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CIRCULATION (ISSN 0009-7322) is published monthly by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231-4596. For rates in Japan, contact Nankodo Co., Ltd., 42-6 Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan. In the United States, individuals may subscribe for their personal use at the following rates: $80 for members of an American Heart Association scientific council and $112 for nonmembers. Outside the United States, add $68 for postage. Contact AHA for single copy rates and subscription rates for medical professionals in training and for libraries, reading rooms, and other multiple-use institutions. Second class postage paid at Dallas, Texas, and additional mailing offices. POSTMASTER: Send address changes to CIRCULATION, American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231-4596.
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The 1985–1986 National Heart, Lung, and Blood Institute’s percutaneous transluminal coronary angioplasty (PTCA) registry collected data at 16 clinical centers on consecutive, first-PTCA cases. Twenty-six percent of the 2,136 patients were women. Although women were an average of 4.5 years older than the male patients and had more cardiovascular risk factors and more severe angina than did the men, their anatomic coronary artery disease was not more extensive. The clinical success rate of PTCA was 79% for both women and men. Women had more initial complications (29% versus 20%, p<0.001) and a considerably higher procedural mortality rate (2.6% versus 0.3%, p<0.001). For patients who survived the initial procedure, 4-year survival was not different for men and women. Women had slightly fewer events (myocardial infarction, repeat PTCA, and/or coronary artery bypass grafting) but were much more likely to report angina and medication use 4 years after initial PTCA.

Epidemiology of Low Cholesterol Levels in Older Adults: The Cardiovascular Health Study |
| Teri A. Manolio, MD, MHS; Walter H. Ettinger, MD; Russell P. Tracy, PhD; Lewis H. Kuller, MD, DrPH; Nemati O. Borhani, MD, MPH; James C. Lynch, MS; and Linda P. Fried, MD, MPH, for the CHS Collaborative Research Group |

Associations between low cholesterol levels and other markers of disease were explored in 5,201 elderly men and women. Cholesterol levels ≤160 mg/dl were present in 11.6% of men and 3.7% of women. After adjustment for age, low cholesterol levels were associated with a twofold increased prevalence of diabetes and with lower levels of lipoproteins, hemoglobin, albumin, and factor VII, suggesting a link with hepatic synthetic function. On multivariate analysis, factors most strongly associated with low cholesterol were decreased factor VII levels, decreased albumin, and diabetes. Cross-sectional associations with low cholesterol differ by sex and suggest poorer health by some measures.

Radiofrequency Catheter Ablation of Mahaim Fibers at the Tricuspid Annulus |
| Lawrence S. Klein, MD; F. Kevin Hackett, MD; Douglas P. Zipes, MD; and William M. Miles, MD |

Four patients with preexcited reciprocating tachycardia due to Mahaim fibers underwent radiofrequency catheter ablation. Three patients had atriofascicular fibers, and one patient had an atrioventricular fiber. Pathways conducted only anterogradely and could be blocked by adenosine. The atrial insertion was right lateral in one patient, right posterolateral in two patients, and right posterior in one patient. Stimulus to delta wave mapping helped localize the atrial insertion of the atriofascicular connections. Radiofrequency energy delivered to the tricuspid annulus in posterior to lateral regions eliminated accessory pathway conduction in all patients. There was no recurrent arrhythmia in any patient. Thus, radiofrequency current applied to the tricuspid annulus safely eliminated tachycardia in these patients with Mahaim fibers.
Quantitative Ultrasonic Analysis of Myocardium in Patients With Thalassemia Major and Iron Overload
Fabio Lattanzi, MD; Paolo Bellotti, MD; Eugenio Picano, MD; Francesco Chiarella, MD; Alessandro Mazzarisi, Caterina Melevendi, MD; Gianluca Forini, MD; Luigi Landini, PhD; Alessandro Distante, MD; and Carlo Vecchio, MD

Quantitative operator-independent measurements of the reflectivity of myocardial wall in 38 young patients with β-thalassemia major, without signs of myocardial dysfunction, and 20 age- and sex-matched controls were obtained by means of an on-line analysis of the ultrasonic radiofrequency signal. The integrated values of the radiofrequency ultrasound signal were normalized for the pericardial interface in each subject and expressed in percent (IB%). Thalassemie patients had been under transfusion therapy for 16±5 years and had received 313±138 transfusion units; they all had been under chelation treatment (desferrioxamine) for 9±2 years. The IB% values were higher in patients with thalassemia major than in controls for both septum (35±14% versus 21±6%, p<0.001) and posterior wall (16±6% versus 11±3%, p<0.001). In conclusion, our data demonstrate that myocardial reflectivity is abnormally increased in patients with thalassemia major under transfusion treatment, probably due to myocardial iron deposits and/or secondary structural changes, even when no signs of myocardial functional involvement are apparent.

