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Special Notice

Circulation will be published twice each month beginning in January 1995. This will allow us to publish high-quality manuscripts dealing with cardiovascular problems in a more timely manner and in a smaller journal, which will best serve the general cardiovascular community.

James T. Willerson, MD, for the American Heart Association and current editors of Circulation
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Deletion Polymorphism of the Angiotensin I–Converting Enzyme Gene Is Associated
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The angiotensin I-converting enzyme (ACE) is a key component of the renin-angiotensin system
thought to be important in the pathogenesis of hypertension and cardiovascular disease. Deletion
polymorphism in the ACE gene may be a risk factor for myocardial infarction in the Caucasian population.
However, this finding has not yet been investigated in the Japanese population. A 287-bp insertion/deletion polymorphism in intron 16 of the ACE gene was examined by polymerase chain reaction in a cross-sectional study of 100 healthy subjects and 178 patients with coronary artery disease (CAD) (70 angioplasty and 36 myocardial infarction); whose serum ACE levels were concomitantly measured. Polymorphism of the ACE gene was characterized by three genotypes: two deletion alleles (genotype DD), two insertion alleles (genotype II), and heterozygous alleles (genotype ID). No differences could be detected among the three genotypes for total cholesterol, HDL cholesterol, and body mass index. Serum ACE levels were 11.4±2.7, 14.5±3.5, and 16.6±4.6 IU/mL for genotypes II, ID, and DD, respectively. In the study population, the genotype DD was more closely associated with CAD than the two other genotypes (ID and II). The frequency of deletion alleles was higher (0.58) in the CAD group than in healthy control subjects (0.42) (P<.05). Furthermore, multi-vessel disease was more strongly associated with deletion alleles than with insertion alleles (P<.05). A deletion polymorphism of the ACE gene is associated with serum ACE activity and increased risk for CAD in the Japanese.

Inhibition of Integrin Function by a Cyclic RGD-Containing Peptide Prevents Neointima Formation
Hiroyuki Matsumo, PhD; Jean Marie Stassen; Jos Vermylen, MD, PhD; Hans Deckmyn, PhD ................................................. 2203

RGD-containing peptides are able to prevent binding of ligands to certain integrins such as αIIbβ3 (glycoprotein IIb/IIIa) and αvβ3, and as such are inhibitors for platelet aggregation and smooth muscle cell migration, both of which are involved in neointima formation. Hamster carotid arteries were damaged, and neointima formation was determined at different time points. G4120, a cyclic RGD-containing peptide, was administered continuously intravenously by an implanted osmotic pump. Neointima formation was inhibited dose dependently. The inhibition was strongest when treatment was started before the vascular injury and continued for the full observation period. Treatment started after the damage and maintained until neointima assessment or started before and stopped earlier was less effective. Inhibition of integrin function by an RGD-containing peptide results in reduction of the development of a neointima. This effect is due both to an early event, which could be due to inhibition of secretion of PDGF by the platelets with blocked αIIbβ3, and to a late event, possibly by interference with smooth muscle cell αvβ3.
Clinical Investigation and Reports

Cellular and Molecular Cardiology

A Polymorphism of the Angiotensinogen Gene Associated With Variation in Blood Pressure in a Genetic Isolate

Robert A. Hegele, MD; J. Howard Brunt, PhD; Philip W. Connelly, PhD

We hypothesized that variation of the angiotensinogen (AGT) and angiotensinogen-converting enzyme genes would be associated with variation in resting blood pressure in a genetic isolate of Hutterites. We observed that genotypes of AGT codon 174 were significantly associated with variation in systolic blood pressure only in men and accounted for 3.1% of the total variation in systolic blood pressure in men. We conclude that the association of AGT variation with resting blood pressure in men is consistent with the existence of important structural elements within or proximal to the AGT gene, whose functional impact might be related to differences in sex.

Alterations in Muscarinic K⁺ Channel Response to Acetylcholine and to G Protein–Mediated Activation in Atrial Myocytes Isolated From Failing Human Hearts

Shin-i chi Koumi, MD; Carl E. Arentzen, MD; Carl L. Backer, MD; J. Andrew Wasserstrom, PhD

We characterized the inwardly-rectifying K⁺ channel (I_K) and the muscarinic K⁺ channel [I_K(ACh)] in atrial myocytes isolated from patients with heart failure (HF) and compared electrophysiological characteristics with those from donors (control) by the patch-clamp technique. In HF, resting membrane potentials were lower, the action potential response to acetylcholine (ACh) was attenuated, and the whole-cell membrane current density and sensitivity to ACh were less compared with donors. Although single-channel behavior of I_K and I_K(ACh) was unchanged in HF, I_K(ACh) required higher concentrations of ACh, GTP, and GTPγS to activate the channel compared with donors. These results suggest that the membrane and action potential alterations in HF are caused by reduced I_K and I_K(ACh) channel density and reduced I_K(ACh) channel sensitivity to G protein-mediated channel activation.

Coronary Heart Disease/Myocardial Infarction

Symptoms of Anxiety and Risk of Coronary Heart Disease: The Normative Aging Study

Ichiro Kawachi, MD; David Sparrow, DSc; Pantel S. Vokonas, MD; Scott T. Weiss, MD

We prospectively examined the association of anxiety symptoms to coronary heart disease (CHD) in the Normative Aging Study, a cohort of 2,280 men aged 21 to 80 years in 1961. An anxiety symptoms scale was administered to the cohort at baseline. During 32 years of follow-up, 131 cases of fatal CHD occurred, including 26 cases of sudden death. Compared to men reporting no symptoms of anxiety, men reporting two or more symptoms had elevated risks of fatal CHD (age-adjusted odds ratio [OR]=3.20, 95% confidence interval [CI]: 1.27 to 8.09), and sudden death (age-adjusted OR=5.73, 95% CI: 1.26 to 26.1). The multivariate-adjusted OR was 1.94 (95% CI: 0.70-5.41) for fatal CHD and 4.46 (95% CI: 0.92-21.6) for sudden death.

Plasma Triglycerides and Three Lipoprotein Cholesterol Fractions Are Independent Predictors of the Extent of Coronary Atherosclerosis

Heinz Drexel, MD; Franz W. Amann, MD; Jan Beran, PhD; Katharina Rentsch, PhD; Reto Candinas, MD; Jörg Muntwyler, MD; Antonia Luethy, MD; Theo Gasser, PhD; Ferenc Follath, MD

The angiographically defined extent of coronary atherosclerosis was related to plasma lipid and lipoprotein levels with particular attention to triglycerides and HDL subfractions in 500 patients. By a polychotomous logistic regression model, it was found that age, sex, LDL cholesterol, HDL₂ cholesterol, HDL₃ cholesterol, and triglycerides were independently predictive (P<.05) of the extent of coronary atherosclerosis. An increase in age of 10 years was associated with an increase of the odds ratio for falling into a higher-extent category by a factor of 1.64, and the same increase of the odds ratio was obtained by increasing LDL cholesterol by 0.92 mmol/L or triglycerides by 1.01 mmol/L and by decreasing HDL₂ cholesterol by 0.20 mmol/L or HDL₃ cholesterol by 0.46 mmol/L.

