

BASIC SCIENCE CURRICULUM

1. EMBRYOLOGY OF THE VASCULAR SYSTEM

1. Embryologic development

Initial formation of the vascular system (arteries and veins).

Development of the aortic arch.

Development of the thoracic and abdominal aorta.

Development of the arteries to the extremities.

Development of the superior vena cava.

Development of the inferior vena cava.

2. Embryologic anomalies

Aortic arch anomalies (including double aortic arch, right aortic arch, retroesophageal right subclavian artery, absence of the internal carotid artery, patent ductus arteriosus and coarctation of the aorta).

Lower extremity arterial anomalies (including persistent sciatic artery, single umbilical artery, and popliteal entrapment syndrome).

Superior vena cava anomalies (including double superior vena cava and left-sided superior vena cava).

Inferior vena cava anomalies (including transposition or left-sided inferior vena cava, retroaortic left renal vein, circumaortic left renal vein, retrocaval ureter and absent suprarenal inferior vena cava).

References

Skandalakis JE, Gray SW eds. Embryology for surgeons: the embryological basis for the treatment of congenital anomalies. Baltimore: Williams & Wilkins, 1994.

Against a background of normal embryology, the authors describe the specific pathological conditions and critically review the embryogenesis of a large number of congenital defects, supplying estimates of their frequency, their distribution within the population, and their prognosis. The diagnostic approach and the principles underlying their surgical correction are also discussed.

Richardson JV, Doty DB, Rossi NP, Ehrenhaft JL. Operation for aortic arch anomalies. Ann Thorac Surg 1981;31:426-432.

This paper reviews a 30-year experience of a single center with aortic arch anomalies. Their clinical presentation, diagnosis and treatment are also briefly reviewed.

Brantley SK, Rigdon EE, Raju S. Persistent sciatic artery: embryology, pathology, and treatment. J Vasc Surg 1993;18:242-248.

This article describes the embryologic development and anomalous persistence of the sciatic artery, the pathologic changes that may occur in the persistent sciatic artery and the management of complications related to these pathologic changes.

Lambert AW, Wilkins DC. Popliteal artery entrapment syndrome. Br J Surg 1999;86:1365-1370.

Popliteal entrapment is an uncommon condition that may cause claudication in young males, some of whom have normal resting pedal pulses. This article reviews popliteal artery entrapment syndrome; it includes the embryology of the arterial supply to the leg and the non-invasive imaging techniques now used in the diagnosis of the condition.

Giordano JM, Trout HH 3rd. Anomalies of the inferior vena cava. J Vasc Surg 1986;3:924-928.

Anomalies of the inferior vena cava are uncommon but important entities to the radiologist and the vascular surgeon. Improper embryogenesis of the inferior vena cava may result in four anatomic anomalies: duplication of the inferior vena cava, transposition or left-sided inferior vena cava, retroaortic left renal vein and circumaortic left renal vein. This paper presents two patients with inferior vena cava anomalies and reviews the embryologic basis and the diagnosis of these rare clinical entities.

2. MOLECULAR BIOLOGY

I. Molecular biology

Cell growth cycle.

Replication, transcription, translation.

DNA and RNA structure and function.

Plasmids, vectors and transfection.

Gene expression, promoters, enhancers.

Basic techniques and assays (Western blot, Northern blot, polymerase chain reaction, in vitro transcription assay, in situ hybridization).

Basic terms in molecular biology.

II. Molecular diagnostics

Aims.

Techniques.

Indications.

III. Molecular biology in the treatment of vascular disease

Gene therapy (systemic and local) including methods and indications.

Cell therapy (ex vivo gene therapy).

Therapy with recombinant protein.

Ethical considerations.

References

Alberts B. Molecular biology of the cell. New York: Garland Science, 2002.

This landmark textbook in the field of molecular cell biology summarizes a wide range of knowledge from a basic discussion of cells, genomes and cell chemistry to recent advances in biotechnology, cellular mechanisms, infection and immunity.

Pang CP. Molecular diagnostics for cardiovascular disease. Clin Chem Lab Med 1998;36:605-614.

The etiology of cardiovascular diseases is known to be multi-factorial. Some of them are caused by environmental factors, some others by specific gene defects, while others result from complex gene-environment interactions. This review article presents molecular diagnostic techniques that have been applied for rapid and reliable detection of specific gene defects. These techniques can provide unequivocal diagnosis beneficial for appropriate drug therapy and genetic counseling.

Morishita R. Recent progress in gene therapy for cardiovascular disease. Circ J 2002;66:1077-1086.

Gene therapy is emerging as a potential strategy for the treatment of cardiovascular diseases, such as peripheral arterial disease, ischaemic heart disease, restenosis after angioplasty, vascular bypass graft occlusion and transplant coronary vasculopathy, for

which no known effective therapy exists. This review presents recent progress in gene therapy for cardiovascular disease.

Richter G, Bacchetta MD. Interventions in the human genome: some moral and ethical considerations. *J Med Philos* 1998;23:303-317.

This paper discusses the need for development of a new framework for the ethical discussion of genetic interventions into the human genome. It also presents the core arguments for the acceptance of somatic gene therapy and those for the rejection of genetic interventions into germ-line cells.

Hiltunen MO, Turunen MP, Laitinen M, Yla-Herttuala S. Insights into the molecular pathogenesis of atherosclerosis and therapeutic strategies using gene transfer. *Vasc Med* 2000;5:41-48.

Gene transfer to the vascular system can be performed both via intravascular and extravascular periadventitial routes. This review describes both of these techniques, their aims and initial results.

3. PHYSIOLOGY AND PATHOPHYSIOLOGY OF BLOOD VESSELS

1. Physiology

Circumferential, longitudinal and radial deformation and stresses of blood vessels.
Properties of collagen, elastin and glycosaminoglycan ground substance.
The length-active stress curve of the vascular muscle.
Changes induced by aging.

2. Pathophysiology

Aneurysms
Histological changes
Causes of aneurysms (including the role of proteases, inflammation, autoimmunity and atherosclerosis)
Mechanisms preventing instantaneous enlargement of aneurysms.

3. Poststenotic dilatation

Histological changes.
Mechanisms for poststenotic dilatation.

4. Autogenous vein grafts

Histological changes.
Mechanisms for the beneficial effects of vein grafts.
Distribution and causes of intimal hyperplasia in end-to-side vascular anastomoses.

5. Arteries of hypertensive subjects

Histological changes.
Behavior and control of the precapillary resistance vessels.
Atherosclerotic arteries
Histological and mechanical changes.
Distribution of vasa vasorum.

References

1. Dobrin PB, Baker WH, Gley WC. Elastolytic and collagenolytic studies of arteries. Implications for the mechanical properties of aneurysms. Arch Surg 1984;119:405-409.

Results of elastolytic and collagenolytic studies on canine and human arteries are presented. Treatment with elastase caused the vessels to dilate but to remain intact, while all vessels treated with collagenase ruptures. The authors conclude that wall integrity depends on intact collagen rather than elastin.

