Annotated Table of Contents

**Circulation Electronic Pages**

**Cardiology Patient Page**

Treatment of Blood Clots
Samuel Z. Goldhaber, MD; Nicole Grasso-Correnti, RN, BSN

**Web Site Feature**

**Correspondence**

Passage of Inhaled Particles Into the Blood
Circulation in Humans
Letter . . . . . . William M. Burch
Response . . . . . . A. Nemmar, DVM, PhD; P.H.M. Hoet, PhD; M. Thomeer, MD; B. Nemery, MD, PhD; B. Vangriekenborne, MD; H. Vanbilloen, PhD; L. Mortelmans, MD, PhD; M.J. Hoylaerts, PhD; A. Verbruggen, Pharm, PhD; D. Dinsdale, PhD

**Web Site Feature**

**Letter**

No-Reflow Phenomenon
Letter . . . . . . H. Richard Hellstrom, MD
Response . . . . . . Shereif H. Rezkalla, MD; Robert A. Kloner, MD, PhD

**Web Site Feature**

**Letter**

Further In Vivo Evidence That Cellular Senescence Is Implicated in Vascular Pathophysiology
Letter . . . . . . Jorge D. Erusalimsky, PhD; Mark Fenton, MA, MRCP
Response . . . . . . Tohru Minamino, MD, PhD; Hideyuki Miyachi, MD; Toshikiko Yoshida, MD; Issie Komuro, MD, PhD; Yasuo Ishida, MD, PhD; Hideo Yoshida, MD, PhD

**Web Site Feature**

**Letter**

Circulating and Exhaled Markers of Nitric Oxide and Antioxidant Activity After Smoking
Letter . . . . . . S.L. Nuttall, PhD; H.C. Routledge, BSc, MRCP; S. Manney, BSc
Response . . . . . . Masahiko Tsuchiya, MD, PhD; Akira Asada, MD, PhD; Mitsuo Shindo, MD, PhD; Emiko Kasahara; Eisahe F. Sato, PhD; Masayasu Inoue, MD

**Web Site Feature**

**Letter**

Angiotensin-(1-7) Attenuates the Development of Heart Failure After Myocardial Infarction in Rats
Letter . . . . . . John McMurray, BSc(Hons); MBChB(Hons), MD, FRCP, FESC; Andrew P. Davie, BSc(Hons), MBChB, MD, MRCP
Response . . . . . . Annemarieke E. Loot, MSc;
Anton J.M. Roks, PhD;
Robert H. Henning, MD, PhD;
Wiek H. van Gilst, PhD; René A. Tio, MD, PhD;
Albert J.H. Suurmeier, MD, PhD;
Frans Boomsma, PhD

**Web Site Feature**

**Letter**

Misinformation on Plant Proteins
Letter . . . . . . John McDougall, MD
Response . . . . . . Barbara Howard, PhD

**Web Site Feature**

**Editorial**

Low-Density Lipoprotein, Non–High-Density Lipoprotein, and Apolipoprotein B as Targets of Lipid-Lowering Therapy
Scott M. Grundy, MD, PhD

**Brief Rapid Communications**

Effect of Diet and Exercise Intervention on Blood Pressure, Insulin, Oxidative Stress, and Nitric Oxide Availability
Christian K. Roberts, PhD; Nosratola D. Vaziri, MD; R. James Barnard, PhD

The present study examined the effects of a short-term, rigorous diet and exercise intervention on blood pressure, hyperinsulinemia, and nitric oxide (NO) availability. Eleven men were placed on a low-fat, high-fiber diet combined with daily exercise for 45 to 60 minutes for 3 weeks. Both systolic and diastolic blood pressure, fasting insulin, and 8-isoprostaglandin F2α decreased, and urinary NO metabolite excretion increased. The intervention resulted in dramatic improvements in blood pressure, oxidative stress, NO availability, and metabolic profile within 3 weeks, mitigating the risk for atherosclerosis progression and its clinical sequelae.