Plasma Concentration of Cross-Linked Fibrin Degradation Product (D-Dimer) and the Risk of Future Myocardial Infarction Among Apparently Healthy Men

Paul M. Ridker, MD; Charles H. Hennekens, MD; Andrew Cerskus, PhD; Meir J. Stampfer, MD

Plasma levels of D-dimer, the primary degradation product of cross-linked fibrin, are elevated in several acute thrombotic disorders. However, whether elevated D-dimer levels among healthy individuals are associated with future coronary thrombosis is unknown. To evaluate whether levels of D-dimer are associated with the occurrence of future myocardial infarction (MI) among apparently healthy men, levels were measured in plasma samples collected at baseline from 296 participants in the Physicians' Health Study who later developed a first MI and from an equal number of age- and

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smoking status-matched control subjects who remained free of vascular disease during a mean follow-up period of 60.2 months. In univariate analyses, baseline plasma concentrations of D-dimer in the upper ranges of normal were associated with elevated risks of MI. Specifically, the relative risk of future MI for individuals with baseline D-dimer concentration exceeding the 95th percentile of the control distribution was two times higher than that of individuals with lower levels (relative risk [RR], 2.02; 95% confidence interval [CI], 1.04 to 4.20; P = .04). This association persisted in multivariate analyses controlling for nonlipid cardiovascular risk factors (RR, 2.12; 95% CI, 1.05 to 4.28; P = .04) and for lipoprotein(a) (RR, 2.02; 95% CI, 1.04 to 3.94; P = .03). In contrast, this association was attenuated and no longer statistically significant in analyses that controlled for total and high-density lipoprotein cholesterol (RR, 1.74; 95% CI, 0.78 to 3.91; P = .2) or for endogenous tissue-type plasminogen activator and its primary inhibitor, plasminogen activator inhibitor type 1 (RR, 1.58; 95% CI, 0.67 to 3.77; P = .3). Elevated levels of D-dimer are associated with increased risks of future MI, although they do not appear to be an independent predictor when other risk factors are considered. As the presence of D-dimer in plasma reflects ongoing fibrin degradation, these data support the hypothesis that activation of the endogenous fibrinolytic system occurs many years in advance of coronary arterial occlusion.

Short Stature and Risk for Mortality and Cardiovascular Disease Events:
The Framingham Heart Study
Joseph P. Kannam, MD; Daniel Levy, MD; Martin Larson, ScD; Peter W. F. Wilson, MD

Several studies have observed an inverse association between height and risk for coronary disease, but it is unclear whether other traditional coronary disease risk factors may have confounded this association. We examined the original Framingham Heart Study cohort to determine whether short stature is associated with all-cause mortality, cardiovascular disease mortality, and myocardial infarction after adjusting for age and other traditional coronary heart disease risk factors. A total of 2019 men and 2585 women were followed up to 35.6 years. Subjects were stratified by sex and divided into quartiles according to height. Risk ratios were calculated from proportional hazards analyses comparing the first, second, and third quartiles of height to the tallest quartile before and after adjusting for age, hypertension, smoking, serum cholesterol, diabetes, relative weight, and alcohol intake. In both sexes, there were significant differences in the unadjusted event rates between the shortest and the tallest quartile for all-cause mortality, cardiovascular mortality, and myocardial infarction. Once the analyses were age adjusted, differences among height quartiles persisted only for risk of myocardial infarction in women. Further adjustment for other clinical variables had little additional impact on the results. After considering age and other coronary disease risk factors, short stature was not associated with increased risk for all-cause or cardiovascular mortality in either sex. It was associated with increased risk for myocardial infarction in women but not in men.

Angioplasty and Interventional Cardiology
Do Fish Oils Prevent Restenosis After Coronary Angioplasty?
Alexander Leaf, MD; Michael B. Jorgensen, MD; Alice K. Jacobs, MD; Gilles Cote, MD; David A. Schoenfeld, PhD; Judy Scher, RN; Bonnie H. Weiner, MD; John D. Slack, MD; Mirie A. Kellett, MD; Albert E. Raizner, MD; Peter C. Weber, MD; Peter R. Mahrer, MD; Jacques E. Rossouw, MD

Four-hundred and forty-seven well-matched patients who had been randomized to receive a dietary supplement of 8 g/d of the ethyl esters of omega-3 fatty acids or to a placebo of ethyl esters of corn oil starting 12 days before PTCA and continuing until exit or for 6 months after PTCA.

Adjunctive Intracoronary Infusion of Antithrombin III During Percutaneous Transluminal Coronary Angioplasty: Results of a Prospective, Randomized Trial
Volker Schächinger, MD; Michael Allert, BSc; Wolfgang Kasper, MD; Hanjörg Just, MD; Werner Vach, PhD; Andreas M. Zeiher, MD

A local deficiency of antithrombin III, the plasma cofactor for heparin-mediated inhibition of thrombin, might limit the antithrombotic effectiveness of heparin during PTCA. In a double-blind study, we therefore prospectively randomized 615 consecutive patients undergoing PTCA of a total of 713 stenoses to receive a bolus injection of 15 000 U heparin followed by a continuous intracoronary infusion via the guiding catheter of either 250 U heparin per minute or 250 U heparin plus 25 U antithrombin III per minute during the procedure. Procedural success rates were similar, with 85% in the heparin group and 83% in the heparin+anti-thrombin III group. There were no differences between the two groups with respect to mean percent diameter stenosis after PTCA, PTCA-related acute vessel occlusion, angiographic evidence of intracoronary thrombus formation, postprocedure creatine kinase increase, Q-wave myocardial infarction, or emergency coronary artery bypass.
surgery, even in high-risk subgroups. Thus, compared with heparin alone, adjunctive intracoronary antithrombin III therapy does not appear to have any beneficial effect on procedural outcome as well as type and frequency of acute complications during PTCA, indicating that a local deficiency of antithrombin III does not play a major role for the failure of heparin to abolish thrombotic complications during PTCA.

**Influence of Serum Cholesterol and Cholesterol Subfractions on Restenosis After Successful Coronary Angioplasty: A Quantitative Angiographic Analysis of 3336 Lesions**

Andonis G. Violaris, MD, MRCP (UK); Rein Melkert, MD, MS; Patrick W. Serruys, MD, PhD

We evaluated the effect of cholesterol on postangioplasty restenosis using quantitative angiographic analysis in 2753 patients. One hundred sixty patients with 191 lesions (5.73%) had hypercholesterolemia (total cholesterol, >7.8 mmol/L; mean, 8.46±0.75 mmol/L) and 2593 patients with 3145 lesions (94.27%), normal cholesterol (5.67±1.06 mmol/L) at trial entry. The restenosis rates were similar in both groups (31.9% versus 33.7%; relative risk 0.975, 95% CI 0.882 to 1.077; P=.68, respectively), as were the absolute (0.31±0.53 versus 0.32±0.53 mm) and relative loss (0.12±0.20 versus 0.13±0.21, respectively, P=NS for both). Dividing the population into deciles according to total cholesterol revealed no significant differences between deciles with regard to the categorical restenosis rate or absolute or relative loss. Subgroup analysis of 667 lesions with HDL and LDL cholesterol levels available again revealed no differences in the categorical restenosis rate or the absolute or relative loss between deciles according to HDL, LDL, or LDL:HDL ratio. These results indicate that there is no association between restenosis and serum cholesterol levels.

