentrations;
- prevents salt sensitive hypertension in the rat model;
- supplementation improves outcome in heart failure and decreases blood pressure in hypertension.

Orotic acid concentrations, a marker of arginine deficiency, are elevated in cardio-vascular diseases (including hypertension and stroke), diabetes and in some cancers.

Factors regulating arginine concentrations in humans have not been fully elucidated. We examined the relationships between plasma arginine concentrations and other amino acids in subjects without and with hypertension. Patients with hypertension are convenient to study as changes in arginine should reflect as non-invasively measured blood pressure changes.

Aim: To determine relationship between plasma arginine concentrations with other amino acids in Black African patients with hypertension.

Methods: Consecutive subjects being screened for hypertension at the clinic at Chris Hani Baragwanath Hospital were requested to take part in the study and provide a blood and urine sample after an overnight fast. In consenting subjects, ambulatory 24-hour blood pressures (ABPM) were measured and amino acid profiles in blood and urine determined by HPLC-MS. Hypertension was defined in subjects with a mean daytime ABPM >89mm Hg.

Results: Plasma arginine concentrations were increased in hypertension and correlated directly with proline concentrations ($r2=0.91$; $p<0.05$). Weaker associations with amino acids using the y+-transporter, and the branch chain amino acids, were noted.

Discussion: The finding of elevated plasma arginine concentrations in hypertension is consistent with two published reports in the literature. The novel finding of the correlation between plasma arginine and proline, a precursor of arginine, suggest that arginine is being synthesized from proline. The results suggest that arginine synthesis may be up-regulated, as reflected by the increased plasma concentrations. However, the arginine is not available for nitric oxide synthesis in these patients with hypertension. Further studies using non-radioactive isotopes would confirm the conversion of proline to arginine.

Employer based Cardiovascular and Respiratory Disease Management Program (Outcomes Research)

George Nel and Francois Wessels

Objectives: Assess impact of consistent face-to-face, nurse-patient interaction as part of chronic disease management on clinical risk control and economic outcomes in the following disease areas: cardiovascular (cholesterol, hypertension) and respiratory disease.

Methods: A major South African company's employees, undergoing annual occupational health surveillance (on-site) were screened by program nurses to identify risk levels or any patients not controlled. At-risk population was referred to clinician for diagnosis and appropriate treatment. This population was followed over an 18-month period (initiated June 2006). Clinical data was captured by program nurses, medical aid claims from Medical Aid (restricted scheme) and absenteeism due to sick leave from the employer (as well as employee salary bracket as an estimate of productivity). Clinical results were analyzed based on a Last Observation Carried Forward analysis and 12-month pre and post enrolment assessment for economic parameters. Every patient was his/her own control.

Results: 5 506 Employees (Caucasian 59%, African 36.4%, male 90.4%, ave age 42 yr) were screened over a 20.7 month period of which 3 425 presented with a target risk factor and was followed-up. Pre-screenings of 7 592 were performed and 13 358 follow-up consultations were performed (ave 3.9). Total program months were 70 998.

Clinical Profile

	Screening	Follow-up	ARR	RRR
Hypertension	23.0%	11.1%	11.9%	52%
Cholesterol	28.9%	16.9%	12.0%	42%
Respiratory	10.4%	2.8%	7.6%	73%

The economic assessment reflected that total cost of managing this population was R1.5 million per month (equal burden to medical aid and employer, 90% cardiovascular related). This total cost was reduced by 9%.

Medical aid expenditure remained flat but the ratio of acute (hospitalization) vs. chronic management (medication and consultation) increased from 1:1.4 to 1:2.7. Costs were reduced through a decrease of 10% in hospitalizations and a 3% reduction per Rx-line cost. Costs were increased by 33% on Rx utilization/compliance and 32% increase in consultations.

Employer benefitted through a 19% reduction in absenteeism (compared to the unmanaged population).

An Employee Satisfaction Survey indicated that all participants wanted the program to continue. Major benefit was seen in the face-to-face nurse interaction and "knowing the risk number". Printed information was viewed as less valuable. The patients indicated changes to own lifestyle including stopping smoking (33%), taking medication more regularly, being conscious of what they eat and drink and exercising more regularly.

Conclusion: *Clinical* - The high prevalence of cardiovascular risk (5 in 10 employees) is of concern as the population ages but respiratory disease is in line with national expectation (1 in 10). The program achieved significant improvement in clinical risk control; not only through increased Rx but also lifestyle gains. Cardiovascular disease is a huge cost driver and needs to be a primary focus at employer and MA level.

Medical Aid - The shift in MA expenditure from acute (hospital) to chronic management (Rx and consults) should in future benefit all stakeholders (if maintained). The outcomes were achieved without incremental cost to the fund.

Employer - The employer experienced a pronounced benefit due to reduced absenteeism. This analysis only considered direct salary cost of absenteeism (which is very conservative). The productivity benefits experienced by the employer are potentially 10-fold greater.

Outcomes Research Program - The study has proven the benefit across all parameters – the magnitude of the impact might vary in different settings but overall trends observed should be consistent. The clinic nurse can successfully act as the custodian of the disease management process and the patients (employees) respond well to the face-to-face interaction with a dedicated nurse. This Outcomes Research Program should be internalized (by the employer) with dedicated resource to sustain the benefit.

Independent Physician: Prof James Ker; **Principal Investigator:** Dr Laubi Walters

Sponsors: Unconditional grants were received from Pfizer and GSK

A comparative study of the complications of infective endocarditis in patients with and without HIV: an echocardiographic study

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Aim(s): (1) To determine the echocardiographic features of patients with infective endocarditis. (2) To compare the findings in HIV positive versus HIV negative patients.

Method(s): This was a prospective study, conducted over three years using the modified Duke criteria in diagnosis of infective endocarditis. A control group of age-matched patients with clinical and echocardiographic evidence of valvular regurgitation, who did not satisfy the criteria and who underwent surgery, was used in comparison.

Results: During this period 91 patients were screened for infective endocarditis. 77 satisfied the criteria for a definite diagnosis of IE. Blood cultures were positive in 46% cases. The commonest organism was S. aureus. Most patients had advanced valve disruption with heart failure and a high peri-operative mortality. The prevalence of echocardiographic complications was 50.6% in the whole group.

Leaflet aneurysms appeared larger in size in the HIV positive patients compared to the smaller sized aneurysm in the HIV negative patient ($p=0.008$). Aortic root abscesses were of a larger size on echocardiography in the HIV positive patients ($p = .118$). There was no evidence of myocardial abscess formation.

Conclusion: There was no difference in the clinical presentation of infective endocarditis between HIV positive and HIV negative patients.

In the setting of antecedent infection (which is common in HIV positive patients) the use of the modified Duke criteria is associated with a high degree of false positivity. Greater reliance should be placed on blood cultures.

TGF-β delays skeletal myoblast differentiation in an isoform-independent manner

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Introduction: Satellite cells are a quiescent heterogenous population of stem and progenitor cells which, once activated, become myoblasts and differentiate to facilitate skeletal muscle repair or growth. Myoblasts have also been shown to repair significant portions of the infarcted myocardium; their high proliferative capacity and resistance to hypoxic conditions make them ideal donor cells within ischemic muscle. The Transforming Growth Factor-β (TGF-β) superfamily members are elevated post-injury and their importance in the regulation of myogenesis and wound healing has been demonstrated by both in vitro and in vivo research. Studies suggest that whereas TGF-β decreases skeletal muscle differentiation, it induces cardiac differentiation. For the latter, an isoform-specific effect has been shown; knockout models suggest a pivotal role for TGF-β2, and not –β1 or –β3, in cardiac development. Furthermore, wound healing studies in other tissues have shown that TGF-β1, -β2 and -β3 exert differential effects on repair speed and quality. To date however, no in vitro studies have specifically compared the effect of TGF-β1, -β2 and -β3 on skeletal myogenesis.

Methods: We used the C2C12 cell-line to analyze the effect of recombinant active TGF-β1, -β2 and -β3 on myoblast proliferation and differentiation. Proliferation was assessed using Total Nuclear Count and Proliferating Cell Nuclear Antigen (PCNA) expression. Differentiation was determined via expression of MyoD, myogenin and myosin heavy chain (MHC), as well as the rate of MyoD degradation.

Results: We found that, irrespective of the isoform, TGF-β significantly increased proliferation of C2C12 cells by changing the cellular localization of PCNA to promote cell division and prevent cell cycle exit ($p<0.05$). Concomitantly, TGF-β1, -β2 and -β3 significantly delayed myogenic commitment by increasing MyoD degradation ($p<0.05$) and decreasing the expression of myogenin ($p<0.05$). Terminal differentiation, as measured by the expression of MHC, was also decreased ($p<0.05$).

Conclusion: We demonstrate for the first time that TGF-β promotes proliferation and delays differentiation of C2C12 myoblasts in an isoform-independent manner. This underscores the observation by others that a general antagonism of the TGF-β signalling pathway can improve skeletal muscle regeneration in rodents. Given the elevated TGF-β levels post-infarct, these results may also cast more light on why myoblast transplantation to improve cardiac repair has thus far proven to be problematic.