Myocardial Infarction
Progressive Left Ventricular Dysfunction and Remodeling After Myocardial Infarction: Potential Mechanisms and Early Predictors
Peter Gaudron, MD; Christoph Ellies, MD; Ingrid Kugler; and Georg Ertl, MD

To define the relation between left ventricular dilatation and dysfunction and to identify early predictors of chronic heart failure, left ventricular volumes and regional area shrinkage fraction (gated single photon emission computed tomography) and hemodynamics at rest and during exercise were assessed prospectively 4 days, 4 weeks, 6 months, and 1.5 and 3 years after first myocardial infarction. Patients without dilatation (n=38) maintained stable volumes and hemodynamics. In 26% (n=18), limited dilatation developed within 4 weeks, restoring depressed stroke volume thereafter. Wedge pressure during exercise, however, rose progressively. In 20% (n=14), progressive dilatation developed. Depressed performance was also restored by 4 weeks but progressively deteriorated thereafter. Area shrinkage fraction in normokinetic sectors at 4 days deteriorated progressively for 4 weeks, but hypokinetic and dyskineic sectors remained unchanged. Global ejection fraction fell after 1.5 years, whereas right atrial pressure, wedge pressure, and systemic vascular resistance increased. Early predictors (multivariate analysis) of dysfunction and remodeling were ejection fraction and stroke index at 4 days, infarct size, infarct location, and TIMI grade of infarct artery perfusion.

Infarct Artery Patency Predicts Outcome of Serial Electropharmacological Studies in Patients With Malignant Ventricular Tachyarrhythmias
John T.Y. Hii, BMBS; Mougheddin Traboulsi, MD; L. Brent Mitchell, MD; D. George Wyse, MD, PhD; Henry J. Duff, MD; and Anne M. Gillis, MD

We postulated that the outcome of electropharmacological studies would be modulated by the patency of the infarct-related artery (IRA). Sixty-four consecutive patients with remote myocardial infarction and spontaneous and inducible ventricular tachyarrhythmias were studied. Sixteen patients (25%) responded to antiaarrhythmic drug therapy. A patent IRA was associated with antiarhythmic drug response significantly more frequently than was an occluded IRA (45% versus 9%, p=0.001). The presence of a patent IRA was the only independent predictor of antiaarrhythmic drug response. The use of IRA patency for the prediction of successful electropharmacological studies has a balanced sensitivity and specificity of 81% and 67%, respectively.

Body Surface Potential Mapping of ST Segment Changes in Acute Myocardial Infarction: Implications for ECG Enrollment Criteria for Thrombolytic Therapy
Fred Kornreich, MD; Terrence J. Montague, MD; and Pentti M. Rautaharju, MD, PhD

Analysis of body surface potential maps identifies areas on the torso where the most significant ST changes most frequently occur in acute MI. Two leads originating from areas where ST depression and ST elevation, respectively, departed most significantly from normal values achieve optimal classification in each of three MI classes: anterior, inferior, and posterior MI. Five of these six leads are outside the standard precordial lead positions. ST depression is the most potent discriminator for each MI group and contains information independent from ST elevation. Quantitative analysis of ST magnitude at each electrode site allows determination of best site-specific thresholds for ECG criteria. Appropriate selection of ECG leads and measurements may help remove inconsistencies in present ECG selection criteria and improve comparability of treatment results.
Differential Effects of Isoproterenol on Sustained Ventricular Tachycardia Before and During Propranolol and Quinidine Antiarrhythmic Drug Therapy

Michael L. Markel, MD; William M. Miles, MD; Jerry C. Luck, MD; Lawrence S. Klein, MD; and Eric N. Prysowsky, MD

Isoproterenol was administered to 25 patients with hemodynamically stable sustained monomorphic ventricular tachycardia (VT) in the drug-free state and then after intravenous propranolol or oral quinidine therapy. In patients with readily inducible VT, isoproterenol 1) decreased VT cycle length more during propranolol and quinidine therapy than in the drug-free state, 3) decreased right ventricular refractoriness by the same amount before and during propranolol and quinidine drug therapy, and 4) did not alter the number of extrastimuli required for VT induction. To the extent that QRS duration reflects changes in conduction within the VT circuit, these results imply that the attenuation of drug-induced slowing of VT by isoproterenol is due primarily to changes in conduction rather than refractoriness.