**Randomized Comparison of Rescue Angioplasty With Conservative Management of Patients With Early Failure of Thrombolysis for Acute Anterior Myocardial Infarction**

Stephen G. Ellis, MD; Expedito Ribeiro da Silva, MD; Guy Heyndrickx, MD; J. David Talley, MD; Carmelo Crescigiaro, MD; Gabriel Steg, MD; Chris Spaulding, MD; Masakyo Nobuyoshi, MD; Raimund Erbel, MD; Corrado Vassanelli, MD; Eric J. Topol, MD, for the RESCUE Investigators

When used for acute myocardial infarction, intravenous thrombolytic agents fail to achieve early infarction artery patency in 15% to 50% of patients. We tested the hypothesis that immediate balloon angioplasty applied in this setting would improve ventricular function and clinical outcome at 30 days compared with medical management alone. One hundred fifty-one patients with first anterior wall infarction treated with any accepted intravenous thrombolytic regimen and angiographically demonstrated to have an occluded infarct vessel within 8 hours of onset were randomized to medical treatment only or medical treatment and balloon angioplasty. Angioplasty was technically successful in 72 randomized patients (92%). While there was no difference in resting ejection fraction (40±11% versus 39±12%), with exercise patients in the angioplasty group had an increased ejection fraction (43±15% versus 38±13%, respectively; P=.04). Death or severe heart failure occurred in 6% and 17% of the angioplasty and medical treatment groups, respectively (P=.05). When applied to patients with first anterior infarction, rescue angioplasty appears to be useful in the prevention of death or severe heart failure with improvement in exercise, but not resting, ejection fraction.

**Systemic Arterial Hypertension and Vascular Reactivity**

**Role of Nitric Oxide in Reactive Hyperemia in Human Forearm Vessels**

Tatsuya Tagawa, MD; Tsutomu Imaizumi, MD; Toyonari Endo, MD; Masanari Shiramoto, MD; Akira Takeshita, MD

We investigated whether nitric oxide (NO) plays a role in reactive hyperemia (RH) in humans by examining the effects of Nω-monomethyl-L-arginine (L-NMMA) on forearm blood flow (FFB) during RH. FFB was measured by strain-gauge plethysmography. The brachial artery was cannulated for drug infusion and measurement of arterial pressure. Intra-arterial infusion of L-NMMA decreased baseline FFB without changes in arterial pressure. L-NMMA did not affect the peak reactive hyperemic FFB but reduced flow debt repayment. L-Arginine reversed the effects of L-NMMA. NO may play a minimal role during peak RH but does play a significant role in maintaining vasodilation after peak RH.

**Diagnosis of Mild Hypertension by Ambulatory Blood Pressure Monitoring**

Michael A. Weber, MD; Joel M. Neutel, MD; David H.G. Smith, MD; William F. Graettinger, MD

Between 20% and 30% of patients with clinically diagnosed hypertension have normal blood pressure (BP) values during automated ambulatory 24-hour BP monitoring. It has not been clear, however, whether these patients can be regarded as normotensive or whether they should be treated in the same way as confirmed hypertensive patients. Ambulatory BP monitoring was performed in 88 normal control subjects and 171 hypertensive patients (office diastolic BP ≥90 mm Hg on three...
Atrioventricular

William was tested. Hypertensive patients were classified as nonconfirmed or white coat (n=58) if their 24-hour diastolic averages were <85 mm Hg and at least 15 mm Hg lower than their office values. For comparisons, white coat patients were pair-matched with normal subjects by 24-hour diastolic averages and sex, and by similar age and weight; there were 40 such pairs. White coat patients were likewise pair-matched with confirmed hypertensive patients by identical office BPs (51 pairs). Participants were studied by individualized treadmill testing, Doppler echocardiography, and assays of resting plasma catecholamines, upright plasma renin and aldosterone, and lipid, glucose, and insulin concentrations. Because of the matching, compared with normal subjects, patients with white coat hypertension and normal subjects had identical 24-hour BP averages. The white coat patients exhibited slightly greater variability among individual readings (obtained each 15 minutes throughout the day [P<.05]), but there were no differences in hemodynamic responses to exercise. Plasma norepinephrine (P<.05), renin and aldosterone (P<.01 for each), and insulin and low-density lipoprotein cholesterol levels (P<.01 for each) were higher in the white coat group, as were left ventricular septal wall (P<.05) and muscle mass (P=.07) echocardiographic measurements. When compared with the confirmed hypertensive patients, the white coat patients had higher renin (P<.01) but were otherwise similar. Within the white coat group, plasma norepinephrine correlated with total cholesterol and triglycerides (P<.05 for each), and aldosterone correlated with left ventricular mass (P<.01); there were no significant correlations within the normal control subject or confirmed hypertension groups. Patients with white coat hypertension differ in metabolic, neuroendocrine, and cardiac findings from normal control subjects and have greater BP variability. These changes appear to be mediated by heightened activity of the sympathetic and renin-angiotensin systems. Although these characteristics could reflect an alerting reaction in the clinic due to awareness of their diagnosis, the white coat hypertensive patients also have evidence for additional, more-sustained differences from normal subjects. Thus, this condition appears to be a true variant of hypertension.

Electrophysiology/Pacing

Control of Rapid Ventricular Response by Radiofrequency Catheter Modification of the Atrioventricular Node in Patients With Medically Refractory Atrial Fibrillation

Gregory K. Feld, MD; R. Peter Fleck, MD; Osamu Fujimura, MD; David L. Prothro, MD; Tristram D. Bahnson, MD; Manuel Ibarra, MD

Control of rapid ventricular response to atrial fibrillation by modification of atrioventricular (AV) nodal conduction was attempted using radiofrequency energy applied to the low midseptal or posteroseptal right atrium. In 7 of 10 patients, mean maximum heart rate was reduced from 164±12 to 123±16 beats per minute (P<.01) and mean average heart rate from 128±11 to 83±10 beats per minute. Mean minimum heart rate was 54±11 beats per minute after ablation. During 14±8 months of follow-up, these 7 patients remained symptom free from rapid ventricular response, 3 off all AV node-blocking drugs, 3 on digoxin alone, and 1 on β-blocker alone. Three of 10 patients did not respond and received alternative treatment. Radiofrequency modification of AV node conduction controls rapid ventricular response to atrial fibrillation in a significant percentage of patients. A possible mechanism is ablation of the AV nodal slow pathway with its short refractory period.