Comparison between two approaches for doing Aortic Valve Replacement

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During the period Feb 2000 to June 2007 112 patients had aortic valve replacement (AVR) in Sudan Heart Center (SHC) by one surgeon. This study was designed to compare two approaches for access to the AVR.
Ministernotomy (MS) approach was used in 63 patients and the conventional full sternotomy (FS) was used in 49 patients.
Significant shorter crossclamp (XCP) and cardiopulmonary bypass (CPB) time was observed in the MS group (86 +/- 24min & 121 +/- 29 min) respectively vs. (103 +/- 58 min & 139 +/- 48 min) in the FS group. Also significant shorter ICU stay and overall hospital stay was observed in the MS group (2.65 +/- 1.4 days & 9.5 +/- 4.5 days) respectively vs. (4.1 +/- 1.2 days & 12.6 +/- 7.7 days) in the FS group.
No significant difference was found for the post operative complications and the early and late mortality between the two groups.
We conclude that the MS approach is very safe and effective and that it is associated with shorter XCP time, CPB time, ICU stay and overall hospital stay.
We recommend that the minimally invasive approach should be the standard approach for sole AVR. The conventional approach can be reserved for when there is a combined procedure in addition to the AVR.

The Prevalence and Haemodynamic Predictors of Effusive Constrictive Physiology in Stable Patients with Large Exudative Pericardial Effusion

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Introduction: Effusive constrictive pericarditis (ECP) occurs when pericardial effusion and visceral pericardial constriction coexist to cause pericardial compression and constrictive physiology. The definitive diagnosis of ECP requires the presence of persistantly elevated right atrial pressure despite the normalization of intra-pericardial pressure following pericardiocentesis. ECP is thought be a precursor to constrictive pericarditis. The prevalence of ECP in patients with large inflammatory effusions is unknown. We hypothesized that ECP is common in patients with inflammatory exudative pericardial effusion as a result of inflammation of the visceral pericardium.
Objectives: (1) To determine the prevalence of ECP in clinically stable patients with large exudative pericardial effusions suspected to be tuberculous in etiolgy. (2) To determine if there were hemodynamic predictors of ECP.
Methods: Between January 2006 and May 2008 consecutive stable (systolic blood pressure >95) patients with large exudative pericardial effusion suspected to be of tuberculous origin, were recurited. Right atrial and intra-pericardial pressures were measured simultaneously, before and after pericardiocentesis. ECP was defined as failure of the right atrial pressure to fall by 50% or to a new level of ≤12mmHg after the intra-pericardial pressure was lowered to below 2 mmHg. Tamponade was defined as equalization of the intrapericardial and mean right atrial pressure.
Results: 142 consecutive patients underwent pericardiocentesis in the period under review. Eighty-one patients were excluded from analysis because of hemodynamic instability or a diagnosis other than tuberculosis (72) and 9 patients did not have complete hemodynamic data. 61 patients had complete data for analysis. 59/61 (97%) had an inflammatory exudative effusion. 23/61 (38%) met criteria for ECP.
The intracardiac pressure and hemodynamic findings in the 61 patients with complete hemodynamic data were as follows: 21/61 (34%) had opening right atrial pressures ≥ 20mmHg, 11/61 (18%) had opening intra-pericardial pressures ≥ 20mmHg, and 32/61 (52%) met the criteria for cardiac tamponade. The characteristics of the patients with ECP were as follows: 10/23 (43%) were culture positive for tuberculosis, 17/23 (74%) had a RAP ≥ 20mmHg, 8/23 (35%) had an opening intra-pericardial pressure≥ 20mmHg, and 12/23 (52%) met the criteria for cardiac tamponade. 10/21 (47%) of patients with RAP ≥ 20mmHg met criteria for tamponade. By univariate analysis the predictors of ECP were RAP ≥ 20mmHg OR 24.08[5.98, 96.95]) and pericardial pressure ≥ 20mmHg OR 10.93[2.09, 57.12]). The presence of cardiac tamponade was not associated with ECP (OR 0.87)[0.31, 2.49]
By multivariate analysis only RAP ≥ 20mmHg remained significant (OR 18) [3.2-105].
Conclusion: We show, in this first and largest study of its kind in the world, that effusive constrictive pericarditis is relatively common (38% prevalence) in normotensive patients with inflammatory exudative effusions. Right atrial pressure ≥ 20mmHg was strongly associated with ECP.

Rheumatic fever and rheumatic heart disease: geographic area of origin, referral rate, disease severity and disease outcome of patients presenting to our unit

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Background: Acute Rheumatic fever (ARF) and its common complication Rheumatic heart disease (RHD) remains a major cause of mortality and morbidity amongst children and young adults in the developing countries. Poor socioeconomic status including poverty and overcrowding is one of the predisposing factors to the development of ARF. South African health policy has changed since 1994 with a new emphasis on primary health care and this might have influenced the face of rheumatic heart disease in this community that is in transition.

Objective: To assess the demographics and referral rate of the patients seen at the above institution since 1993 and to evaluate whether the change in health policy in South Africa has had an impact on the picture of affected patients at presentation with regard to acute versus chronic disease including disease severity and outcome.

Method and results: We conducted a retrospective record review of all patients seen at our institution with rheumatic fever and rheumatic heart disease for the period of January 1993 to June 2006. There was a fall in the number of new referrals over time. The majority of patients with severe disease seemed to originate from outside the Gauteng province and within the Gauteng province the majority of patients were from the poorly resourced areas.

Conclusion: Although there is a drop in the number of RF and RHD patients presenting to our hospital there still remains a burden to health resources in terms of the need for expensive valvular heart surgery and awareness needs to be increased amongst the health care workers and the department of health.

Transient Heart Block associated with acute Myocarditis

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We present an unusual case of transient heart block associated with acute myocarditis.

A 7-year-old male was referred urgently from a local hospital with bradycardia. He initially presented with two episodes of syncope on the day of admission. This was preceded by abdominal discomfort and vomiting beginning the day before.

He was found on examination to be poorly perfused with poor cardiac output and lethargy. Complete heart block with a ventricular rate of 26 beats per minute was recorded.

An emergency temporary pacemaker was inserted with rapid improvement in the child's general condition.

Investigations at this stage demonstrated high urea related to the poor cardiac output and markedly elevated cardiac enzymes. The chest X-ray was unremarkable as was the echocardiogram with a fractional shortening of 28%. A selective coronary angiogram performed the following day demonstrated no coronary abnormalities.

No steroids, immunglobulin or antifailure treatment was instituted.

Five days following pacemaker insertion sinus rhythm returned and the temporary pacemaker was removed on Day 7 following a normal 24-hour holter. The cardiac enzymes returned to normal and the child was discharged completely recovered.

The data on heart block associated with myocarditis and its clinical course is limited, with complete recovery being documented in approximately two-thirds of cases. Prompt recognition and emergent pacing is lifesaving.

Management of atrio-ventricular septal defects in a developing country: an institutional experience

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Introduction: Atrio-ventricular septal defects (AVSDs) require surgical treatment, either definitive correction or palliation by a pulmonary artery band (PAB) and subsequent delayed repair. We review our institutional experience with both approaches to determine outcome and compare that to current international practice.

Patients and methods: A retrospective review of patients operated between January 2000 and December 2006. Fields determined: patient characteristics, age at presentation, presence of Trisomy 21, pre-operative and post-operative anatomical and functional description of defect, age at surgery, hospital stay, outcome and follow up.

Results: Records of 92 patients were reviewed as identified from the ICU database. Of these 81, were assessed suitable for biventricular repair. Ratio of M: F- 33:48, median age at presentation 7 months (range: 0- 81 months). The incidence of T21 was 52 (65%). The distribution of Rastelli group A, B and C was 54(66.6%), 9 (11.1%) and 4 (4.9%) respectively and not recorded in 14 (17.2%). The total cohort was divided into 3 groups: (A) PAB only, awaiting definitive correction 29 (31.5%), (B) PAB and Correction, 28 (30.4%) and (C) Primary correction, 24(26%). In group A, the median age at PAB application was 8 months. In group B, the median ages at PAB application was 8.5 months and 33 months at definitive repair. The median interval between PAB application and definitive correction was 28 months. In group C the median age at definitive repair was 18 months and ten patients had primary repair under one year of age. The mortality rate in group A as analyzed between the application of a pulmonary artery band and date of review was 17% (5/29). The mortality rate post correction (groups B and C) was 1.9% (1/52).

Conclusion: The mortality at the time of definitive repair following a staged approach is low for those that survive to definitive correction. However, the interval between palliation and definitive repair is long and the inter-stage mortality is high.

Sick Sinus Syndrome (SSS): a potentially malignant arrhythmia

A. Okreglicki

Introduction: SSS is often considered benign albeit occasionally associated with significant morbidity. Despite 101yrs since the discovery of the sinus node, little is known of the natural history of its dysfunction and associated mortality. Some studies suggest overall survival of patients with SSS is the same as of the general population. The supposed benign nature based on this may result in the inappropriate failure to appreciate the potential life-threatening danger.