Comparison of Angioplasty and Surgery for Unoperated Coarctation of the Aorta

Robert E. Shaddy, MD; Mark M. Boucek, MD; Jane E. Sturtevant, RN, BSN; Herbert D. Ruttenberg, MD; Richard B. Jaffe, MD; Lloyd Y. Tani, MD; Victoria E. Judd, MD; L. George Veachy, MD; Edwin C. McGough, MD; and Garth S. Oremond, MD

Thirty-six patients were prospectively randomized to receive either angioplasty (20 patients) or surgery (16 patients) as treatment for unoperated coarctation of the aorta. Reduction in peak systolic pressure gradient across the coarctation was similar (86%) immediately after both balloon coarctation angioplasty and surgery. Aneurysms were seen in the angioplasty group (20%) but not the surgery group (0%). The incidence of other complications was similar in both groups, although two patients experienced neurological complications after surgery. The incidence of restenosis tended to be greater in the angioplasty group (25%) than the surgery group (6%). Although the risk of aneurysm formation after angioplasty is higher than after surgery, balloon coarctation angioplasty of unoperated coarctation of the aorta may provide an effective initial alternative to surgical repair in many patients.

Sudden Cardiac Death and the Use of Implantable Cardioverter-Defibrillators in Pediatric Patients

Michael J. Silka, MD; Jack Kron, MD; Ann Dunnigan, MD; and Macdonald Dick II, MD; for the Pediatric Electrophysiology Society

This collaborative, international study was performed to evaluate the current uses of implantable cardioverter-defibrillators (ICD) in young patients (less than 20 years of age) and their subsequent clinical outcome. Detailed information was obtained regarding 125 patients, 76% of whom had been resuscitated from sudden cardiac death. The predominant forms of associated cardiovascular disease were cardiomyopathy (56%), primary electrical disease (26%), and congenital heart disease (18%). During a mean follow-up of 31 months, at least one appropriate ICD discharge was reported in 59% of the patients. Duration of follow-up greater than 24 months was the primary correlate of ICD discharge (p=0.001). Nine patients died during follow-up, with impaired ventricular function the primary correlate of mortality (p=0.002). Despite the differing substrates of cardiovascular disease, patterns of ICD use in young patient are similar to those of adults. Thus, use of these devices in young survivors of SCD appears valid.

Circadian Variations in Ischemic Threshold and Their Relation to the Occurrence of Ischemic Episodes

Jesala Benhorin, Shmuel Banai, Mady Moriel, Alex Gavish, Andre Keren, Shlomo Stern, and Dan Tzivoni

To determine whether the ischemic threshold during daily activity exhibits a circadian pattern that might relate to the frequency of occurrence of ischemic episodes, we studied the time of occurrence and the heart rate at onset of ischemia (ischemic threshold) in 1,571 ischemic episodes recorded in 41 patients with stable coronary disease who had repeated ischemic episodes during 7 days of ambulatory ECG monitoring. Ischemic episodes exhibited the typical bimodal distribution of occurrence (morning and late afternoon peaks), while the ischemic threshold exhibited a different single-peaked circadian distribution (highest at noon and lowest at midnight). Time series analyses indicated a strong hour-by-hour trend of each of the two circadian distributions, while the two series cross-correlated maximally at a lag of zero hours (p<0.01), indicating a complex interplay between myocardial oxygen demand and supply in determining the occurrence of ischemic episodes during daily activity.
A Predictive Method for Estimating the Late Angiographic Results of Coronary Intervention Despite Incomplete Ascertainment
Richard E. Kuntz, MD, MS; Karen M. Keaney, MS; Cindy Senerchia, RN, MSN; and Donald S. Baim, MD

Coronary restenosis estimates may be biased substantially whenever incomplete angiographic follow-up results from a confounder that affects both an individual's reason for repeat angiography and the restenosis end point under investigation. We examined such a confounder, the clinical indication for angiographic restudy, in 301 treated lesions from 267 consecutive patients who underwent either directional atherectomy or coronary stenting. By categorizing all treated lesions according to their clinical indication for restudy (elective versus nonelective) we could measure the selection bias introduced into the traditional estimation of angiographic restenosis. Simulated models of late percent stenosis or binary restenosis were developed using a novel predictive method that adjusts for such bias and provides a theoretically more accurate estimate. Comparisons between restenosis estimated by this predictive method and by the traditional method demonstrated how various parameters (sample size, percentage of angiographic follow-up, restenosis values, etc.) may influence the selection bias caused by incomplete angiographic follow-up. Therefore, by using readily available clinical information about nonrestudied patients, a predictive method was developed that can provide a closer estimate of the true restenosis end points in clinical trials with incomplete angiographic follow-up and potential selection bias.