Upper Limit of Vulnerability Reliably Predicts the Defibrillation Threshold in Humans

Chun Hwang, MD; Charles D. Swerdlow, MD; Robert M. Kass, MD; Eli S. Gang, MD; William J. Mandel, MD; C. Thomas Peter, MD; Peng-Sheng Chen, MD

The upper limit of vulnerability is the stimulus strength above which electrical stimulation cannot induce ventricular fibrillation even when the stimulus occurs during the vulnerable period of the cardiac cycle. The purpose of this study was to test the hypothesis that the upper limit of vulnerability can accurately predict the defibrillation threshold in patients undergoing implantable cardioverter-defibrillator (ICD) implantation using nonthoraotomotomy lead systems. We studied 77 patients at the time of ICD implantation. Multiple endocardial-endocardial and endocardial-subcutaneous shock pathways were used. Two different protocols were used to test the upper limit of vulnerability. In protocol 1 (n=17), the upper limit of vulnerability was tested with two shocks on the peak or the upper-slope of the T wave of paced rhythm. The shocks were given randomly either at the peak and 20 milliseconds before the peak of T wave (n=7) or at 20 and 40 milliseconds before the peak of T wave (n=10). In protocol 2 (n=60), the upper limit of vulnerability was tested with three shocks delivered at 0, 20, and 40 milliseconds before the peak of the T wave. The weakest shock that failed to induce ventricular fibrillation by a 5-J step-down or step-up method was defined as the upper limit of vulnerability. The defibrillation threshold was also determined by a 5-J step-down or step-up method. In protocol 1, the upper limit of vulnerability (±6 J) was significantly lower than the defibrillation threshold (13±7 J) with a correlation coefficient of .87 and P<.001. In protocol 2, the upper limit of vulnerability (13±6 J) was not significantly different from the defibrillation threshold (13±6 J) with a correlation coefficient of .85 and P<.001. In 45 of the 60 patients, the upper limit of vulnerability was...
Nogami, MD; Akihiko Fumiaki
Turkey. The upper limit of vulnerability accurately predicted the defibrillation threshold in patients undergoing ICD implantation using nonthoracotomy lead systems. This method required either one or no episodes of ventricular fibrillation in most patients.

Sudden Death in the Young: Is Acute Coronary Thrombosis the Major Precipitating Factor?
Domenico Corrado, MD; Cristina Basso, MD; Alessandro Poletti, MD; Annalisa Angelini, MD; Marialuisa Valente, MD; Gaetano Thiene, MD

A morphological study was performed in 45 obstructive coronary plaques from 37 young victims of sudden death (33 men and 4 women, age 18 to 35 years; mean, 29.4 years). Thirty-one plaques (69%) were fibrous, while the other 14 were atheromatous. Single-vessel disease, mostly affecting the left anterior descending coronary artery, was found in 33 patients. At histological study, only 10 plaques from 10 patients were complicated by thrombosis. Compared with the atheromatous lesions, the fibrous plaques were rarely complicated by thrombosis (P<.001) and distinctly exhibited a fairly well-preserved tunica media (P<.001) as well as a stratum of intimal fibrocellular hyperplasia (P<.001). In conclusion, most of the young victims of sudden death with obstructive coronary plaque showed single-vessel disease affecting the left anterior descending coronary artery due to fibrocellular plaques in the absence of acute thrombosis.

Exercise and Rehabilitation

Oxygen Uptake Kinetics Are Determined by Cardiac Function at Onset of Exercise Rather Than Peak Exercise in Patients With Prior Myocardial Infarction
Akira Koike, MD; Michiaki Hiroe, MD; Hiromasa Adachi, MD; Takashi Yajima, MD; Yasuteru Yamauchi, MD; Akihiko Nogami, MD; Hiroshi Ito, MD; Yasuhiro Miyahara, MD; Masayoshi Korenaga, MD; Fumiaki Marumo, MD

To determine whether cardiac function affects VO2 kinetics at onset of exercise rather than VO2 at peak exercise, we measured VO2 during 6 minutes of moderate constant work rate testing and during incremental exercise testing in 40 patients with a history of myocardial infarction. The VO2 time constant during constant work rate exercise was markedly slower in patients with relatively low left ventricular ejection fractions (58.0±7.6 seconds) compared with those with higher ejection fractions (45.8±10.5 seconds), reflecting delayed cardiac output response. However, there was no difference in peak VO2 obtained during incremental exercise testing among the two groups. The VO2 time constant during submaximal constant work rate exercise can be used as a sensitive and discriminant measure of impaired cardiac reserve in these patients.

Effects of Acute β-Adrenergic Receptor Blockade on Age-Associated Changes in Cardiovascular Performance During Dynamic Exercise
Jerome L. Fleg, MD; Steven Schulman, MD; Frances O’Connor, MPH; Lewis C. Becker, MD; Gary Gerstenblith, MD; Jon F. Clulow; Dale G. Renlund, MD; Edward G. Lakatta, MD

The cardiovascular response to β-adrenergic stimulation is markedly blunted with advancing age, and this blunting may underlie some of the prominent age-associated changes in the hemodynamic profile during dynamic exercise. To examine this hypothesis, we administered the nonselective β-adrenergic receptor blocker propranolol (0.15 mg/kg IV) to 25 healthy normotensive men ages 28 to 72 years from the Baltimore Longitudinal Study of Aging (BLSA) immediately before maximal upright cycle ergometry with 99mTc gated cardiac blood pool scintigraphy. Their hemodynamic responses to exercise were compared with those of 70 age-matched healthy unmedicated male BLSA control subjects. The maximal cycle work rate achieved was similar in propranolol-treated men (158±32 W) and control subjects (148±32 W) and declined similarly with age in both groups. Hemodynamics at seated rest were not age-related in either group; however, propranolol-treated men had lower heart rates (HR), systolic blood pressure (SBP), ejection fraction, and cardiac index than control subjects but higher end-diastolic volume index (EDVI) and end-systolic volume index (ESVI) by covariance analysis. At maximal effort, several striking age-drug interactions were evident: Propranolol caused a greater reduction in HR and greater increases in EDVI and stroke volume index (SVI) in younger than in older men. Hence, at maximal work rate, HR declined less with age in the propranolol group (0.46 versus 1.09 beats per minute per year, P<.05 by covariance analysis); EDVI and SVI decreased with age (0.27 and 0.48 mL/m2 per year, respectively) after propranolol compared with increases of 0.47 and 0.16 mL/m2 per year in control subjects, respectively, each P<.05 by covariance analysis. The left ventricular contractility index, SBP/ESVI, at exhaustion was reduced by propranolol to a
greater extent in younger than older men. Thus, acute β-adrenergic blockade reverses the age-associated ventricular dilation at end diastole and end systole observed during upright cycle exercise and blunts the decline in maximal HR and myocardial contractility. These data suggest that the age-associated declines in maximal HR and left ventricular contractility during vigorous exercise are manifestations of reduced β-adrenergic responsivity with advancing age which is partially offset by exercise-induced ventricular dilation.

Cardiac Transplantation

Hemodynamic and Metabolic Effects of Paced Linkage Following Heterotopic Cardiac Transplantation

Jayne Morris-Thurgood; Richard Cowell, BSc, MRCP; Vincent Paul, BSc, MRCP; Kameljit Kalsi, BSc; Anne-Marie Seymour, PhD; Charles Ilsley, FRCP; Andrew Mitchell, FRCP; Asghar Khaghani, FRCS; Magdi Yacoub, FRCS, FRCP

After heterotopic cardiac transplantation, there may be a decline in recipient heart function with resulting clinical deterioration. Temporary paced linkage has the potential of reducing afterload and enhancing coronary flow and heart function of both hearts. Hemodynamic studies were performed on 11 patients. The two hearts were linked with a pacemaker to produce recipient heart systole during different periods of donor diastole. Paced linkage produced a significant improvement in cardiac output, coronary sinus flow, and aortic systolic pressure, with significant functional improvements in both hearts. This short-term study illustrates the hemodynamic benefits of paced linkage after transplant.