2. Dobrin PB. Poststenotic dilatation. Surg Gynecol Obstet 1991;172:503-508.

This paper presents the pathogenetic mechanisms of poststenotic dilatation. According to experimental studies, shear stress and turbulence are the most likely causes. Whatever

the flow disturbance, it must may the wall vibrate to produce poststenotic dilatation. Vibrations are thought to produce alterations in wall elastic and possibly in vascular smooth muscle tone.

3. Dobrin PB, Littooy FN, Endean ED. Mechanical factors predisposing to intimal hyperplasia and medial thickening in autogenous vein grafts. *Surgery* 1989;105:393-400.

This paper presents experimental data showing that intimal hyperplasia is best associated with low flow velocity, a factor correlated with low blood-artery shear stress. By contrast, medial thickening is best associated with increased deformation of the vein wall in the circumferential direction (increased diameter). These findings correlate with clinical responses of vein grafts.

4. Zarins CK, Weisenberg E, Kolettis G, Stankunavicius R, Glagov S. Differential enlargement of artery segments in response to enlarging atherosclerotic plaques. *J Vasc Surg* 1988;7:386-394.

This is a study of the response of artery segments to enlarging atherosclerotic plaques. It shows that coronary arteries enlarge in response to increasing atherosclerotic plaque and that such enlargement can prevent narrowing of the lumen. However, differential segments of the same artery may respond differently. Local differences in the relative rates of plaque growth and artery enlargement may determine progression to stenosis, preservation of normal lumen area, or enlargement.

5. Dobrin PB. Mechanical factors associated with the development of intimal and medial thickening in vein grafts subjected to arterial pressure. A model of arteries exposed to hypertension. *Hypertension* 1995;26:38-43.

Exposure of vein grafts to arterial pressure increases the following nine mechanical factors: deformation in the circumferential, longitudinal, and radial directions; stresses in each of these three directions; pulsatile deformations and pulsatile stresses; and flow velocity. The experiments presented in this article demonstrate that intimal thickening is best correlated with low flow velocity, a correlate of low shear stress, whereas medial thickening is best correlated with deformation in the circumferential direction.

4. HEMODYNAMICS AND ATHEROSCLEROSIS

Physiology – Pathophysiology

Types of blood flow (laminar, turbulent) and their determinants (Reynolds number).

Hemodynamic forces (shear stress, tensile stress): definitions and equations.

Vessel wall properties affecting the development of atherosclerosis (thickness, elasticity, number of vasa vasorum).

Shear stress effects on the endothelium.

Causes and effects of turbulence.

The role of hypertension in atherosclerosis.

Hemodynamic changes associated with arterial stenoses.

Hemodynamics associated with anastomoses.

Clinical implications

Plaque localization in the carotid bifurcation (the effects of low shear stress).

Plaque localization in the coronary arteries (the effects of heart rate).

Plaque localization in the aorta (the effects of low flow velocity, the curvature of the abdominal aorta and the aortic bifurcation).

References

Frangos SG, Gahtan V, Sumpio B. Localization of atherosclerosis: role of hemodynamics. Arch Surg 1999;134:1142-1149.

This review provides fundamental knowledge on the predominant hemodynamic forces that have been characterized: shear stress and cyclic circumferential strain. The role of hemodynamics in the localization of atherosclerosis is discussed as well as the intracellular events that link hemodynamic stimuli and endothelial cell response.

Davies PF, Polacek DC, Shi C, Helmke BP. The convergence of haemodynamics, genomics, and endothelial structure in studies of the focal origin of atherosclerosis. Biorheology 2002;39:299-306.

This article outlines how modern molecular techniques are being utilized in studies of endothelia mechanotransduction associated with controlled shear stress in vitro and hemodynamics in vivo. The value of such techniques as components of an integrated understanding of vascular rheology is emphasized.

Feldman CL, Stone PH. Intravascular hemodynamic factors responsible for progression of coronary atherosclerosis and development of vulnerable plaque. Curr Opin Cardiol 2000;15:430-440.

This review outlines the mechanisms that link hemodynamic factors to plaque development and rupture and describes in some detail recently developed techniques that, for the first time, make it possible to determine these factors in vivo.

Gimbrone MA Jr, Topper JN, Nagel T, Anderson KR, Garcia-Cardena G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. *Ann N Y Acad Sci* 2000;902:230-240.

Phenotypic modulation of endothelium to a dysfunctional state contributes to the pathogenesis of cardiovascular diseases such as atherosclerosis. This article reviews the role of the vascular endothelium in the atherosclerotic disease process, the impact of the various types of hemodynamic forces on vessel wall biology and the mechanisms of endothelial gene regulation by biomechanical forces.

Vorp DA, Trachtenberg JD, Webster MW. Arterial hemodynamics and wall mechanics. *Semin Vasc Surg* 1998;11:169-180.

This article summarizes the basic concepts of arterial hemodynamics and wall mechanics as they relate to the development of arterial pathology. A few practical mathematical relationships and examples are provided for both illustration and utilization. The use of computer models for the estimation of wall stresses in individual abdominal aortic aneurysms is also discussed.

5. PEPTIDE GROWTH FACTORS

1. General considerations

Function of growth factors.

Growth factor receptors and mechanism of action.

2. Specific growth factors

Platelet-derived growth factor (characteristics, receptor, effects, role in proliferative diseases of the vascular system).

Fibroblast growth factor (characteristics, receptor, effects, role in proliferative diseases of the vascular system).

Epidermal growth factor (characteristics, receptor, effects, role in proliferative diseases of the vascular system).

Transforming growth factors α and β (characteristics, receptor, effects, role in proliferative diseases of the vascular system).

Insulin-like growth factors (characteristics, receptor, binding protein, effects, role in proliferative diseases of the vascular system).

References

1. Sidawy AN, Mitchell ME, Neville RF. Peptide growth factors and signal transduction. *Semin Vasc Surg* 1998;11:149-155.

This paper reviews the role of various growth factors, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin, insulin-like growth factor-I (IGF-I), and transforming growth factors alpha and beta (TGF alpha and beta), in the development of arteriosclerosis and intimal hyperplasia.

2. Hughes AD, Clunn GF, Refson J, Demoliou-Mason C. Platelet-derived growth factor (PDGF): actions and mechanisms in vascular smooth muscle. *Gen Pharmacol* 1996;27:1079-1089.

This review describes the vascular biology of PDGF. It particularly focuses on recent findings regarding the intracellular signals activated by PDGF in the context of vascular smooth muscle cell proliferation, migration and contraction.

3. Chen CH, Henry PD. Atherosclerosis as a microvascular disease: impaired angiogenesis mediated by suppressed basic fibroblast growth factor expression. *Proc Assoc Am Physicians* 1997 ;109:351-361.

This paper presents evidence that hypercholesterolemia and oxidized low-density lipoprotein impair endothelial cell growth by suppressing basic fibroblast growth factor expression. Background studies on the subject are briefly reviewed.

4. Topper JN. TGF-beta in the cardiovascular system: molecular mechanisms of a context-specific growth factor. *Trends Cardiovasc Med* 2000;10:132-137.

Transforming growth factor beta isoforms have been strongly implicated in a number of pathophysiologic processes including chronic vascular diseases such as atherosclerosis and hypertension. This article reviews the molecular mechanisms by which these factors exert their complex and pleiotropic actions on cells and tissues of the cardiovascular system.

