840

Safety of Platelet IIb/IIIa Inhibitor Post-Thrombolytic Therapy when given Before or During PCI.

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INTRODUCTION
Platelet IIb/IIIa inhibitors (GP) have been shown to improve outcome when used during percutaneous coronary intervention (PCI), but their safety when given soon after full dose thrombolytic therapy (TL) has yet to be defined. GUSTO V and ASSENT III trials using half dose TL combined with GP showed reduced occlusion rates with no increase in mortality, but with an increase in bleeding complications. Since TL failure remains a significant problem, patients (pts) with ST elevation MI (STEMI) often require cardiac catheterization (CC) with view to rescue PCI. We have utilized eptifibatide (ep) during rescue PCI because of its shorter 1/2 life vs. abciximab. Ep is often given once the decision for PCI has been made, and clinical reperfusion has been observed frequently before PCI was performed. The potential for ep to be used for 'rescue' in failed TL in rural centers could be important.

METHODS
We therefore analyzed our experience in pts who received ep within 12 hrs of TL.
We identified 121 STEMI cases (93 males, 28 females) ranging in age from 33-79 years (from June 2001 to Feb 2004) who had ongoing ischemia post-TL.

RESULTS
The door-to-needle time for TL was 2.3 ± 1.6hrs. Ep was used either before CC, in cases of reperfusion failure/acute reocclusion post-TL (66 pts in group 1), or as adjuvant therapy during rescue PCI (55 pts in group 2). Time between TL and ep was 3.4 ± 2.4hrs. The CK peak was 3578 ± 2920 at 11.6 ± 8.8 hrs. CC was undertaken in all pts with a mean time to cath of 15 ± 18hrs. One pt had a subdural bleed, 6% had moderate bleeding, and 11% minor bleeding. The risk of moderate bleeding was higher in group 2 (17.3%) vs group 1 (7.7%) with an odds ratio of 7.3. The 30-day survival was 94%, similar to the GUSTO V results, with fewer deaths in group 1 (5.2%) vs. group 2 (15.4%).

CONCLUSIONS
Use of ep within 12 hrs of failed TL appears to be well tolerated in pts, with no increase in bleeding or mortality when given before as compared to during facilitated PCI.

841

RIGHT PRECORDIAL LEADS AND LEAD AVR AT EXERCISE ELECTROCARDIOGRAPHY. DOES IT CHANGE TEST RESULTS?

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Background: A recent study on exercise testing (ET) suggested that ST-segment changes in the right precordial leads (RPL) may increase its sensitivity substantially. However, this study looked at a highly selected population of patients who all underwent thallium-201 scintigraphy and coronary angiography. The present study evaluated the clinical utility of ST-segment changes in the RPL and lead aVR in an unselected population of patients undergoing ET.
Methods: 906 consecutive patients who received ET were included in the study. ET was done using the Bruce Protocol with a 12 lead electrocardiogram (ECG) substituting V4R and V6R for V1 and V6. Leads V1 and V6 were selected for omission as these two leads hardly ever manifest changes in isolation. Substituting two leads would obviate the need for a more complex recording system, thus improving clinical utility.
Results: On the basis of horizontal/downsloping ST-segment depression (STD) of 1.0 mm or more (the usually accepted criterion for a positive ET), 159 (17.5 percent) patients had a positive ET. In those patients with a negative ET (545 patients), 4 patients (0.7 percent) manifested STD and 5 patients (0.9 percent) manifested ST-segment elevation (STE) in leads V4R and/or V6R. Of note, 44.7 percent of the positive ET group had STE in lead aVR.
Conclusion: The use of ST-segment changes in RPL during exercise stress testing does not appreciably change the test results of a standard ET. If one was to consider an additional marker, STE in aVR may be more useful, as it shows a stronger correlation with positive tests and does not require the recording of additional leads.

842

Transgenic mice with cardiac specific expression of wildtype or mutant PRKAG2 display similar effects on AMPK activity, while having profound differences in glycogen deposition: Clues to the development of Wolff-Parkinson-White Syndrome?

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AMP-activated protein kinase (AMPK) is an enzyme centrally involved in regulating cellular energy homeostasis. Recently, an Arg302Gln mutation in the γ2 subunit of AMPK (the PRKAG2 gene) has been identified as an AMPK loss-of-function mutation responsible for a familial form of Wolff-Parkinson-White syndrome (WPW). Transgenic mice with cardiac restricted expression of this mutation (TG γ2 R302Q) also develop cardiac hypertrophy and dramatic increases in myocardial glycogen deposition, which is thought to occur as a result of a perturbation in AMPK signaling. Since the role AMPK plays in these processes is not clearly defined, we investigated if changes in AMPK activity, glycogen deposition, and cardiac hypertrophy were specific to the Arg302Gln mutation in the γ2 subunit of AMPK. Transgenic mice expressing either the non-mutated form of the γ2 subunit (TG γ2 WT) or the mutated form (TG γ2 R302Q) both displayed increases in heart weight/body weight ratio compared to control (1.5-fold, vs 2.7-fold, respectively). In addition, hearts from TG γ2 WT and TG γ2 R302Q mice both displayed a significant 2-fold reduction in AMPK activity compare to control, wildtype hearts. This decrease in AMPK activity was also accompanied by a reduction in phosphorylation of AMPK at its activation site, threonine 172, in both groups of transgenic mice. Despite this comparable decrease in AMPK activity, glycogen levels in hearts from TG γ2 R302Q mice were significantly higher as compared to TG γ2 WT mice (107.4 ± 14.6 vs 29.4 ± 3.2 µmol glucosyl units/ g wet weight), suggesting that AMPK activity alone is not responsible for the profound increase in glycogen in hearts from TG γ2 R302Q mice. While hearts from TG γ2 R302Q mice have similar decreases in AMPK activity and phosphorylation status as hearts from TG γ2 WT mice, only the TG γ2 R302Q mice develop WPW. Taken together, these data suggest that excessive glycogen accumulation is the major contributor to the cause of WPW and not AMPK activity per se.

843

Angiotensin Recptor Blockers and Risk of Myocardial Infarction: A Systematic Review

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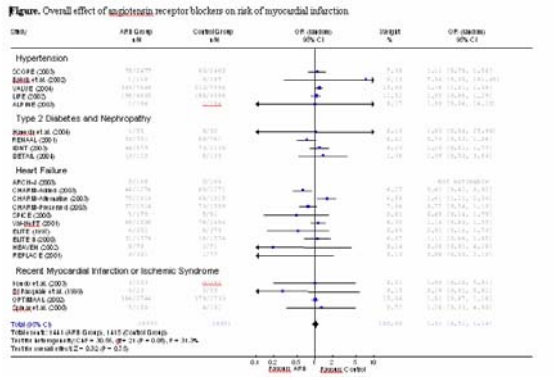
PURPOSE: Controversy exists as to whether angiotensin receptor blockers (ARBs), prescribed for a variety of indications, are associated with increased rates of myocardial infarction (MI). To evaluate the effect of ARBs on risk of MI in a broad spectrum of patients at risk for cardiovascular events, we undertook a systematic review of the existing literature.
METHODS: We performed a systematic review of controlled trials of ARBs. Data sources included MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, hand search, and contact with investigators. Predefined criteria were used to select controlled clinical trials comparing ARB use with angiotensin converting enzyme (ACE) inhibitors, placebo, or other active treatment in patients at risk for adverse cardiovascular events. Data were extracted for patient characteristics, interventions, quality of trials and MI.
RESULTS: Twenty-three studies with 57488 patients were included in our overall analysis. There were 5 studies of ARB use in hypertensive patients, 4 studies in patients with diabetes and nephropathy, 10 studies in patients with heart failure, and 4 in patients with recent MI/ischemic syndrome. Eleven studies of 21062 patients allowed for pre-specified comparison between ARBs and placebo; 9 studies of 10625 patients allowed for pre-specified comparison between ARBs and ACE inhibitors. In the overall analysis (ARBs vs any control therapy), there was a neutral effect of ARBs on risk of MI (odds ratio [OR]1.02, 95% confidence interval[CI] 0.91-1.14) (Figure). ARB use was not associated with increased risk of MI versus placebo (OR 0.94, 95% CI 0.75-1.16) and was not associated with increased risk of MI versus ACE inhibitor therapy (1.01, 0.87-1.17).
CONCLUSIONS: Treatment with ARBs does not confer an increased risk of MI. Until further information specifically addressing this issue is available from large prospective trials, our findings may alleviate recent concerns over the safety of this class of medications.



844

IMPROVED HEART TRANSPLANT SURVIVAL IN PATIENTS BRIDGED WITH VENTRICULAR ASSIST DEVICE

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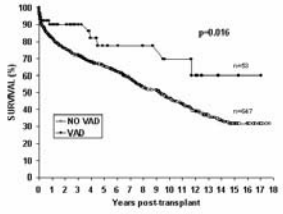
INTRODUCTION:
Due to donor shortage and increasingly more patients with heart failure, more heart transplants (HTx) are being performed on status 3 & 4 patients. While awaiting HTx these patients can deteriorate and require a ventricular assist device (VAD) as a bridge to HTx. We report our single center experience.

METHODS:
We reviewed our VAD database. Those who survived to HTx were compared to non-VAD HTx patients. Survival curves of these two groups were generated.

RESULTS:
From 1984 to 2001, 86 patients had VADs. The devices were: Novacor(59), Thoratec(22), ABiomed(4), and Heartmate(1). Six patients received bi-ventricular(V) support. Two patients had right-V support, and the others received left-V support. There were 69 males and 17 females. Body surface area was 1.98±0.25 m2 (1.32 to 2.58). Etiologies of heart disease were idiopathic dilated cardiomyopathy(CM)(53), ischemic CM(19), acute myocardial infarction(7), peripartum CM(4), restrictive CM(1), myocarditis(1), and congenital heart disease(1). Duration of support on VAD was 53±82 days (0 to 452). Thirty patients(35%) died while on VAD support. They were significantly older than those who survived to transplant (47±11 vs 38±15 years, p=0.005). Causes of death were multi-organ failure(16), bleeding(5), sepsis(4), stroke(2), respiratory failure(2), and right-V failure(1). Fifty-six patients (65%) survived to HTx. When compared to non-VAD supported HTx patients, survival was better in the VAD-supported group: (see graph)

CONCLUSION: With increasing number of critically ill patients on the HTx waiting list, the need for VAD as a bridge to HTx will also increase. Our study shows that these patients have a good chance of surviving to HTx and a better survival rate after HTx.



845

USE OF ECHOCARDIOGRAPHY TO ASSESS FUNCTION OF hDAF-TRANSGENIC PIG CARDIAC XENOGRAFTS

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INTRODUCTION:
The current standard of hand palpation may not be a sensitive method to detect rejection in heterotopic heart xenotransplants (HHTx). We sought to assess the use of echocardiography (echo) to detect rejection of pig heart xenografts.

METHODS:
Four cynomolgus monkeys (cyno) received HHTx from hDAF-transgenic pigs. Immunosuppression was cyclophosphamide induction, cyclosporine, steroids, sodium mycophenolate, alpha-Gal trisaccharide polymer, ±soluble complement receptor type 1. Echo was performed immediately after HHTx and 3 times a week post-op. Contractility on echo was scored as 1(none), 2(severely impaired), 3(moderate to severely impaired), 4(moderately impaired), 5(mild to moderately impaired), 6(mildly impaired), or 7(normal). Left ventricle wall thickness (LVWT) was measured in the anterior, inferior, posterior, lateral, and septal walls; the average was calculated. Impaired contractility and/or increase in LVWT were considered rejection and treated with steroid (Rx) (solumedrol 15 mg/kg iv for 3-5 days). Palpation score (4-strong to 1-none) was recorded daily. Myocardial biopsies were obtained infrequently.

RESULTS:
At time of first rejection, all 4 cynos had increase in LVWT and decrease in contractility on echo. Steroid Rx enhanced contractility in 4/4 cynos and decreased LVWT in 3/4 cynos. Palpation score remained at 4/4 during initial rejection episodes. (SEE TABLE ATTACHED)
Final graft failure was steroid-resistant and associated with severe vascular rejection.

CONCLUSION:
Decrease in contractility and increase in LVWT on echo appear to signify graft injury, since steroid Rx results in improvement. Compared to palpation, echocardiography is more sensitive for assessing function of heterotopic pig heart xenografts. Echo has therefore the potential to detect and treat early rejection episodes of heterotopic heart xenografts in non-human primates. This may help to achieve longer graft survival.

Cyno	Survival (d)	Baseline LVWT (cm)	LVWT at 1st rejection (cm)	LVWT post-Rx (cm)	Contractility score pre-Rx	Contractlity score post-Rx
1	35	4.9	6.2	4.8	3	5
2	22	4.6	7.7	8.0	2	3
3	20	7.7	9.3	8.6	5	6
4	36	7.1	8.2	5.6	4	5
Mean	28±8	6.1±1.5*	7.9±1.3*	6.7±1.8	3.5±1.3	4.7±1.2
*p=0.033						

846

Characterization of an Inhibitor Resistant Mutant of the Na+/H+ Exchanger

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The Na+/H+ exchanger is a plasma membrane protein present in all mammalian cells. In the heart the NHE1 isoform functions to remove excess intracellular acid removing one H+ in exchange for one extracellular sodium. Evidence has suggested that the protein is involved in the damage that occurs to the myocardium with ischemia and reperfusion. It is suggested that the excess intracellular acid removed by the Na+/H+ exchanger results in increased intracellular sodium. The sodium is removed by the Na+/Ca2+ exchanger resulting in calcium overload and cell damage. Numerous studies have demonstrated that inhibition of the Na+/H+ exchanger results in decreased calcium influx into the myocardium during ischemia and reperfusion. To study the mechanism by which the Na+/H+ exchanger modulates calcium overload and regulates intracellular pH, we made a mutant drug resistant form of the Na+/H+ exchanger. The Na+/H+ exchanger is composed of a 500 amino acid membrane domain consisting of 12 transmembrane regions plus a cytosolic tail. Residues leucine 163 and glycine 174 of transmembrane segment IV were mutated to phenylalanine and serine. The protein was then transfected into Na+/H+ exchanger deficient CHO cells (AP-1 cells) and stable cell lines were made of transfectants. A hemagluttin tag confirmed that the cell lines had expressed the mutated protein. We characterized the resistance of the mutant to the Na+/H+ exchanger inhibitor HOE694. The Ki of inhibition for the mutant was 37.1?M while that for the wild type was 0.15?M. The results confirm that we created a Na+/H+ exchanger protein that is resistant to drug inhibition. In future studies we will transfect various regulatory mutants of this drug resistant Na+/H+ exchanger into isolated cardiomyocytes and treat cells with HOE694 to inhibit the wild type Na+/H+ exchanger and study the regulation of the transfected protein. Supported by CIHR of Canada.