Feasibility of Serial Intracoronary Ultrasound Imaging for Assessment of Progression of Intimal Proliferation in Cardiac Transplant Recipients

Fausto J. Pinto, MD; Adrian Chenzbraun, MD; Javier Botas, MD; Hannah A. Valentine, MD; Frederick G. St.Goar, MD; Edwin L. Alderman, MD; Stephen N. Oesterle, MD; John S. Schroeder, MD; Richard L. Popp, MD

Serial quantitative coronary angiography is used to assess progression of coronary disease; however, pathology studies have demonstrated angiographic insensitivity for determining atheroma. Intracoronary ultrasound (ICUS) can define and measure the components of the arterial wall and offers the potential for precise quantitative assessment of disease progression on serial examinations. The present study was done to test the feasibility of serially assessing intimal proliferation at the same coronary site with ICUS imaging in cardiac transplant recipients. ICUS imaging was done with a 30-MHz, 5F or 4.3F ultrasound imaging catheter at the time of angiography in 70 cardiac allografts (3.8 sites per patient) initially and 1 year later. Mean intimal thickness (IT), luminal area (LA), and total area (TA) of lumen plus intima and an index of intimal thickness (IT=TA−LA/TA) were measured at each site. Additionally, vessels were graded using a scale incorporating criteria of intimal thickness and circumferential involvement. Side-by-side comparisons of paired angiograms were performed both to verify the similarity of ICUS imaging site to detect new angiographic abnormalities. At least one site could be assessed serially by ICUS in 100% of patients, but only 189 of the original 263 coronary sites (72%) (2.7 sites per patient) could be matched satisfactorily on the second study. Thirty-nine patients (56%) had mild IT and 31 patients (44%) had moderate or severe IT on the initial study. Both groups showed the same IT progression the following year (Δ=0.05±0.13 versus 0.07±0.15 mm; P=NS). Twenty-seven of the 70 patients (39%) showed progression by ICUS. The 23 patients with ICUS progression and angiographically normal vessels had the same progression in intimal thickening as the 4 patients with ICUS progression but showing angiographic disease (Δ=0.17±0.13 versus 0.22±0.10 mm; P=NS). Replication of the intracoronary imaging site by judgment of two observers at an initial study and at a second study 1 year later was possible in at least one vessel site in 100% of the 70 patients and in 72% (189 of 263) of the original imaging sites (2.7 sites per patient). Serial ICUS demonstrates progression of intimal thickening at specific sites in only some cardiac transplant patients. Progression of intimal proliferation can occur in individuals in the presence or absence of initially increased intimal thickening or of angiographic disease at the time of the initial studies. Angiography is insensitive for recognizing early intimal thickening of the coronary vessels.

Coronary Bypass Surgery

Relation of Regional Function, Perfusion, and Metabolism in Patients With Advanced Coronary Artery Disease Undergoing Surgical Revascularization

Juergen von Dahl, MD; Daniel T. Eitzman, MD; Ziad R. Al-Aouar, MD; H. Lee Kanter, MD; Rodney J. Hicks, MBBS, MD; G. Michael Deeb, MD; Marvin M. Kirsh, MD; Markus Schweiger, MD

Myocardial viability was assessed by PET with [15N]ammonia and [18F]fluorodeoxyglucose in 37 patients with advanced coronary artery disease and reduced left ventricular function who underwent surgical revascularization. Ventricular function was evaluated by radionuclide ventriculography pre-
operate and 13±13 weeks after revascularization. Preoperatively impaired wall motion improved significantly in hypoperfused but viable regions, whereas regions with nonviable tissue by PET characterization did not improve. The negative predictive value of PET was 86%, while the positive predictive value for functional recovery in hypoperfused regions ranged from 48% to 86% depending on severity of baseline wall motion abnormalities.

A Comparison of Internal Mammary Artery and Saphenous Vein Grafts After Coronary Artery Bypass Surgery: No Difference in 1-Year Occlusion Rates and Clinical Outcome

Jan van der Meer, MD; Hans L. Hilleges, MD; Wiek H. van Gilst, PhD; Aart Brutel de la Rivière, MD; Peter H.J.M. Dunselman, MD; Václav Fiderl, PhD; Gerrit J. Kootstra, MD; Barbara J.M. Mulder, MD; Matthias Pfisterer, MD; Kong I. Lie, MD. A report of the CABADAS Research Group of the Interuniversity Cardiology Institute of the Netherlands.

One-year angiographic graft patency was assessed in 494 patients with internal mammary artery (IMA) plus vein grafts and in 418 patients with only vein grafts. Occlusion rates in both groups were compared for IMA versus vein grafts, and IMA plus vein versus vein grafts. These were 5.4% versus 12.7% (P<.0001) and 10.4 versus 12.7% (P=.14). Multivariate analysis revealed several risk factors for graft occlusion. When adjusted for these factors, IMA and vein grafts showed no difference in risk of occlusion (P=.089). Clinical outcome was similar for both groups. In conclusion, 1-year patency of IMA and vein grafts depends on other characteristics than graft material. One-year clinical outcome is not improved by IMA grafting.

Pericardial Tamponade

Cardiac Tamponade Complicating Proximal Aortic Dissection: Is Pericardiocentesis Harmful?

Eric M. Isselbacher, MD; Joaquin E. Cigarroa, MD; Kim A. Eagle, MD, FACC

Little is known about how best to manage cardiac tamponade when it complicates acute proximal aortic dissection. We retrospectively identified 10 patients presenting to our hospital over a 13-year period who were diagnosed with both aortic dissection and cardiac tamponade. Three presented with fatal electromechanical dissociation and seven were hypotensive or normotensive on presentation. Of this latter group, three of four undergoing successful pericardiocentesis died, while none of those having either no pericardiocentesis or an unsuccessful pericardiocentesis died. These observations raise the possibility that in patients with cardiac tamponade complicating aortic dissection pericardiocentesis may be harmful rather than beneficial.

Congenital Heart Disease

Origin of Both Coronary Arteries From the Pulmonary Artery

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Origin of both coronary arteries from the pulmonary artery is generally a lethal condition from progressive ventricular failure. We report the clinical and surgical course of two infants, ages 3 and 6 months, with this anomaly. One patient had normal intracardiac anatomy with low pulmonary artery pressures (30/12 mm Hg). The second patient had a restrictive subpulmonic ventricular septal defect with a moderately elevated pulmonary artery pressure (50/13 mm Hg). Left ventricular ejection and shortening fractions were profoundly depressed in both patients. The common coronary trunk arose from the right anterior facing sinus in one patient and from the left posterior facing sinus in the other. Both patients underwent repair by direct coronary implantation to the aorta. Left ventricular function improved with shortening fractions near normal at a follow-up of 6 months for one patient and 1 year for the other. Early diagnosis and prompt repair is compatible with survival and return of normal shortening fraction.