Methods: *Case 1:* A 47-year-old woman visited the EU 6 days after her 1st and only syncopal episode. She had no past history, other symptoms or medications. All was normal except for pulse of 50 bpm. The ECG showed intermittent S.arrest with junctional escape. She was discharged to return for a Holter in 3 days. She never arrived. She died 2 days after her visit.

Case 2: An 80-year-old woman with a 2-year history of "tachy-brady" SSS (with palpitations and pre-syncope) was admitted to the Cardiac Unit after her 1st syncope. The only abnormal finding was S.bradycardia of 39 bpm. A permanent pacemaker implant was planned in 2 days time. The following day, while waiting for the procedure, she had syncope again with injury. Telemetry records showed a 12sec run of polymorphic ventricular tachycardia (PMVT) / Torsade de Pointes. She was paced urgently.

Case 3: A 74-year-old woman was transferred following recurrent syncope. At the referring hospital the ECGs showed S.bradycardia of 38 bpm and intermittent S.arrest with junctional escape. A chance observation of recurrent non-sustained PMVT precipitated her transfer for urgent pacing.

Results: Review of the 3 cases showed the common finding of a long QT: 640,802,656ms and QTc: 610, 658, 598ms respectively and bifid T waves in the anterior chest leads. No electrolyte abnormalities or drugs could account for these ECG findings. In cases 2 and 3, since pacemaker implantation, no further symptoms attributable to SSS have been reported.

Conclusions: These cases highlight that dismissing the danger of a diagnosis of sick sinus syndrome and considering it as benign may result in inappropriate delay in pacing. It is mandatory to examine the ECGs of patients with SSS for the malignant signs of marked QT prolongation and T notching.

The accuracy of NT-proBNP as a measure of the LV filling pressure

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Cardiac catheterization is the "gold standard" for the measurement of the LV filling pressure. Since Brain Natriuretic Peptide (NT-proBNP) is released in response to LV dilatation, it has been used as an estimate of the LV filling pressure. The ratio of the mitral inflow velocity to early diastolic velocity of the mitral annulus (E/Ea) derived non-invasively from Tissue Doppler Imaging (TDI) has also been shown to correlate with the mean left ventricular (LV) filling pressures.

Aim: We investigated the potential of NT-proBNP and TDI in measuring LV filling pressure and determined their accuracy in comparison to established invasive methods of measuring the LV filling pressure.

Method: Fifty consecutive patients (25 males/ 25 females) admitted to the Cardiology Ward at Inkosi Albert Luthuli Central Hospital for coronary angiography were examined by conventional echocardiography and Tissue Doppler Imaging (TDI). Plasma NT-proBNP levels were measured simultaneously. BNP levels were log transformed for statistical analysis.

Results: Mean BNP levels were elevated in this population, and showed a significant correlation with the systolic blood pressure (r=0.292), left ventricular mass index (r=0.319), wall stress (r=0.290) and E(annulus) (r=-0.362).

The E/Ea(l) had a low sensitivity of 23%, but was the most specific parameter of 93%. The AUC =0.683 for E/Ea, was marginally better than that for NT-proBNP (AUC=0.676) which had the highest sensitivity of 91%, but a low specificity of 36%.

Multivariate linear regression showed that with every 1 log unit increase in BNP the risk of abnormal LV filling pressure increased significantly by 10 times (p=0.009). The other factors which were significantly independently associated with abnormal LV filling pressure were the male gender and E/Ea (1.6 times increase in risk with 1 unit increase in E/Ea).

Conclusion: Although correlation of the E/Ea(l) with the LV filling pressure was significant (p=0.039), it was only marginally stronger than NT-proBNP (p=0.108).

NT-proBNP may well be a useful marker and a surrogate for left heart catheterization in identifying raised LV filling pressure in patients exclusively with coronary artery disease.

Impact of Highly Active Anti-Retroviral Therapy on Pediatric Human Immuno-deficiency Virus Associated Left Ventricular Dysfunction within the Johannesburg Teaching Hospital Complex

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Objective: To analyze the outcome of pediatric patients with left ventricular dysfunction who have been placed on Highly Active Anti-Retroviral Therapy (HAART) within the Johannesburg Academic Hospital Complex.

Method: Retrospective analysis of records of 34 HIV positive children with echocardiographically-documented left ventricular dysfunction who were managed and followed up at Chris Hani Baragwanath, Coronation and Johannesburg Hospitals. Baseline characteristics and changes in the following variables were reviewed and compared: fractional shortening (FS), CD4 percentage, viral load and nutritional status. The various HAART combinations assigned to each patient and treatment duration were documented.

Results: Eighteen of the 34 patients with left ventricular dysfunction (group 1) received HAART for a mean duration of 24 months, and 16 patients (group 2) were HAART naïve (pre HAART era). There was no statistically significant difference between group 1 and group 2 regarding FS, nutritional Z-scores at the initial visit. There was no immunological monitoring in group 2 as these patients never received HAART. Only seven patients in group 2 had follow-up echocardiograms and of those, three had improved FS. Nine of group 2 patients (pre-HAART roll-out) demised and the rest were lost to follow-up (presumed dead).

	Group 1 (HAART) n= 18
Treatment duration	24 months
Male: Female ratio	9: 9
Mean age (initial visit)	75 months
Died	1
Lost to follow up	1
Improved LV function	17

Group 1	Pre HAART n = 18	Post HAART n = 18	p-value
FS (mean)	18.2 %	32.8 %	<0.0001
CD4 (median)	12 %	30.5 %	<0.0001
Viral copies (median)	24 9000	25	<0.0001
Weight gain Median Z-score	- 1.70	-1.32	0.0083

Discussion: The above findings are in keeping with other reports that have shown improvement in left ventricular function in patients with HIV associated cardiomyopathy treated with HAART. The recovery of myocardial function is associated with improvement of their initially poor immunological and nutritional status emphasizing the importance of initiation of HAART in patients with LV dysfunction.

Conclusion: It is possible that viral suppression induced by HAART prevents HIV viral replication within the cardiac myocyte, thereby preventing damage to the myocardium and resulting in improved cardiac function. Failure of initiation of HAART is associated with increased mortality.

Nursing post operative cardiac children with pulmonary hypertension - the art of maintaining a balance

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Introduction: Pulmonary hypertension (PHT) is a relatively common life-threatening peri-operative problem in pediatric cardiac surgery. In the context of staff shortages, loss of skilled nurses, high patient turnover and patients requiring complex care it is essential that Pediatric Intensive Care Unit (PICU) nurses are competent, i.e. possess the necessary knowledge and skills to recognize and appropriately manage PHT. A full understanding of precipitating factors for PHT together with the ability to differentiate between a pulmonary hypertensive event or crisis is essential for the PICU nurse. "The better the nurse's understanding of the child's congenital heart disease, pre-operative condition, surgical procedures and potential postoperative complications, the more able that nurse will be to anticipate, recognize and treat postoperative complications" Hazinski (1999).

The aim of this case presentation is to discuss the role of the nurse in the management of the post operative cardiac child with PHT by means of eliminating factors that promote pulmonary vasoconstriction and instituting measures that promote pulmonary vasodilation.

Method - Case Presentation: A 3-month-old female patient post surgical repair of supracardiac total anomalous pulmonary venous drainage (TAPVD) was admitted to the PICU with a pulmonary artery line, arterial line, central venous line and cardiac monitoring. She was initially hemodynamically stable but presented with episodes of pulmonary hypertension.

Various strategies using a basic and integrated approach were instituted to limit stimulation of pulmonary hypertension including control of pain and anxiety, reduction of agitation, limitation of routine suctioning and precautionary measures during suctioning. Other strategies included careful monitoring and management of fluids to prevent over or under hydration, pharmaceutical management of PHT such as magnesium chloride, pulmonary vasodilators (including nitric oxide), moderate alkalosis and the prevention and management of sepsis.

A multi-disciplinary team approach with regular reviews is essential for good results. A collaborative project with US-based Children's HeartLink provided support with resources and additional training possibilities.

Conclusion: This case presentation will provide an understanding of the role of nurses caring for post operative cardiac children with pulmonary hypertension. It will succinctly describe how general nursing therapies and directed medical therapies are manipulated in children to maintain the balance and improve the outcome.

Orientation to PICU - developing a workable programme with limited time

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Critically ill patients require the care of knowledgeable and highly skilled nurses. The challenges nurses face daily, such as extreme staff shortages, the loss of highly skilled nurses, high patient turnover and patients requiring complexed care have major implications on the delivery of quality care. Thomason, 2006 states: "Today's nursing educators and clinical nurse specialists are faced with the challenge of how to present the necessary information during new employee orientation in order to facilitate the greatest amount of learning".