Long-Term Clinical Follow-up in Patients With Angiographic Restudy After Successful Angioplasty
William S. Weintraub, MD; Ziyad M.B. Ghazzal, MD; John S. Douglas Jr., MD; Henry A. Liberman, MD; Douglas C. Morris, MD; Caryn L. Cohen, RN, MN; and Spencer B. King III, MD

To determine the incidence of clinical events after coronary angioplasty in patients undergoing angiographic restudy after coronary angioplasty, 1,793 patients without and 1,570 patients with restenosis were identified. The restenosis patients were older, had more hypertension, diabetes, angina, multivessel coronary disease, more severe stenoses, and less satisfactory original results. At restudy, in patients without restenosis, 38.7% had angina versus 70.7% in patients with restenosis \(p<0.0001\). At 6 years, the survival was 0.95 without restenosis and 0.93 with restenosis \(p=0.16\). At 6 years, freedom from myocardial infarction was 0.88 without restenosis and 0.85 with restenosis \(p=0.0001\). Repeat revascularization was much more frequent in the restenosis group.

Quantitative Doppler Assessment of Valvular Regurgitation
Maurice Enriquez-Sarano, MD; Kent R. Bailey, PhD; James B. Seward, MD, FACC; A. Jamil Tajik, MD, FACC; Mary J. Krohn, RDCS; and Janet M. Mays, RN, RDCS

Accuracy of Doppler assessment of valvular regurgitation is controversial. Therefore, 120 patients (20 normal, 19 with aortic regurgitation, and 81 with mitral regurgitation) were studied by quantitative Doppler echocardiography in conjunction with measurement of left ventricular volumes by two-dimensional echocardiography using Simpson's biapical rule. In normal patients, regurgitant volume was calculated at 4.4±4.4 ml and regurgitant fraction at 5.3±4.5% by Doppler. There were good correlations between Doppler and ventricular methods for measurement of stroke volume, regurgitant volume, and regurgitant fraction in aortic and mitral regurgitation. The potential limitation of quantitative Doppler was identified as overestimation of mitral regurgitation; however, it becomes minimal with increased experience. Quantitative Doppler provides an accurate quantitation of aortic and mitral regurgitation. Regurgitant volume can also be reliably measured.

Abnormal Baroreceptor-Mediated Vasodilation of the Peripheral Circulation in Congestive Heart Failure Secondary to Idiopathic Dilated Cardiomyopathy
Henrik Wroblewski, MD; Jens Kastrup, MD, PhD; Svend Aage Mortensen, MD, PhD; and Stig Haunse, MD, PhD

Baroreceptor-mediated regulation of subcutaneous blood flow of the lower leg was studied in healthy subjects and in patients with moderate and severe congestive heart failure. When the central baroreceptor reflex alone was activated, subcutaneous blood flow increased significantly in patients with both severe and moderate congestive heart failure compared with the decrease in blood flow observed in control subjects. Patients with congestive heart failure have an abnormal baroreceptor-mediated vasodilation in subcutaneous tissue of the lower leg during upright position, which increases with the severity of the disease. This abnormal vasodilation may be a pathogenetic factor in the development of edema in these patients.

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Signal-Averaged Electrocardiogram: Improved Identification of Patients With Ventricular Tachycardia Using a 28-Lead Optimal Array

David S.W. Ho, MBBS, FRACP; Robert A. Dennis, MD, FRACP; John B. Uther, MD, FRACP; David L. Ross, MBBS, FRACP, and David A.B. Richards, MD, FRACP

The sensitivity and specificity of signal-averaged ECG using a 28-lead optimal array were compared with an orthogonal array in 223 patients with prior myocardial infarctions (62% with inducible VT). From the optimal array, 28 QRS durations were obtained, each defined as the duration from the earliest onset of any leads to the offset of that lead. QRS duration >120 msec in ≥3 leads were considered abnormal. While the specificity of each array was comparable (84%), the optimal array (70%) was more sensitive than the orthogonal array when analyzed either as a combined vector magnitude (54%, \(p=0.001\)) or as three individual leads (59%, \(p=0.004\)). The increase in sensitivity was equal for anterior (\(n=120\)) and inferior (\(n=103\)) infarctions. Application of the 28-lead optimal array improves the sensitivity of signal-averaged ECG without loss of specificity.