5. Bayes-Genis A, Conover CA, Schwartz RS. The insulin-like growth factor axis: A review of atherosclerosis and restenosis. *Circ Res* 2000;86:125-130.

Dysregulated actions of insulin-like growth factors I and II have been found to contribute to coronary atherosclerosis and restenosis. This article first reviews the basic physiology of the IGF axis and then discusses specific autocrine and paracrine actions of IGFs in atherosclerotic plaque progression and the neointimal hyperplasia of restenosis.

6. ENDOTHELIAL CELLS

1. Development of the endothelium
2. Structure of the endothelium
 - Extracellular matrix.
 - Endothelial cell cytoskeleton.
 - Endothelial cell integrins.
3. The endothelium as a metabolic organ
4. Endothelial interactions
 - Endothelium and platelets.
 - Endothelium and lymphocytes.
 - Endothelium and leukocytes.
5. Culture of endothelial cells
 - Large vessel endothelial cells (including human umbilical vein endothelial cells and bovine aortic endothelial cells).
 - Microvascular endothelial cells.
 - Identification of endothelial cells.
 - Endothelial cell culture media.

References

1. Behrendt D, Ganz P. Endothelial function. From vascular biology to clinical applications. *Am J Cardiol* 2002;90:40L-48L.

This paper reviews the role of endothelium on atherogenesis and emphasizes the profound prognostic and therapeutic implications of endothelial dysfunction.

2. Blann AD, Lip GY. The endothelium in atherothrombotic disease: assessment of function, mechanisms and clinical implications. *Blood Coagul Fibrinolysis* 1998;9:297-306.

This article reviews the scientific and clinical evidence showing that changes in endothelial cell physiology are an important component of inflammatory and atherosclerotic vascular disease.

3. Schiffrin EL. The endothelium and control of blood vessel function in health and disease. *Clin Invest Med* 1994;17:602-620.

The endothelium is critically involved in the regulation of vascular function through its barrier role, via interaction with circulating cells such as platelets, which then release vasoactive or growth regulating agents, and through production of substances which may modulate vascular tone, smooth muscle cell growth and coagulation. This article reviews

the role of the endothelium in health as well as in various diseases such as hypertension, atherosclerosis, diabetes, heart failure, ischemic heart disease, sepsis, and shock.

4. Luscher TF, Tanner FC. Endothelial regulation of vascular tone and growth. *Am J Hypertens* 1993;6:283S-293S.

The endothelium regulates vascular tone and growth by releasing factors involved in relaxation and contraction, in coagulation and thrombus formation, and in growth inhibition and stimulation. The role of various chemical and physical stimuli, mediators and endothelium-derived factors is summarized.

5. Katusic ZS, Shepherd JT. Endothelium-derived vasoactive factors: II. Endothelium-dependent contraction. *Hypertension* 1991;18:III86-92.

Endothelial cells may produce and release vasoconstrictor substances in response to a number of agents and physical stimuli. This brief review discusses the mechanisms of endothelium-dependent contractions and speculates about the possible importance of such contractions for venous graft function, development of vasospasm, increased vascular resistance in hypertension, and vascular complications in diabetes.

7. VASCULAR SMOOTH MUSCLE CELLS

Smooth muscle cells in vivo

Histology.

Function.

Culture of smooth muscle cells

Isolation, identification and culturing of smooth muscle cells.

Smooth muscle cell media.

Phenotypic modulation of smooth muscle cells in culture (including contractile protein expression, Na⁺ pump activity, receptor changes and extracellular matrix formation).

Smooth muscle cell signal transduction

Signaling pathways (including the role of calcium, protein kinase C, tyrosine kinase and cyclic AMP).

Smooth muscle cell agonists (including ATP, serotonin, angiotensin II, endothelin, α_1 -adrenergic agonists, prolactin, atrial natriuretic polypeptide, heparin, thrombin, nitric oxide and vasopressin).

Growth factors produced by smooth muscle cells (including platelet-derived growth factor, heparin-binding epidermal growth factor, fibroblast growth factor, transforming growth factor β_1 and insulin-like growth factor).

References

Berk BC. Vascular smooth muscle growth: autocrine growth mechanisms. *Physiol Rev* 2001;81:999-1030.

VSMCs exhibit several growth responses to agonists that regulate their function including proliferation, hypertrophy, endoreduplication, and apoptosis. This review discusses the autocrine and paracrine growth factors important for VSMC growth in culture and in vessels. Four mechanisms by which individual agonists signal are described: direct effects of agonists on their receptors, transactivation of tyrosine kinase-coupled receptors, generation of reactive oxygen species, and induction/secretion of other growth and survival factors. Additional growth effects mediated by changes in cell matrix are discussed.

Rivard A, Andres V. Vascular smooth muscle cell proliferation in the pathogenesis of atherosclerotic cardiovascular diseases. *Histol Histopathol* 2000;15:557-571.

This article reviews the different factors that are involved in the control of VSMC proliferation, especially in the context of cardiovascular disease. Therapeutic approaches that targeted specific cell-cycle control genes or growth regulatory molecules which effectively inhibited neointimal lesion formation are also discussed.

McCarthy NJ, Bennett MR. The regulation of vascular smooth muscle cell apoptosis. *Cardiovasc Res* 2000;45:747-755.

Apoptosis describes the morphological changes that identify a specific form of regulated cell death. This article reviews the role of apoptosis in the maintenance of vascular homeostasis. Specifically, it addresses the role of vascular smooth muscle cell death, how this may be regulated at the molecular level and whether any of these molecular mediators will provide targets for intervention in diseases such as atherosclerosis.

Williams B. Mechanical influences on vascular smooth muscle cell function. *J Hypertens* 1998;16:1921-1929.

This review focuses on an emerging field of cardiovascular research in which the direct effects of mechanical strain on VSM cells and isolated blood vessels in organ culture have been characterized, in vitro.

Delafontaine P. Growth factors and vascular smooth muscle cell growth responses. *Eur Heart J* 1998;19 Suppl G:G18-22.

The accumulation of vascular smooth muscle cells plays an important role in the development of atherosclerotic plaques and in the restenotic process occurring after balloon angioplasty. This paper reviews the role of various growth factors and cytokines in vascular smooth muscle cell proliferation and migration.

8. MACROPHAGES

General considerations
Macrophage production.
Macrophage kinetics.
Macrophage function.

The role of macrophages in vascular disease
Chemoattractants.
Monocyte endothelial cell adherence.
Monocyte migration.
Macrophage activation.

Macrophage secretory products
Proteases and local tissue destruction.
Cytokines (including interleukin-1, interleukin-6, interleukin-8, interferon, tumor necrosis factor and colony stimulating factors).
Growth factors (including platelet-derived growth factor, fibroblast growth factor and transforming growth factor- β).

The role of macrophages in lipid metabolism

References

Plenz G, Robenek H. Monocytes/macrophages in atherosclerosis. *Eur Cytokine Netw* 1998;9:701-703.