An orientation programme was developed and implemented in a general PICU with a high turnover. The aim was to provide new registered nurses (RNs) with the necessary knowledge and skills to improve their performance and confidence as soon as possible in order to meet the unit's needs. Some recruits had pediatric nursing experience but most are new graduates. It seemed important to design a multipronged approach and to include current PICU staff in the programme.

Traditional classroom training was the initial method of orientating new RNs in the unit, but staff challenges soon necessitated a shift towards a practical and more integrated approach. Strategies like requesting the newly qualified RNs to prepare and present specific topics during in-service training sessions supported the unit. The benefit of a collaborative project with US-based Children's HeartLink provided support with resources and additional training possibilities.

This presentation will explain the orientation process of RNs over a 2-year period. It will include challenges, practice shifts as well as evaluation to date.

Food choices and their nutritional value in black African patients with heart failure: How affordable is a healthy diet?

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Background: Heart failure (HF), an emerging health problem in one of Africa's largest urban concentrations of black Africans, requires targeted prevention and management strategies. The study aim was to provide a detailed description of the dietary habits and potential nutritional deficiencies of black African patients diagnosed with HF. It specifically focused on the impact of inherently varied cultural and dietary patterns, the poor socio-economic status of many patients and the affordability of healthy versus unhealthy food choices.

Methods: Fifty consecutive black African patients with HF attending the Baragwanath Hospital in Soweto were surveyed about their food choices and dietary intake via the validated quantitative food frequency questionnaires (QFFQ). Data were translated into nutrient data using Food Finder based on South African food composition tables and compared to recommended values.

Results: Overall, 27 (54%) of patients were female with a mean age of 49.9 ± 16.4 (range 23 to 79) years. In women, notable food choices likely to negatively impact on heart health included added sugar (75% of women: mean daily intake 15 ± 9.6g), sweet drinks (51%: 310 ± 356ml) and salted snacks (61%: 15 ± 22g). The same food choices in men were 94% (15 ± 11g added sugar), 65% (438 ± 567ml sweet drink) and 74% (16 ± 18g salted snacks). Relative to age-specific recommendations, on average women derived 66% of their calcium, 37% of vitamin C and 40% of vitamin E daily requirements. The equivalent figures for men were 66%, 87% and 67%, respectively. Most significantly, in this HF group, the overall mean daily intake of sodium was 1470 ± 1280% (range 238 to 5523%) greater than recommended consumption levels for a healthy population. Current intake as indicated in the table requires an expenditure of approximately R15.62/day (49%) of the disability grant, which in 2008 was R940 per month. The recommended food intake however would require an expenditure of only R13.81/day (44%) of this benefit.

Conclusions: These data highlight a significant potential to improve the health status of black African patients with HF by recommending and supporting healthier food choices. Healthy food choices can be more affordable than current intake.

TABLE 1: Cost of healthy eating compared with habitual intake

Current Intake			Recommended Intake		
Food Item	Weight (g/mL)	Cost(R)[1]		Weight (g/mL)	Cost(R)[1]
Bread	150	2.25	Mabele (coarse)	40	0.30
Margarine	15	0.40			
Polony	30	0.62			
Milk ((full cream)	150	1.28	Milk (full cream)	500	4.25
Sugar	15	0.12			
Maize meal porridge	1 000	3.60	Maize meal porridge	1 000	3.60
Chicken (cooked)	90	2.00	Chicken	90	2.00
			Carrots	75	0.83
Tomato	45	0.50	Spinach	75	0.83
Apple	160	1.60	Apple	160	1.60
			Orange	180	0.40
Cold drink	500	3.25			
TOTAL cost		**R15.62**			**R13.81**

[1]Based on food prices in Soweto, July 2008.

Novel interactors: additional functions of N-terminal cardiac myosin-binding protein C?

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Cardiac myosin-binding protein C (cMyBPC) is a large multi-domain protein (C0 to C10) that is anchored, in the C-zone of the sarcomere, to myosin and titin via its C-terminal domains. While the function and some interactors of the C-terminal are known, those of the N-terminal (C0C2) are not as well characterized. The N-terminal is proposed to modulate cardiac contractility via phosphorylation of the cMyBPC motif (located between domains C1 and C2), which results in the rearrangement of myosin crossbridges and the structure of the thick filament upon β-adrenergic stimulation. Since domain C0C2 has a rigid scaffolding structure and sufficient length to extend into the interfilament space, it is possible that this region modulates cardiac contractility by cycling between binding partners, dependent perhaps on the phosphorylation status of the MyBPC motif. That this region may be of vital importance is further emphasized by reports of mutations linked to hypertrophic cardiomyopathy.

The present study aimed to identify interactors of the C1C2 region of cMyBPC by yeast two-hybrid (Y2H) analyses, under conditions that mimic the various phosphorylation states of the cMyBPC motif, with a view to gaining insight into the function of the N-terminal of cMyBPC. C1C2 bait constructs mimicking the native, monophosphorylated, trisphosphorylated and dephosphorylated conditions of the cMyBPC motif were used to screen cardiac cDNA libraries, in separate Y2H library screens. Putative C1C2 interactors were subjected to in vitro co-immunoprecipitation (Co-IP) and three-dimensional in vivo co-localization analyses to verify interaction with N-terminal cMyBPC.

The four library screens yielded a total of 27 putative interactors of domains C1C2, of which 4 [copper metabolism gene MURR1 domain 4 (COMMD4); β-enolase (ENO3); phosphodiesterase 4D interacting protein (PDE4DIP); heat shock 27kDa protein family, member 7 (HSPB7)], that may plausibly relate to the functions of cMyBPC, were investigated. In vitro Co-IP experiments confirmed the interactions of HSPB7 and PDE4DIP with C1C2 cMyBPC, no interactions were observed with COMMD4 while the interaction of C1C2 cMyBPC with ENO3 could not be assessed. Three-dimensional in vivo co-localization, using fluorescence microscopy, in differentiated H9C2 cardiac myocytes showed that COMMD4, PDE4DIP, HSPB7 and ENO3 exist in the same subcellular space as cMyBPC.

The present study has identified and verified numerous novel interactors of C1C2 cMyBPC. These interactors may shed light on the dynamics of PKA-mediated phosphorylation (PDE4DIP), the turnover of cMyBPC in the sarcomere (COMMD4), the preservation of cMyBPC integrity (HSPB7) and the means to generate energy to power the additional work during β-adrenergic stimulation (ENO3). This study has identified exciting and novel interactors that will extend our knowledge of cMyBPC and will serve as a platform for future studies on the role and function of cMyBPC, as well as novel potential contributors to cardiac dysfunction.

Genetic Variants Associated with Insulin Resistance and Metabolic Syndrome in Young Asian Indians with Myocardial Infarction

Naresh Ranjith, Rosemary J. Pegoraro, Datshana P Naidoo, Rebecca Shanmugam and Lee Rom

Background: The objective of this study was to assess whether an association exists between the metabolic syndrome and polymorphisms in genes involved in insulin resistance in young Asian Indian patients presenting with acute myocardial infarction (AMI).

Methods: The study population comprised 467 patients who were 45 years or younger. The National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF) definitions were used to assess the prevalence of metabolic syndrome. We examined the genotype and allele frequencies of the IRS-I G972R, PPAR-γ P12A, KCNJ11 E23K, and TNF-α -308G/A polymorphisms in relation to the metabolic syndrome determined by both definitions.

Results: The metabolic syndrome as defined by the NCEP ATP III criteria was found in 282 (60.4%) patients, and in 278 (59.5%) patients according to the IDF criteria. This gave only a moderate level of agreement of 79% between the two definitions (Cohen's kappa = 0.554). No association was found between the IRS-I G972R, PPAR-γ P12A, and KCNJ11 E23K, or TNF-α -308G/A polymorphic variants and the metabolic syndrome, or its components, for either definition.

Conclusion: Although the metabolic syndrome is a common finding in young Asian Indian patients with AMI, there was only a moderate level of agreement between the NCEP ATP III and IDF definitions of the syndrome. Our findings do not support a role for any of the polymorphic variant alleles in the four insulin resistance related genes examined in the etiology of insulin resistance, and reinforces the notion of a multifactorial etiology for the metabolic syndrome.

Metabolic syndrome in young Asian Indian patients with myocardial infarction

N. Ranjith, R.J. Pegoraro, D.P. Naidoo and T.M. Esterhuizen

Objectives: This study assessed the prevalence of the metabolic syndrome and its impact on hospital outcomes in young South African Indians (≤ 45 years) with acute myocardial infarction (AMI) using both the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF) definitions.

Methods and Results: The study population comprised 389 patients with AMI. The metabolic syndrome as defined by the NCEP ATP III criteria was found in 235 (60%) patients and in 223 (57%) according to the IDF criteria, with a 79% concordance between the two definitions. When ethnic-specific waist circumference cut-offs were included as a criterion for the NCEP ATP III definition, the number of patients with the metabolic syndrome increased significantly to 270 (69%) ($p < 0.01$).