**Sympathetic Neural Activation in Visceral Obesity**

Guy E. Alvarez, MS; Stacy D. Beske, PhD; Tasha P. Ballard, MS; Kevin P. Davy, PhD

We tested the hypothesis that muscle sympathetic nerve activity (MSNA) would be increased in men (age = 18 to 40 years, body mass index = 35 kg/m²) with higher abdominal visceral fat (HAVF) compared with their age-, total body-, and abdominal subcutaneous fat levels (LAVF). MSNA was ≈55% higher in men with HAVF compared with men with LAVF. Furthermore, MSNA was more closely associated with the level of abdominal visceral fat than total body or abdominal subcutaneous fat. Our observations are consistent with the idea that abdominal visceral fat may be an important adipose tissue depot that links obesity with elevated MSNA in humans.

**Clinical Investigation and Reports**

Non–High-Density Lipoprotein Cholesterol Levels Predict Five-Year Outcome in the Bypass Angioplasty Revascularization Investigation (BARI)
Vera Büttner, MD, MSPH; Regina Hardison, MS; Sheryl F. Kelsey, PhD;

*Pfizer provides an unrestricted gift for subscriptions to Circulation for Cardiology Fellows in training.*
We determined the relationship between non–high-density lipoprotein cholesterol level (non-HDL-C) and clinical outcomes over 5 years of follow-up in the Bypass Angioplasty Revascularization Investigation. Non-HDL-C was a strong and independent predictor of nonfatal myocardial infarction and angina pectoris, but it was not related to mortality. Our data suggest that non-HDL-C is an appropriate treatment target among patients with coronary heart disease.

Low-Density Lipoprotein Level Reduction by the 3-Hydroxy-3-Methylglutaryl Coenzyme-A Inhibitor Simvastatin Is Accompanied by a Related Reduction of F2-Isoprostane Formation in Hypercholesterolemic Subjects: No Further Effect of Vitamin E
Raffaele De Caterina, MD; Francesco Cipollone, MD; Francesca Paola Filardo, MD; Francesco Cipollone, MD; Marco Zimarino, MD; Walter Bemini; Guido Lazzarini; Tonino Bucciarelli, MD; Angela Falco, MD; Paola Marchesani, MD; Raffaella Muraro, MD; Andrea Mezzetti, MD; Giovanni Ciabattoni, MD

We randomized 43 hypercholesterolemic patients to simvastatin or simvastatin plus 600 mg/d vitamin E for 2 months, with crossover to the alternative treatment for 2 additional months. We assessed urinary 8-iso-prostaglandin F2α (8-iso-PGF2α) as a marker of oxidative stress. Simvastatin significantly reduced 8-iso-PGF2α, but the addition of vitamin E did not produce any additive effect. LDL cholesterol was a strong direct correlate of 8-iso-PGF2α, whereas vitamin E levels were only a weak inverse correlate. In hypercholesterolemic patients, simvastatin causes a drastic reduction of oxidative stress to a level that is not further reduced by the addition of vitamin E.

Ability of Recombinant Factor VIIa to Reverse the Anticoagulant Effect of the Pentasaccharide Fondaparinux in Healthy Volunteers
Nick R. Bijsterveld, MD; Arno H. Moons, MD; S. Matthijs Boekholt, MD; Benien E. van Aken, PhD; Hein Fennema, PhD; Ron J.G. Peters, MD; Joost C.M. Meijers, PhD; Marcel Levi, MD; Harry R. Builler, MD; Lynn Bason, MS; David A. Piccoli, MD; Doff B. McElhinney, MD; Ian D. Krantz, MD; Karan M. Emerick, MD; Nancy B. Spinner, PhD; Elizabeth Goldmuntz, MD; L. Stavenow, MD, PhD; L. Janzon, MD, PhD; F. Lindgärde, MD, PhD