Venous Thrombosis/Treatment and Prevention

Use of Hirulog in the Prevention of Venous Thrombosis After Major Hip or Knee Surgery

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The study objective was to determine whether Hirulog, a direct thrombin inhibitor, has potential efficacy and safety in the prevention of deep vein thrombosis (DVT) in orthopedic patients. A phase 2 open-label, dose-escalating design was used to study 222 unselected patients undergoing major hip or knee surgery in tertiary-care, university-affiliated hospitals. Subcutaneous Hirulog was initiated postoperatively. PA-
patients were evaluated for bleeding and symptomatic pulmonary embolism, and mandatory bilateral pulmonary venography was performed before discharge. Dose escalations were made on the basis of observed rates of bleeding and venous thrombosis. There were five dosage regimens used: 0.3 mg/kg every 12 hours, 0.6 mg/kg every 12 hours, 1.0 mg/kg every 12 hours for 3 days followed by 0.6 mg/kg every 12 hours for up to 11 days, 1.0 mg/kg every 12 hours, and 1.0 mg/kg every 8 hours. One hundred seventy-seven patients who had technically adequate bilateral venography or objectively documented pulmonary embolism were included in the primary analysis of efficacy. The highest dosage regimen (1.0 mg/kg every 8 hours) provided the lowest rates of total DVT (17%) and proximal DVT (2%), both of which were significantly lower (P=.010 and P=.023, respectively) than the pooled rates of total (43%) and proximal (20%) DVT seen with the first four regimens. Bleeding rates were low (<5%) with all regimens. This study demonstrates that 1.0 mg/kg Hirulog every 8 hours started postoperatively is potentially efficacious and safe for the prevention of DVT after major hip or knee surgery.

Basic Science Reports

Cellular and Molecular Cardiology

A Novel Sialyl Lewisβ Analog Attenuates Neutrophil Accumulation and Myocardial Necrosis After Ischemia and Reperfusion

David J. Lefer, PhD; David M. Flynn, MS; M. Laurie Phillips, PhD; Murray Ratcliffe, PhD; Andrew J. Buda, MD

We studied a novel carbohydrate analog of Sialyl Lewisβ that blocks selectin-mediated neutrophil-endothelial cell interactions in a canine model of myocardial reperfusion injury. Anesthetized dogs were subjected to 1.5 hours of regional ischemia and 4.5 hours of reperfusion. Administration of the carbohydrate selectin blocker CY-1503 just before reperfusion significantly reduced the extent of myocardial reperfusion injury. Plasma creatine kinase activity was significantly reduced (P<.05) during reperfusion, and neutrophil infiltration into the reperfused myocardium was reduced by greater than 60% (P<.05) compared with dogs receiving vehicle. In addition, treatment with CY-1503 attenuated myocardial necrosis within the area at risk by 65% (P<.01) and significantly preserved coronary artery vascular reactivity. Our results strongly suggest that the selectins play a significant role in neutrophil-mediated myocardial reperfusion injury and that therapies aimed at neutralization of the selectins may prove beneficial.

Percutaneous Transluminal In Vivo Gene Transfer by Recombinant Adenovirus in Normal Porcine Coronary Arteries, Atherosclerotic Arteries, and Two Models of Coronary Restenosis

Brent A. French, PhD; Wojciech Mazur, MD; Nadir M. Ali, MD; Robert S. Geske, BA; J. Patrick Finnigan, MD; George P. Rodgers, MD; Robert Roberts, MD; Albert E. Raizner, MD

The major obstacle to gene therapy for preventing coronary restenosis is the low efficiency of gene transfer afforded by conventional methods. A replication-deficient adenovirus carrying the luciferase reporter gene was constructed, and in vivo coronary gene transfer with percutaneous catheters was performed comparing the adenovirus with Lipofectin in normal porcine arteries, atherosclerotic arteries, and in two atherosclerotic models of restenosis (using balloon injury or stent deployment). Atherosclerosis or previous arterial injury had little effect on either gene transfer method; however, the mean level of reporter gene expression in the adenovirus cohort was 100-fold higher than in the Lipofectin cohort. Luciferase expression peaked within 7 days after deployment of the adenoviral vector and declined to low levels by 28 days. Histochemical analysis of coronary arteries treated with a second adenovirus expressing a nuclear-localized β-galactosidase gene demonstrated gene transfer to infrequent cells in the media and adventitia.

Direct In Vivo Gene Transfer Into Porcine Myocardium Using Replication-Deficient Adenoviral Vectors

Brent A. French, PhD; Wojciech Mazur, MD; Robert S. Geske, BA; Roberto Bolli, MD

Replication-deficient recombinant adenoviral vectors carrying either the luciferase or lacZ reporter genes were injected directly into the ventricular myocardium of adult domestic swine for evaluation of reporter gene expression. This procedure did not affect regional myocardial function as assessed by systolic wall thickening using ultrasonic crystals. Luciferase activity was detected 3 days after injection, increased markedly at 7 days, and then declined progressively at 14 and 21 days. Luciferase production was comparable in the right and left ventricular walls and increased with increasing amounts of virus. The injection of 200 µg of plasmid DNA (pRSVL) produced significant levels of luciferase; however, when normalized to the number of genes injected, the adenovirus was 140 000 times more efficient than plasmid DNA. Histochemical analysis of β-galactosidase activity demonstrated that nearly all (>95%) of the stained cells were cardiomyocytes, but prominent leukocytic infiltration was also documented. This study evaluates for the first time the potential of direct
intramyocardial injection of replication-deficient adenovirus as a method of introducing recombinant genes into the cardiomyocytes of a large animal species with relevance to human physiology.

Role of Protein Kinase C–Mediated Pathway in the Pathogenesis of Coronary Artery Spasm in a Swine Model
Akira Ito, MD; Hiroaki Shimokawa, MD; Ryuchi Nakaike, MD; Tohru Fukai, MD; Makoto Sakata, MT; Tsuneo Takayanagi, MT; Kensuke Egashira, MD; Akira Takeshita, MD ........................................ 2425

The role of protein kinase C (PKC)–mediated pathway in the pathogenesis of coronary artery spasm was examined in an in vivo swine model. Intracoronary serotonin and histamine repeatedly induced coronary spasm at the atherosclerotic site, where phorbol-12,13-dibutyrate (PDBu), a PKC-activating phorbol ester, also induced the spasm. PDBu-induced coronary spasm was completely blocked by staurosporine, a PKC inhibitor. Coronary spasm induced by the autacoids was significantly augmented by pretreatment with PDBu and partially inhibited by staurosporine. Thus, these results suggest that the PKC-mediated pathway is importantly involved in the pathogenesis of coronary spasm in our in vivo swine model.

Experimental Myocardial Ischemia/Infarction
Inhibition of Growth of Thrombus on Fresh Mural Thrombus: Targeting Optimal Therapy
Beat J. Meyer, MD; Juan J. Badimon, PhD; Alessandra Mailhac, MD; Antonio Fernández-Ortiz, MD; James H. Chesebro, MD; Valentín Fuster, MD, PhD; Lina Badimon, PhD ........................................ 2432

We used an ex vivo perfusion model to study the growth of arterial thrombus onto preformed thrombus. We hypothesized that direct thrombin inhibition would block acute thrombus growth better than current medical therapies. Thrombus growth as measured by deposition (D) of 131I-in-labeled platelets (P) (×10^9/cm²) and 125I-labeled fibrinogen (F) (×10^11 molecules/cm²) was mildly but not significantly reduced by aspirin (1034±92 and 436±78, respectively) compared with baseline (1113±67 and 545±52, respectively). Inhibition of thrombus growth with heparin was dose dependent. Recombinant hirudin profoundly inhibited growth of thrombus (PD, 30±12; FD, 109±21) significantly more than even the highest dosage of heparin (250 IU/kg per hour). This study suggests that growth of a thrombus on a vascular surface covered with fresh thrombus appears to be primarily thrombin mediated.