847

Na+/H+ exchanger over-expression elevates diastolic Ca2+-overload in myocardial ischemia/reperfusion

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Na+/H+ exchanger over-expression elevates diastolic Ca2+-overload in myocardial ischemia/reperfusion

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The Na+/H+ exchanger is a plasma membrane protein that is present in all mammalian cells. In the heart, the NHE1 isoform removes one intracellular H+ in exchange for one extracellular Na+. Recent evidence shows that NHE1 is an important contributor to myocardial ischemia/reperfusion injury. The intracellular acidification caused by ischemia results in increased [Na+]i that leads to calcium overload and irreversible cell damage due to reverse-mode Na+/Ca2+ exchanger activity. It is also known that NHE1 levels vary widely in the heart and other tissues – stimuli such as chronic acidosis dramatically increase protein and mRNA levels. To examine the effect of increased NHE levels, we created a transgenic model that over-expresses NHE1 in the mouse myocardium using the alpha myosin heavy chain promoter. A hemagglutinin tag on the protein confirmed that the NHE1 was over-expressed in the myocardium. Western blot analysis showed that expression of the NHE1 transgene was specific to the myocardium. Ventricular cardiomyocytes were isolated from transgenic and control mouse hearts. We then examined the sensitivity of field-stimulated cardiomyocytes to IR injury using a cellular model of metabolic inhibition and reoxygenation. The increase in diastolic [Ca2+]i associated with reoxygenation was significantly larger in myocytes isolated from NHE1 overexpressor animals (42 ± 6.8% vs. 22 ± 5.5% in controls, n = 7 and 9, respectively, $P<0.05$). This increase in diastolic [Ca2+]i was attenuated in NHE1 over-expressor myocytes that were reoxygenated with a solution containing the NHE1 inhibitor HOE 694 (5 mM). The results demonstrate that overexpression of NHE1 directly causes increased diastolic Ca2+ overload during cardiac ischemia/reperfusion. Supported by CIHR.
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848

Matrix metalloproteinase-2 mediated degradation of alpha-actinin in peroxynitrite-induced myocardial injury

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Matrix metalloproteinases (MMPs) are best known for their ability to remodel the extracellular matrix. We previously reported that peroxynitrite (ONOO-)-induced myocardial injury is mediated by MMP-2. The sarcomeric protein troponin I is one target of MMP-2 proteolytic activity, however, MMP-2 was also found to localize to the cytoskeleton. We therefore examined whether MMP-2 may degrade cytoskeletal proteins to contribute to ONOO- -induced myocardial injury. Methods: Isolated rat hearts were perfused in Langendorff mode and subjected to a 15-min infusion of 80 microM ONOO- in the presence or absence of the MMPs inhibitor PD-166793 (2 microM) or glutathione (GSH, 300 microM), a ONOO- scavenger. Control hearts were infused with decomposed (dec.) ONOO-. Heart homogenates were prepared to perform immunoblots of cytoskeletal proteins and in vitro degradation assays were done to measure their susceptibility to proteolysis by MMP-2. Results: At the end of perfusion, mechanical function of ONOO-infused hearts was depressed (10 ± 1 vs. dec. ONOO- 21 ± 1 mmHg x min^-1 x 10^3). PD-166793 or GSH abolished the ONOO-induced decline in mechanical function. A 45% decrease in alpha-actinin levels in ONOO- infused hearts was observed by immunoblot ($p<0.05$ vs. dec. ONOO-; n=3/group). PD-166793 or GSH normalized alpha-actinin levels to that of the controls. Levels of desmin, and alphaII spectrin were unchanged in hearts following ONOO- infusion. In vitro degradation assays using purified alpha-actinin, desmin or spectrin and purified human recombinant MMP-2 (1-2 hr, 37 degrees C) showed that alpha-actinin and to a lesser extent desmin (but not spectrin) are susceptible to proteolysis by MMP-2. Tissue inhibitor of metalloproteinase-2 blocked the in vitro degradation of alpha-actinin and desmin by MMP-2. Conclusions: Here for the first time we demonstrate a novel action and target of MMP-2 to degrade alpha-actinin in hearts subjected to ONOO- -mediated oxidative stress injury. This may contribute to the impairment in contractile function.

849

Spontaneous Pulmonary Arterial Hypertension in Fawn Hooded Rats Results from Abnormalities on Chromosome I That Impair Mitochondrial Oxygen Sensing Causing an Hypoxic Phenotype During Normoxia

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Fawn Hooded rats (FHR), like humans, spontaneously develop pulmonary arterial hypertension (PAH), an idiopathic condition characterized by obstruction of the pulmonary vascular bed, right ventricular hypertrophy and a high mortality rate. We report that FHR have an inherited, mitochondrial defect that disrupts oxygen-sensing within the pulmonary artery smooth muscle cell (PASMC), triggering a response normally seen only with chronic hypoxia. In FHR, despite normal PO2, there is HIF-1± activation, decreased Kv1.5 expression and PASMC hypertrophy. FHR PASMC mitochondria are swollen and hyperpolarized with altered expression of mitochondrial complexes I and III and reduced production of reactive O2 species, prior to onset of PAH. Early dysregulated genes in FHR relate to mitochondrial function or apoptosis. Substitution of chromosome 1 (consomic rats FHR/BN1) prevents both the mitochondrial defect and PAH, suggesting that the relevant genes are on chromosome 1. PAH is reversed and survival enhanced by dichloroacetate (DCA), a mitochondrial pyruvate dehydrogenase kinase inhibitor, that restores mitochondrial function. This first description of inherited mitochondrial dysfunction as a cause for PAH is relevant to human PAH and suggests a therapeutic strategy of mitochondrial modulation with DCA.

850

Matrix metalloproteinase-2 activity is modulated by peroxynitrite

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Several cardiac pathologies, including ischemic and inflammatory heart diseases, are characterized by a rapid increase in reactive oxygen species and loss of cardiac contractile function. In particular, peroxynitrite (ONOO-), generated by the reaction of superoxide and nitric oxide, can alter the function and/or structure of several proteins. Although many enzymes can be inhibited by ONOO-, some matrix metalloproteinases (MMPs) (-1, -8 and -9) are activated by low micromolar concentrations of ONOO- in a glutathione (GSH)-dependent manner. As MMP-2 is activated in the heart under several conditions in which ONOO- levels increase and this results in the degradation of intracellular targets such as troponin I (TnI), the aim here was to understand whether MMP-2 activity can be modulated by ONOO- and GSH.

Methods: MMP-2 (either secreted from human HT1080 cell line or purified human recombinant enzyme) was incubated with ONOO- (0.3-300 microM, 15 minutes at 37°C) in the presence or absence of GSH (10-100 microM). MMP-2 activity was measured by gelatin zymography or by collagen or TnI degradation assays.

Results: In the absence of GSH, low concentrations of ONOO- (1-30 microM) increased MMP-2 gelatinolytic activity, whereas high concentrations (100-300 microM) significantly decreased activity. GSH did not potentiate the effect of ONOO-, but prevented the loss of MMP-2 activity induced by high concentrations of ONOO-. Collagen degradation by MMP-2 was not affected by ONOO- and/or GSH treatment. Preliminary results suggest that TnI degradation was enhanced by ONOO- and GSH.

Conclusions: Our results show that low micromolar concentrations of ONOO- enhance MMP-2 activity, and suggest that an imbalance between ONOO- and GSH in the heart can lead to MMP-2 activation or inactivation, with possible consequences in the development of heart diseases caused by oxidative stress.

851

Matrix Metalloproteinase-2 and Vascular Hypocontractility in Two Models of Sepsis

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An enhanced proteolytic state caused by an increase in matrix metalloproteinase (MMP) activity has been implicated in numerous cardiovascular pathologies. Recent evidence implicates a role of MMPs in vascular hyporeactivity to vasoconstrictor agents during sepsis. Bacterial lipopolysaccharide (LPS) is an important instigator and interleukin-1β (IL-1β) is an essential downstream mediator in the septic cascade. We investigated the changes in blood vessel contractility and MMP activity using two models of sepsis. METHODS: In an in vitro model of sepsis, aortas isolated from male Sprague-Dawley rats were incubated for 6 hr at 37 °C with IL-1β (10 ng/mL) in the presence or absence of GM6001 (10μM and 30μM), an inhibitor of MMPs. Concentration-response curves to phenylephrine were performed in organ baths, and MMP activity in similarly treated rings was examined by gelatin zymography. In order to examine changes in vascular MMPs in vivo, male Sprague-Dawley rats were injected with LPS (4 mg/kg) and aortas were excised after 6 hours. These were fixed, sectioned, and immunohistochemical analysis was performed. RESULTS: Functional in vitro studies of IL-1β treated rings showed a marked decrease in phenylephrine-induced contraction. This was inhibited by GM6001 in a concentration-dependent manner, indicating a role of MMPs in mediating vascular dysfunction by IL-1β. IL-1β treated aortic rings exhibited a decrease in MMP-2 activity (71% of control) accompanied by an increase in MMP-2 activity in the incubation culture media (116% of control), indicating the possible release of MMP-2 into the media. Immunohistochemical analysis revealed a decrease in MMP-2 protein in aortas taken from rats subjected to LPS. CONCLUSIONS: This study demonstrates that MMP-2 is involved in the development of vascular hyporeactivity, triggered by IL-1β in vitro or LPS in vivo. The loss of MMP-2 from vascular tissue may reflect its intracellular activation and release. Further work is required to identify the target(s) of MMP-2 in the vascular wall.

852

The potential Role Of Expensive New Technologies In Heart Failure In Canada: Lessons From The University Of Alberta Heart Function Clinic

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INTRODUCTION: Cardiac resynchronization therapy (CRT) devices and implantable cardioverter-defibrillator (ICDs) have been proven in trials to reduce morbidity and mortality in heart failure (HF). However, these therapies are expensive and their impact on total health care resources is unknown given the paucity of information on how many pts qualify for these devices; current estimates regarding eligibility range as high as 50% of all pts with HF. Our study was done to determine what proportion of pts attending a specialized heart failure clinic meet trial eligibility criteria for these devices.

METHODS: We applied trial eligibility criteria to consecutive pts seen at the University of Alberta Heart Function Clinic between Aug 2003 and Jan 2004.

RESULTS: Of the 309 pts in our cohort, 46 were excluded. Of the 263 pts with ischemic or dilated cardiomyopathy, 94% were prescribed ACE inhibitors, 75% beta-blockers, 47% spironolactone, and 48% digoxin - NYHA class was assessed on "optimal medical therapy". CRT trial eligibility criteria (ischemic or dilated cardiomyopathy, LVEF < 0.35, QRS > 120 msec, and NYHA class III or IV symptoms despite optimal pharmacotherapy i.e. - ACE inhibitor/ARB, beta-blocker, and spironolactone in pts without contraindications) were met by 48 pts (18%). MADIT II criteria (ischemic cardiomyopathy, LVEF < 0.30, and NYHA Class I-III symptoms) were met by 85 pts (32%), whereas 134 pts (51%) met SCD-HeFT criteria (ischemic or non-ischemic cardiomyopathy, LVEF < 0.35, and NYHA Class II or III symptoms), including 35 (13%) pts who qualify for both CRT and ICD.

CONCLUSIONS: If evidence-based medications are optimally applied, only a minority of symptomatic HF pts potentially require CRT, whereas the proportion who require ICD is substantially higher. Given the referral bias in any specialized HF clinic, these estimates should be considered as worst case scenarios for purposes of resource planning.

% eligibility in pts with ischemic or dilated cardiomyopathy:				
n = 263	ICD			CRT
	MADIT II criteria	Additional pts using SCD-HeFT criteria	Total	
% eligible when on optimal medical therapy	32%	19%	51%	18%

853

Enriching the Prognostic Value of the Baseline ECG in STEMI

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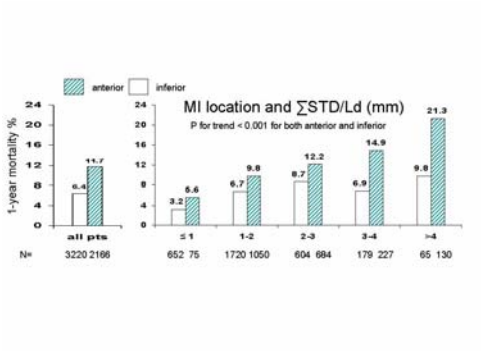
Background: Baseline sum of ST elevation (ΣST↑) and the composite of ST elevation and depression i.e. deviation (∑STD), as well as the number of leads with ST elevation have all been shown to be individual predictors of mortality in pts with acute STEMI. However, the integration of these ECG features to risk stratify pts has not been explored. Accordingly we examined this issue in ECGs of 5386 pts in a sub-study of ASSENT-3.

Methods: ΣSTD was determined by summing ΣST↑ and associated ST depression. The figure below shows the relationship between ΣSTD normalized for the number of leads involved (ΣSTD/Ld) & 1-year mortality, as well as the impact of infarct location on mortality.

Results: A comparison of the impact of ∑ST↑, ∑STD, and ∑STD/Ld on mortality revealed that baseline ∑ST↑ was associated with 1-yr mortality for anterior (p for trend = 0.001) but not inferior MI. However baseline ∑STD was associated with 1-yr mortality for both locations (p for trend = 0.001 for anterior and 0.019 for inferior). When analyzed using a multivariable model, ∑STD significantly predicted mortality only for anterior MI (OR 1.033, 95% CI, 1.02-1.05). The figure demonstrates that the extent of ∑STD/Ld predicted mortality for both anterior and inferior MI in univariate as well as multivariable analysis (OR 1.36 and 1.22 for each 1 mm increment in ∑STD/Ld, 95% CI 1.19-1.55 and 1.03-1.43, respectively). Irrespective of infarct location, the best discriminator of 1-yr mortality risk was provided by ∑STD/Ld.

Conclusion: These novel findings indicate that baseline ∑STD/Ld enhances risk stratification of pts with acute STEMI. Hence, when triaging and making treatment decisions for these pts, the integration of ∑STD, # of leads involved and MI location is desirable.



854

Risk Stratification In STEMI Is Enhanced By Using Both Baseline ST Deviation And ST Resolution At 180 Min

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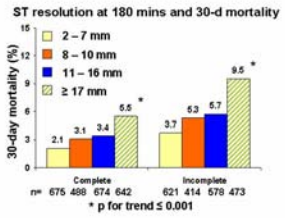
Background: Although ST resolution post fibrinolytic therapy and baseline sum of ST deviation (ΣSTD), i.e. sum of ST elevation and associated ST depression, have been shown to be prognostically useful in pts with acute STEMI, the integration of these ECG variables to risk stratify pts has not been studied. Accordingly, we examined this issue in a sub-study of ASSENT 3.

Methods: ST resolution was determined using Schroder's criteria in 4565 pts with interpretable ECGs at 180 min post fibrinolysis. The figure shows 30-day mortality in pts with complete (i.e. >70%) vs. incomplete ST resolution according to quartiles of absolute baseline ΣSTD in mm.