We investigated whether the anticoagulant effects of fondaparinux, a selective factor Xa inhibitor, could be neutralized by recombinant factor VIIa (rFVIIa) in healthy male volunteers. We performed a randomized, placebo-controlled trial comparing fondaparinux (10 mg SC) plus rFVIIa (90 μg/kg IV; n=8), fondaparinux alone (n=4), or rFVIIa alone (n=4). rFVIIa after fondaparinux increased prothrombin activation fragments 1+2 (F1+2) and normalized 2 ex vivo thrombin-generation tests up to 6 hours after rFVIIa injection. We conclude that rFVIIa is capable of normalizing coagulation times and thrombin generation during fondaparinux treatment, which makes rFVIIa a potential candidate in case of serious bleeding complications in fondaparinux-treated patients.

Lung Function and Cardiovascular Risk: Relationship With Inflammation-Sensitive Plasma Proteins
G. Engström, MD, PhD; P. Lind, MD; B. Hedblad, MD, PhD; P. Wollen, MD, PhD; L. Stavenow, MD, PhD; L. Janzon, MD, PhD; F. Lindgärde, MD, PhD

This study explored the relationships between forced vital capacity (FVC), inflammation-sensitive plasma proteins (ISP; ie, fibrinogen, α1-antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid), and incidence of cardiovascular disease in 5064 healthy men followed up over an 18-year period. Low FVC was associated with higher ISP levels. Adjustments for ISP levels reduced the cardiovascular risk among men with low FVC. Among men with low FVC, cardiovascular risk was significantly increased if ISP levels also were high. Relationships with ISP contribute to but cannot fully explain the increased cardiovascular risk among men with low FVC.

Arterial Stiffness and Endothelial Function in Patients With β-Thalassemia Major
Y.F. Cheung, MBBS; Godfrey C.F. Chan, MD; S.Y. Ha, MBBS

Arterial stiffness and endothelial function were assessed noninvasively in 30 patients with β-thalassemia major. Whereas indexes of left ventricular systolic and diastolic function were similar to those of 30 age- and sex-matched control subjects, thalassemia patients had greater absolute (P=0.04) and indexed (P<0.001) left ventricular mass, stiffer carotid artery (P<0.001), faster brachioradial pulse-wave velocity (P=0.03), and less brachial artery flow-mediated dilation (P<0.001). Stiffness index and pulse-wave velocity correlated inversely with magnitude of flow-mediated dilation and positively with left ventricular mass. Our findings suggest increased arterial stiffness and endothelial dysfunction in iron-overloaded thalassemia patients.

Analysis of Cardiovascular Phenotype and Genotype-Phenotype Correlation in Individuals With a JAG1 Mutation and/or Alagille Syndrome
Doff B. McElhinney, MD; Ian D. Krantz, MD; Lynn Bason, MS; David A. Piccoli, MD; Karan M. Emerick, MD; Nancy B. Spinner, PhD; Elizabeth Goldmuntz, MD

The cardiovascular phenotype was characterized in 200 individuals with a mutation in the JAG1 gene or Alagille syndrome. A variety of right- and left-sided cardiovascular anomalies was documented (n=150) or suspected on the basis of clinical examination (n=37) in 94% of subjects. The most common cardiovascular anomaly was branch pulmonary artery stenosis/hypoplasia, which was documented by imaging or inferred from physical examination in 76% of subjects. There was no correlation between the presence or type and location of JAG1 mutation and the cardiovascular phenotype.
Annotated Table of Contents

Coronary Artery Pattern and Outcome of Arterial Switch Operation for Transposition of the Great Arteries: A Meta-Analysis
Sara K. Pasquale, MD; Vic Hasselblad, PhD; Jennifer S. Li, MD; David F. Kong, MD; Stephen P. Sanders, MD ................................. 2575

We assessed the relationship between coronary anatomy and mortality after arterial switch operation in patients with transposition of the great arteries through combining results of 9 series in a meta-analysis. Compared with the normal pattern, intramural (OR 6.5, 95% CI 2.9 to 14.2) and single (OR 2.9, 95% CI 1.3 to 6.8) coronary arteries were associated with significantly increased mortality. These 2 patterns remained associated with significant added mortality after adjustment for time-trend effects.