A Population Study of the Natural History of Wolff-Parkinson-White Syndrome in Olmsted County, Minnesota, 1953–1989

Thomas M. Munger, MD; Douglas L. Packer, MD; Stephen C. Hammill, MD; Barry J. Feldman, MD; Kent R. Bailey, PhD; David J. Ballard, MD, PhD; David R. Holmes Jr., MD; and Bernard J. Gersh, MB, ChB, DPhil

During the period 1953–1989, 113 residents of Olmsted County, Minnesota, were identified as having the Wolff-Parkinson-White (WPW) syndrome. The incidence of newly detected cases was approximately four per 100,000 per year. Approximately one half the population was asymptomatic at diagnosis; however, symptoms had developed in 30% of younger patients (<40 years) at 10 years of follow-up. Two sudden cardiac deaths occurred in the entire cohort, yielding an overall sudden cardiac death rate of 0.0015 (95% confidence interval, 0.0002–0.0054) per patient-year. No sudden deaths were noted in patients who were initially asymptomatic; this confirms previous data suggesting that routine electrophysiological investigation of asymptomatic WPW patients is not warranted.

Interaction Between Thromboxane A2 and 5-Hydroxytryptamine Receptor Subtypes in Human Coronary Arteries

Adrian H. Chester, PhD; Sean P. Allen, BSc; Samad Tadjkarimi, MD; and Magdi H. Yacoub, FRCS

The interaction between 5-hydroxytryptamine (5-HT) and thromboxane A2 (TXA2) was assessed in human epicardial coronary arteries. In the presence of 5-HT, receptor antagonist ketanserin, the contractile response of 5-HT could be significantly enhanced by the presence of either the EC30 or EC50 concentrations of the thromboxane mimetic U46619. This potentiation was inhibited by methiothepin, a nonselective 5-HT-like/5-HT2 receptor antagonist. These data indicate that a synergistic interaction may occur between U46619 and 5-HT acting specifically at 5-HT-like receptors.

Laboratory Investigation

Loss of Myocardial Protection After Preconditioning Correlates With the Time Course of Glycogen Recovery Within the Preconditioned Segment

Christopher L. Wolfe, MD; Richard E. Sievers, BS; Frank L.J. Visseren, MD; and Thomas J. Donnelly, MD

To test the hypothesis that preconditioning reduces infarct size by depleting cardiac glycogen stores and attenuating the degree of intracellular acidosis during subsequent prolonged left coronary artery (LCA) occlusion, preconditioned and control rats were subjected to 45 minutes of LCA occlusion and 120 minutes of reflow immediately after preconditioning or after 30 minutes, 1 hour, or 6 hours of nonischemic recovery after preconditioning. Compared with controls, preconditioned rats demonstrated marked glycogen depletion in the ischemic region, attenuation of intracellular acidosis during ischemia, and marked infarct size reduction. In rats allowed to recover after preconditioning, the time course of glycogen recovery paralleled the loss of protection from ischemic injury. We conclude that glycogen depletion and the attenuation of intracellular acidosis during ischemia appear to be important factors in delaying irreversible injury and reducing infarct size in this animal model of myocardial preconditioning.

Regional Ischemic ‘Preconditioning’ Protects Remote Virgin Myocardium From Subsequent Sustained Coronary Occlusion

Karin Pryklenk, PhD; Barbara Bauer, MD; Michel Ovize, MD; Robert A. Kloner, MD, PhD; and Peter Whitaker, PhD

One or more brief episodes of coronary artery occlusion "precondition" the myocardium perfused by that artery and limit infarct size caused by a subsequent period of sustained ischemia. We used
the anesthetized canine model to determine whether preconditioning protects only those myocytes subjected to brief ischemia or whether brief occlusions in one vascular bed also protects remote virgin myocardium from subsequent coronary occlusion. Infarct size produced by 60 minutes of left anterior descending coronary artery occlusion was significantly smaller in dogs that underwent four episodes of 5 minutes of circumflex branch occlusion plus 5 minutes of reperfusion before the sustained left anterior descending coronary artery occlusion compared with controls. Thus, the benefits of preconditioning are not limited to those myocytes subjected to brief ischemia: Brief coronary occlusion in one vascular bed also protects remote myocardium from subsequent sustained ischemia.