Elevated fasting blood glucose (86%) was the major NCEP ATP III determinant. All determinants were found more frequently in patients with the metabolic syndrome ($p < 0.001$). Similar significant differences were observed for the IDF definition. The frequency of adverse cardiovascular events, including death, was low although 44% of patients had triple vessel disease on cardiac catheterization studies.

Conclusion: The metabolic syndrome is a common finding in young Indian patients with AMI who frequently presented with extensive atherosclerotic disease. There was no significant difference in the prevalence rate of the metabolic syndrome as determined by the NCEP ATP III and IDF definitions, but there was only a moderate level of agreement between the two definitions. Inclusion of ethnic-specific waist circumference cut-offs as a criterion for the NCEP definition may improve prediction of the metabolic syndrome.

An Initiative aimed at Best Outcomes for Nursing Children with Excellence (BOuNCE)

Charmain Rinquist, Sandy Staveski, Marleen Petersen, Natalie Möller, Jenny Knobel, Hilary Barlow, Johanna Lucas, Linda Jonker, Candice Bonaconsa, Andreas Tsakistos and Minette Coetzee

Introduction: Children's Heartlink (CHL), a United States based NGO, approached the Red Cross Children's Hospital (RCCH), a specialist children's hospital in Cape Town, South Africa to collaborate on a project aimed at retention of PICU nurses. At RCCH, this coincided with a newly appointed nurse leadership team and an existing child nurse practice development initiative working on participative protocol development with an interdisciplinary Pediatric Intensive Care (PICU) team.

During a series of meetings, the BOuNCE project was conceptualized. The main aim was to support resource development and PICU nurse training. Lucile Packard Children's Hospital (LPCH) in the United States became the other project partner.

Methods: The mainstay of any successful collaboration is communication. The BOuNCE collaborative is enhanced by teleconference meetings, on- site visits 2-3 times per year and augmented by regular electronic communication. We used a mutli-modal, participative approach to enhance clinical care delivery. Methods included: (1) Resource development consisting of protocol development process and pocket reference booklets for use in PICU, (2) Training including joint seminars, formal cardiac care courses and ad-hoc in-service sessions, (3) Skills fair, (4) Preceptor workshop and (5) Information posters.

Results: There was an increase in the number of staff who could participate in training. Eight professional nurses are currently completing a cardiac care course designed to provide skills caring for children after cardiac surgery. Twenty-four nurses completed a High Care Course preparing staff to care for very sick children. Eighteen new Prof Nurses successfully completed the induction and orientation requirements to work in the PICU unit. This assisted in staffing the PICU for 18 patients (increase of 2 beds). Ten preceptors were trained to support new staff during orientation and induction. One hundred nurses attended the skills fair. Staff of RCWMCH and LPH presented two workshops that were attended by 180 persons from the Health Sector in the Western Cape Province.

Conclusions: Our collaboration has taught us many lessons including cultural and practice differences. We have shared information and become acquainted with one another's contexts by communicating across oceans and time zones.

CHL funding increases what we are able to achieve and offers opportunities for travel to a different country and clinical settings in hopes of retaining nurses both in the United States and South Africa and improving our patients' outcomes.

Acute Type A Dissection - Surgeon as Risk Factor

Richard Schulenburg, Polychronis Antonitsis and Stephan Westaby

Introduction: Acute Type A dissection is an immediately life threatening event. In most countries the patient is secondarily referred from a district hospital to the closest cardiovascular centre, then operated on by the duty cardiac team. Under this system hospital mortality and morbidity are substantial. The International Registry of Acute Aortic Dissection reported 26% surgical mortality overall for 12 large tertiary referral centres. In contrast individual specialist aortic surgeons have recorded mortality rates as low as 5-6%. To what extent does the surgical team feature as a risk factor for death and can measures be taken to improve these results?

Methods: We performed a retrospective audit of outcomes for 201 consecutive acute Type A dissection patients operated at a single centre between April 1990 and April 2007. Demographic variables, presenting clinical features, time from presentation to surgery and perioperative variables, including surgical team were analyzed and correlated with hospital mortality.

Results: Five surgical teams operated on 201 patients; 150 (75% male) and 51 (25% female). Ages ranged from 26 to 87 years (mean 64 +/-9). Twelve patients (6%) had Marfans syndrome. Surgery took place within 24 hours of first hospital admission in 76%. Mean cardiopulmonary bypass (CPB) time ranged from 5.7% to 37.5%. Overall hospital mortality was 14%, a relatively low rate because the specialist aortic team had operated on 52% of the patients. For patients who had CPB<90 minutes overall mortality was 6.8%. In contrast more prolonged CPB provided 21.4% mortality ($p<0.05$). The surgeons with most experience had shorter CPB time. Catastrophic presenting features including cardiogenic shock, acute myocardial ischemia and renal impairment were risk factors for hospital mortality whereas advanced age, female gender, Marfan's syndrome and preoperative acute cerebral injury were not.

Conclusions: Successful outcome after Acute Type A dissection surgery depends in part on the experience of the surgical team, and the ability to perform the corrective procedure in a limited time frame. If results are to improve these patients should be conveyed urgently to centres with aortic surgery expertise to be operated by the specialist team.

The prevalence of myocarditis in HIV-associated cardiomyopathy in Cape Town

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The cause of HIV-associated cardiomyopathy is largely unknown. A number of potential etiologies have been postulated, including myocardial inflammation due to cardiac infection with HIV itself. We conducted an endomyocardial biopsy study of the prevalence of myocarditis in HIV-associated cardiomyopathy in patients presenting at Groote Schuur Hospital, Cape Town.

We used lightmicroscopy and immunohistochemistry to define the histopathological phenotype of HIV-associated cardiomyopathy. We compared the endomyocardial biopsies of fourteen HIV-associated cardiomyopathy patients, with eight idiopathic dilated cardiomyopathy cases and eleven heart transplant recipients. We applied the two classification systems for the diagnosis of myocarditis: the Dallas and Marburg criteria.

By pooling the data of both grading systems we showed that active myocarditis accounted for a minority of patients with HIV-associated cardiomyopathy (approximately 25%) in Cape Town, with 32% of individuals exhibiting borderline myocarditis and the remainder (~43%) displaying no evidence of myocardial inflammation. However, by utilizing only the Dallas criterion we illustrated that 29% (4/14) showed active myocarditis, 43% (6/14) displayed borderline myocarditis and 29% (4/14) of HIV-associated cardiomyopathy cases displayed no inflammation. Conversely, the Marburg criterion showed active myocarditis to occur in 21% (3/14) of HIV-associated cardiomyopathy cases, 21% (3/14) displayed borderline myocarditis and no evidence of inflammation was found in 57% (8/14) of cases. Light microscopy revealed variable amounts of interstitial fibrosis. Immunohistochemistry revealed a sparse cellular infiltrate made up mainly of inflammatory markers CD3 and CD8. The tissues stained negative for the p24 antigen of HIV and other cardiotropic viruses.

To the best of our knowledge, this is the first study to apply both qualitative (i.e. Dallas criteria) and quantitative (i.e. Marburg criteria) criteria to determine the prevalence of myocarditis in HIV-associated cardiomyopathy. We show that HIV-associated cardiomyopathy encompasses the full spectrum of inflammatory disease – with active myocarditis occurring in only a minority of patients. This is in contrast to others who have suggested that active myocarditis is the pathological hallmark of HIV-associated cardiomyopathy. Our results also indicate that the criteria should not be used exclusively of each other but that both of these grading systems should be used in conjunction in order to obtain the most reliable indication of myocarditis.

Echocardiographic Assessment of Left Ventricular Involvement (Dysfunction) in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia

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Arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) is a non-ischemic cardiomyopathy involving mainly the right ventricle. However, the left ventricle can be occasionally involved. It is characterized by myocyte atrophy and progressive replacement of the myocardium by fatty tissue and/ or fibrosis which leads to wall motion abnormalities, impaired function and arrhythmias.

Aim: To assess the prevalence of left ventricular involvement in patients with ARVC.

Method: The South African ARVC Registry was assessed retrospectively and only participants with confirmed ARVC and the relevant echocardiographic data were included in the study. Two-dimensional trans-thoracic echocardiographic data was obtained for analysis. The echocardiographic parameters obtained were: left ventricular (LV) dimensions, wall thickness (e.g. LVH), ejection fraction (EF), and wall motion abnormalities (WMA). Right ventricular (RV) size was also assessed to evaluate the effect of RV size on LV function. Statistical analysis was done using Microsoft Excel. For the EF the data is presented as mean ± Standard Deviation (SD), otherwise other data is presented as a percentage (%) of the patient data set.