In this chapter the role of the monocyte/macrophage in the genesis of the atherosclerotic plaque is discussed. As it is demonstrated, the pivotal role of the macrophage in atherosclerosis depends not only on its ability to handle lipids but also on its physical and secretory functions and its role as a mediator of inflammation.

Yla-Herttuala S. Macrophages and oxidized low density lipoproteins in the pathogenesis of atherosclerosis. *Ann Med* 1991;23:561-567.

This article describes the role of macrophages and oxidized low density lipoproteins in the pathogenesis of atherosclerosis. The clarification of this role offers an interesting possibility to reduce atherosclerosis by antioxidants, enzyme inhibitors and other compounds that protect LDL against oxidative damage and/or reduce the subsequent harmful effects of oxidized LDL on various cellular functions.

Rosenfeld ME, Palinski W, Yla-Herttuala S, Carew TE. Macrophages, endothelial cells, and lipoprotein oxidation in the pathogenesis of atherosclerosis. *Toxicol Pathol* 1990;18:560-571.

This review outlines the complex interactions between macrophages, endothelial cells, and lipoprotein oxidation in the pathogenesis of atherosclerosis. The basic steps of the

pathogenetic pathway including trapping of LDL, oxidation of LDL, monocyte chemotaxis, cell transformation into macrophage-derived foam cells, endothelial cell injury and formation of mural thrombi are summarized.

Aviram M, Fuhrman B. LDL oxidation by arterial wall macrophages depends on the oxidative status in the lipoprotein and in the cells: role of prooxidants vs. antioxidants. *Mol Cell Biochem* 1998;188:149-159.

All major cells in the arterial wall including endothelial cells, smooth muscle cells and monocyte derived macrophages can oxidize LDL. Oxidized LDL is highly atherogenic as it stimulates macrophage cholesterol accumulation and foam cell formation, it is cytotoxic to cells of the arterial wall and it stimulates inflammatory and thrombotic processes. This review article summarizes the above issues with an emphasis on the authors' own data.

DiCorleto PE. Cellular mechanisms of atherogenesis. *Am J Hypertens* 1993;6:314S-318S.

The interactions of endothelial cells, smooth muscle cells, and monocyte-derived macrophages as well as the role of thrombin, monocyte adhesion proteins and platelet-derived growth factor in atherogenesis has been the focus of great interest over the past decades. The resultant information is summarized in this brief review.

9. PLATELETS

General considerations

Platelet production and structure.

Platelet kinetics and life span.

Platelet membrane glycoproteins.

The role of platelets in vascular disease

Adhesion.

Aggregation.

Secretion, including dense bodies, alpha granules, platelet specific proteins (platelet factor 4, β -thromboglobulin, platelet-derived growth factor and thrombospondin).

Inhibition of secretion.

Biochemistry of platelet activation and inhibition

The importance of thromboxane.

Other agonists of platelet activation (including thrombin, collagen, ADP, epinephrine, platelet activating factor and ristocetin).

Platelet inhibitors (including aspirin, indomethacin and sulindac, phenylbutazone and sulfinpyrazone, nonsteroidal anti-inflammatory drugs, dipyridamole, prostacyclin, thromboxane synthetase inhibitors, thromboxane receptor antagonists, ticlopidine and glycoprotein IIb-IIIa inhibitors).

Platelet interactions with coagulant proteins

Coagulation proteins in platelets (including fibrinogen, factor V, von Willebrand factor, high-molecular weight kininogen, factor XI, factor XIII and plasma protease inhibitors).

Platelet contribution to the coagulation mechanism (including contact activation and factor X).

References

Rendu F, Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. *Platelets* 2001;12:261-273.

Although anucleated, blood platelets are highly organized cells rich in different types of organelles. Dense granules contain small non-protein molecules that are secreted to recruit other platelets. alpha-Granules contain large adhesive and healing proteins. Lysosomes contain hydrolases able to eliminate the circulating platelet aggregate. Granules' constituents, secretion and functions as well as typical platelet disorders resulting from a storage granule abnormality are described in this review article.

Savage B, Cattaneo M, Ruggeri ZM. Mechanisms of platelet aggregation. *Curr Opin Hematol* 2001;8:270-276.

This review focuses on recent developments in elucidating the mechanisms that regulate platelet aggregation. The role of platelet receptors for collagen, von Willebrand factor, thrombin and adenosine diphosphate is briefly reviewed.

Sachais BS. Platelet-endothelial interactions in atherosclerosis. *Curr Atheroscler Rep* 2001;3:412-416.

This article reviews recent evidence showing how the interaction between platelets and endothelial cells may play an important role in the pathogenesis of atherosclerosis, suggesting an underappreciated potential locus for pharmacologic intervention.

Bennett JS. Novel platelet inhibitors. *Annu Rev Med.* 2001;52:161-84.

This review addresses our current understanding of platelet function and how this information has been applied to the discovery of novel platelet inhibitors. Platelet inhibitors include inhibitors of prostaglandin-stimulated platelet activation, inhibitors of ADP-mediated platelet activation, phosphodiesterase inhibitors, inhibitors under development (CD39/ATP diphosphohydrolase and thrombin receptor inhibitors) and antagonists of ligand binding to $\alpha\text{IIb}\beta\text{3}$. The evidence on the efficacy of each platelet inhibitor is summarized.

Oforu FA. The blood platelet as a model for regulating blood coagulation on cell surfaces and its consequences. *Biochemistry (Mosc)* 2002;67:47-55.

This review is divided into three sections. The first section considers the contributions of platelet-derived and plasma-derived reactants to prothrombin activation on platelets. The second section briefly reviews the mechanisms of platelet activation and the critical role of platelet activation in hemostasis. The third section reviews some of the pathological consequences that can arise from inadequate regulation of platelet activation.

10. RESPONSE OF THE ARTERIAL WALL TO INJURY AND INTIMAL HYPERPLASIA

General considerations

Degrees of vascular injury.

General characteristics of intimal hyperplasia (including its differentiation from restenosis).

Types of injury resulting in intimal hyperplasia

Angioplasty, stenting, endarterectomy.

Vein grafting.

Prosthetic grafting.

The three-wave model of intimal hyperplasia

Medial smooth muscle cell proliferation (including the role of platelet-derived growth factor, basic fibroblast growth factor and angiotensin II).

Smooth muscle cell migration (including the role of extracellular matrix, platelets, migratory factors and the endothelium).

Intimal expansion (including the regulation of the extent of intimal hyperplasia).

Prospects for control of intimal hyperplasia

Surgical technique.

Promoting endothelialization.

Pharmacologic control of smooth muscle cell activity (including systemic and local drug delivery techniques).

Brachytherapy.

Strategies for the future (including antibodies to growth factors, antisense nucleotides, gene therapy etc).

References

Newby AC, Zaltsman AB. Molecular mechanisms in intimal hyperplasia. *J Pathol* 2000;190:300-309.

The underlying causes of intimal hyperplasia are migration and proliferation of vascular smooth muscle cells provoked by injury, inflammation, and stretch. This review discusses, at a molecular level, both the final common pathways leading to smooth muscle migration and proliferation and their (patho)-physiological triggers. It emphasizes the key roles played by growth factors and extracellular matrix-degrading metalloproteinases, which act in concert to remodel the extracellular matrix and permit cell migration and proliferation.