Results: Overall, pts with complete ST resolution had lower 30-day mortality compared to those with incomplete ST resolution (3.5 % vs. 5.9 %, respectively, p < 0.001). Irrespective of ST resolution, increased baseline ΣSTD was strongly associated with higher 30-day mortality (p for trend ≤0.001 in fig). After adjustment for key baseline risk factors in multivariable analysis, pts in the highest quartile of ΣSTD had a higher risk of 30-day mortality than those in the lowest quartile in both complete (OR 2.33, 95% CI 1.21-4.47) and incomplete ST resolution groups (OR 2.72, 95% CI 1.58-4.70).

Conclusion: These findings indicate that % ST resolution alone is an inadequate guide to 30-day mortality and that it should be combined with measurement of baseline ΣSTD to enhance risk stratification of STEMI pts treated with fibrinolysis. This integration of both the baseline and post fibrinolysis ECG will assist in triage and treatment of such patients.



855

NFAT regulates Kv1.5 expression, a voltage-gated K+ channel which is selectively downregulated in animal and human pulmonary hypertension

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The proliferative vascular remodeling in Pulmonary Hypertension (PHT), in humans is characterized by a selective downregulation of Kv1.5, an oxygen-sensitive voltage gated K+ channel. Kv1.5 inhibition or deficiency in pulmonary artery smooth muscle cells (PASMC), leads to enhanced proliferation (due to depolarization-induced influx of Ca++) and suppressed apoptosis (due to K+-induced caspase inhibition). Although acute hypoxia inhibits Kv1.5 by a redox mechanism, the mechanism by which chronic hypoxia downregulates Kv1.5 expression is unknown. We hypothesized that Kv1.5 is downregulated by NFAT, a transcription factor activated by calcineurin, when [Ca++]i increases. Activation of NFAT (i.e. de-phosphorylation) allows its translocation to the nucleus, where it increases or decreases the expression of target genes. We studied hypoxic PASMC, a model relevant to chronic hypoxic PHT, with qRT-PCR, whole-cell patch clamping and multiphoton confocal microscopy. Chronically hypoxic human PASMC (10%O2x96hrs) had decreased Kv1.5 expression (mRNA-protein) and function (outward K+ current, Ik) at -30mV, current density was 18 ± 6 pA/pF in control (N=4) versus 5 ± 1.5 pA/pF in hypoxia (N=5). [Ca++]I increased by 30% in hypoxic cells (N=35) compare to control (N=47) and activated NFAT. Triple staining studies showed that Kv1.5 was particularly decreased in PASMC with activated NFAT (i.e. translocated to the nucleus). Inhibition of Ca++ influx in hypoxic PASMC, by nifedipine (10°M), blocked NFAT activation (i.e. cytoplasmic and not nuclear pattern) and increased Kv1.5 expression. Direct NFAT inhibition in hypoxic PASMC (by a competing peptide 4°M) completely reversed the decrease in Kv1.5 expression (mRNA+protein), Ik (N=7), and the increase in [Ca++]I (N=34). We show that the activation of NFAT pathway in human PASMC is responsible for Kv1.5 downregulation. We suggest that this pathway might be operative in proliferative vascular remodeling states and that it might be a potential therapeutic target in PHT.

856

Decellularization reduces the immune response to aortic valve allografts in the rat

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INTRODUCTION Cryopreserved valve allografts used in congenital cardiac surgery are associated with a significant cellular and humoral immune response. This may be reduced by removal of antigenic cellular elements (decellularization). The aim of this study was to determine the immunological impact of decellularization in a rat allograft valve model.

METHODS Brown Norway and Lewis rat aortic valves were decellularized with a series of hypotonic and hypertonic buffers, protease inhibitors, gentle detergents (Triton X-100), and phosphate buffered saline. Valves were implanted into Lewis rats in syngeneic and allogeneic combinations. Cellular (CD3, CD8) infiltrates were assessed using morphometric analysis and the humoral response was assessed using flow cytometry.

RESULTS Morphometric analysis identified a significant reduction in CD3+ cell infiltrates (cells/ square mm leaflet tissue) in decellularized allografts as compared to nondecellularized allografts at 1 (79 ± 29 vs. 3310 ± 223; $P < 0.001$), 2 (26 ± 11 vs. 109 ± 20; $P = 0.004$), and 4 weeks (283 ± 122 vs. 984 ± 145; $P < 0.001$). Anti-CD8 staining confirmed the majority of infiltrates were cytotoxic T cells. Flow cytometry mean channel fluorescence intensity identified a negative shift (abrogated antibody formation) for decellularized allografts compared to non-decellularized allografts at 2 (19 ± 1 vs. 27 ± 3; $P = 0.033$), 4 (35 ± 2 vs. 133 ± 29; $P = 0.001$), and 16 weeks (28 ± 2 vs. 166 ± 54; $P = 0.017$).

CONCLUSIONS Decellularization significantly reduces the cellular and humoral immune response to allograft tissue. This could prolong the durability of valve allografts and may prevent immunologic sensitization of allograft recipients.

857

Can Prophylactic Intravenous Immunoglobulin Prevent Sensitization to Cryopreserved Allograft Tissue Used in Congenital Cardiac Surgery?

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INTRODUCTION Cryopreserved allograft tissue used in the Norwood procedure for infants with hypoplastic left heart syndrome (HLHS) causes profound immunologic sensitization which may complicate future transplantation. Intravenous immunoglobulin (IVIG) has been shown to reduce sensitization after it has developed, allowing for successful transplantation. The purpose of this pilot trial was to determine whether IVIG given prospectively could prevent sensitization to cryopreserved allograft patches used in the initial repair of HLHS.
METHODS IVIG (2gm/kg) was given preoperatively, 3 weeks postoperatively, and 4 months postoperatively to 7 infants undergoing the Norwood procedure. Panel reactive antibodies (PRA) were measured preoperatively and at 1 and 4 months postoperatively using flow cytometry and compared to a contemporary cohort of 12 infants undergoing the Norwood procedure who did not receive IVIG.
RESULTS The two groups were well matched for age and weight at the time of surgery. There were no differences in transfusion requirements. At four months, there was no difference in the degree of sensitization for the two groups (table). In addition, antibody specificity analysis confirmed antibodies were specific for the HLA type of the donor allograft or well-known cross reactive antigens.
CONCLUSIONS The use of allograft tissue in the repair of HLHS is associated with profound donor specific immunologic sensitization which may complicate or prevent future transplantation. While IVIG has shown to reduce sensitization after it has occurred, giving IVIG prior to sensitization has no benefit.

	Preoperative PRA (%)	1 month postop PRA (%)	4 month postop PRA (%)
Class I PRA			
No IVIG	1 ± 4	20 ± 30	62 ± 40
IVIG	6 ± 17	4 ± 9	73 ± 41
	p = 1.000	p = 0.443	p = 0.813
Class II PRA			
No IVIG	1 ± 2	17 ± 27	49 ± 42
IVIG	0	20 ± 17	54 ± 41
	p = 0.267	p = 0.400	p = 0.706

858

Feasibilty of Incorporating a CPR/AED Course within a Cardiac Rehabilitation Program

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Introduction: Survival rate from out-of hospital cardiac arrests(CA) can be greatly improved by immediate by-stander cardio-pulmonary resuscitation(CPR) together with early defibrillation whenever automated external defibrillators (AED) are available. Although CA are most frequent in patients(pts) with known cardiac disease, the majority of the pts/spouses remain untrained in CPR/AED use. The present study examined the feasibility of incorporating such a program within the cardiac rehabilitation program (CRP)
Methods: All pts enrolled in the CRP (since March 2004) were strongly encouraged to attend CPR/AED training(with a family member). A 2-hr class was run by certified instructors and provided free of charge.
Results:Over a 1-year period, 133/370(36%) pts and 105 family members(78.9%) undertook the course. Ten individuals(4.2%) couldn't be adequately trained. The pts who attended the course differed significantly ($p<0.05$) from those who did not attend by way of age (62.5 +/- 1.1 Vs 59.7 +/- 0.7yrs), the index event (AMI=40.5%: Unstable angina = 33.8%: CAB=36.6%; Stable angina = 19.2%), The frequency of attendance did not significantly differ ($p>0.05$) by way of gender(F=35.3%; M=36.1%), ethnicity (Caucasians=36.9%; South Asians=32.6%), educational level (less than High School Diploma= 38.3%:. High School Diploma=35.6%; College/University=35.8%), number of wks. prior to return to work (8.6 +/- 1.0 wks vs 7.9 +/- 0.6 wks). There appeared to be a trend for pts with higher weights (87.4 +/- 1.3 kg vs 84.0 +/- 1.6 kg) and those unemployed/on disability (2/15 =13.3%; employed 71/204=34.8%; homemaker/retired 60/150=40.0%) to not attend. A pt who took the course performed CPR on a golfer who had a CA on the fairway until defibrillation was done by the EMS. The golfer recovered to leave hospital with minimal neurological deficit.
Conclusion:It is feasible to incorporate a CPR/AED training program for pts attending a CRP and achieve competence in the majority. However additional measures are needed to improve participation.

859

Innovative Cardiology Care Delivery Utilizing Nurse Practitioners (NP): the University of Alberta Model

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The role of NPs in Cardiology is new and evolving. The Canadian Nurses Association is endeavoring to standardize NP education and certification. We propose that a model for NPs, used by Cardiology at the University of Alberta for the past 5 years could inform this process. Our model, developed with a team of 6 NPs, combines a variable mix of clinical, research and administrative responsibilities. NPs are utilized in innovative and traditional services, including: a Pulmonary Hypertension Program, a rapid-evaluation consultative clinic, a chest pain program, a cardiology ward and a stress-testing laboratory. Our model operates on the following principles: All NPs a) have significant clinical experience (~8 years); b) are matched with physician preceptors; c) participate in divisional CME d) undergo training and skill validation in each area (1-3 months) e) participate in 3-month rotations f) receive strong support for graded independence, as outlined by a scope of practice document. In some cases, NP's function autonomously, as in the stress-test laboratory; in other venues a more traditional physican-partnering model applies. Our model: a) optimizes and extends the efficiency of physicians time; b) improves waiting times; c) enhances follow-through thereby reducing medical error and d) enhances the practice of evidence-based Medicine. This model promotes NP independence while maintaining traditional nursing strengths, including patient education, enhancing compliance and increased availability for patient concerns. NPs have significant administrative responsibilities and, since our innovation programs host translational research, research skills are both desired and developed. This experience might assist efforts to develop a model for NP training and certification that would be applicable in other institutions.

860

Left Ventricular Lead Implantation Via Left Mini-Thoracotomy: A Viable Alternative or a Better Approach for Cardiac Resynchronization Therapy?

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INTRODUCTION: Transvenous placement of LV epicardial leads is limited by long procedure times, high procedural failure rates and limited sites for lead placement. Open surgical approaches are used primarily after failure of the transvenous approach, but provide several important benefits. The main objective of this study was to assess surgical outcomes of left anterior mini-thoracotomy for the implantation of left ventricular (LV) epicardial leads in cardiac resynchronization therapy (CRT). Mid-term lead function was assessed.

METHODS: Nine patients were referred for open LV epicardial lead placement. Mean patient age was 67 +/- 7 years. Patients had New York Heart Association Class 3.0 +/- 0.5 heart failure, mean left ventricular ejection fraction of 18 +/- 5% and mean QRS duration of 177 +/- 29 milliseconds. Patient data was reviewed retrospectively.

RESULTS: LV epicardial leads were successfully placed in all patients. There was one small left ventricular injury and one minor exacerbation of heart failure. Mean surgical time was 101 +/- 33 minutes and intraoperative lead thresholds were: R-wave 12.1 +/- 7.1 millivolts, lead threshold 1.5 +/- 1.0 Volts at 0.5 milliseconds and impedance 928 +/- 658 Ohms. There were no statistically significant 25 weeks: lead threshold 2.1 +/- differences in lead parameters at 40 1.6 Volts (p = 0.359) and impedance 571 +/- 198 Ohms (p=0.129).

CONCLUSIONS: Epicardial LV lead implantation via left anterior mini-thoracotomy is safe and effective. Given its benefits over transvenous techniques, the mini-thoracotomy approach should be reconsidered for first-line LV lead implantation for CRT

861

Practice Patterns and Outcomes in Patients Presenting to the Emergency Department With Acute Heart Failure

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INTRODUCTION
Heart failure (HF) is a common emergency department (ED) presentation and a leading reason for hospital admission in Canada. Contemporary Canadian practice patterns for acute HF have not been described. The objective of the study is to describe current treatment patterns of patients presenting to the ED with acute HF.

METHODS
A multi-centre, retrospective, health record review was performed on patients who presented to EDs from 04/2002 to 03/2003 with a most responsible diagnosis of acute HF. Thirty percent of patient records from each of 6 ED's in Edmonton, Alberta were randomly selected for review.

RESULTS
A total of 96 patients were included in this preliminary analysis; 42% were female and the mean age was 79 (±12) y. Common comorbidities were: hypertension 56%, diabetes 44%, previous myocardial infarction 43%, atrial fibrillation 25%, and COPD 25%. In the first 72h, patients were treated with IV furosemide77%, oxygen 58%, ACE inhibitors or angiotensin receptor blockers 36%, salbutamol 34%, ipratropium 31%, anticoagulants 28%, oral furosemide 27%, ASA 26%, transdermal nitroglycerin 22%, beta-blockers 16%, and digoxin 15%. Mean ED length of stay was 14 (±9)h, 48% of patients were admitted to hospital (average length of stay 10 (±14)d, and 12% of patients died.

CONCLUSIONS
The current treatment patterns for acute HF include mostly IV furosemide and bronchodilators. Proven efficacious HF therapies (ACE inhibitors and beta-blockers) were used in relatively few patients. Future research on predictors of readmission, treatments to reduce rehospitalization, and small area practice variation are warranted.

862

Pravastatin Reverses the Down-Regulating Effect of Inflammation on β Adrenergic

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INTRODUCTION: Inflammatory conditions reduce electrocardiographic (ECG) response to cardiac β-adrenergic antagonists such as propranolol. We hypothesize that pravastatin, an anti-cholesterol drug, may reverse this, and that it may correct Th1/Th2 immune imbalance associated with the Th1-skewed Pre-Adjuvant Arthritis model (Pre-AA).
METHODS: PR-interval response to propranolol, a measure of cardiac conduction, was measured in four groups of rats (n=14-16/group): Healthy/Placebo, Arthritis/Placebo, Healthy/Statin, and Arthritis/Statin. Day 0: 38 mg/kg Mycobacterium butyricum in squalene, or placebo. Day 4: 6 mg/kg of pravastatin twice daily, or placebo. Day 8: final ECG measurement.
RESULTS: As expected, response to propranolol was reduced in inflamed rats.Interestingly, however, treatment with pravastatin reversed the down-regulation so that it enabled the inflamed rat to maintain expected propranolol response: Area Under the % Effect Curve (%.min) was 714±214 in Healthy/Placebo, 256±249 in Arthritis/Placebo, 1534±367 in Healthy/Statin, and 1713±393 in Arthritis/Statin. Significantly fewer rats had detectable IFN-gamma in Arthritis/Statin versus Arthritis/Placebo. Pravastatin does not appear to correct the elevated plasma propranolol concentrations associated with Pre-AA.
CONCLUSIONS: Inflammation lowered drug response despite increased plasma propranolol concentration. Pravastatin reversed the effects of inflammation on propranolol's PR-interval response. Restoration of cardiac response with pravastatin was not associated with a correction of plasma propranolol levels, but coincides with attenuation of the inflammatory cytokine interferon-gamma. This indicates that response may be related to the anti-inflammatory effects of pravastatin. Patients in inflammatory status may benefit from statins during cardiovascular treatment.
Supported by: CIHR and RX&D Health Research Foundation.