Time Course of Coronary Endothelial Healing After Injury Due To Ischemia and Reperfusion
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We studied the time course of coronary vascular endothelial injury after 1 hour of coronary artery ligation in dogs killed at 1 hour, 48 hours, 2 weeks, or 9 weeks of reperfusion. At 1 hour and 48 hours of reperfusion we observed abnormal endothelium-dependent relaxation of coronary vascular rings excised from the ischemic/reperfused epicardial coronary artery, and increased regional protein leak, an index of coronary microvascular permeability, in the previously ischemic myocardium. There were histological abnormalities in the endothelium in the epicardial coronary artery and microvasculature at 48 hours of reperfusion. However, nearly complete functional and complete histological healing occurred within 2 weeks, and complete functional healing occurred within 9 weeks of reperfusion.

Thrombolytic Effects of Recombinant Fibrolase or APSAC in a Canine Model of Carotid Artery Thrombosis
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Thrombolytic agents used clinically rely on the activation of plasminogen to plasmin. Plasmin possesses multiple actions including increasing thrombin activity and activation of platelets. Thus, after successful thrombolytic therapy, arterial hyperactivity and reocclusion may be the result of a predominant plasmin-induced thrombogenic action at the site of the residual thrombus. Fibrolase, a direct-acting fibrinolytic enzyme from southern copperhead snake venom, induces rapid clot lysis in vitro. Fibrolase does not rely on plasminogen activation or any other bloodborne components for activity and is not inhibited by any of the rapidly acting serine proteinase inhibitors in blood. We investigated the efficacy of fibrolase to lyse an occlusive thrombus formed in the carotid artery of the anesthetized dog. Electrolytic injury was initiated in both the right and left carotid arteries. Thirty minutes after both arteries were occluded, each vessel was infused with either fibrolase (4 mg/kg over 5 minutes) or physiological saline (over 5 minutes). In two separate groups of dogs, anisoylated plasminogen streptokinase activator complex (APSAC) (0.1 U/kg) was infused into the occluded vessel. In the artery infused with fibrolase, five of five dogs exhibited patency within 6±1 minutes of the infusion (P<.05 versus vehicle-treated artery; Fisher's exact test). In the contralateral carotid artery that received vehicle, the occlusion was maintained throughout the experimental protocol.
APSAC alone lysed the thrombus in each vessel within 17±3 minutes. Five minutes after the end of fibroblast administration and in one of the groups administered APSAC, a glycoprotein (GP)IIb/IIIa antibody, 7E3 (0.8 mg/kg IV), was administered to prevent reocclusion of the patent artery. After 7E3 administration, the vessel treated with fibroblast remained patent in four of five dogs, and six of six APSAC-treated vessels were patent for the remainder of the observation period (2 hours). These studies demonstrate that local administration of fibroblast lyses a carotid arterial thrombus rapidly without excessive hemorrhage or hemodynamic compromise. The enzyme in combination with antiplatelet therapy (7E3) offers a unique mechanism for clot dissolution and may prove useful as a clinically efficacious alternative to presently used thrombolytic agents or may act in a synergistic manner with plasminogen activators.

Survival After Myocardial Infarction in the Rat: Role of Tissue Angiotensin-Converting Enzyme Inhibition

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The beneficial effects of ACE inhibition have been attributed, in part, to inhibition of an activated tissue RAS. However, a relation between tissue ACE inhibition and long-term efficacy has not been established. The present study evaluated the impact of low-dose ACE inhibition and high-dose ACE inhibition on LV hypertrophy and 1-year mortality after myocardial infarction in the rat. Infarcted rats were randomized to placebo, low-dose lisinopril, or high-dose lisinopril (each, n=80) and compared with sham-operated animals (n=40). In a separate group of animals, tissue ACE-activity was determined after 6 weeks of therapy, demonstrating that both regimens were effective with regard to both plasma and pulmonary ACE inhibition; however, only high-dose lisinopril inhibited renal ACE. Neither dose affected LV ACE-activity and ACE mRNA levels. High-dose lisinopril reduced arterial blood pressure, normalized right ventricular and LV weight, reduced LV ANF mRNA levels, and affected a substantial reduction of 1-year mortality, whereas the low dose did not (placebo, 56.3%; low dose, 53.3%; high dose, 22.9%; P<.0001 versus low dose and versus placebo). Hemodynamically effective ACE inhibition is required to reduce LV hypertrophy and mortality after infarction in the rat. Low-dose lisinopril, although exerting sustained inhibition of plasma ACE, does not improve survival.

Angioplasty and Neointimal Proliferation

Mithramycin Inhibits Myointimal Proliferation After Balloon Injury of the Rat Carotid Artery In Vivo

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This study tested the hypothesis that mithramycin inhibits transcription of the c-myc protooncogene and prevents myointimal proliferation after balloon injury of the rat carotid artery in vivo. Sprague-Dawley rats received mithramycin (150 μg/kg, i.p.) or vehicle 1 hr before and 1 hr after balloon catheterization. Two weeks later, the areas of neointima and the ratios of neointimal to medial area of the injured arteries were significantly less in mithramycin treated than in control rats. Mithramycin treatment reduced c-myc mRNA expression in the injured arteries within 2 and 6 hrs after the balloon catheterization. Thus, inhibition of c-myc with mithramycin may be therapeutically useful in preventing the proliferative lesion after arterial injury.

Local Delivery of r-Hirudin by a Double-Balloon Perfusion Catheter Prevents Murial Thrombosis and Minimizes Platelet Deposition After Angioplasty

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We evaluated the effects of local delivery of r-hirudin on platelet deposition and mural thrombus formation compared with three different levels of systemic anticoagulation. These studies demonstrate that local drug therapy with the specific thrombin inhibitor r-hirudin significantly reduces quantitative platelet deposition and macroscopic mural thrombus formation following balloon angioplasty with respect to systemic treatment at conventional doses of heparin and hirudin.