Results: The SA ARVC registry included 80 probands of which 38 had the relevant echocardiographic data. Of the 38 patients 36% were females, and the mean age was 40 years (range: 12-84). Of the 38 patients, EF measurements were obtained in 37. The mean EF % was 54.8 ±13 (range: 20-70). Other echocardiographic findings of all 38 patients were: normal LV-22/38 (57.9%); abnormal LV- 21/38 (55.3%) of which LV dilatation occurred in 11/38 (28.9%), left ventricular hypertrophy (LVH) in 2/38 (5.3%), LV non-compaction in 2/38 (5.3%), paradoxical septal wall motion in 4/38 (10.5%), reduced LV systolic function (LVEF%) in 8/38 (21.1%), septal hypertrophy in 1/38 (2.6%), and LV hypokinetic inferior wall in 3/38 (7.9%). Of the 38 patients 30 had RV measurements and 20/30 (66.7%) had abnormal RV function and/ or size.

Conclusion: In the majority of patients in this study with ARVC associated RV dysfunction the LV was also affected. Some of the patients irrespective of their having normal LV size still had reduced systolic function and wall motion abnormalities. These could have been due to an enlarged RV compressing the LV, thus interfering with normal LV function. Even though this investigation has shown that LV dysfunction may be associated with ARVC, a prospective study is indicated over a longer period of time with a larger study population. This could help determine the stages at which changes take place in the LV and if they arise following RV dysfunction or independently.

Cardiac allografts – A 24-year South African experience

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Introduction: A homograft program was initiated in 1984 in Bloemfontein. The program started with fresh storage at 4 degrees Celsius in antibiotic serum medium and progressed to a fresh frozen program in 1992. Initially glycerol was used as cryoprotectant but in 2007 dimethylsulfoxide (DMSO) was introduced.

Methods: Retrospective analysis of the allograft data collected at the Bloemfontein Homograft Bank over a 24-year period.

Results: Two thousand five hundred and eleven aortic and pulmonary homografts were processed, of which 1 573 were accepted for transplantation, of which 1 187 were implanted. Of the harvested valves, 923 were discarded mainly due to human immunodeficiency virus (HIV) (26.0%), hepatitis (110%) and other venereal diseases (23.0%).

Forty percent of donors were murdered and 36.0 % succumbed to motor vehicle related accidents.

Mean donor age peaked between 17 and 40 years with male predominance (1 318 male vs. 398 female).

Three hundred and sixty-two aortic and 135 pulmonary homografts were implanted in Bloemfontein. Fifty-five valves were exported to Germany and a total of 640 homografts were used in South African units. Of the valves used in Bloemfontein, 85.0 % of the aortic homografts were used for aortic valve replacement and 99.0% of the pulmonary homografts were used for right ventricular outflow tract reconstruction.

Harvest times ranged between 3 and 90 hours post mortem with a mean ischemic time of 33 hours. Eighty-nine percent were harvested before 48 hours.

Recent research projects in our department are addressing the availability of homografts and focus on the effects of varying ischemic times on valve autolysis. Results will include differential scanning calorimetry (DSC), tensile strength and histology (hematoxilyn and eosin staining and scanning electron microscopy).

Conclusion: The Bloemfontein Homograft Bank provides an important service to the cardiac surgery community of South Africa. The expanded use of homografts should be investigated as the valve implant of choice in Africa.

The presentation relates to the incidence of transient ischemic attacks (TIA) with Barlow's Syndrome

H.D. Solomons

Barlows syndrome is a posterior billowing mitral syndrome with associated chest pain and a mid-systolic click.

There is a high incidence of TIAs with this syndrome. This relates to activation of platelets as they hit the billowing leaflet.

Scanning electron microscopy shows activation of the platelets. They change from a disc to a sphere. These platelets then aggregate to form microemboli. These then lodge in the brain and form infarcts. These microinfarcts cause major neurological signs which manifest as cerebro-vascular infarcts. A double blind analysis skows the beneficial results of asprin versus dipyridomol!

There is a high incidence of transient ischemic attacks in billowing mitral leaflet syndrome and the majority of these cases are preventable with cyclo-oxygenase inhibitors. So theoretically or teleologically speaking it is possible to use any non-steroidal anti-inflamatory to prevent these harsh sequele!

Sphingosine-1-phosphate (S1P) can mimic ischemic postconditioning via activation of the JAK/STAT-3 pathway

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Introduction: Ischemic postconditioning (PostC; small episodes of ischemia at the onset of reperfusion) is a powerful protective mechanism with potential for clinical application. Sphingosine-1-phosphate (S1P) is a derivative of the sphingolipid pathway and a component of High Density Lipoprotein (HDL) cholesterol that has recently been implicated in cardioprotection. We propose that exogenous S1P can mimic PostC in an isolated mouse heart model and that this protective effect is mediated via the JAK/STAT-3 pathway.

Methods: Control hearts from wildtype and cardiac deficient STAT-3 male mice were perfused on a Langendorff apparatus and subjected to 35min global ischemia and 45min reperfusion. Alternatively, S1P (10nM) was administered at the onset of reperfusion for the first 7min. At the end of the experiment, myocardial infarct size was assessed. Additionally, phosphorylated levels of STAT-3 were examined by Western blot analysis after 15min of reperfusion in S1P-treated wildtype hearts with/without a known JAK/STAT-3 inhibitor, AG490.

Results: S1P successfully reduced myocardial infarct size in wildtype mice (32.2±2.1% in control vs. 12.1±2.5% in S1P-treated hearts; $n \geq 6$; $p<0.05$) but its protective effect was abolished in the cardiac deficient STAT-3 mice (30.3±2.8% in control vs. 34.2±4.3% in S1P-treated hearts; $n \geq 5$; p=ns). Levels of phosphorylated STAT-3 were significantly increased in the nuclear extract after S1P administration (5±1 AU in control vs. 10±2 AU in S1P-treated hearts; n=4; $p<0.05$). In contrast, STAT-3 phosphorylation was abrogated in the presence of AG490 (4±1 AU vs. control; n=4; p=ns).

Conclusion: Our data strongly suggest that S1P is cardioprotective when administered as a postconditioning mimetic and its beneficial effects are mediated by the JAK/STAT-3 pathway. The further delineation of this protective pathway may provide a greater insight into development of novel pharmacologic agents for future experimental research and clinical applications.

Cardiopulmonary bypass

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Introduction: Cardiopulmonary bypass (CPB) is a complex process in which oxygen delivery and tissue perfusion are maintained via mechanical pump and oxygenator during cardiac surgery. Comprehensive understanding of CPB and the effects of bypass on the developing child can improve nursing care delivery and optimize patient outcomes.

Methods: This session will provide an evidenced-based approach to understanding the CPB pump and oxygenator, processes associated with CPB (e.g. anticoagulation, hemodilution), the effects of CPB on the pediatric physiology, and the nurse's role in optimizing patient outcomes in children receiving CPB. Additionally, long-term issues related to quality-of-life and developmental outcomes for children after CPB, novel educational concepts for novice nurses, and interdisciplinary team approach receiving the child from the operating theater will be discussed.

Results: Proactive nursing care can occur through a better understanding of CPB, CPB process, and the physiology associated with CPB. Proactive care has been positively linked with better patient outcomes.

Conclusion: Through improved understanding of physiology and CPB process, nurses are able to provide vigilant, proactive nursing care to children undergoing CPB.

Nitric oxide synthase (NOS) is regulated by the PI3-K / PKB pathway in hypoxic cardiac cells

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Introduction: The roles of eNOS, and its putative association with PKB, and iNOS are not well characterized in hypoxic cardiac cells and there is a lack of studies that measure NO directly. We aimed to measure NO-production in cardiomyocytes and cardiac microvascular endothelial cells (CMECs) under baseline and hypoxic conditions and evaluate the expression, regulation and activation of eNOS, iNOS and PKB. The effect of PI3-K/PKB inhibition on NO-production and eNOS expression/activation was also investigated.

Methods: Adult rat cardiomyocytes and rat CMECs were made hypoxic by cell pelleting and low PO2 incubation. Intracellular NO was measured by FACS analysis of DAF-2/DA fluorescence and eNOS, iNOS and PKB were evaluated by Western blotting or flow cytometry. Upstream PKB-inhibition was achieved with wortmannin.

Results: (1) NO levels increased in both cell types after exposure to hypoxia. (2) In hypoxic CMECs, eNOS was upregulated and activated, no iNOS expression was observed, and PKB was activated. (3) In myocytes, hypoxia did not affect eNOS expression, but increased its activation. Activated PKB also increased during hypoxia. FACS analysis showed increased iNOS in hypoxic myocytes. (4) Wortmannin resulted in decreased hypoxia-induced NO-production, and reduced activated eNOS levels.

Conclusions: Cardiomyocytes and CMECs show increased NO production during hypoxia. eNOS seems to be the main NOS isoform involved as source of the increased NO generation, although there may be a role for iNOS and other non-eNOS sources of NO in the hypoxic myocytes. Hypoxia-induced PKB and eNOS activation occurred simultaneously in both cell types, and the PI3-K/PKB pathway was associated with hypoxia-induced NO-production via eNOS activation.