Purcell C, Tennant M, McGeachie J. Neo-intimal hyperplasia in vascular grafts and its implications for autologous arterial grafting. *Ann R Coll Surg Engl* 1997;79:164-168.

In this article the structure and development of neointimal hyperplasia in vascular grafts, both venous and arterial, are reviewed briefly. The clinical outcomes of various arterial grafts that are now being used, including the radial, the internal mammary and the

gastroepiploic arteries, as well as the underlying cell biology of their adaptation to the grafted environment are also reviewed.

Davies MG, Hagen PO. Pathobiology of intimal hyperplasia. Br J Surg 1994;81:1254-1269.

Intimal hyperplasia may be defined as the abnormal migration and proliferation of vascular smooth muscle cells with associated deposition of extracellular connective tissue matrix. In this article, the pathology of intimal hyperplasia is reviewed with particular attention to its physiology, pharmacology, cell biology and molecular biology.

Neville RF, Sidawy AN. Myointimal hyperplasia: basic science and clinical considerations. Semin Vasc Surg 1998;11:142-148.

The development of the intimal hyperplasia at the outflow anastomosis of a prosthetic bypass or in autogenous saphenous vein bypass placed in the arterial system is responsible for most bypass failures. This article reviews current knowledge on the pathogenesis of myointimal hyperplasia and addresses possible therapeutic considerations for the future.

Tennant M, Dilley RJ, McGeachie JK, Prendergast FJ. Histogenesis of arterial intimal hyperplasia and atherosclerosis. Aust N Z J Surg 1990;60:79-85.

This article briefly reviews the histological evidence for the genesis of intimal hyperplasia and atherosclerosis in arteries. It concentrates upon the origin, structure, behaviour and interactions of vascular smooth muscle cells in the intimal (subendothelial) layer.

11. ATHEROSCLEROSIS: THEORIES OF ETIOLOGY AND PATHOGENESIS

1. Atherosclerotic lesions
 - Fatty streaks.
 - Gelatinous plaques.
 - Fibrous plaques.
 - Complicated plaques.
2. Theories of atherogenesis
 - Lipid hypothesis.
 - Thrombogenic hypothesis.
 - Mesenchymal hypothesis.
 - Monoclonal hypothesis.
 - Response to injury hypothesis.
3. Lesion arrest and regression
 - Risk factor modification.
 - Modification of the plaques.

References

1. Tegos TJ, Kalodiki E, Sabetai MM, Nicolaides AN. The genesis of atherosclerosis and risk factors: a review. *Angiology* 2001;52:89-98.

In this review the microscopic appearance of the normal arterial wall, the definition of atherosclerosis and the five theories of atherogenesis are described (the lipid theory, the hemodynamic theory, the fibrin incrustation theory, the nonspecific mesenchymal hypothesis and the response to injury hypothesis). The classification of the atherosclerotic lesions according to Stary (types I-VI) as well as the epidemiology and the role of various risk factors are presented in detail.

2. Willeit J, Kiechl S. Biology of arterial atheroma. *Cerebrovasc Dis* 2000;10 Suppl 5:1-8.

This review article provides insights into the complex biology of arterial atheroma and the etiologic peculiarities of advanced complicated plaques. This knowledge may serve as a basis for identifying high-risk subjects and for novel vascular prevention strategies with focus on plaque stabilization and antithrombotic/anticoagulant measures.

3. Hegele RA. The pathogenesis of atherosclerosis. *Clin Chim Acta* 1996;246:21-38.

Pathogenesis of atherosclerosis is reviewed including genetic factors, environmental factors, pathological stages and cell types involved in the disease process. Therapeutic implications of this knowledge are also briefly reviewed.

4. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr, Rosenfeld ME, Schwartz CJ, Wagner WD, Wissler RW. A definition of advanced types of

atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* 1995;92:1355-1374.

This report describes the characteristic components and pathogenic mechanisms of the various advanced atherosclerotic lesions. An attempt is also made to correlate the appearance of lesions noted in clinical imaging studies with histological lesion types and corresponding clinical syndromes.

5. Dzau VJ. Pathobiology of atherosclerosis and plaque complications. *Am Heart J* 1994;128:1300-1304.

Endothelial dysfunction, which results from biochemical and hemodynamic stresses associated with cardiovascular risk factors, causes an imbalance in the expression of vasodilating and vasoconstricting substances, as well as excess production of chemoattractant molecules and growth factors. The role of these parameters in the process of atherosclerosis is briefly described.

12. HISTOPATHOLOGIC FEATURES OF NONARTERIOSCLEROTIC DISEASES OF THE AORTA AND ARTERIES

Degenerative changes of the aorta and arteries

Age-related changes in the aorta.

Aortic dissection.

Heritable disorders of connective tissue (including Marfan's syndrome and Ehlers-Danlos syndrome).

Acquired structural defects

Cystic adventitial disease.

Developmental or acquired structural abnormalities of arteries

Fibromuscular dysplasia

Inflammatory conditions of the aorta and arteries

Vasculitis.

Syphilitic aortitis.

Inflammatory aortic aneurysms and retroperitoneal fibrosis.

Rheumatoid aortitis.

Seronegative spondyloarthritides.

Takayasu's aortitis.

Giant cell aortitis.

Infectious aortitis.

Collagen vascular diseases.

Scleroderma.

Giant cell arteritis.

Polyarteritis nodosa.

Allergic granulomatosis and angiitis.

Polyangiitis overlap syndrome.

Thromboangiitis obliterans.

Ergot-alkaloid associated arterial disease.

References

Pyeritz RE. The Marfan syndrome. *Annu Rev Med* 2000;51:481-510.

This chapter briefly reviews the historical evolution of this heritable disorder of connective tissue and related conditions, discusses the important developments of the past few years, and suggests where progress is most needed in the immediate future.

Luscher TF, Lie JT, Stanson AW, Houser OW, Hollier LH, Sheps SG. Arterial fibromuscular dysplasia. *Mayo Clin Proc* 1987;62:931-952.

This is a comprehensive review of fibromuscular dysplasia including its pathology, pathogenesis, natural history, clinical presentation, diagnosis and treatment.

Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. *J Clin Pathol* 2002;55:481-486.

Takayasu arteritis is a well known yet rare form of large vessel vasculitis. This review details the history, clinical features, differential diagnoses, classification, and immunology of the disorder. Current evidence-based treatments are also presented and discussed.

Levine SM, Hellmann DB. Giant cell arteritis. *Curr Opin Rheumatol* 2002;14:3-10.

This review paper summarizes myriad basic science studies on the pathogenesis of giant cell arteritis. It also reviews the expanding knowledge of the epidemiology, clinical presentation, diagnosis and treatment of this systemic vasculitis.

Aqel MB, Olin JW. Thromboangiitis obliterans (Buerger's disease). *Vasc Med* 1997;2:61-66.

Thromboangiitis obliterans (Buerger's disease) is a nonatherosclerotic segmental inflammatory obliterative disease that most commonly affects the small- and medium-sized arteries and veins in both upper and lower extremities. The outline of Buerger's disease is described in this article.