Ventricular Function/Pericardial Abnormalities

Nonuniform Course of Left Ventricular Pressure Fall and Its Regulation by Load and Contractile State

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The effects of clamp elevations of systolic left ventricular pressure on left ventricular pressure fall were analyzed in open-chest dogs. Effects of aortic occlusions timed at early, mid, and late ejection allowed subdivision of pressure fall into an initial accelerative phase, an intermediate decelerative phase, and a terminal decelerative phase. Early pressure elevations of 12 mm Hg induced variable
Right Atrial and Right Ventricular Transmural Pressures in Dogs and Humans:
Effects of the Pericardium

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To determine the transmural pressure-dimension relations of the right atrium (RA) and right ventricle (RV) before and after pericardectomy, six open-chest dogs were instrumented with pericardial balloons placed over the RA and RV free walls. RA appendage dimensions and RV free-wall segment lengths were measured using sonomicrometry. Intact-pericardium RA and RV transmural pressures were calculated by subtracting the pericardial pressures (measured using balloons) from the cavitary pressures. Pooled data from six animals with pericardium intact indicate that at RA and RV cavitary pressures of 5, 10, and 15 mm Hg, RA pericardial pressure was 4.3±0.3, 8.6±1.0, and 13.3±1.5 mm Hg respectively, and RA pericardial pressure was 4.8±0.3, 9.6±0.6, and 14.6±0.6 mm Hg, respectively (mean±SD). With calculated unstressed dimensions, the cavity dimension data were normalized to strain (in percent). We determined that in the dog, RV strain would increase by 14% and RA by 68% to maintain cavitary pressure at 10 mm Hg on pericardectomy. To compare these results with clinical data, RV (n=7) and RA (n=6) transmural pressures were measured using balloons in patients (age, 19 to 76 years) undergoing cardiac surgery. RA transmural pressure of six patients was 1.0±1.5 mm Hg when central venous pressures (CVPs) ranged from 3 to 16 mm Hg. RV transmural pressure equaled 1.2±1.9, 2.3±1.9, and 3.4±2.0 mm Hg when CVP was 5, 10, and 15 mm Hg, respectively. Pericardial constraint (as evaluated by the ratio of pericardial to intracavitary pressures when CVP is 10 mm Hg) accounted for 96% of RA cavitary pressure in the dog and 89% in humans and at least 86% of RV cavitary pressure in the dog and 77% in humans.

Relation Between Shock-Related Myocardial Injury and Defibrillation Efficacy of Monophasic and Biphasic Shocks in a Canine Model

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Jeremy N. Ruskin, MD; Hasan Garan, MD

Data from in vitro and in vivo experimental models have shown that certain waveforms are not only more efficient at defibrillation but also affect myocardial function to a different extent than others. However, to date the relation between defibrillation efficacy and myocardial injury of clinically used waveforms has not been extensively studied. We investigated whether the higher efficacy of asymmetrical biphasic shocks may also be associated with more-injurious effects and, therefore, may not provide a true biological advantage compared with monophasic waveforms. In the canine model, myocardial lactate extraction rate and hemodynamic performance as measures of defibrillation injury were significantly more suppressed after two monophasic shocks in sinus rhythm compared with two biphasic shocks of the same energy. However, the defibrillation thresholds were significantly lower for biphasic shocks. Given this higher defibrillation efficacy as well as the less-injurious effects on myocardial oxidative metabolism and hemodynamic function, the “therapeutic range” of biphasic waveforms is better, which might provide an important long-term benefit in patients receiving frequent shocks from implantable cardioverter-defibrillators.

Cellular Factors in Blood Pressure Control and Hypoxia

Role of Endothelin in the Maintenance of Blood Pressure in Conscious Rats With Chronic Heart Failure: Acute Effects of the Endothelin Receptor Antagonist

Ro 47-0203 (Bosentan)

John R. Teerlink, MD; Bernd-Michael Löffler, MD; Patrick Hess; Jean-Paul Maire; Martine Clozel, MD;
Jean-Paul Clozel, MD

This study demonstrates increased endothelin-1 (ET-1) concentrations in rats with chronic heart failure (CHF) secondary to coronary artery ligation that may be due to increased conversion of big ET-1 into ET-1. Oral administration of the mixed (ET\(_R\) and ET\(_A\)) endothelin receptor antagonist bosentan to CHF rats resulted in significant decreases in mean arterial pressure, which were additive to those of cilazapril, an ACE inhibitor. These findings demonstrate that endothelin plays a role in the maintenance of blood pressure in CHF rats and suggests that endothelin antagonists may be useful therapeutic agents in the treatment of CHF.
17β-Estradiol Inhibits Flow- and Acute Hypoxia-Induced Prostacyclin Release From Perfused Endocardial Endothelial Cells
E.M. Redmon, PhD; M.N. Cherian, MD; R.C. Wetzel, MBBS

The effect of 17β-estradiol pretreatment (100 ng/mL, 72 hours) on cultured sheep endocardial endothelial cell (EEC) PGI2 release in response to multiple stimuli was studied. 17β-Estradiol had no effect on arachidonic acid-, A23187-, or bradykinin-stimulated PGI2 release from static cultures of EECs in six-well plates, but it inhibited the flow- and acute hypoxia-induced increase in PGI2 release from perfused EECs on microcarrier beads. These effects of 17β-estradiol could account for some of the sex-related differences in cardiovascular function because EECs are involved in modulating myocardial activity and potentially in downstream pulmonary activity and systemic vascular tone.

Interventional Devices
Endocarditis Risk of the USCI PDA Umbrella for Transcatheter Closure of Patent Ductus Arteriosus
Larry A. Latson, MD; Bruce M. McManus, MD, PhD; Cynthia Doer, MD; Karen Kilzer; John P. Cheatham, MD

Susceptibility of the USCI PDA Umbrella to infection and effectiveness of the PDA Umbrella in reducing endocarditis risk was assessed in an animal model. Two of 10 control animals developed vegetations after intravenous injection of group L streptococcus. All animals with a significant shunt through a PDA with (n=3) or without (n=7) a PDA Umbrella in place developed endocarditis in the ductus and valvular vegetations. Infection of the device itself was present in only 1 of 1 animal in which the device was free in the left pulmonary artery. Animals with a PDA Umbrella resulting in complete (n=6) or nearly complete (n=2) closure of the ductus had no endocarditis of the ductus or infection of the device, and the rate of development of valvular vegetations was not different from the rate in controls.

Current Perspectives
Universal Angiographic Follow-up in Trials of New Interventional Devices: A Concept Whose Time Has Passed
Frank Litvack, MD; Neal L. Eiger, MD; Geoffrey O. Hartzler, MD; John H.K. Vogel, MD; James S. Forrester, MD

Sudden Cardiac Death in Heart Failure: The Role of Abnormal Repolarization
Gordon F. Tomaselli, MD; Dirk J. Beuckelmann, MD; Hugh G. Calkins, MD; Ronald D. Berger, MD, PhD; Paul D. Kessler, MD; John H. Lawrence, MD; David Kass, MD; Arthur M. Feldman, MD, PhD; Eduardo Marban, MD, PhD

Congestive heart failure is a highly lethal cardiovascular disorder claiming over 200,000 lives a year in the United States alone. Some 50% of the deaths in heart failure patients are sudden, and most of these are probably the result of ventricular tachyarrhythmias. Methods designed to identify patients at risk have been remarkably un rewarding, as have attempts to intervene and prevent sudden death in these patients. The failure to impact favorably on the incidence of sudden death in heart failure patients stems largely from a lack of understanding of the underlying mechanisms of arrhythmogenesis. This article explores the role of abnormalities of ventricular repolarization in heart failure patients. We will examine evidence for the hypothesis that alteration of repolarizing K+ channel expression in failing myocardium predisposes to abnormalities in repolarization that are arrhythmogenic. The possible utility of novel electrophysiological and ECG measures of altered ventricular repolarization will be explored. Understanding the mechanism of sudden death in heart failure may lead to effective therapy and more accurate identification of patients at greatest risk.

Clinicopathological Conference
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