Basic Science Reports

Enzymatically Modified Nonoxidized Low-Density Lipoprotein Induces Interleukin-8 in Human Endothelial Cells: Role of Free Fatty Acids
Prapat Suriyaphol, PhD; Dominic Fenske, PhD; Ulrich Zähringer, PhD; Shan-Rui Han, MD; Prapat Suriyaphol, PhD; Dominic Fenske, PhD; Ulrich Zähringer, PhD; Shan-Rui Han, MD; Sucharit Bhakdi, MD; Matthias Husmann, MD . . . 2581

Enzymatic, nonoxidative modification transforms low-density lipoprotein (LDL) to a potentially atherogenic molecule (E-LDL) in vitro, and E-LDL is present in early atherosclerotic lesions. E-LDL has a high content of free cholesterol due to liberation of free fatty acids from cholesterol esters. We report that free fatty acids associated with E-LDL selectively stimulate production of interleukin-8 in endothelial cells. Interleukin-8 is required for rolling monocytes to adhere firmly to the endothelium, and thus a possible link is provided between subendothelial entrapment of LDL and monocyte recruitment to the lesion.

Hypotension Caused by Extracorporeal Circulation: Serotonin From Pump-Activated Platelets Triggers Nitric Oxide Release
Piet Borgdorff, PhD; Durk Fekkes, PhD; Geert Jan Tangelder, MD, PhD ................................. 2588

In rats, a heparin-coated extracorporeal shunt was placed between the proximal part of a carotid artery and the distal part of a femoral artery. Pump perfusion immediately elicited strong platelet aggregation, serotonin release, and systemic hypotension, which could be prevented by blockade of 5-hydroxytryptamine (5-HT)2 receptors or nitric oxide (NO) synthase inhibition. Pumping the blood into the aortic arch yielded a similar and NO-dependent hypotension, but venous return did not. We conclude that with arterial blood, return pumping-induced hypotension is caused by endothelial release of NO, which in turn is triggered by serotonin from activated platelets.

Reverse Ventricular Remodeling Reduces Ischemic Mitral Regurgitation: Echo-Guided Device Application in the Beating Heart
Judy Hung, MD; J. Luis Guerrero, BS; Mark D. Handschumacher, BS; Gregory Supple, BS; Suzanne Sullivan, BS; Robert A. Levine, MD ................................. 2594

Therapy for ischemic mitral regurgitation remains difficult because of persistent papillary muscle displacement after annuloplasty. In a model of inferior infarction with ischemic mitral regurgitation, we placed a Dacron patch containing an inflatable balloon over the papillary muscle. In all 10 sheep, such an external device repositioned the papillary muscles and reduced mitral regurgitation without compromising left ventricular function. Echocardiographic guidance allowed application of this technique in the beating heart.

Preoperative Glutamine Administration Induces Heat-Shock Protein 70 Expression and Attenuates Cardiopulmonary Bypass–Induced Inflammatory Response by Regulating Nitric Oxide Synthase Activity
Yoshitaka Hayashi, MD, PhD; Yoshiki Sawa, MD; Naoto Fukuyama, MD; Hiroe Nakazawa, MD; Hikaru Matsuda, MD ................................. 2601

Gluatamine administration for 1 week before cardiopulmonary bypass induced heat-shock protein 70 expression before the onset of inflammation in rats. Three hours after the termination of 60 minutes of cardiopulmonary bypass, pretreatment with glutamine enhanced heat shock protein 70 expression and attenuated cardiopulmonary bypass–induced inflammation by regulating nitric oxide synthase activity. Preoperative glutamine administration may be a prospective management for conferring tolerance to cardiopulmonary bypass–induced inflammatory response through a self-protective mechanism.