COMMD4 implicates a role for protein degradation and turnover in MYBPC3-derived hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is the most common inherited form of cardiac hypertrophy. Cardiac myosin binding protein C (cMyBPC), the second most common HCM-causing gene, modulates cardiac contractility in a manner dependent on phophorylation of the MyBPC-motif. Previously, in a yeast two-hybrid (Y2H) library screen, we found that Copper metabolism MURR1-domain containing protein 4 (COMMD4) bound to the N-terminal of cMyBPC, in an interaction similarly regulated by phosphorylation of the MyBPC-motif. The function of COMMD proteins is still unclear, but has been linked to copper metabolism as well as the ubiquitin-proteasome pathway (UPS). Intriguingly, recent studies have shown that the UPS plays a role in at least MyBPC-derived HCM, while dietary copper-depletion causes cardiac hypertrophy. We therefore set out to investigate the function of COMMD4 by identifying its protein binding partners by Y2H analysis.

A COMMD4 Y2H bait construct was generated and used to screen a cardiac cDNA-library. Putative interactors were identified by direct sequencing and analyzed using bioinformatics tools.

These interactors implicate COMMD4 in protein trafficking and turn-over, providing support for the link between cMyBPC-related HCM and protein degradation. This may further elucidate the mechanism by which some cMyBPC gene mutations cause HCM.

Differential induction of apoptosis during simulated ischemia and hypoxia in myotubes: The role of the phosphatidylinositol 3-kinase (PI3-K) signaling pathway

Mark Thomas and Anna-Mart Engelbrecht

Muscle displays a remarkable potential to react to myotrauma and endure external stresses. Under conditions of chronic, decreased cellular oxygen availability, PI3K signaling pathways are thought to facilitate in survival and proliferation. Indeed, many reports suggest an increase in PI3K/Akt activation during chronic hypoxia. In addition, decreased flux through the mTOR pathway, also situated downstream of PI3K/Akt, tries to conserve valuable energy resources during these conditions. These actions may contribute to cell survival during a chronic hypoxic insult in some cell lines. Ischemia is characterized by depletion in oxygen and other vital nutrients, and ischemic cell death is believed to be associated with an increasingly harsh environment where pH levels decrease and potassium levels increase. Our model employs a modified ischemic buffer which mimics acute ischemia in a recently differentiated murine myogenic cell line. Using vital staining techniques, we demonstrate greater cell death and apoptosis after three hours of ischemia versus hypoxia in cultured C2C12 myotubes. MTT assays show a diminished level of cell activity during ischemia while cultures incubated during hypoxia alone showed no significant decrease. Using Western blot analysis, a PI3K ELISA assay as well as known inhibitors of the PI3K pathway in conjunction with the MTT assay, we show a significant decrease in activity of the PI3K/Akt pathway in simulated ischemia but not during hypoxia in C2C12 myotubes. We also demonstrated that downstream effectors of Akt, known to amplify apoptosis and reduce protein synthesis, become activated during simulated ischemia in our model. We propose that, in contrast to chronic hypoxia, a severe ischemic insult leads to rapidly decreased flux through the PI3K/Akt/mTor pathway in an attempt to conserve valuable, rapidly depleting resources. A concomitant down regulation of survival pathways initiates increased flow through apoptotic pathways regulated by PI3K/Akt thereby committing severely depleted cells to death. This rapid switch to a survival state in severe simulated ischemia could prove crucial during ischemic heart disease.

ECG Characteristics in Peripartum Cardiomyopathy

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Introduction: The incidence of peripartum cardiomyopathy (PPCM) is high in Africa. The ECG is a simple, accessible, and widely available screening test for peripartal heart disease. However, the nature, frequency and evolution of ECG abnormalities in PPCM is, to the best of our knowledge, not well defined. This study assessed the prevalence of ECG abnormalities in newly diagnosed PPCM patients at baseline and at 6 months of follow-up.
Methods: Data analysis was performed on 39 consecutive patients presenting to a tertiary centre in South Africa with PPCM, for whom 12-lead ECGs were performed on diagnosis and follow-up at six months. A standardized approach to ECG analysis was adopted using the Minnesota code; with the reviewer blinded to all patients' clinical details, as to whether they were reviewing baseline or follow-up ECGs.
Results: Most patients included were black African women, of mean age 29 ±6.4 years and median body mass index of 23.9 (IQR22.1-27.4)kg/m2. At baseline, mean systolic and diastolic blood pressures were 112 ±18mmHg and 96 ±19mmHg, respectively.
On first diagnosis, most ECGs were in sinus rhythm (90%), with mean baseline heart rate of 103 (IQR22-33) beats per minute. Abnormalities in baseline ECGs included the following: (1) abnormal frontal plane QRS axis (26%;95%CI 13-42), with left axis deviation evident in 18% (95%CI 8-34), right axis deviation in 5% (95%CI 0.6-17) and 3% with indeterminate axis (95%CI 0.006-13); (2) Bundle-branch block was observed in 18% (95%CI 8-34), while 5% (95%CI 0.6-17) had an idioventricular pattern; (3) Atrial abnormality was detected in 13% (95%CI 19-50), all being right atrial abnormality; (4) T-wave changes were evident in 44% of ECGs (95%CI 28-60).
At six months follow-up, only 32% of ECGs remained in sinus rhythm ($Z=-2.67$, $p=0.008$). The mean heart rate was significantly lower than at baseline (mean of 76 beats per minute;$t=8.47$, $p<0.001$). At six months, abnormal axis was detected in one-fifth of ECGs, while bundle-branch block occurred 5% less frequently than at baseline. Atrial abnormalities were evident in 18% of ECGs at follow-up: with only 8% showing right atrial abnormalities, 5% ECGs now also showing left atrial abnormalities, and 5% having bi-atrial abnormalities. The prevalence of left ventricular hypertrophy was similar from baseline to follow-up; while the prevalence of T-wave abnormalities decreased to 31% at six months.
Conclusions: This is the first known descriptive analysis of serial ECG data on PPCM women in South Africa. Most women with newly diagnosed PPCM were in sinus tachycardia, almost half having T-wave abnormalities; both of which, together with bundle-branch block, appeared to improve at six months. We note that the ECG in PPCM is abnormal in 93% of patients and may serve as a screening tool for women presenting with non-specific peripartal symptoms of heart failure.

Myomegalin is an AKAP involved in the phosphorylation of cardiac MyBPC

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Speed and energy efficiency of cardiac muscle contraction has to be regulated in order to match the body's needs. One way contractility is regulated is by dynamic phosphorylation of proteins within the sarcomere, usually by means of cAMP-activated protein kinase A (PKA). Kinases regulate a broad range of cellular responses, and therefore need to be compartmentalized close to their targets. This will ensure control over which proteins are phosphorylated in response to second messenger signaling. Kinase compartmentalization is either achieved by direct docking to the target protein, or by means of an adaptor protein, called A-kinase anchoring proteins (AKAPs) in the case of PKA.

Cardiac Myosin Binding Protein C (cMyBPC) is a highly modular sarcomeric protein which regulates contractility in response to PKA phosphorylation. Mutations in the gene encoding for cMyBPC causes hypertrophic cardiomyopathy (HCM). During a previous yeast two-hybrid screen conducted in our laboratory, a phosphodiesterase 4D interacting protein-like ligand was identified of the triphosphorylated mimic of the MyBPC motif. This was interesting because it is known that cases exist where the same adaptor protein interacts with and anchors both PKA and phosphodiesterase 4D. We therefore hypothesized that this PDE4D interacting protein, also known as myomegalin, acts as an AKAP, anchoring both PKA and PDE4D to the MyBPC motif.

Yeast two-hybrid assays were conducted to establish whether myomegalin anchors PKA, and also what its other ligands are. The myomegalin cDNA was cloned into a bait vector, which was directly assessed for interaction with two distinct PKA regulatory-subunit preys. This bait was also used to screen a cardiac cDNA library for novel myomegalin interactors, and the prey clones sequenced to determine their identity.

Myomegalin bound both PKA regulatory subunits as well as other proteins that are PKA targets, including cardiac troponin (cTNI), also a HCM-causing sarcomeric protein. These putative interactors were further analyzed via in vivo Z-stacked 3D co-localization to establish true interaction. Preys were cloned into mammalian vectors that allowed expression of various fluorescent fusion proteins and the constructs were transfected into the mammalian H9C2 cells along with a construct encoding a fluorescently labeled PDE4DIP. After transfection, co-localization in live cells was done and it was found that COMMD4, SNX3, ENO3 and the PKA regulatory 2A subunit co-localized in three dimensions with myomegalin.

Our hypothesis is therefore supported that myomegalin acts as an AKAP in the phosphorylation of sarcomeric proteins involved in the regulation of cardiac contractility. This may have implications for understanding the effect of HCM-causing mutations in cMyBPC and cTNI.