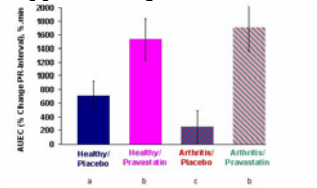

Figure 1. Effect of pravastatin and inflammation on propranolol response in the Pre-AA SD Rat. Same characters indicate no significant difference.

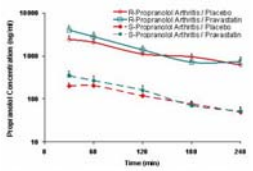

Figure 7. Effect of pravastatin on plasma R- and S-propranolol concentration in the Pre-AA SD rat. The groups were not significantly different.

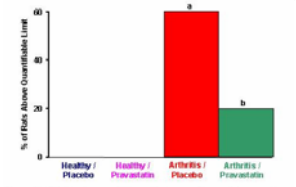

Figure 2. Effect of pravastatin and inflammation on the percentage of rats above IFNγ quantifiable limit in the Pre-AA SD rat. Same characters indicate no significant difference.

863

Differences in Psychosocial Correlates of Exercise Tolerance in Men and Women Attending Cardiac Rehabilitation

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INTRODUCTION: Poor exercise tolerance, as indicated by an exercise stress test (EST), is a predictor of recurrent events and mortality after a heart attack. Aside from disease severity, recent evidence (Ruo et al., 2004) suggests that psychological factors can add to the explanation of exercise tolerance. PURPOSE: To examine the impact of stress and types of social support (tangible, emotional, belonging) on EST time in men and women at cardiac rehabilitation (CR), and to explore sex differences in how these psychosocial variables might affect EST times. METHODS: Men (n = 333, mean age = 57, SD = 10) and women (n = 85, mean age = 57, SD = 11) recruited upon entry into CR completed measures of stress and social support followed by an EST using the Bruce protocol. RESULTS: Regression analyses were used to examine the relationship between stress, social support and EST times controlling for age. Given the exploratory nature of comparing the impact of the psychosocial variables between men and women on exercise tolerance, a relaxed confidence level was used (i.e., $p < .10$). Results showed that age and the psychosocial variables explained 20% ($p < .001$) and 12% ($p < .01$) of the variability in EST times for men and women, respectively. For men, stress and age were both negatively related EST time (both p's $< .05$), and belonging support was positively related to EST time ($p = .08$). For women, age and tangible support were negatively related to EST times ($p < .01$ and $p = .05$, respectively), and emotional support was positively related EST times. CONCLUSIONS: Psychosocial variables may provide additional explanation for the results of an EST. The influence of these factors seems to vary between men and women where EST times were negatively influenced by stress for men but not for women. These results confirm earlier studies suggesting psychosocial factors can influence EST times. Future research should determine if this effect reflects motivation to perform on the test or some other mechanism like cardiovascular reactivity.

864

Sex Differences in Psychosocial Predictors of Depressive Mood upon Entry into a Cardiac Rehabilitation Program

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INTRODUCTION: Symptoms of depression are prevalent in newly diagnosed cardiac patients and are a significant predictor of recurrent cardiac events within the first year after a myocardial infarction (Bush et al., 2001). PURPOSE: The purpose of this study was to examine the differential influence of psychosocial predictors on depressive mood prior to beginning cardiac rehabilitation (CR) among men and women. METHODS: Participants referred to CR were mailed a questionnaire assessing depressive mood, perceived stress, and three types of social support: emotional, tangible and belonging. Demographic information was collected from patient medical records. Participants (men =129, women = 38) returned the questionnaire at an introductory CR orientation session prior to beginning the rehabilitative program. RESULTS: Two regression analyses were used to separately examine the influence of the psychosocial factors on depressive mood for men and women. Results showed that perceived stress and social support accounted for significant variability in depressive symptoms among both men ($R^2_{adj} = .50$, $p < .001$) and women ($R^2_{adj} = .49$, $p < .001$). For men, being younger, having less tangible support, and reporting more stress were significantly related to depressive mood. Among women, a lack of belonging support and stress were significantly related to depressive mood. CONCLUSIONS: Results support previous research on the occurrence of depressive mood in cardiac patients. However, this study highlights the importance of examining stress and different types of social support in both men and women prior to attending CR. In furthering our understanding of depressive mood following a cardiac event, tangible support may be particularly important for men and belonging support for women.

865

Angiotensin Converting Enzyme I/D Gene Polymorphism Influences Serum C-reactive Protein Level in Hypertensive Individuals.

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Objectives: The angiotensin converting enzyme (ACE) gene has been associated to inflammatory conditions and to the risk of cardiovascular disease. We investigated whether the I/D polymorphism of the ACE gene influences . plasma levels of C-reactive protein (CRP), IL-6 and TNF
Methods and results: Inflammatory markers and ACE genotype were ascertained in 64 hypertensive and 20 normotensive subjects without history of atherosclerotic disease. High sensitivity ELISA tests were used to measure inflammatory markers and polymerase chain reaction was used for genotyping. Participants were 30-64 years old (mean age 48 9), 37% were male, and 25 % were obese. The prevalence of the D allele was 61% and the polymorphisms were in Hardy-Weinberg equilibrium were log-transformed and (p=0.98). Values of CRP, IL-6 and TNF subjects with the DD allele (n=31) were compared to those with the II/ID alleles using linear regression. Crude means (95% confidence intervals) for inflammatory markers in individuals with II/ID vs. DD genotype were: CRP (mg/dl): 0.35 (0.26, 0.46) vs. 0.22 (0.16, 0.32); IL-6 (pg/ml): 8.94 (6.56, 12.18) vs. 6.59 (3.75, 11.59); and TNF (pg/dl): 10.37 (6.20, 17.37) vs. 13.98 (7.36, 26.57), respectively. After adjustment by age, gender, body mass index, hypertension and levels of the other two markers, DD subjects had a 32.7% (1.91, 53.8; p=0.04) lower CRP. This difference in CRP was similar in hypertensive and non-hypertensive subjects (p-value for interaction test=0.90). The prevalence of the D allele by quartiles of CRP (lowest to highest) was: 69.0%, 61.9%, 57.1%, and 54.8%. No significant differences were (p=0.34 and p=0.16, respectively). observed for levels of IL-6 and TNF
Conclusions: Subjects with the DD variant of the ACE gene have significantly lower levels of CRP than carriers of the I allele. These results indicate that the ACE gene is involved on the modulation of CRP levels.

866

Feasibility Of Determining Myocardial Infarction Type From Retrospective Medical Record Review

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Feasibility Of Determining Myocardial Infarction Type From Retrospective Medical Record Review

Background: Hospital discharge data are used extensively in health research. Given the clinical differences between ST segment elevation myocardial infarction (STEMI) and non ST segment elevation myocardial infarction (NSTEMI), it is important that these 2 entities be distinguishable in the medical record. In this study, we sought to determine the extent to which the type of MI is recorded in hospital medical records, and the consistency of this designation within records.
Methods: A chart review of all MI cases discharged from a Canadian tertiary care center between March 31, 2000 and March 31, 2001 was performed to establish documentation of STEMI or NSTEMI in 4 parts of the medical record: admission history, physician progress notes, CCU summary and the discharge summary.
Results: The use of the term STEMI decreased during the hospital stay, while the use of NSTEMI increased (Table1). Only 9 (1.6%) STEMI patients and 38 (6.5%) NSTEMI patients had these terms used consistently. In 49 (8.4%) of patients, neither STEMI nor NSTEMI was used in any areas of the charts, and in 73(12.6%), the chart referred to both STEMI and NSTEMI in the same patient – a finding that makes it impossible to assign MI status to those inconsistent cases.
Conclusion: The designation of MI cases as STEMI vs. NSTEMI is both incomplete and inconsistent in hospital records. This has implications for health services research conducted retrospectively using medical record data, as it is impossible to adequately study processes and outcomes of MI care if MI type can not be retrospectively determined.

Table 1: Use of STEMI and Non-STEMI in the hospital chart (n=581)

Source	STEMI Designated	NSTEMI Designated	No specific Designation of AMI Type
Admission History	274 (47.2%)	105 (18.1%)	202 (34.7%)
Progress	124 (21.3%)	173 (29.8%)	284 (48.9%)
CCU Summary	132 (22.7%)	133 (22.9%)	316 (54.4%)
Discharge Summary	65 (11.2%)	141 (24.3%)	375 (64.5%)
Any place in chart	305(52.9%)	196(33.7%)	

868

Efficacy of PCI in Revascularization of Patients with Early Recurrence of Ischemia Post-CABG

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OBJECTIVE: To examine the efficacy of PCI in pts with symptomatic CAD within 1 year post-CABG.
BACKGROUND: There is scant recent literature on efficacy of PCI in revascularization (rv) of pts with symptomatic CAD post-CABG. Repeat CABG is associated with a higher mortality than first time CABG. Furthermore, CABG within 1 year independently predicts greater morbidity and mortality.
METHODS: Retrospective study using data from the APPROACH database and chart review. Primary endpoint was presence any major adverse cardiac events (MACE). Secondary endpoints were presence of inducible ischemia on EST or MIBI, unstable angina or MI at follow up.
RESULTS: From Jan2000-Apr2005, 33 pts underwent PCI < 1 year post-CABG at Royal Alexandra Hospital. Mean time between CABG and PCI was 172 ± 94 days. There were 24 male pts(72.7%). Mean age was 62±9. Seven pts(21.2%) were diabetic. Pre-CABG angiogram showed 2 vessel disease(42.4%); 3 vessel(57.6%), including 6% with L main disease. Number of bypasses per pt was 3.2 ± 0.9. Two pts did not receive a LIMA graft. Graft failure occurred in 41.9%(13/31) of LIMA and 25%(19/76) of SVG. Indications for PCI post-CABG were: symptomatic or provocable ischemia 48.5%, acute coronary syndrome 48.5% and STEMI 3%, due to graft failure 72.7%and missed culprit lesion 27.3%. There were 90.9% Grade C, 3.0% B2 & 6% B1 lesions. IIb/IIIa inhibitors were used in 48.5% and stents in 84.8% of pts, including drug eluting stents(DES) in 46.4%. There were no MACE immediately post-PCI.
Mean time to follow up was 347 ± 292 days. One pt died of unknown cause at 840 days. Ischemia on EST or MIBI was present in 3 pts (9.1%), 2 of which underwent repeat PCI with DES(1 a new lesion, 1 in stent restenosis). Two pts with angina were managed with medical therapy. No MACE was observed in the remaining 27 pts(81.8%), including all pts who received DES.
CONCLUSION: PCI is an effective option for early rv in pts with symptomatic CAD post-CABG. The low restenosis rate of DES may further expand the utilization and efficacy of PCI in these pts.

869

Multi-Center Analysis of Octogenarians Undergoing Mitral Surgery

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INTRODUCTION: To compare octogenarians to younger patients undergoing mitral valve surgery, and to identify risk factors specific to octogenarians.
METHODS: Data were collected prospectively from 1996 to 2004 at three centers from Alberta and Nova Scotia. Of 2101 consecutive patients with mitral valve surgery, 120 (5.7%) were aged > 80 years. Survival data were analyzed using Cox proportional hazards modeling.
RESULTS: Octogenarians and younger patients were similar in most pre-operative factors; however, octogenarians were more likely to have renal dysfunction, CHF, and a history of strokes ($p < 0.05$). Operative characteristics for ocotogenarians and younger patients are similar in their rate of mitral valve replacement (MVR) (58.3% versus 57.8%, $p > 0.05$); however, octogenarians were more likely to require urgent surgery, combined mitral valve and coronary artery bypass surgery (MV+CABG), increased cardio-pulmonary bypass (CPB) and aortic cross clamp (ACX) times, and increased length of hospital stay (LOS) ($p < 0.05$). Octogenarians had higher in-hospital mortality than younger patients (18.3% versus 6.0%, $p < 0.05$). Independent risk factors of mortality for the entire cohort were: age > 80, renal dysfunction, hypertension, peripheral vascular disease (PVD), urgent surgery, MVR, MV+CABG, increased CPB and ACX times, and increased LOS ($p < 0.05$). A sub-group analysis was performed on octogenarians ($n = 120$) and the independent risk factors specifically to the elderly patients were PVD (OR = 9.48, $p < 0.05$), MVR (OR = 7.68, $p < 0.05$), and increased CPB time (OR = 1.01, $p < 0.05$).
CONCLUSIONS: Octogenarians undergoing mitral valve surgery have greater incidence of urgent surgery, MV+CABG, longer operative times, increased LOS, and decreased rates of survival. Age specific risk factors for mortality in octogenarians were PVD and MVR. Thus, caution must be used in evaluating octogenarians for mitral valve surgery with pre-operative PVD, and where mitral valve repair is unlikely based on echocardiographic evaluation of anatomy.

870

Same Day Discharge Radial Access PCI in Selected Patients with Stable Angina

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OBJECTIVE: To assess the safety of same day discharge(SDD) of selected pts after radial access PCI.
BACKGROUND: There are 3 major barriers to SDD after PCI: risk of acute closure, use of IV IIbIIIa inhibitors requiring hospital stay of 12-18 hrs, and access complications. In pts with low risk of acute closure, IIbIIIa inhibitors are rarely required. In these pts, radial access PCI where access complications are infrequent, provide the ideal setting for SDD. While there are reports on the safely of SDD in uncomplicated PCIs, there is no literature on its safety in uncomplicated, unsuccessful PCI pts.
METHODS: Retrospective chart review on all radial access SDD pts. This included both successful and unsuccessful PCI pts. Since pts typically stay < 24 hrs in hospital post-PCI, the primary endpoint was any major adverse cardiac events(MACE) within 24 hrs of PCI. Secondary endpoint was any MACE from PCI to follow up.
RESULTS: From Jan02-Dec04, 52 pts with stable angina had SDD after radial access PCI (ad hoc 62.3%). There were 39(73.4%) males, and 7(13.2%) diabetics. There were 41(77.4%) pts with one-vessel PCI, 2(3.8%) in 2 vessels and 10(18.9%) where PCI was unsuccessful. Stent length was17±8mm and size 3.1±0.4mm. Lesion grades were: A - 2(3.3%); B1 - 9(15.1%); B2 - 14(23.3%); C - 35(58.3%). All unsuccessful PCI pts had C lesions. Drug eluting stents were used in 11(21.2%) pts and 17(28.3%) lesions. There was no unstented coronary dissection, perforation, thrombus or decrease of TIMI flow grade from baseline in any pt. Hospital stay post-PCI was 5.6±1.8 hrs. MACE was not recorded in any pt within 24 hrs of PCI. Only 1 pt attended ER within 24 hrs after successful PCI with non-ischemic chest pain. Over a follow up period of 550±328 days, 4 pts (7.5%) underwent repeat revascularization – 1 CABG, 2 PCI, and 1 CABG and PCI. Mean time to revascularization was 244 days. One pt died of unknown cause 247 days after PCI.
CONCLUSION: In selected radial access PCI pts, SDD is safe after both successful and unsuccessful procedures.