Adenosine Alters Glucose Use During Ischemia and Reperfusion in Isolated Rat Hearts
Barry A. Finegan, MB, FRCP; Gary D. Lopaschuk, PhD; Chandani S. Coulson, PhD; and Alexander S. Clanchan, PhD

The effect of adenosine (100 μM) on mechanical function, glucose oxidation, glycolysis, and metabolic levels was studied in paced working rat hearts. Adenosine increased recovery of mechanical function after ischemia. Glucose oxidation, which was inhibited during ischemia, was increased by adenosine during reperfusion. Glycolysis was inhibited by adenosine during ischemia and during reperfusion. Adenosine reduced H+ production from glucose, depressed lactate levels, and increased ATP levels during reperfusion. The effects of adenosine on glucose metabolism that would tend to decrease cellular acidosis and hence, Ca2+ overload, may explain the beneficial cardioprotective effects of adenosine.

Interstitial Dendritic Cells of the Rat Heart: Quantitative and Ultrastructural Changes in Experimental Myocardial Infarction
Jun Zhang, MD; Zu-Xi Yu, MD, PhD; Shinsuke Fujita, MD, PhD; Maria L. Yamaguchi, BS; and Victor J. Ferrans, MD, PhD

Light and electron microscopic immunohistochemical methods using specific (OX 6 and W3/25) monoclonal antibodies were used to investigate the changes that interstitial dendritic cells (IDCs) of the heart undergo in myocardial infarction. The numbers of OX 6-positive IDCs per mm² were 82±10 in the left ventricle of unoperated rats. IDCs in the border zone of myocardial infarction were markedly increased (796±79, 528±98, and 159±15 at 7, 14, and 21 days, respectively) and were associated with clusters of T-helper lymphocytes. These findings suggest that interstitial dendritic cells participate in the activation of lymphocytes and in the initiation of immune responses in myocardial infarction.

The Renin–Angiotensin System and Volume Overload–Induced Cardiac Hypertrophy in Rats: Effects of Angiotensin Converting Enzyme Inhibitor Versus Angiotensin II Receptor Blocker
Marcel Ruzicka, MD; Baouxue Yuan, MD; Eel Harmsen, PhD; and Frans H.H. Leenen, MD, PhD

The development of volume overload–induced right ventricular hypertrophy and left ventricular (LV) eccentric hypertrophy (i.e., increased LV volume and decreased wall thickness/radius ratio) was associated with significant increases in plasma and cardiac renin activity shortly after induction of an aortocaval shunt. Although chronic treatment with either enalapril or losartan similarly lowered LV end-diastolic pressure, only losartan but not enalapril significantly attenuated the hypertrophic responses of the heart. These results appear to reflect other than hemodynamical determinants of the hypertrophic response to cardiac volume overload.

Effect of Selective Angiotensin II Receptor Antagonism and Angiotensin Converting Enzyme Inhibition on the Coronary Vasculature In Vivo: Intravascular Two-dimensional and Doppler Ultrasound Studies
Krishnankutty Sudhir, MD, PhD; John S. MacGregor, MD, PhD; Mukesh Gupta, MD; Sophie D. Barbant, MD; Rita Redberg, MD; Paul G. Yock, MD, FACC; and Kanu Chatterjee, MB, FRCP

We examined the effects of an AT1-receptor antagonist Losartan on coronary arteries in dogs, using intravascular ultrasound. At peak effect, Losartan increased coronary cross-sectional area and average peak velocity, resulting in an increase in coronary blood flow. The maximal effect of Losartan on coronary blood flow was significantly greater than that of Enalapril. Relative to adenosine (6 mg i.c.), flow increase from baseline was 0.37 with the AT1-receptor antagonist and 0.19 with the angiotensin converting enzyme inhibitor. Losartan-induced epicardial vasodilation was partially inhibited by L-NAME. These acute canine studies suggest that inhibition of AT1-receptors in the coronary circulation results in vasodilator responses greater in magnitude than angiotensin converting enzyme inhibition and partly endothelium dependent.
Cholinergic Modulation of the Coronary Vasoconstriction Induced by Cocaine in Conscious Dogs
Richard P. Shannon, MD; Bruce S. Stambler, MD; Kazuo Komamura, MD; Tedashi Ihara, PhD; and Stephen F. Vatner, MD

We studied the mechanisms of cocaine-induced coronary vasoconstriction in 10 conscious, chronically instrumented dogs. We observed a 24±3% (p<0.05) increase in calculated coronary vascular resistance, whereas coronary blood flow increased by 13±3% (p<0.05), to meet the 41±9% (p<0.05) increase in measured myocardial oxygen consumption associated with cocaine administration (1 mg/kg). Importantly, we observed that cholinergic blockade significantly attenuated the coronary vasoconstrictor response to cocaine in both the presence and absence of β-blockade. Combined α-, β-, and cholinergic blockade abolished the vasoconstrictor effects. Of note, cocaine administration was associated with increased myocardial oxygen delivery achieved through a significant increase in arterial oxygen content (control value, 15±0.6 vol%; peak value, 17.8±0.5 vol%; p<0.05). Thus, the effects of cocaine on the coronary circulation are the sum of increased metabolic demand and adrenergic vasoconstriction, which is modulated significantly by parasympathetic tone.