13. REGULATION OF VASOMOTOR TONE AND VASOSPASM

General considerations

Regulation of vasomotor tone (including the role of mechanical forces, blood elements, vasoactive substances and ions).

Definition of vasospasm and its role in atherogenesis.

Experimental models for the study of blood vessel contractile responses (including the muscle bath, ex vivo perfusion devices, angiography, cell culture and fresh vascular smooth muscle cells).

Vasoconstriction

Molecular mechanisms of vasoconstriction.

Mediators of vascular smooth muscle contraction.

Vasorelaxation

Molecular mechanisms of vasorelaxation.

Mediators of vascular smooth muscle relaxation.

References

Fields CE, Makhoul RG. Vasomotor tone and the role of nitric oxide. *Semin Vasc Surg* 1998;11:181-192.

This review describes the physiology and biochemistry of NO as it relates to the control of vasomotor tone. Methods of measuring NO in basic science and clinical settings are outlined, and the derangements of endothelial NO production and release (endothelial dysfunction) in pathophysiologic and disease states are discussed. Potential therapies aimed at preserving endothelial function and augmenting NO production are also reviewed.

De Artinano AA, Gonzalez VL. Endothelial dysfunction and hypertensive vasoconstriction. *Pharmacol Res* 1999;40:113-124.

This review article discusses several of the mechanisms which may undergo change and substantiate the endothelial dysfunction which accompanies experimental arterial hypertension and arterial hypertension in humans. The synthesis and effect of nitric oxide and endothelin as well as the production of free radicals and vasoconstrictor peroxides is also analyzed.

Gutstein WH. Vasospasm, vascular injury, and atherogenesis: a perspective. *Hum Pathol* 1999;30:365-371.

Based on early work by the author and a selective review of the literature, evidence is presented to show how a common cardiovascular event, vasospasm, may be one of the factors responsible for vessel wall injury, producing a substantial arteriopathy in the very vessel in which it occurs.

Woodman OL. Modulation of vasoconstriction by endothelium-derived nitric oxide: the influence of vascular disease. Clin Exp Pharmacol Physiol 1995;22:585-593.

The endothelium makes a significant contribution to the regulation of vascular tone through the release of potent vasodilator agents such as nitric oxide (NO) and prostacyclin (PGI₂) as well as vasoconstrictor compounds such as endothelin. This article describes the mechanisms underlying these functions and their impact on vascular disease.

Frelin C. Mechanisms of vasoconstriction. Am Heart J 1991;121:958-960.

The contractility of vascular smooth muscle cells is controlled in a complex manner by both extracellular and intracellular messages. This review describes briefly each step of these signalling pathways which are possible sites for potential therapeutic interventions.

14. VENOUS SYSTEM OF THE LOWER EXTREMITIES: PHYSIOLOGY AND PATHOPHYSIOLOGY

1. Anatomy

- The superficial system of veins.
- The deep system of veins.
- The perforating veins.
- Structure of venous wall.

2. Physiology

- Venous hemodynamics.
- Venous pressures.
- The calf muscle pump.
- The thoracoabdominal muscle pump.
- Venous tone.
- Venous endothelium.

3. Clinical tests of physiologic function of the venous system

- Ambulatory venous pressure.
- Arm-foot pressure differential.
- Ascending and descending venography.
- Air-plethysmography.
- Photoplethysmography.
- Duplex ultrasound.

4. Pathophysiology

- Varicose veins (epidemiology, pathology, pathophysiology).
- Chronic venous insufficiency (epidemiology, pathology, pathogenesis).

References

Nicolaides AN. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). *Circulation* 2000;102:E126-63.

This consensus document provides an up-to-date account of the various methods available for the investigation of chronic venous insufficiency of the lower limbs, with an outline of their history, usefulness, limitations and indications of which patients should be subjected to the tests and when and of what clinical decisions can be made.

Somjen GM. Anatomy of the superficial venous system. *Dermatol Surg* 1995;21:35-45.

This paper is aimed at providing basic anatomic information of the lower extremity venous system. It also highlights the new research areas and the changing concepts on the pathophysiology of varicose veins.

Marston WA. PPG, APG, duplex: which noninvasive tests are most appropriate for the management of patients with chronic venous insufficiency? *Semin Vasc Surg* 2002;15:13-20.

Numerous noninvasive tests including venous duplex ultrasound, photoplethysmography and air plethysmography have been described for assistance in the diagnosis and treatment of patients with chronic venous insufficiency. These tests are reviewed including the typical information obtained, the usefulness of this information, and the relevance for clinical management of patients with CVI. Based on the clinical class, recommendations for a noninvasive testing protocol are outlined.

Gschwandtner ME, Ehringer H. Microcirculation in chronic venous insufficiency. *Vasc Med* 2001;6:169-179.

In this review, the anatomy and physiology of the venous system and its pathophysiology are described. Theories regarding the possible causes of disturbances in venous microangiopathy as well as the recently discovered pattern of perfusion in microcirculation within and around venous ulcers are also discussed.

Schmid-Schonbein GW, Takase S, Bergan JJ. New advances in the understanding of the pathophysiology of chronic venous insufficiency. *Angiology* 2001;52 Suppl 1:S27-34.

Chronic venous insufficiency is inseparably linked to elevated venous pressure and is accompanied by vascular, dermal, and subcutaneous tissue damage and restructuring. Among several possible mechanisms (hypoxia, humoral stimulation), a shift in fluid shear stress from normal physiological levels and endothelial distension under the influence of elevated venous pressure may serve as trigger mechanisms for inflammation. The key role of inflammation in chronic venous insufficiency including its trigger mechanisms and consequences is summarized in this review.

15. STRUCTURE AND FUNCTION OF THE LYMPHATIC SYSTEM

Embryology

Structure and function

Peripheral lymphatic system.

Lymph nodes.

Central lymphatic system.

Cellular components of the lymphatic system.

Physiology

Lymph formation.

Lymph flow.

Lymph visualization

Lymphangiography.

Lymphoscintigraphy.

References

Swartz MA. The physiology of the lymphatic system. *Adv Drug Deliv Rev* 2001;50:3-20.

This paper presents an overview of the anatomy, physiology, and biology of the lymphatic system specifically relevant to lymphatic drug delivery. It briefly reviews the classic fluid and solute transport literature, and also examines the current research in lymphatic endothelial cell biology and tumor metastasis in the lymphatics because of the increasing potential for targeted delivery of immunomodulators, chemotherapeutics, and genetic material to specific lymph nodes.

Sallustio G, Giangregorio C, Cannas L, Vricella D, Celi G, Rinaldi P. Lymphatic system: morphofunctional considerations. *Rays* 2000;25:419-427.

This article reviews current knowledge of lymph node cellular architecture as well as of the structure and course of lymphatic vessels. The function of the lymphatic system is also summarized along with its response to pathologic processes.

Witte CL, Witte MH. Diagnostic and interventional imaging of lymphatic disorders. *Int Angiol* 1999;18:25-30.