871

IMPROVING BLOOD PRESSURE TREATMENT AND CONTROL IN PEOPLE WITH DIABETES: THE DESIGN OF THE SCRIP-HTN STUDY

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BACKGROUND: Cardiovascular disease is the major cause of mortality in people with diabetes, yet risk factors such as hypertension are very poorly controlled, with about 88% not reaching recommended targets of <130/80mmHg. An active, community-based, multidisciplinary strategy is needed.

PURPOSE: To determine the efficacy of a community-based, multidisciplinary screening and intervention program on blood pressure control in people with diabetes.

METHODS:
Design: Multicentre randomized controlled trial.
Patients: 220 adults with diabetes and BP >130/80mmHg (measured on 2 separate occasions 1-2 weeks apart using BPTru®), identified through 14 Medicine Shoppe pharmacies in Edmonton.
Interventions: Consenting subjects will be randomized to Intervention or Usual Care. Intervention includes nurse and pharmacist assessment and follow-up (regular BP monitoring, BP wallet card, education on risk factors, and referral to their primary care physician for further assessment and treatment).
Follow-up: Repeat BP measurement, education, and further referrals as necessary will be conducted at 6, 12, 18, and 24 weeks. All interventions will follow the Canadian Hypertension Education Program.
Usual care patients receive information on diabetes management and minimal follow-up.
Outcome measures: Primary outcome is difference in change systolic BP between groups. Other outcomes will include proportion with BP<130/80, receiving ACE inhibitors or angiotension receptor blockers, and changes in antihypertensive therapy.

STUDY STATUS: Training of pharmacists and nurses is complete, and the study began enrolling patients on May 4, 2005. We anticipate completion of recruitment in December, 2005.

872

Use of Drug Eluting Stents in a Modified Balloon Crush Technique for Improved Outcomes in Bifurcation Coronary Interventions

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Even with drug eluting stents(DES), PCI of the bifurcation lesion(BL) remains a significant challenge. Restenosis is often due to lack of stent coverage at the side branch(SB) ostium. One solution is the modified T-stenting technique with crushing where 4-5mm of the SB stent was crushed by the main branch(MB) stent. However, this results in crowding of stent struts proximal to the SB which increases the risk of subacute stent thrombosis(SST), required 7/8F guide catheters via femoral approach which increases the risk of access complications, and cannot be applied to trifurcation(TL) or quadrifurcation lesions(QL). To overcome these shortcomings, we developed a 6F, radial access compatible modified balloon crush technique(MBCT) applicable to TL and QL, where the SB stent protrusion of only 0.5-1mm is crushed by a balloon in the MB, followed by MB stenting. Kissing balloon inflation (KB) was done at the operator's discretion.

From Feb04-Mar05, 48 pts(age 64±10, male 83%, diabetic 38%)with BL underwent PCI(ad hoc 31%) using MBCT with DES. Clinical diagnosis was stable angina 54%, unstable angina 4%, NSTEMI 21%, STEMI 21%. Radial approach was used in 63%. Guide catheter size was 6F 85%, 7F 4% and 8F 11%. Target lesions were LAD/diagonal 81%, LCx/OM 8%, RCA/PD 6% and L main 4%. There were 2 TL(LAD/ramus/diagonal) & 1 QL (LAD/ramus/D1/D2). IIbIIIa inhibitors were used in 81%. Mean stent length & size(mm) were 23±6 & 3±0.3 in MB and 16±5 & 2.6±0.3 in SB. KB was done in 52.1%of pts. Procedural success was achieved in all pts. Mean follow up was 217±100 days, with major adverse cardiac event(MACE) in 4 pts(8.3%). Three pts had SST in small SB (two 2.25 & one 2.5 DES, none had KB) within 1 week of PCI, of which one died. One pt had instent restenosis at 141 days requiring CABG. The remaining 44 pts(91.3%) were free of MACE.

Conclusion: Excellent procedural success and low restenosis rates can be achieved in BL PCI by MBCT with DES. KB should be considered in all pts to reduce the incidence of SST.

873

Overlapping Drug Eluting Stents for Diffuse Coronary Disease: Outcomes from the Royal Alexandra Hospital Drug Eluting Stent Registry(RADER)

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Preliminary data from drug eluting stent(DES) trials seems to indicate that unlike bare metal stents, the total length of drug eluting stents(DES) deployed is not associated with increased risk of restenosis, whereas subacute stent thrombosis(SST) risk is increased with overlapping DES. We examined the outcomes of pts who had at least 2 overlapping DES with total stent length >=40mm in our DES registry.

From Nov03 to Mar05, 78 pts with 79 lesions satisfied the selection criteria. Mean age was 62±11 with 75.6% male and 30.8% diabetic pts, CCS Class IV(35 pts, 44.9%), II(30 pts, 38.5%) and III(13 pts, 16.7%). Clinical diagnosis included STEMI 17.9%, NSTEMI 21.8%, unstable angina 9% and stable angina 51.3%. Radial access was used in 62 pts(79.5%) and 52.6% of PCIs were ad hoc. IIbIIIa inhibitors were used in 47 pts(60.3%) and prePCI Plavix in 33 pts(42.3%). Vessels stented include LAD - 35(44.3%), RCA - 31(39.2%), Cx/OM - 8(10.2%), Diagonal - 3(3.8%), Ramus - 1(1.3%) and SVG - 1(1.3%). There were 2 overlapping stents in 66 vessels, 3 stents in 12 vessels and 4 stents in 1 vessel. Length of stents deployed was 51.5±10.3mm, and size 2.8±0.4mm.

Over a follow up of 245±133 days, major adverse cardiac event(MACE) rate was 3.8%(3 pts – 1 in segment restenosis and 2 deaths). One death occurred one day after successful PCI when pt and family refused further treatment; the other after exploratory abdominal aortic aneurysm surgery 2 months 11 days post-PCI, with cardiogenic shock as cause of death on death certificate. Angiographic follow up data was available in 11 pts at a mean of 84 days post-PCI – 6 showed no restenosis, 5 required repeat PCI(4 for new lesions and 1 for in segment restenosis). There was no pt with documented SST. None of the 53 pts(67.9%) followed for over 180 days had MACE.

Our data showed that excellent medium to long term outcomes are achievable with overlapping DES covering long coronary segments. This has potential impact on the choice of revascularization options in pts with long segments of diffuse CAD.

874

Long-Term Outcome of Diabetic Patients Undergoing Heart Transplantation

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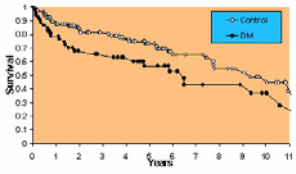
BACKGROUND:
In the early days of heart transplantation (HTX), pre-existing diabetes mellitus was considered to be a contraindication. With the advent of cyclosporine and better surgical results, selected patients with pre-existing diabetes are now routinely undergoing HTX. We sought to determine long-term results in patients with pre-existing diabetes who underwent HTX.

METHODS:
Between January 1986 and June 2000, 487 adults underwent first HTX at Stanford University Hospital. The study group (DM) consisted of 52 recipients with pre-existing diabetes who survived beyond the first month after HTX. One hundred and four age-matched patients without DM before HTX were selected from the same cohort to serve as controls.

RESULTS:
No significant differences were seen between the groups in terms of donor age, heart failure etiology, ischemic time or baseline creatinine. Kaplan-Meier survival analysis with Wilcoxon test showed poorer outcomes at 10 years in DM patients (p=0.0276). (see Figure)
DM patients were more likely to experience severe infections and develop chronic renal failure. In addition, infections were more likely to lead to death in these patients. There was no statistical difference in the incidences of coronary artery disease, cancer or rejection between the groups. Deaths due to rejection and coronary artery disease also were not significantly different.

CONCLUSION:
Our results show a poorer long-term survival outcome in patients with pre-existing diabetes mellitus who underwent HTX. We suggest a more detailed assessment and careful selection of patients with pre-existing diabetes for HTX, especially an evaluation for pre-existing diabetic nephropathy. Infections in these recipients should be treated aggressively.

Figure: Kaplan-Meier Survival Curves



875

GLUCOSE INTOLERANCE AS REFLECTED BY HEMOGLOBIN A1C LEVEL IS ASSOCIATED WITH THE INCIDENCE AND SEVERITY OF TRANSPLANT CORONARY ARTERY DISEASE

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BACKGROUND:
Several studies have suggested that glucose intolerance is one of the risk factors for transplant coronary artery disease (TxCAD). However, a correlation between TxCAD and hemoglobin A1c concentration (HbA1c) has not yet been reported.

METHODS:
HbA1c was measured in 151 consecutive adult patients undergoing routine annual coronary angiography, at a mean of 4.1 years post-transplant. Intracoronary ultrasound (ICUS) examination was also performed in 42 of the patients. TxCAD was graded by angiography as follows: No disease (None); stenosis in any one vessel < 30% (Mild); 31-69% (Moderate); > 70% (Severe) and by ICUS as mean intimal thickness = 0.3 mm or > in any coronary artery segment. HBA1c and other established risk factors were compared for association with each grade of TxCAD by analysis of variance. Risk factor variables analyzed by logistic regression were HbA1c, total cholesterol, donor age, body weight, and rejection score derived from the ISHLT grading.

RESULTS:
HbA1c levels increased progressively with increasing grade of TxCAD (None: Mild: Moderate: Severe, 5.6: 5.8: 6.4: 6.2%, respectively; p= 0.05 for None-vs-Moderate and/or Severe). Similarly, HbA1c was higher in patients with coronary artery intimal thickness >0.3 mm compared to =0.3 mm (6.4-vs- 5.7%, p= 0.05). By multivariate analysis, HbA1c was identified as an independent predictor of TxCAD (OR=1.55, p=0.011). No correlation of HbA1c and immunosuppressive regimen was demonstrated.

CONCLUSIONS:
Persistent glucose intolerance as reflected by plasma HbA1c is associated with a high incidence of TxCAD; therefore, glucose intolerance plays an important role in the disease process.

876

Successful Treatment to Guideline Recommended LDL-Cholesterol Targets in Heart Transplant Recipients

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INTRODUCTION: The association between hyperlipidemia and development and progression of coronary allograft vasculopathy (CAV) is well established. While national cholesterol treatment guidelines do not address orthotopic heart transplant (OHT) recipients, the 2001 CCS Consensus Conference on Cardiac Transplantation recommends this population be treated with a statin to an LDL-cholesterol goal of <2.5 mmol/L for prevention of CAV. We sought to determine the proportion of patients reaching the CCS recommended LDL target and evaluate patterns of use for lipid-lowering agents among our OHT recipients.
METHODS: The medical records of all adults transplanted since January 1996, who were >6 months post-OHT, and actively followed in our outpatient cardiac transplant clinic were reviewed retrospectively.
RESULTS: 135 patients (105 men; mean age 57.4 yrs; mean time since OHT 4.7 yrs) were included. There were 126 (93.3%) patients at target. The mean LDL was 1.88 mmol/L (±0.58; range 0.57-4.94) for all patients and 3.41 mmol/L (±0.69; range 2.81-4.94) for those not at target. Statins were used in 127 (94.1%) patients. The agents prescribed (mean dose ± SD) were: atorvastatin (23.6 ± 20.1 mg/day) in 117 (92.1%) patients, pravastatin (24 ± 8.9 mg/day) in 6 (4.7%) and simvastatin (30 ± 11.5 mg/day) in 4 (3.2%). Reasons for not prescribing a statin: LDL <2.5 mmol/L and non-ischemic indication for OHT (n=5), and statin-induced myalgias (n=2) or depression (n=2). Among the patients who failed to achieve target LDL, 5 were on a statin at the maximum recommended dose (n=2) or the maximum tolerated dose (n=3), limited by myalgias.
CONCLUSIONS: It is possible to achieve the CCS consensus recommended LDL target of <2.5 mmol/L in a significant proportion of OHT recipients. Despite concerns regarding the potential for pharmacokinetic drug interactions between statins and calcineurin inhibitors, they can be safely combined in this special population when patients are followed regularly with close biochemical and clinical monitoring.

877

Can We Safely Intervene on Ultra-Small Coronary Vessel Disease with Drug-Eluting Stents? Results from the Royal Alexandra Hospital Drug Eluting Stent Registry (RADER).

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Introduction: Ultra-small coronary vessels (USCV) with diameters of 2.25 mm or less have a high risk of restenosis following percutaneous intervention. Results of intervention this subset with drug-eluting stents have never been previously published. Methods: Clinical and lesion characteristics of all patients receiving drug-eluting stents were tracked prospectively in a patient data registry. Clinical events were collected through APPROAH database and chart review. Results: Since Mar-04, 84 paclitaxel-eluting stents with 2.25 mm diameter have been implanted in 68 patients in our institute. Average age of patients was 61.8+/- 11.1. Average length of stents was 18.5+/-5.1 mm. Clinical characteristics and clinical event rate at mean follow-up 165 days are shown below. Periprocedural success rate was 98.5%. All clinical events occurred in patients with either bifurcation lesion or multiple stents deployment suggestive of increased event risk as observed in the preliminary TAXUS V trial results.

Clinical characteristics:N(%)
Diabetic:32(47.1)
Acute coronary syndromes:41(60.3)
LAD lesion: 22(32.4)
In-Stent restenosis:1(1.5)
IIbIIIa used:46(67.6)
Bifurcation:17(25.0)
Two or more stents:23(33.8)

Clinical Event:N(%)
TVR:6(8.8)
Death:2(2.9)
Combined:7(10.3)

Conclusion: Although our registry data demonstrates intervening in USCV is feasible, concerns remains in increased events of subacute thrombosis in patients with ultra-small coronary vessels with overlapping stents in long segments and bifurcations.

878

The Effect of Timing on Surgical Results for Coronary Artery Bypass Grafting after Acute Myocardial Infarction

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Introduction: Optimal timing of coronary artery bypass graft (CABG) surgery in the presence of or after an acute myocardial infarction (MI) remains controversial.
Objectives: To determine the relationship between timing of revascularization after acute MI and 30-day survival in a large series of patients over 12 years.