CD14-Deficient Mice Are Protected Against Lipopolysaccharide-Induced Cardiac Inflammation and Left Ventricular Dysfunction
Pascal Knuefermann, MD; Shintaro Nemoto, MD, PhD; Arunima Misra, MD; Naoki Nozaki, MD; Gilberto Defreitas, BS; Sanna M. Goyert, PhD; Blase A. Carabello, MD; Douglas L. Mann, MD; Jesus G. Vallejo, MD ................................. 2608

Administration of lipopolysaccharide (LPS) induced a rapid and robust increase in tumor necrosis factor, interleukin-1β, and NOS2 in hearts of wild-type mice. In contrast, tumor necrosis factor and interleukin-1β expression was significantly blunted in hearts of CD14-deficient mice. In wild-type mice, LPS significantly decreased left ventricular fractional shortening, velocity of circumferential shortening, and dp/dtmax. LPS-treated CD14-deficient mice maintained normal cardiac function. These results suggest that CD14 is important in mediating the proinflammatory response in the heart and that CD14 is necessary for LPS-induced left ventricular dysfunction.

Mini-Review: Current Perspective

Update on Myocardial Bridging
Stefan Möhlenkamp, MD; Waldemar Hort, MD; Junbo Ge, MD; Raimund Erbel, MD ................................. 2616
AHA Scientific Statement

Medication Errors in Acute Cardiac Care: An American Heart Association Scientific Statement
From the Council on Clinical Cardiology
Subcommittee on Acute Cardiac Care, Council on Cardiopulmonary and Critical Care, Council on Cardiovascular Nursing, and Council on Stroke
Jane E. Freedman, MD; Richard C. Becker, MD; Jesse E. Adams, MD; Steven Borzak, MD; Robert L. Jesse, MD; L. Kristin Newby, MD; Patrick O’Gara, MD; John C. Pezzullo, MD; Richard Kerber, MD; Bernice Coleman, MD; Joseph Broderick, MD; Sally Yasuda, MS, PharmD; Christopher Cannon, MD

AHA Special Report

Report of the American Heart Association Task Force on Strategic Research Direction:
Executive Summary
Robert Roberts, MD; Robert O. Bonow, MD; Joseph Loscalzo, MD, PhD; Lori Mosca, MD, MPH, PhD

Basic Science Subgroup
Joseph Loscalzo, MD, PhD, Chair; Robert Balaban, PhD; Lance B. Becker, MD; Geoffrey S. Ginsburg, MD, PhD; Vladimir C. Hachinski, MD; John E. Hall, PhD; Donald D. Heistad, MD; Leslie A. Leinwand, PhD; Claude J. Lenfant, MD; Eduardo Marban, MD, PhD; Eric N. Olson, PhD; Stephen M. Schwartz, PhD

Clinical Science Subgroup
Robert Bonow, MD, Chair; Edward B. Clark, MD; Gregory D. Curfman, MD; Alan Guttmacher, MD; Martha N. Hill, PhD; D. Craig Miller, MD; Aubrey R. Morrison, MD; Robert J. Myerburg, MD; Michael D. Schneider, MD; Myron L. Weisfeldt, MD; James T. Willerson, MD; James B. Young, MD

Population/Outcomes/Epidemiology/Social Science Subgroup
Lori Mosca, MD, MPH, PhD, Chair; Donna K. Arnett, PhD; Kathleen Dracup, RN, DNASC; Barbara C. Hansen, PhD; Darwin R. Labarthe, MD; James S. Marks, MD; Karen A. Matthews, PhD; Thomas A. Pearson, MD, PhD; William Weintraub, MD; Walter Wilson, MD

Web Site Feature

Classified Advertising