Recent developments in diagnostic and interventional imaging of lymphatic disorders are reviewed. Several imaging techniques are presented, including lymphangioscintigraphy, magnetic resonance imaging, ultrasonography, fluorescent microangiolympography, and intradermal brominated fluorocarbon. The use of these techniques in the treatment of certain lymphatic disorders is also discussed.

Szuba A, Rockson SG. Lymphedema: anatomy, physiology and pathogenesis. *Vasc Med* 1997;2:321-326.

The authors review the anatomy and physiology of the lymphatic system. The current understanding of the pathophysiology of lymphedema is also discussed, including its congenital and acquired causes, pathophysiologic consequences and clinical results.

Stewart KC, Lyster DM. Interstitial lymphoscintigraphy for lymphatic mapping in surgical practice and research. *J Invest Surg* 1997;10:249-262.

The development of lymphoscintigraphy for surgical research and practice is reviewed. The characteristics of the radiopharmaceutical used, the technique of injection and imaging as well as the most common applications of these nuclear medicine techniques is discussed.

16. DIABETIC VASCULAR DISEASE

1. Insulin

- Structure.
- Synthesis.
- Mechanisms of action.
- Insulin as a growth factor.

Diabetes mellitus and peripheral vascular disease

Macrovascular disease.

Microvascular disease.

The diabetic foot.

References

Katabchi AE, Duckworth WC, Stentz FB. Insulin synthesis, proinsulin and C-peptides. In: Rifkin H, Porte D Jr (eds). Diabetes Mellitus: Theory and Practice. 4th ed. New York: Elsevier, 1990:71-88.

This section provides the reader with some basic knowledge on the structure of human insulin and the conversion sequence of proinsulin to insulin. The significance of this knowledge for the clinical practice is also discussed.

Standl E. Hyperinsulinemia and atherosclerosis. Clin Invest Med 1995;18:261-266.

The high prevalence of macrovascular disease in non-insulin-dependent diabetes appears to be related to insulin levels and to the degree of hyperinsulinemia as measured in the blood of these patients. The various components of the Metabolic syndrome or Syndrome X are presented in this review along with the suggested therapeutic strategies in these patients.

Tooke JE. Possible pathophysiological mechanisms for diabetic angiopathy in type 2 diabetes. J Diabetes Complications 2000;14:197-200.

This article reviews possible pathophysiological mechanisms for diabetic angiopathy in type 2 diabetes. The key role of oxidative stress, endothelial function, and insulin resistance in this process is emphasized.

Schaper NC, Nabuurs-Franssen MH, Huijberts MS. Peripheral vascular disease and type 2 diabetes mellitus. Diabetes Metab Res Rev 2000;16 Suppl 1:S11-5.

In this review potential mechanisms for the high prevalence and altered distribution of peripheral vascular disease in patients with type 2 diabetes are explored. It is hypothesized that the metabolic abnormalities in the prediabetic phase predispose to a more distal and aggressive atherosclerosis. Once diabetes has developed this process is accelerated due to chronic hyperglycaemia. Furthermore, endothelial damage, non-

enzymatic glycosylation and polyneuropathy could lead to impaired vascular remodelling and collateral formation.

Shaw JE, Boulton AJ. The pathogenesis of diabetic foot problems: an overview. *Diabetes* 1997;46 Suppl 2:S58-61.

Diabetic peripheral neuropathy and peripheral vascular disease have been recognized as the most important etiologic factors of diabetic foot problems. The complex interplay between these abnormalities and a number of other contributory factors, such as altered foot pressures, limited joint mobility, glycemic control, ethnic background, and cardiovascular parameters is presented in this brief review article.

6. Akbari CM, LoGerfo FW. Microvascular Changes in the Diabetic Foot. in *The Diabetic Foot* (Veves A, Giurini J, LoGerfo FW eds.) Humana, Totowa, NJ, 2002, pp 99-112

This summarizes the complex interaction of neuropathy and vascular disease, including an explanation of the neuroinflammatory response and its role in the pathogenesis of ulceration.

17. PLASMA LIPOPROTEINS AND VASCULAR DISEASE

PHYSIOLOGY

Structure of lipoproteins.
Categories of lipoproteins.
Lipoprotein metabolism.

PATHOPHYSIOLOGY

Abnormal chylomicron metabolism.
Abnormal VLDL metabolism.
Abnormal LDL metabolism.
Abnormal HDL metabolism.

THERAPEUTIC INTERVENTIONS

Diet.
Drug therapy.
Surgical therapy.

THE RELATIONSHIP OF LIPOPROTEINS TO ATHEROGENESIS AND CLINICAL VASCULAR DISEASE

The role of LDL in atherogenesis.
The role of VLDL and chylomicron remnants in atherogenesis.
The role of HDL in atherogenesis.
The relationship of lipoproteins to clinical vascular disease.

References

Ginsberg HN. Lipoprotein physiology. *Endocrinol Metab Clin North Am* 1998;27:503-519.

This review article describes in detail the composition and transportation of lipoproteins and apolipoproteins, including a discussion of cellular receptors and the enzymes relevant to lipoprotein metabolism.

Batiste MC, Schaefer EJ. Diagnosis and management of lipoprotein abnormalities. *Nutr Clin Care* 2002;5:115-123.

This article provides the reader with an update on the current status of the diagnosis and management of lipid disorders. The guidelines of the National Cholesterol Education Program Adult Treatment Panel III are presented including the current recommendations for treatment by diet and drugs.

Kruth HS. Lipoprotein cholesterol and atherosclerosis. *Curr Mol Med* 2001;1:633-653.

This article reviews the pathways of cholesterol entry and removal, the metabolism, and the physical changes of cholesterol in the vessel wall. How these processes are believed to contribute to cholesterol buildup in atherosclerotic plaques is discussed.

de Winther MP, Hofker MH. New mouse models for lipoprotein metabolism and atherosclerosis. *Curr Opin Lipidol* 2002;13:191-197.

Mouse models have greatly advanced our understanding of the pathology associated with altered lipoprotein levels, including cellular uptake, intracellular metabolism, cellular efflux mechanisms and transcriptional regulation. This review article describes progress in all of these areas and shows that animal models are likely to remain important to our view of gene function in the context of the whole organism.

Breslow JL. Genetics of lipoprotein abnormalities associated with coronary artery disease susceptibility. *Annu Rev Genet* 2000;34:233-254.

This review discusses the genetic basis of the principal lipoprotein abnormalities associated with coronary heart disease susceptibility in the general population. Individual sections discuss genes regulating LDL cholesterol, HDL cholesterol, and triglyceride levels. A section is included on the effects of the common apo E genetic variation on lipoprotein levels, as well as sections on the genetic regulation of lipoprotein(a) levels, genes regulating the inverse relationship between triglyceride-rich lipoproteins and HDL cholesterol levels, and our current understanding of the genetic basis of familial combined hyperlipidemia.

18. CIGARETTE SMOKING AND VASCULAR DISEASE

Smoking and the development of atherosclerosis

The effects of smoking on endothelial cells.

The effects of smoking on plasma lipoproteins.

The effects of smoking on platelet function.

The effects of smoking on white blood cells.

Pharmacology of nicotine

Pharmacokinetics.

Mechanisms of action.