Methods: Data was collected retrospectively on 6042 consecutive patients with MI treated by CABG +/- concomitant procedures between 1991 and 2003. Logistic regression analysis was performed on 32 pre- and intra-operative variables for mortality.

Conclusion: Operative mortality is highest in patients operated on the same day as their MI, but is markedly less when more than 24 hours after MI. Surgical results have continued to improve in the modern era and operative risk is relatively similar when more than 24 hours have elapsed since the MI (1.4-2.6%).

Results:

1991-1999	**<6 hrs**	**6-24 hrs**	**1-7 d**	**7-21 d**	**>21 d**
n	12	39	147	487	2415
30d Mortality	33.3%	28.2%	7.5%	3.9%	4.4%
2000-2003	**<6 hrs**	**6-24 hrs**	**1-7 d**	**7-21 d**	**>21 d**
n	9	13	114	462	1689
30d Mortality	11.1%	7.7%	2.6%	1.5%	1.4%

Multivariate analysis	**Odds Ratio**	**p**
Intra-aortic Balloon Pump	9.65	<0.0001
Left Ventricular Assist Device/ECMO	6.63	<0.0001
Peri-operative MI	6.48	<0.0001
Pre-op Resuscitation	6.22	0.004
Emergent Status	2.94	0.007
Urgent Status	1.87	0.006
Concomitant Procedures	1.72	0.01
Female Gender	1.65	0.007

879

Superiority of Retrograde Cerebral Perfusion during Hypothermic Circulatory Arrest for Complex Aortic Arch Surgery

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Introduction: The interruption of cerebral circulation during complex aortic arch surgery or aortic dissection repair can lead to significant neurological morbidity and mortality.

Methods: Clinical data were retrospectively collected for 84 consecutive patients who underwent aortic arch repair using circulatory arrest from 1994 to 2004. Patients had either deep hypothermic circulatory arrest (DHCA), DHCA + retrograde cerebral perfusion (RCP) or DHCA + antegrade cerebral perfusion (ACP). Pre- and intra-operative variables were entered into a logistic regression equation to determine predictors of mortality and stroke.

Logistic regression analysis revealed method of cerebral protection was the only independent predictor for stroke:
ACP: Odds ratio 8.61, p=0.01.

Conclusion: Retrograde cerebral perfusion can provide additional brain protection during aortic arch surgery. Our series demonstrates that retrograde cerebral perfusion is safe with markedly improved survival and reduced neurological morbidity.

Results	RCP	ACP	DHCA	p
n	34	11	39	-
Age	59 ± 2	58 ± 3	66 ± 4	0.4
Concomitant AVR	15%	27%	13%	0.5
Previous surgery	9%	18%	21%	0.4
Emergent Status	50%	27%	62%	0.2
Aortic dissection	71%	64%	87%	0.1
Systemic temp (ºC)	21	20	19	0.001
Circulatory arrest (min)	42 ± 4	43 ± 4	43 ± 4	1.0
Intubation (hours)	76 ± 20	122 ± 49	103±21	0.5
ICU stay (days)	6 ± 1	16 ± 3	16 ± 5	0.2
Hospital stay (days)	18 ± 4	24 ± 5	25 ± 8	0.5
Renal Failure	15%	27%	23%	0.6
Stroke	9%	46%	15%	0.02
30-Day Survival	100%	73%	74%	0.005

880

The First Step Program – Picking Up the Pace: A Pedometer Based Approach to Assessing and Setting Walking Intensity Goals.

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INTRODUCTION
The First Step Program is a practical, pedometer-based physical activity (PA) program that helps people with type 2 diabetes become more physically active. Despite previous demonstration of efficacy for increasing daily PA volume (walking), improvements in cardiovascular disease risk factors were modest. Hence, the purpose of this pilot study was to test the feasibility of increasing daily walking intensity and frequency within a 3-phase, 12-week pedometer based program.
METHODS
Baseline self-selected walking intensity was determined during a 10-minute track test (TT) where participants wore a pedometer an Activity Monitoring Pod and a heart rate monitor to measure steps/10min, walking speed and heart rate response respectively: from this, individual pedometer determined Picking Up the Pace intensity goals were set as a 10% increase in steps/30 min/phase.
RESULTS
For the TT (mean ± SEM; n = 11) total steps, walking speed, final heart rate and rating of perceived exertion (Borg) were: 1216 ± 39 steps, 4.7 ± 0.2 km/hr, 112.5 ± 2.6 bpm and 9.2 ± 0.3 respectively.
CONCLUSIONS
Assessing 'normal' walking speed is necessary before setting realistic and attainable walking intensity goals within a pedometer based PA program. The assessed walking speed, heart rate and rating of perceived exertion in this cohort represent a self-selected walking intensity that meets or exceeds current recommendations for moderately intense exercise (> 3 METS). Moreover, based on these data and with the use of a pedometer and stopwatch, participants will be capable of monitoring their intensity progression to 'brisk walking' during the intervention period.

881

Resveratrol, a Red Wine Polyphenol, Exerts Cardioprotective Effects via a Novel Mechanism Involving Persistent Sodium Current Block and Improvements in Calcium Handling

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INTRODUCTION The cardiovascular benefits of the consumption of red wine and other bioactive foods have been linked to their polyphenolic constituents, such as resveratrol and quercetin, and are largely attributed to antioxidant effects. However, due to structural similarities between polyphenols and sodium channel blockers, and to their potential use as anti-ischemic agents, we hypothesized that some of their cardioprotection may be mediated by inhibition of persistent sodium current, a feature of long QT syndrome type 3 (LQT3) and reperfusion injury.
METHODS Voltage clamp of tsA201 cells expressing wild-type human heart sodium channels was used to investigate the effects of various polyphenols on peak sodium current. Persistent current was examined by the use of ATXII, an inhibitor of sodium current inactivation, and with the LQT3 sodium channel mutant R1623Q. Electrically stimulated rat right ventricular cardiomyocytes were used to determine the effects of resveratrol on ATXII-induced myocyte dysfunction. Calcium transients were measured using calcium green-1AM fluorescence and contractility was monitored via video edge detection.
RESULTS Quercetin and resveratrol blocked peak current with IC50s of 22.5 mM and 77.3 mM respectively. Resveratrol blocked ATXII-induced late current with an IC50 of 26.1 mM and blocked mutation-induced late current to a 2.5-fold greater extent than peak current at a concentration of 50 mM. Treatment of myocytes with ATXII increased diastolic calcium by 30%; resveratrol prevented and reversed this effect. Resveratrol also produced a 3-fold delay in ATXII-induced contractile dysfunction.
CONCLUSIONS Our results indicate that resveratrol and structurally related polyphenols may protect against excessive sodium influx, known to contribute to reperfusion injury and LQT3 arrhythmias.

882

Early Steps in the Validation of Plethysmographic Technique to Assess Endothelial Function in Humans - Correlation with Results in Isolated Internal Mammary Arteries

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INTRODUCTION Impairment of vasodilator response to acetylcholine (ACH) is indicative of endothelial dysfunction and represents the earliest stage of atherosclerotic disease. The peripheral assessment of endothelial function may, therefore, identify individuals with subclinical vasulcar disease. A validated measurement of endothelial function could be useful in the early detection of disease and assessment of medical therapies that improve endothelial function.
METHODS Assessment of endothelial function as measured in vivo by forearm plethysmography and in vitro, from the left internal mammary artery (LIMA) was compared in subjects (n=7) undergoing elective CABG. Pre-operative mercury strain-gauge plethysmography of the forearm measured the endothelium-dependent response to ACH and the endothelium-independent response to nitroprusside. Endothelial function was measured in distal LIMA rings harvested from the same patients during CABG, using standard ring bath techniques. Normal endothelial function on plethysmography was defined as a doubling of the ACH-induced capactitance change rate (versus saline control). In LIMA rings, "normal" was defined as 75-100% loss of phenylephrine (PE)-induced tension.
RESULTS All subjects had >doubling of forearm capacitance to nitroprusside. The five subjects with intact endothelial function in vitro demonstrated intact forearm response to acetylcholine. The two subjects with IMA endothelial dysfunction also had evidence of endothelial dysfunction in vivo.
CONCLUSIONS Plethysmography holds promise as a method of assessing global endothelial dysfunction. Further validation, with larger numbers, is required.

883

Mesenchymal stem cells (MSC) protect from O2-induced lung injury in experimental bronchopulmonary dysplasia (BPD)

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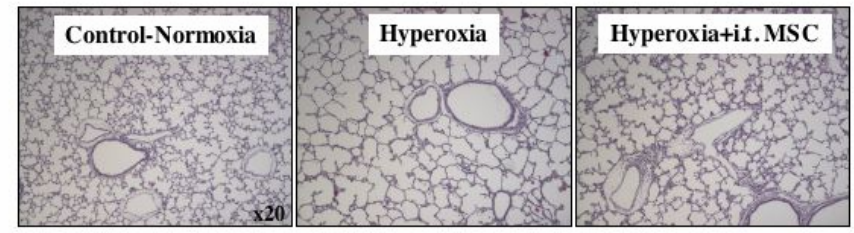
BACKGROUND. BPD is characterized by an arrest in alveolar growth. The regenerative capacity of the developing lung and the risk of long-lasting consequences into adulthood remains unknown. Recent evidence suggests that MSC can repair injured tissue. This potential has never been tested in the developing lung.
OBJECTIVES. To determine whether MSC can protect from O2-induced lung injury in experimental BPD.
METHODS. MSC were obtained from adult rat bone marrow. In vitro, MSC were placed in the upper chamber of a migration assay and randomized to 3 culture conditions 1) DMEM-vehicle, 2) normoxic lung, and 3) hyperoxic lung, in the lower chamber. MSC migration was assessed after 6 hours. In vivo, rat pups were exposed from birth to P14 to normoxia (control group), hyperoxia (95%O2, BPD group) or 95%O2+MSC. MSC were labeled with the green fluorescent dye CFSE and administered i.v. or intratracheally (i.t.) at P4. Lungs were harvested at P14 and processed for various analyses.
RESULTS. Compared with DMEM and normoxic lungs, hyperoxic lungs increased in vitro migration of MSC. Accordingly, i.v.-injected MSC migrated to the O2-injured lungs, but green fluorescence was sparse. Conversely i.t. MSC administration resulted in more widespread lung distribution and some engraftment. Using fluorescence microscopy, we show that the MSC adopt the phenotype of a type 2 alveolar epithelial cell through the co-localization of SP-C expression (Figure 1a). Hyperoxia interrupted lung growth and resulted in larger and fewer alveoli, mimicking human BPD. I.t. BMSC restored normal alveolarization in hyperoxic animals (Figure 1b).
CONCLUSION. Injured lungs secret a homing factor to recruit MSC for tissue repair. Exogenously administered MSC protect from O2-induced lung injury and may have therapeutic potential in lung diseases characterized by alveolar damage.

+Figure



884

Impending Paradoxical Embolism: Saddle Thrombus Traversing a Patent Foramen Ovale

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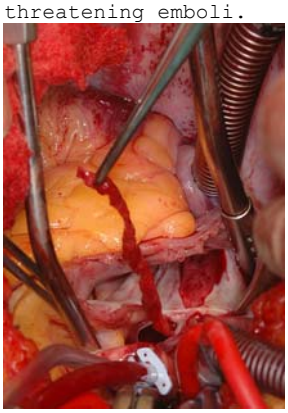
Introduction: Paradoxical embolism is an uncommon yet potentially life-threatening phenomenon in which a thrombus traverses through an atrial septal defect. Such an embolic event can result in stroke, vascular occlusion of the limbs, and less commonly, myocardial infarction.

Methods: We describe the case of a 28 year-old female who presented with acute shortness of breath and chest heaviness two days after being treated for a deep vein thrombosis and multiple pulmonary emboli. On examination a new mild systolic heart murmur was documented. Transesophageal echocardiography revealed a saddle embolus spanning the interatrial septum through a patent foramen ovale and extending across the mitral valve into the left ventricular outflow tract. The patient met all four diagnostic criteria of paradoxical embolism: presence of a deep venous thrombosis, thrombus in the arterial circulation, a patent foramen ovale and known recent pulmonary embolus accounting for the increased right chamber pressure leading to the development of a right-to-left shunt. She underwent surgical removal to prevent systemic embolization, and recovered without any complication.

Conclusion: Sources of venous thrombosis and emboli are not always discovered due to limitations in ultrasonography. A definitive diagnosis of paradoxical embolism can only be made with evidence of thrombus traveling though the venous-arterial communication. As such, accurately diagnosing a paradoxical embolism remains a problem in many patients. It is recommended that systemic heparinization, followed by emergent surgical embolectomy and closure of the defect, be the treatment of choice. Paradoxical embolism is a serious event and patients with this suspected diagnosis should receive intervention to prevent further life-threatening emboli.



885

Re-examining the Canadian Cardiovascular Society Angina Score After a Quarter Century of Use

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INTRODUCTION: Since its publication in 1976, the Canadian Cardiovascular Society Angina (CCSA) score has been used extensively to evaluate patients with stable angina pectoris. While its practicality and ease of use is well established, there is limited data on the validity of the CCSA relative to other measures of functional status. Accordingly, we examined the correlation between CCSA and the Duke Activity Status Index (DASI). The prognostic significance of CCSA on long-term mortality was also examined.

METHODS: The study population consisted of 1,407 patients with significant coronary artery disease (CAD) (defined as >75% stenosis) undergoing cardiac catheterization at Duke University Medical Center between 01/92 and 01/96. The DASI incorporates four major activity domains (personal care, ambulation, household tasks, and sexual function/recreation) and ranges from 0 to 58, with higher scores reflecting better functional status.

RESULTS: CCSA Class IV patients were more likely female and had 16.7 in higher rates of comorbidities. DASI scores ranged from 31.4 14.9 in CCSA Class IV patients (Figure 1). With CCSA Class I to 15.5 the exception of Class IV patients, increasing CCSA class was associated with worse survival (Figure 2).

CONCLUSION: CCSA and DASI appear to be strongly correlated in patients with Class I-III symptoms. However, the similarity in functional status and outcomes among Class III and IV patients indicates a need for re-evaluation in Class IV patients.