PDE4DIP is an AKAP involved in phosphorylation of cMyBPC

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Cardiac contractility is regulated by dynamic phosphorylation of proteins within the sarcomere by kinases such as cAMP-activated protein kinase A (PKA). PKA is anchored close to its targets by A-kinase anchoring proteins (AKAPs) to control phosphorylation. Cardiac Myosin Binding Protein-C (cMyBPC) and cardiac troponin I (cTNI) are hypertrophic cardiomyopathy-(HCM)-causing sarcomeric proteins which regulate contractility in response to PKA phosphorylation. We identified a phosphodiesterase4D-interacting protein-like (PDE4DIP) ligand of the N-terminal of cMyBPC via a yeast two-hybrid (Y2H) screen. Because AKAPs sometimes anchor both PKA and phosphodiesterases, we hypothesized that this protein acts as an AKAP, and tested this by Y2H analyses.

The PDE4DIP cDNA was cloned into a bait vector, which was directly assessed for interaction with two distinct PKA regulatory-subunit preys. This bait was also used to screen a cardiac cDNA library for novel PDE4DIP interactors, and the prey clones sequenced to determine their identity.

PDE4DIP bound both PKA regulatory subunits as well as with other cardiac proteins that are PKA targets, including cTNI. Thus, PDE4DIP acts as an AKAP in the phosphorylation of sarcomeric proteins involved in the regulation of cardiac contractility. This may have implications for understanding the effect of HCM-causing mutations in cMyBPC and cTNI.

Outcome of different cross-linking methods on the tissue properties of bovine pericardium

J.J. van den Heever, W.M.L. Neethling, F.E. Smit and D. Litthauer

Introduction: Glutaraldehyde (GA)-fixed bovine pericardium is widely used as substitution material in cardiac and other surgical procedures, but calcifies severely. Pretreatment with glycosaminoglycans(GAG) before final fixation with GA to mitigate calcification without sacrificing other requirements, was investigated and compared with Glycar commercial patches.

Methods: Fresh pericardium was treated with a) 0.625% GA, b) 0.1M AlCl3, c) 0.0025M, 0.005M, 0.01M, 0.1M and 0.2M GAG and with Glycar patches (GA + propylene glycol) implanted subcutaneously in Wistar albino rats for 8 weeks to evaluate calcification potential and immunogenicity. Histology, tensile testing, protein denaturation temperatures (DSC) and resistance to enzymatic digestion were also determined for unimplanted tissue.

Results: Tissue treated with GA and AlCl3 calcified severely (179.48 and 140.99µg Ca^{2}+/mg DM respectively) when compared to GAGs- and Glycar-treated tissue (9.11 and 0.93µg Ca^{2}+/mg DM), and also had significantly ($p<0.0001$) lower extractable water content (36.01 & 46.5% compared to 75.9 & 64.79%). Thus GA-fixed tissue demonstrated a significantly ($p=0.03$) reduced tensile strength compared to GAG- and Glycar-treated tissue, due to reduced elasticity. Protein denaturation temperatures (DSC) decreased with an increase in GAG concentration and eventually fell below the benchmark of 80°C, while that for GA (85.46°C) and Glycar (87.32°C) were significantly ($p<0.0005$) higher, indicating a very high degree of cross-linking. On histological evaluation superficial GAG was bound only to the outer surface of the pericardium, making it highly prone to mechanical damage during handling and accelerating the tissue's calcification and degradation. GAG also leached out into surrounding host tissue following subcutaneous implantation, as well as during storage in GA before implantation. Cross-linking of proteins with GAG before final GA fixation resulted in significant reduction in calcification of tissue, while maintaining good structural integrity, mechanical properties and low antigenicity.

Conclusions: Future research will require fixation strategies that will allow deeper penetration of the GAG into the tissue layers (mechanical or chemical) before final fixation with GA. More effective methods of stabilizing the cross-links formed by GAG-fixation will also be required in order to prevent GAG leaching out, without sacrificing tissue properties. Permanent cross-linking and fixation, producing stable and durable bioprostheses, will be required before they can be used safely and with confidence, especially in a pulsatile hemodynamic system.

QTC prolongation prior to coronary angiography is associated with poorer cardiac systolic and diastolic function and increased mortality

Pieter van der Bijl, Marshall Heradien, Innocentia Louw, Pearl Fredericks, Elizabeth Schaafsma and Anton Doubell

Introduction: The QT interval is measured from the beginning of the QRS complex to the end of the T wave. It varies with gender, age and heart rate, and can be shortened or prolonged by a multitude of factors. A prolonged, corrected QT interval (QTc) is a risk factor for polymorphic, ventricular tachycardia and sudden cardiac death.

Methods: > 900 patients underwent coronary angiography at Tygerberg Academic Hospital during the period 11/2006 - 01/2008. Complete records (215) were examined for the: QTc, left ventricular ejection fraction (measured by ventriculography or transthoracic echocardiography), left ventricular, end-diastolic pressure (measured directly at the time of ventriculography), presence of triple-vessel, coronary artery disease and the presence of major risk factors for ischemic heart disease (IHD). Patients were telephoned at six-monthly intervals to determine survival. Atrial fibrillation, bundle branch blocks and a creatinine level > 200 µmol/l were exclusion criteria. Kaplan-Meier survival curves and other statistical tests (Mann-Whitney and chi-squared) were utilized to analyze data.

Results: QTc prolongation in the presence of ischemic heart disease demonstrated a significant association with: mortality, systolic and diastolic dysfunction of the left ventricle, a family history of ischemic heart disease and hypercholesterolemia.

Conclusion: QTc prolongation prior to coronary angiography is significantly associated with increased mortality, left ventricular systolic and diastolic dysfunction, hypercholesterolemia and a family history of IHD.

Genetic variation in angiotensin-converting enzyme 2 gene is associated with extent of left ventricular hypertrophy in hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM), a common, inherited cardiac muscle disease, primarily caused by mutations in sarcomeric protein-encoding genes, is characterized by overgrowth of ventricular muscle that is highly variable in extent and location. This variability has been partially attributed to locus and allelic heterogeneity of the disease-causing gene, but other factors, including unknown genetic factors, also modulate the extent of hypertrophy that develops in response to the defective sarcomeric functioning. Components of the renin-angiotensin-aldosterone system (RAAS) are plausible candidate hypertrophy modifiers because of their role in control of blood pressure and biological effects on cardiomyocyte hypertrophy.

We investigated four Single Nucleotide Polymorphisms in the gene encoding angiotensin converting enzyme 2 (ACE2), a gene on the X-chromosome whose RAAS product modulates cardiac structure and function, for association with hypertrophic traits in 227 individuals belonging to 22 HCM families with known founder disease-causing mutations.

After adjustment for hypertrophy-influencing factors, including the particular disease-causing mutation, we find association between the G-allele of rs879922 and increased left ventricular mass (effect size: 18.7g), maximum interventricular septal thickness (effect size: 1.9mm) as well as maximum posterior wall thickness (effect size: 0.7mm).

These data demonstrate that ACE2 plays a role in modifying the extent of hypertrophy that develops in HCM, independent of the effect of the disease-causing mutation or blood pressure.

Focus on 2007: A clinical audit of the Red Cross Children's Hospital Pediatric Cardiac Surgery Program

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Introduction: Pediatric Cardiac Surgery has a long and rich history in South Africa with the first cardiopulmonary bypass operation performed by Prof Chris Barnard in a child at Red Cross Children's Hospital in 1958. Since the 1990s though, severe budget restrictions, the emergence of private health care and ever-increasing numbers of indigent patients have put significant strains on the delivery of specialized cardiac care within the public service. The largest of these units is that based at Red Cross Children's Hospital with upwards of 250 cases per year. It is the referral centre for the Western Cape Pediatric Cardiac Services based at Red Cross and Tygerberg Hospitals as well as the satellite hospitals within the metropole. In addition, referrals from the Eastern Cape and other parts of the Western and even Northern Cape comprise a significant part of the service. In recent times, with even more stringent budget restrictions and increasing referrals from the neonatal service, the waiting list has reached unprecedented figures of over 150. In order to critically review areas of deficiencies within the service and to define ways of managing our reduced resources in a more efficient fashion, we undertook a clinical audit of all patients operated upon in 2007.

Setting: The folders of all patients operated upon between 1 January 2007 and 31 December 2007 were reviewed and demographic, surgical and other patient outcome data were recorded and analyzed. Only cardiac surgical procedures were reviewed and all strictly thoracic cases were excluded.

Results: 244 patients were identified although 4 folders were lost and therefore excluded from our audit. A total of 252 surgical procedures were reviewed. Demographic parameters that were reviewed included age, age at time of initial diagnosis and then at surgery, the referral pathway to our service as well as mortality, days spent in ICU and total days spent in hospital. Surgical parameters included time of surgery, bypass times, re-operations and re-intervention rates. The total mortality was 7.5% with in-hospital mortality rates at 5.8%. 43% of patients resided within the Cape Metropole while 22% resided in provinces other than the Western Cape. 64% of patients were diagnosed within the first year of life, most as neonates.

The true waiting period for surgery could not be reliably determined from this review.

Conclusion: In this audit we sought to focus on 2007 and critically appraise as many aspects of our surgical service as possible. We hope to now institute clinical audit as a regular part of our program in particular to aid us in managing our limited resources in a more efficient way and hopefully in so doing, decreasing our waiting list and improving our service delivery.