Electrophysiological Effects of High Cocaine Concentrations on Intact Canine Heart: Evidence for Modulation by Both Heart Rate and Autonomic Nervous System
Craig W. Clarkson, PhD; Chuntong Chang, MD; Adrienne Stoffi, BGS; William J. George, PhD; Shirou Yamasaki, MD; and Arthur S. Pickoff, MD

In dogs anesthetized with morphine and α-chloralose, cocaine (2–11 μg/mL) increased both atrial and ventricular refractory periods and produced rate-dependent increases in atrial, atrioventricular, His-Purkinje, and ventricular conduction intervals. The use-dependent effects of cocaine on conduction intervals were similar to values reported for class Ib antiarrhythmic agents. Cocaine produced a rate-dependent increase in QT interval that was greatest at high heart rates yet produced no change in the ST (QT-QRS) interval. Cocaine’s effects on both atrioventricular and intraventricular conduction were significantly larger in autonomico blocked than in autonomically intact animals.

Heat-Shock Response and Limitation of Tissue Necrosis During Occlusion/Reperfusion in Rabbit Hearts
R.W. Currie, PhD; R.M. Tanguay, PhD; and J.G. Kingma Jr., PhD

To test the hypothesis that induction of the heat-shock response delays the progression of myocyte injury, rabbits were initially pretreated with whole-body hyperthermia and then subjected to acute regional ischemia and coronary reperfusion either 24 or 40 hours later. Infarct area (tetrazolium staining) was normalized to anatomic risk area (microsphere autoradiography). Western blot analysis of ventricular tissue biopsies from both ischemic and nonischemic myocardium indicated expression of HSP71 in heat-shocked rabbits. Infarct size was significantly reduced at 24 but not 40 hours after heat shock in rabbits undergoing 30 minutes of regional ischemia with 3 hours of reperfusion compared with control rabbits. Myocyte injury was not reduced when the duration of ischemia was increased to 45 minutes in rabbits treated with whole-body hyperthermia and 40 hours of recovery. These findings suggest that whole-body hyperthermia delays the onset of irreversible myocyte injury in this animal model of acute myocardial infarction.

Beneficial Effect of Carnitine on Mechanical Recovery of Rat Hearts Repерfused After a Transient Period of Global Ischemia Is Accompanied by a Stimulation of Glucose Oxidation
Tom L. Broderick, MSC; H. Arthur Quinney, PhD; Collin C. Barker, BSc; and Gary D. Lopaschuk, PhD

We determined whether the beneficial effects of carnitine in ischemic hearts was accompanied by a stimulation in glucose use. Isolated working rat hearts were perfused under aerobic conditions with 11 mM glucose, 1.2 mM palmitate, and 100 μU/ml insulin and then subjected to a period of global ischemia followed by aerobic reperfusion. Myocardial carnitine content was first increased by perfusing hearts with 10 mM carnitine for a period of 60 minutes. This resulted in a twofold increase in total myocardial carnitine content. Glycolysis rates in carnitine-treated hearts were not significantly altered compared with control hearts, whereas glucose oxidation rates were increased approximately threefold compared with control hearts. During reperfusion of ischemic hearts, glycolysis rates returned to preischemic values in both control and treated hearts. Glucose oxidation rates also recovered to preischemic values in these hearts and remained significantly higher in carnitine-treated hearts. In these hearts, recovery of mechanical function was 71% of preischemic values compared with 44% in control hearts. This suggests that the beneficial effects of carnitine in ischemia can be explained by a stimulation in glucose oxidation.
Superoxide Dismutase Restores Contractile and Metabolic Dysfunction Through Augmentation of Adenosine Release in Coronary Microembolization

Seiji Takashima, MD; Masatugu Hori, MD; Masafumi Kitakaze, MD; Hiroshi Sato, MD; Michitoshi Inoue, MD; and Takenobu Kamada, MD

Coronary blood flow, fractional shortening, and the lactate extraction ratio were measured with and without administration of human recombinant superoxide dismutase before and after an injection of microspheres into the coronary artery in 78 dogs. Pretreatment with superoxide dismutase increased coronary blood flow by enhancement of the release of adenosine. The enhancement of coronary blood flow and adenosine release, which are associated with the restoration of 5'-nucleotidase activity, attenuated the contractile and metabolic dysfunction. Administration of superoxide dismutase at 10 and 30 minutes but not at 60 minutes after coronary embolization restored both contractile and metabolic dysfunction. This restoration of the contractile and metabolic dysfunction was blunted by 8-phenylethylpyline and coronary submaximal vasodilation induced by papaverine and adenosine. We conclude that superoxide dismutase restores the ischemic injury in coronary microembolization by preservation of 5'-nucleotidase activity and augmentation of adenosine production.