Figure 1

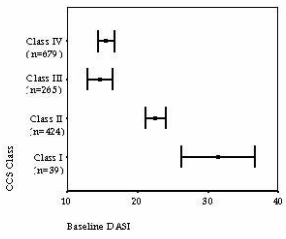
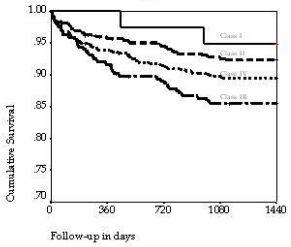


Figure 2



886

Peroxisomal Localization of Malonyl CoA Decarboxylase in Neonatal Rat Cardiac Myocytes

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Recent evidence suggests that inhibition of malonyl CoA decarboxylase (MCD) improves post-ischemic recovery of the heart by raising malonyl CoA levels, which inhibits fatty acid uptake into mitochondria. Despite this important role of MCD, little is known about the subcellular localization of MCD. Subcellular location of MCD is difficult to predict based on protein sequence alone, since MCD has two putative targeting sequences: an N-terminal mitochondrial and C-terminal peroxisomal targeting sequence. MCD also has two potential translational start sites, only one of which contains the mitochondrial targeting sequence. Immunocytochemistry on cultured neonatal rat cardiac myocytes shows that MCD immunofluorescence co-localized best with a fluorescent peroxisomal marker. In addition, western blots performed on pure peroxisomes isolated from rat heart demonstrated the presence of the MCD protein. To determine the function of the two putative targeting sequences, four mammalian expression vectors were produced that expressed either full-length or truncated forms of MCD. These forms of MCD were also tagged at either the N- or C-terminus with a 10 amino acid MYC tag to block the mitochondrial or peroxisomal targeting sequences. Transfection of these expression vectors into neonatal myocytes indicated that both of the proteins tagged on the N-terminus co-localized with peroxisomes, while the protein tagged at the C-terminus (which lacks the mitochondrial targeting sequence) was localized to the cytosol. The MCD protein that contained a mitochondrial targeting sequence and C-terminal MYC tag, was localized to the mitochondria. Although both targeting sequences are functional the majority of cardiac MCD is localized to the peroxisomes. Since each targeting sequence is sufficient to target MCD to either organelle we postulate that cardiac MCD is not a cytosolic protein. This novel finding suggests that MCD may have additional roles in the heart, which may involve aspects of peroxisomal metabolism.

887

Opportunities for Improving Care of Patients with Diabetes in the Community

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Chronic diseases such as diabetes are commonly managed in the community. As such, efforts to improve the care of these individuals (e.g. for management of cardiovascular risk factors) should also be community-based. Quantification of these opportunities for care (visits to healthcare professionals) has not been described.

OBJECTIVE:
To identify the opportunities for care of diabetic patients in the community by pharmacists and physicians.

METHODS:
Data were obtained from the administrative databases of Saskatchewan Health for all insured prescription drug dispensations and physician service claims since 1991. A retrospective review of the year 2001 was used to compare the number of pharmacy and physician visits of diabetic patients. A pharmacy visit was defined as a day in which one or more dispensations occurred while physician and specialist visits were defined as a day in which one or more claims were recorded. Patients without insurance coverage for the selected timeframe were excluded. A paired sign test was used to evaluate differences in pharmacist, physician and specialist visits.

RESULTS:
A total of 36,493 patients with diabetes were selected from the database (age 57.76 ± 16.28, 47% female). The median number of pharmacy visits per year was 15.0 (Interquartile Range (IQR) 9.0 – 24.0) compared to 11.0 (IQR 6.0 – 18.0) total physician visits per year (7.0 (IQR 4.0 – 13.0) general practitioner visits and 0.0 (IQR 0.0 – 1.0) specialist visits per year). Patients visited their pharmacy more frequently than physicians ($p < 0.0001$).

CONCLUSIONS:
This population – based analysis of a large sample of people with diabetes showed that patients visit a community healthcare professional as frequently as once a month. Therefore, there is a substantial opportunity for the care of people with diabetes in the community, validating the use of community – based (especially pharmacist – initiated) disease management programs.

888

Dual Therapy with Rapamycin and Atorvastatin does not significantly improve Monocrotaline Pulmonary Arterial Hypertension in Rats

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INTRODUCTION: Human Pulmonary Arterial Hypertension (PAH) is a disease with few effective treatments. Investigators have published that rapamycin, when given orally at 2.5mg/kg/d to rats injected with 60mg/kg of monocrotaline (MCT) , attenuates MCT-PAH. These results have not been duplicated, and it is not known if rapamycin would reverse established MCT-PAH. Others have published evidence that oral simvastatin (2mg/kg/d) reverses established MCT-PAH. Both drugs are purported to have "antiproliferative" effects on endothelial and pulmonary arterial smooth muscle cells, reducing remodeling of resistance PAs. We hypothesized that combination therapy with rapamycin (3mg/kg/d) and atorvastatin (10mg/kg/d), a more potent statin, would reverse established PAH.
METHODS: We randomized 51 age-matched male Sprague-Dawley rats to either vehicle or MCT 60mg/kg injection. Beginning on day 10, when PAH begins in our model, we gavage fed either rapamycin. rapamycin and atorvastatin, or vehicle to the MCT-injected rats. We studied the rats with echocardiography and left and right heart catheterization on days 21-24.
RESULTS: Pulmonary Vascular Resistance Index was not significantly reduced with either rapamycin or rapamycin+atorvastatin, though there was a strong trend ($p = 0.07$ for both)for a 15% reduction in PVRI for both arms. This was accompanied by excess mortality in the rapamycin (n=5) and rapamycin+atorvastatin (n=2) groups compared to MCT (n=1).
CONCLUSIONS: Treatment with rapamycin (3mg/kg/d) was associated with increased mortality in rat MCT-PAH, although the mechanism is not known. Adverse effects, possibly due to immunosuppression, may limit rapamycin therapy for animal and therefore human PAH. Further studies are required to determine the utility of atorvastatin monotherapy for MCT-PAH.

889

AMPK as a Treatment for Insulin Resistance

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INTRODUCTION
Skeletal muscle insulin resistance has been implicated as a major contributor to the development of Type II diabetes. In obese individuals, chronically high levels of plasma fatty acids result in increased triglyceride (TG) stores within the skeletal muscle, which has been postulated to perturb insulin signaling. As skeletal muscle accounts for 80-90% of insulin-stimulated glucose uptake, strategies to decrease skeletal muscle insulin resistance may aide in the treatment of Type II diabetes. AMP-activated protein kinase (AMPK) activation has been shown to increase fatty acid oxidation and may reduce TG stores. In addition, AMPK activation promotes skeletal muscle glucose uptake in an insulin-independent manner. Thus AMPK activation provides multiple mechanisms that may improve insulin sensitivity. We hypothesize that activation of AMPK within the skeletal muscle can reverse and/or prevent insulin resistance.
METHODS
We have overexpressed the activating mutations within the gamma1 and gamma3 subunits of AMPK in cultured C2C12 skeletal muscle cells (using adenoviral vectors) and in mouse gastrocnemius muscle in vivo (using electroporation). Insulin signaling as well as metabolic parameters (glucose uptake, glycolytic rates and fatty acid oxidation rates) will be analyzed in the presence or absence of high fatty acids.
RESULTS
We have determined that electroporation of injected DNA is an effective method of in vivo gene delivery. Using this technique, we have shown that transfection of gastrocnemius muscle with the gamma1 mutaion results in activation of AMPK as indicated by an increase in phospho-threonine 172 and phosphorylation of the downstream target acetyl-CoA carboxylase.
CONCLUSIONS
Taken together, we have shown that delivery of the gamma mutations to skeletal muscle cells, in vitro and in vivo, increases AMPK activity and can be used to provide proof of principle evidence that AMPK activation can be used to treat skeletal muscle insulin resistance.

890

Outcome of combined Sirolimus-eluting stents and Paclitaxel-eluting stents implantation in same patient.

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Purpose: Drug-eluting stents (DES) have been shown to improve event free survival after implantation in native coronary arteries. Limitation of size and length selection of DES in stock has resulted in some patients have been implanted with both Sirolimus-eluting stent (SES) and Paclitaxel-eluting stent (PES). The aim of this study was to evaluate clinical outcomes, safety and effectiveness of combined SES and PES implantation in the same patient.

Methods and Results: We retrospectively analyzed 75 patients who undergoing PCI and implanted with both SES and PES from registry data, since October 2002 to March 2005. Thirty-five patients (46.7%) were implanted both SES and PES in same artery, which are overlapping stents in 26 patients (34.7%). Implantation of both SES and PES in LAD, RCA and LCX were 21 (28%), 11 (14.7%) and 3 (4%) respectively.

Baseline Patients characteristic were: number (percent)
Male 61(81.3%) Smoker 7(9.3%)
DM 25(33.3%) Dyslipidemia 59(78.7%)
Hypertension 54(72%) Prior MI 25(33.3%)
PriorPCI 26(34.7%) GP IIbIIIa used 54(72%)

Coronary lesion subsets included: in-stent restenosis (13.3%), bifurcation lesion (25.3%), crush technique (12%) and chronic total occlusion (1.3%). In mean follow up period of 8.2 months, clinical outcomes and major adverse cardiac events (MACE) including death, myocardial infarction (MI), target vessel revascularization (TVR) or coronary bypass surgery (CABG) were collected. There was no incidence of acute or subacute stent thrombosis event. Incidence of death, TVR and CABG was 2.7%, 1.3% and 1.3% respectively.

Conclusion: PCI with implantation both SES and PES in same patient appears to be safe and effective with no acute or subacute stent thrombosis event and is associated with less MACE.

891

Outcome of Using Drug Eluting Stents in Aorto-Ostial Coronary Lesions

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Introduction: The effectiveness and safety of coronary stenting of aorto-ostial lesions remains uncertain. Before, ostial Right coronary and Left main lesions have been revascularized with Coronary Artery Bypass Grafting (CABG). Recently, some studies have suggested angioplasty with stenting as a reasonable and effective alternative.The use of drug-eluting stents in these high risk lesions is new and evidence of its benefit and safety is incomplete.
Objective: This study aims to describe the experience of our center's use of drug-eluting stents on aorto-ostial coronary lesions.
Patients/Methods: All patients undergoing percutaneous coronary intervention of the Ostial Right coronary and Left Main coronary using drug-eluting stents at our center from October 2002 until March 2005 were included. Patients, procedure and outcomes were identified.
Results: A total of 25 patients were identified. Fifteen (60%) had Left main involvement. Ten (40%) had ostial Right coronary artery involvement with 1 patient having both. Angiographic success of coronary intervention was documented in all 25 patients. All patients survived to hospital discharge. Ten (40%) of the patients had prior coronary bypass to either the left anterior descending artery, left circumflex arteries. A cutting balloon was used in 10 (40%) of lesions and 1 patient needed Rotational arthrectomy. A GP IIB IIIA inhibitor was used in 13 (53%) of cases. Four (16%) patients came for routine repeat angiography at 14 weeks, no significant restenosis was seen. Procedural complications included 3(12%) ventricular fibrillations treated with defibrillation, 1 transient No Reflow, 1 Intra-Aortic Balloon Pump and 2 intracoronary dissections treated by coronary stenting. One (4%) patient went on to have CABG 4 months after stenting. Only 1 patient died after 1 year of a non-cardiac cause.
Conclusions: These data suggest, that aorto-ostial lesions, with or without prior coronary artery bypass graft protection, treated with drug-eluting stenting is safe and effective.

892

Treatment-specific mortality in the stent era of patients with significant left main disease

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Introduction: Since the 1970's CABG vs medicine trials, patients with significant (>50%) left main disease (SLM) have been excluded from trials. Case series of stenting in SLM are encouraging, but an inclusive outcome analysis of SLM treatments currently used would be important in reevaluating preference for CABG.

Methods: APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart disease) is an outcome-focused database of all Alberta patients who have received a cardiac catheterization (cath) since 1995. Between 1995 and 2003, 4777 (7.4%) patients with SLM were identified. Within the first year after cath the first treatment received was CABG in 3245 (67.9%), PCI of only non-LM lesions (NLMPCI) in 266 (5.6%), PCI including LM lesion (LMPCI) in 90 (1.9%) and no intervention (NONINT) in 1176 (24.6%). Patient characteristics and 1-year mortality were assessed.

Results: Selected clinical features and 1-year mortality for each group follows:

Variables	NLM PCI (%) (N=266)	LM PCI (%) (N=90)	CABG (%) (N=3245)	NONINT (%) (N=1176)	P-value
CHF	23.7	33.3	17.9	35.0	<0.0001
Renal Disease	5.3	12.2	3.5	8.3	<0.0001
Diabetes Mellitus	25.6	36.7	23.9	29.8	<0.0001
Prior CABG	55.6	46.7	6.0	40.4	<0.0001
Indication:					
Stable Angina	20.7	23.3	35.0	30.0	<0.0001
MI	43.6	42.2	27.9	29.8	
Unstable Angina	31.6	31.1	31.3	28.9	
One year Mortality	13.9	32.2	6.4	25.1	<0.001
Risk Adj. 1 year Mort.	11.4	23.0	5.6	16.6	<0.001

A restricted analysis confined to non-emergent and non-AMI cases yielded the same relative mortality pattern.

Conclusion: The motivation for treatment of SLM disease requires further study. Patients receiving non-CABG treatment had the highest risk profile and higher 1-year mortality, which remained high even after risk-adjustment, particularly in those with LM intervention. This observational data would appear to support continuance of a 25-year preference for CABG in SLM patients. Further study into specific circumstances such as "protected" LM and the emergency NLMPCI in acute MI may alter this preference.

893

A Randomized Control Trial of Daclizumab versus Anti-thymocyte Globulin Induction for Heart Transplantation

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Introduction: Rejection remains a significant cause of morbidity and mortality following heart transplantation. The purpose of this study was to test the efficacy and safety of Daclizumab (DZM) versus Anti-thymocyte Globulin (ATG) as a component of induction therapy following heart transplantation.

Methods: Thirty heart transplant patients were randomized to receive either ATG or DZM during induction therapy. Patients in the DZM group received an initial dose of 2mg/kg i.v. at the time of transplant and 1mg/kg i.v. on post-op day 4. All but 7 patients have completed their one-year follow up.

Results: Recipient, donor, and intra-operative variables did not differ significantly between groups. The cost of induction therapy and total drug cost was significantly less for the DZM group. Average absolute lymphocyte and platelet counts were significantly higher in the DZM group. There were no adverse drug reactions. There were no significant differences in the incidence of rejection, infection, malignancy or steroid-induced diabetes. The one malignancy in the DZM group was a basal cell carcinoma which was successfully treated. Actuarials using the Kaplan-Meier method revealed no significant difference between groups for time to first rejection, infection, as well as survival for one year.

Conclusion: Daclizumab is a safe component of induction therapy in heart transplantation. Cost of induction therapy and total drug cost was significantly less with Daclizumab.

	ATG (n = 15)	DZM (n = 15)	P value
Diagnosis	ICM (11), Other (4)	ICM (10), Other (5)	1.0
Avg Absolute Lymphocyte Count	0.5 ± 0.04	0.9 ± 0.10	<0.0001
Avg Platelet Count	114 ± 9	150± 9	0.008
Induction Therapy Cost	$7400 ± 800	$5400 ± 300	0.04
Total Drug Cost	$8100 ± 800	$6200 ± 300	0.04
Infections	24	18	0.5
Rejections	2	0	0.2
Malignancy	0	1	0.2
1 Month Survival	93%	100%	1.0
1 Year Survival	85%	80%	0.6

894

Effect of Physical Fitness and Gender on Arterial Compliance in Adolescents

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Introduction: Cardiovascular disease presents clinically in adulthood, however atherogenesis begins in childhood. Changes in small artery structure and function occur before overt atherosclerosis and hypertension, yet little information on arterial compliance and its relationship to fitness, gender and body habitus is known in youth.

Methods: The relationship between physical fitness and arterial compliance was examined in 247 adolescents (13 to 17 years). Participants were grouped into four fitness quartiles based on a Leger 20m shuttle run score (Quartile 4=fittest group). Large (C1) and small (C2) arterial compliance were assessed using diastolic pulse wave analysis. Predictors of C1 and C2 were determined with linear regression analysis.

Results: Adolescents in the lowest fitness quartile had lower C2 compared to adolescents in the highest fitness quartile. In addition, shuttle run score was an independent predictor of both C1 and C2. C2 was significantly higher in males than in females, however, after adjusting for anthropometric differences, the gender difference no longer existed.

Conclusions: Vascular function is affected by physical fitness at an early age. Increased physical fitness, as measured by shuttle run score, is associated with enhanced small artery compliance in 13-17 year old adolescents. Neither male nor female adolescents are at increased risk of developing arterial stiffness.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p
n	79	59	52	56	-
Shuttle run score	3.8 ± 1.0	6.4 ± 0.6	8.3 ± 0.7	11.3 ± 1.2	<0.0001
Gender (F/M)	76%/24%	61%/39%	38%/62%	30%/70%	<0.0001
Height (cm)	164 ± 8	165 ± 10	170 ± 10	168 ± 10	0.001
BMI (kg/m^2)	23 ± 5	21 ± 3	21 ± 3	21 ± 3	0.001
C1 (ml/mmHg)	13.9 ± 5.3	12.5 ± 3.3	14.1 ± 3.5	14.2 ± 4.7	0.1
C2 (ml/mmHg)	7.6 ± 2.7	7.5 ± 2.1	8.4 ± 2.2	8.4 ± 2.7	0.08

(p=interquartile differences)

Predictors of C1	p	β	Predicators of C2	p	β
Systolic BP	<0.0001	-0.582	Weight	<0.0001	0.433
Weight	<0.0001	0.480	Systolic BP	<0.0001	-0.257
Diastolic BP	<0.0001	0.295	Systemic vascular resistance	<0.0001	-0.236
Stroke Volume	<0.0001	0.280	Shuttle Run Score	<0.0001	0.227
Shuttle Run Score	<0.0001	0.126			

895

Antennapedia enhances ex vivo adenoviral gene delivery of the O2-sensitive channel Kv1.5 in human ductus arteriosus: A strategy to enhance therapeutic gene-delivery.

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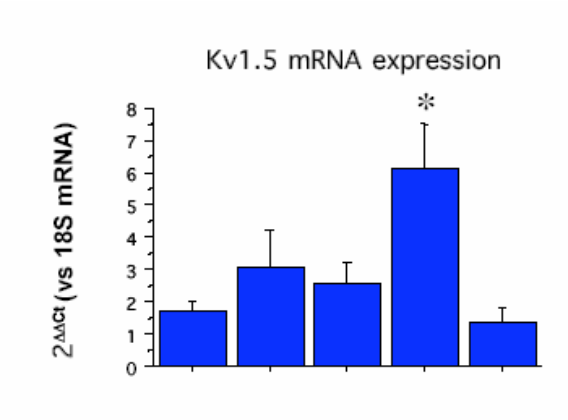
Introduction: Targeted gene delivery is sometimes ineffective in animal and humans due to inefficient DNA transfer. Although, use of viral vectors in high titres enhances expression it also triggers cytotoxicity in vitro and can trigger deleterious immune response in vivo. Antennapedia is an 11 amino acid peptide, involved in targeting the location of the antennae in Drosophila. Antennapedia can to penetrate the cell membrane and acts as a shuttle molecule that can transfer other proteins via a receptor-independent mechanism. We hypothesized that incubation of antennapedia with an adenovirus carrying the O2-sensitive, voltage-gated potassium channel, Kv1.5, would enhance Kv1.5 expression and restore oxygen-sensitivity in ionically remodeled human ductus arteriosus (DA) that have lost O2 constriction due to ex vivo incubation.
Methods: Human DAs were obtained from neonates undergoing palliative surgery for single ventricle. Adenovirus carrying Kv1.5 driven by a smooth-muscle 22a (SM22a) promoter (Ad-SM22aKv1.5) was incubated with vehicle or 0.5 mM of antennapedia for 15 minutes prior to the infection of the human DA. DA constriction was studied in a ring set-up pre and post-infection (PO2 120 mmHg). Quantitative RT-PCR was used to determine Kv1.5 mRNA expression.
Results: Incubation of Ad-SM22aKv1.5 with antennapedia significantly increased Kv expression about two-fold in all 8 DA tested (see Figure). Furthermore, enhanced expression of Kv1.5 increased vascular reactivity in 6/8 ionic-remodeled DA. DAs infected with Ad-SM22Kv1.5 incubated with antennapedia also showed increased constriction to 4-aminopyridine (a Kv channel blocker) versus those incubated with Ad-SM22aKv1.5 alone. Conclusion: Incubation of Ad-SM22??Kv1.5 with antennapedia enhances the Kv1.5 expression and in most cases, partially restores O2-constriction in human DAs. Antennapedia is a simple peptide that enhances the efficiency of adenoviral gene therapy and may permit greater transgene expression with lower viral exposures.



896

Improved Clinical Outcomes Associated with Metformin in Diabetic Heart Failure Patients

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Introduction – Metformin is considered contraindicated in patients with heart failure (HF) due to concerns over lactic acidosis despite increasing evidence of potential benefit. The aim of this study was to evaluate the association between metformin and clinical outcomes in patients with HF and type 2 diabetes.

Methods - Using the Saskatchewan Health databases, 12,272 new users of oral antidiabetic agents were identified between the years 1991-1996. Subjects with incident HF (n=1,833) were identified through administrative records based on ICD-9 code 428 and grouped according to antidiabetic therapy: metformin monotherapy (n=208), sulfonylurea monotherapy (n=773), or combination therapy (n=852). Multivariate Cox proportional hazards models were used to assess differences in all-cause mortality, all-cause hospitalization, and the combination (i.e., all cause hospitalization or mortality).

Results – Average age of subjects was 72 years, 57% were male, and average follow-up was 2.5 (SD 2.0) years. Compared to sulfonylurea therapy, fewer deaths occurred in subjects receiving metformin: 404 (52%) for sulfonylurea monotherapy vs. 69 (33%) for metformin monotherapy [hazard ratio (HR) 0.70 (95% CI 0.54-0.91)] and 263 (31%) for combination therapy [HR 0.61 (95% CI 0.52-0.72)]. A reduction in deaths or hospitalizations was also observed: 480 (63%) for sulfonylurea monotherapy vs. 115 (55%) for metformin monotherapy [HR 0.83 (95% CI 0.70-0.99)] and 480 (56%) for combination therapy [HR 0.86 (95% CI 0.77-0.96)]. There was no difference in time to first hospitalization between study groups.

Conclusion – Metformin, alone or in combination, in subjects with HF and type 2 diabetes was associated with reduced morbidity and mortality compared to sulfonylurea monotherapy.

898

INTERMEDIATE TERM OUTCOMES OF ARTERIAL SWITCH OPERATION FOR TRANSPOSITION OF THE GREAT ARTERIES IN NEONATES – ALIVE BUT WELL?

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INTRODUCTION Transposition of the great arteries (TGA) is a challenging surgical problem that has seen a great improvement in operative outcomes over the last few years. The late neurodevelopmental outcomes however are still uncertain. We reviewed our experience with TGA including late outcomes.
METHODS 88 consecutive patients under the age of 6 weeks underwent arterial switch operation (ASO) for transposition of the great arteries between September 1996 and August 2004 with full flow cardiopulmonary bypass (100-125 mL/kg/min) and moderate hypothermia. Age at surgery was 10 ± 7 days. Patients were divided into 3 groups based on anatomy: Group A: simple TGA (52); Group B: TGA+VSD only (22); Group C: Complex TGA (14). Additional diagnoses in Group C included double outlet right ventricle (4), aberrant coronary arteries (9), interrupted aortic arch or hypoplastic aortic arch (4). The Bayley Scales of Infant Development II for Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were assessed at 18-24 months of age.
RESULTS : There was one (1.1 %) operative mortality. There were two perioperative neurological events (CVA). Average length of stay was (mean±SD) 24.8±18.9 days. At average 4 years follow-up, freedom from reintervention (surgical or percutaneous) was 91.8%, and survival was 98.8%. 63 children underwent neurodevelopmental assessment. None had cerebral palsy or vision or hearing loss. Average MDI was 88±17 (range: 49-118) and average PDI was 91±18 (range: 49-125). 11 patients had an MDI below 70. Factors associated with poor MDI included autistic spectrum disorder, pre-op PPHN requiring nitric oxide, complex anatomy, ECMO, pre-op infarction, high pre-op lactate or meningitis.
CONCLUSIONS TGA, including complex types, can be successfully treated with low surgical risk and good intermediate survival but neurodevelopmental status is a concern. Optimization of preoperative factors may further improve long term neurodevelopmental outcomes.

902

Predictive Value of Cardiac Troponin I for Perioperative Myocardial Infarction Post Cardiac Surgery: A Systematic Review of the Literature

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INTRODUCTION: A perioperative myocardial infarction (PMI) is a frequent complication post cardiac surgery with a prevalence between 1-50%, and a morbidity and mortality rate of 70%. The diagnostic value of cardiac troponin I (cTnI), in identification of PMI is controversial, with studies producing contradictory findings.
OBJECTIVES: The objectives of this systematic review were to: (1) identify the cTnI kinetics of patients diagnosed with a PMI, (2) identify the sensitivity and specificity of cTnI for diagnosing PMI, and (3) identify the prognotic value of cTnI for clinical outcomes post cardiac surgery.
METHODS: An electronic search of MEDLINE, PUBMED, and CINAHL from 1990 through 2005 was conducted using cTnI to predict outcomes post cardiac surgery. Key search terms included "perioperative myocardial infarction", "cardiac surgery", "troponin I", and "postoperative outcomes". Articles were limited to studies in English, adult cardiac surgery, and examining the predictive value of cTnI.
RESULTS: Twenty-two studies met the inclusion critieria and were reviewed. Peak cut-off values for cTnI in patients with a diagnosed PMI were: 6 hr at 1.84 ug/L, 10 hr at 14.9 ug/L, 12-24 hr from 9.4 ng/ml to 17 ug/L, 20-24 hrs at 15 ug/L, and 24 hrs from 2 ng/ml to 36 ug/L. In patients with no diagnosed PMI, the peak value was reported 8-12 hrs post cardiac surgery. The sensitivity and specificity of cTnI for diagnosing a pMI ranged from 76% to 100%. Only four studies examined the prognostic value fo cTnI for limited clinical outcomes.Results varied due to the use of different criteria for the diagnosis of PMI, different cTnI collection times, peak levels and cut-off values in the cardiac surgical patient.
CONCLUSION: The sensitive and specific time points and the cut-off value of cTnI for diagnosing a PMI remain undertermined. A diagnosis of PMI portends a risk for patient survival and quality of life. Further study is needed to determine the predictive value of cTnI post cardiac surgery to risk stratify patients for complications.

903

Are Decellularized Allografts Strong Enough To Implant?

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Introduction: Allograft patches, which are essential for many of the complex reconstructions of congenital cardiac disease, have a limited durability due to a well-documented host immune response. A proposed option to attenuate this alloreactive response is decellularization. The purpose of this study was to determine the effect of decellularization on the biomechanical properties of an allograft patch.

Methods: Porcine pulmonary trunk and ascending aorta were decellularized with a combination of hypotonic and hypertonic buffers, protease inhibitors, and gentle detergents (1.0 % Triton X-100) followed by a prolonged washout in phosphate buffered saline. A tensile testing machine (MTS Synergie 500) was used for testing non-decellularized (fresh) and decellularized tissue to fracture in order to compare biomechanical properties.

Results: Stress to fracture testing showed that the mechanical properties of decellularized allograft tissue were similar to that of non-decellularized allograft tissue (table).

Conclusions: Decellularized porcine pulmonary trunk and ascending aortic wall retained the mechanical properties of non-decellularized allograft tissue. Therefore, decellularized allograft tissue appears strong enough to be used as a patch in congenital cardiac surgery. Given the accumulating evidence that decellularized allograft tissue is associated with a reduced alloreactive immune response, this could have a significant benefit for children requiring congenital cardiac surgery.

Specimen	Stress to Fracture (mmHg) n = 12	P-value[a]
Pulmonary Trunk		
Non-Decellularized	10217 ± 3336	0.945
Decellularized	10294 ± 2887	
Aortic Wall		
Non-Decellularized	7668 ± 1901	0.416
Decellularized	7414 ± 1964	

[a] Paired T – Test

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904

New Insights Into Gender-Based Delay In Acute Myocardial Infarction

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INTRODUCTION As part of a randomized trial (WEST) assessing which strategies best serve patients with ST elevation myocardial infarction we prospectively studied, in two regional centres, the factors that influence patients' decisions to seek medical attention and to what extent these are influenced by gender.
METHODS The 51 item survey was administered to 99 patients by study coordinators in Edmonton, AB and Surrey, BC.
RESULTS The table describes key patient characteristics and behaviors, according to gender, relating to the environment in which their symptoms arose, personal responses to symptom onset and involvement of other persons prior to hospital arrival. As compared to men, women were 11 years older, less likely to be employed and more frequently at home (77%) when symptoms occurred. Women were more likely to be in the company of family and more likely to relay their symptoms to others prior to seeking medical assistance. There was no difference in the mode of transportation to hospital; 82% of women and 73% of men traveled to hospital via ambulance. Women classified the severity of their pain as more intense and were more likely to communicate their concerns to another person than men. Despite this, women tended to arrive in hospital later after symptom onset than men, largely related to delay in calling 911.
CONCLUSIONS These data provide new insights into gender specific differences in the response to STEMI onset that will be of assistance in patient education and the enhancement of process of health care delivery.

Characteristic	Male n = 77	Female n = 22	ρ
Median Age (years)	55	66	0.003
Employed	65%	41%	0.040
Symptoms began at home	56%	77%	0.070
Alone when symptoms began	43%	18%	0.035
With family when symptoms began	43%	68%	0.036
Response to Symptoms: Tried to Relax	26%	5%	0.030
Response to Symptoms: Told Someone	12%	41%	0.002
Pain Classified: High	51%	77%	0.026
Transport to Hospital via Ambulance	73%	82%	0.400
Time from Symptom Onset to Hospital Arrival (via ambulance n = 72)	93 (75, 145)	109 (89, 181)	0.140
Time from Symptom Onset to Hospital Arrival (All)	91 (67, 132)	108 (74, 181)	0.135