Comparative Immunogenicity and Thrombolytic Properties Toward Arterial and Venous Thrombi of Streptokinase and Recombinant Staphylokinase in Baboons

Désiré Collen, MD, PhD; Frans De Cock; and Jean-Marie Stassen

The relative immunogenicity and thrombolytic properties toward arterial and venous thrombi of streptokinase and recombinant staphylokinase were studied in baboons. Baboon plasma contained streptokinase-neutralizing activity (neutralizing 0.39±0.25 μg streptokinase per milliliter of plasma) that increased to 4.4±4.6 μg/ml after 4 weekly administrations of 0.30 mg/kg streptokinase and was associated with marked allergic reactions and partial resistance to lysis of a blood clot inserted into an extracorporeal loop. Staphylokinase-neutralizing antibodies could not be detected at baseline or after five repeated administrations of recombinant staphylokinase in three of four animals, and resistance to renewed administration did not occur. Staphylokinase had a thrombolytic potency toward jugular vein blood clots similar to that of streptokinase (50% lysis of a 125I-fibrin–labeled clot requiring 0.140 mg/kg [3.25 nmol/kg] streptokinase and 0.058 mg/kg [3.22 nmol/kg] recombinant staphylokinase) but had a higher thrombolytic potency toward platelet-rich femoral arterial erosion graft thrombi, as evidenced by more frequent and more persistent recanalization (p<0.05).

Thrombolytic Profiles of Clot-Targeted Plasminogen Activators: Parameters Determining Potency and Initial and Maximal Rates

Paul Holvoet, PhD; Maria Dewerchin, PhD; Jean Marie Stassen; Henri Roger Lijnen, PhD; Tom Tollenaere; Patrick J. Gaffney, PhD; and Désiré Collen, MD, PhD

Clot targeting of recombinant single-chain urokinase-type plasminogen activator (rcsu-PA) with fibrin-specific monoclonal antibodies was found to enhance its thrombolytic potency toward experimental pulmonary emboli in hamsters 40–60-fold. The thrombolytic potency of rcsu-PA/antifibrin conjugates was determined by their clearance, rate, and extent of initial binding to the emboli as well as by changes in binding during clot lysis. Clot targeting with fibrin-specific antibodies did not increase the maximal rate of clot lysis or shorten the minimal lag phase of clot lysis; these parameters were indeed very similar to those obtained with rcsu-PA or with recombinant tissue-type plasminogen activator (rt-PA). Thus, clot targeting reduces the dose required to obtain maximal clot lysis, but the minimal lag-phase and the maximal rate of lysis are independent of the nature of the plasminogen activator or of targeting. These observations suggest that there may be intrinsic limitations to the maximal achievable speed of thrombolysis.

Interruption of Vascular Thrombus Formation and Vascular Lesion Formation by Dietary n-3 Fatty Acids in Fish Oil in Nonhuman Primates

Laurence A. Harker, MD; Andrew B. Kelly, DVM; Stephen R. Hanson, PhD; William Krupski, MD; Arie Bass, MD; Bjarni Osterud, PhD; Garret A. FitzGerald, MD; Scott H. Goodnight, MD; and William E. Connor, MD

This study demonstrates that dietary ω-3 fatty acids are rapidly incorporated into blood and vascular tissues, modestly reduce the thrombotic responses of flowing blood to thrombogenic surfaces, and interrupt both the thrombotic and proliferative responses at sites of mechanical vascular injury without significantly impairing hemostatic function or producing other adverse effects when administered to baboons.

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Special Article

A History of the American Heart Association's Council on Clinical Cardiology
W. Bruce Fye, MD, MA ....................................................................................................... 1057

This essay reviews the history of the Council on Clinical Cardiology of the American Heart Association. It stresses the factors that led to the council's formation and shaped its agenda. The direct stimulus for its creation was the American College of Cardiology's first membership drive in 1951. The Section (later Council) on Clinical Cardiology was formally established the following year to "facilitate and encourage investigation, prevention, treatment and education in the field of clinical cardiology." Originally strained, the relations between the AHA and the ACC improved as the organizations came to view each other as potential partners rather than rivals.
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