References

Michael Pittilo R. Cigarette smoking, endothelial injury and cardiovascular disease. *Int J Exp Pathol* 2000;81:219-230.

This review concentrates on new evidence regarding the precise components of cigarette smoke responsible for the relationship between cigarette smoking and cardiovascular disease as well as the mechanisms by which they exert their effect.

Villablanca AC, McDonald JM, Rutledge JC. Smoking and cardiovascular disease. *Clin Chest Med* 2000;21:159-172.

The relationships between smoking and cardiovascular disease result from multiple mechanisms that interact to contribute to atherosclerosis, vascular injury, thrombosis, and vascular dysfunction. This article reviews our current understanding of how smoking contributes to the genesis and progression of these disorders.

Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. *Vasc Med* 1998;3:21-28.

This article reviews the mechanisms of arterial wall damage caused by smoking. Several products of tobacco combustion, including nicotine, free radicals and aromatic compounds, have been shown to cause release of catecholamines, endothelial injury, oxidation of LDL, increase of plasma fibrinogen and alteration of platelet activity. All these proatherogenic effects of smoking are summarized in this paper.

Benowitz NL. The role of nicotine in smoking-related cardiovascular disease. *Prev Med* 1997;26:412-417.

This article review current evidence showing that nicotine contributes, via its hemodynamic effects, to acute cardiovascular events. However, the effects of nicotine are much less important than are the prothrombotic effects of other products of tobacco combustion. Another issue that is emphasized is that the dose response for cardiovascular events of nicotine appears to be flat, suggesting that if nicotine is involved, adverse effects might be seen with relatively low-level cigarette exposures.

Krupski WC. The peripheral vascular consequences of smoking. *Ann Vasc Surg* 1991;5:291-304.

Nicotine and carbon monoxide produce acute cardiovascular consequences, including altered myocardial performance, tachycardia, hypertension, and vasoconstriction. Smoking injures blood vessel walls by damaging endothelial cells, thus increasing permeability to lipids and other blood components. Among metabolic and biochemical changes induced by smoking are a tendency for increased serum cholesterol, reduced high density lipoprotein, elevated plasma free fatty acids, elevated vasopressin, and a thrombogenic balance of prostacyclin and thromboxane A2. In addition to rheologic and hematologic changes from increased erythrocytes, leukocytes, and fibrinogen, smokers have alterations in platelet aggregation and survival that produce thrombosis. All of these interactive mechanisms by which smoking exerts its deleterious effects are summarized in this article.

19. COAGULATION AND DISORDERS OF HEMOSTASIS

1. Physiology

Basic mechanisms of coagulation (extrinsic/intrinsic pathways of coagulation, the role of platelets).

Natural anticoagulant mechanisms (antithrombin III, proteins C and S, heparin cofactor II).

Fibrinolysis.

2. Hypercoagulable states

Heparin-associated thrombocytopenia.

Antithrombin III deficiency.

Protein C and S deficiency.

Factor V Leiden mutation.

Lupus anticoagulant/antiphospholipid syndrome.

Abnormalities of fibrinolysis.

Abnormal platelet aggregation.

Disseminated intravascular coagulation.

3. Bleeding disorders

Hemophilia A.

Hemophilia B.

von Willebrand disease.

Factor XI deficiency.

Factor V deficiency.

Factor VII deficiency.

Deficiencies of fibrinogen.

Platelet disorders.

4. Pharmacologic – nonpharmacologic interventions

Anticoagulant agents (structure, mechanism of action, complications, monitoring of the anticoagulant effect).

Heparin (unfractionated and low molecular weight).

Heparinoids (danaparoid).

Warfarin.

Hirudin.

Ancrod.

Antiplatelet agents (mechanism of action, complications).

Aspirin.

Dipyridamole

Ticlopidine.

Clopidogrel.

Abciximab.

Fibrinolytic agents (source, mechanism of action, complications, monitoring of the fibrinolytic effect).

First-generation agents (streptokinase and urokinase).
Second-generation agents (recombinant tissue plasminogen activator and antistreplase).
Third-generation agents (reteplase).
Nonpharmacologic interventions.
Mechanical measures (early ambulation, elastic stockings, electrical calf muscle stimulation, external pneumatic compression).
Vena cava filters.
Pulmonary embolectomy.

References

Hassouna HI. Laboratory evaluation of hemostatic disorders. *Hematol Oncol Clin North Am* 1993;7:1161-1249.

This article is abroad review presenting in detail the roles of coagulation testing in the management of bleeding and thrombotic disorders. Limitations of coagulation testing in defining the hemostatic state, interpretation of abnormal coagulation test results and the possible relationship to excessive bleeding and thrombosis are thoroughly discussed.

Whiteman T, Hassouna HI. Hypercoagulable states. *Hematol Oncol Clin North Am* 2000;14:355-377.

The focus of this article is understanding mechanisms in the hypercoagulable state that enhance and maintain the production of thrombin in circulating blood while preventing its progression to thrombosis. These mechanisms include reactions that produce thrombin from prothrombin, feedback loop mechanisms that affect the rate of thrombin production from prothrombin and the inactivation of thrombin in blood.

Van Cott EM, Soderberg BL, Laposata M. Activated protein C resistance, the factor V Leiden mutation, and a laboratory testing algorithm. *Arch Pathol Lab Med* 2002;126:577-582.

This report describes the protein C/protein S pathway, the significance of activated protein C resistance and the factor V Leiden mutation, and the clinical testing used to detect activated protein C resistance and the factor V Leiden mutation. A proposed laboratory testing algorithm is also provided.

Triplett DA. Coagulation and bleeding disorders: review and update. *Clin Chem* 2000;46:1260-1269.

This review considers laboratory tests used to evaluate coagulation, including prothrombin time, activated partial thromboplastin time, thrombin time, and platelet count. It discusses hereditary disorders of platelets and/or coagulation proteins that lead to clinical bleeding as well as acquired disorders, including disseminated intravascular coagulation and acquired circulating anticoagulants.

Frangos SG, Chen AH, Sumpio B. Vascular drugs in the new millennium. J Am Coll Surg 2000;191:76-92.

This review discusses pharmacologic therapy of cardiovascular disorders including antiplatelet agents, anticoagulants, thrombolytics, and claudication-alleviating drugs. Each drug category is introduced with a brief review of the current "gold standard" medication, with emphasis on the limitations and weaknesses that the newer agents have been designed to overcome.

20. BLOOD RHEOLOGY AND THE MICROCIRCULATION

Blood rheology

Definitions of rheologic parameters (shear stress, shear rate, viscosity, Newtonian fluid, non-Newtonian fluid, yield stress, Hagen-Poiseuille law, Reynold's number).

Measurement of viscosity (rotating cylindrical viscometers and the cone on plate viscometers).

Viscosity of plasma.

Viscoelastic properties of erythrocytes and leukocytes.

Viscosity of blood.

Effects of vessel diameter on the viscosity of blood.

Microcirculation

Topographic features.

Measurement of microvascular hemodynamics (microvessel pressures, microvessel blood flow).

Pressure-flow relations in the microcirculation.

Microvessel hematocrit and apparent viscosity.

Blood flow through bifurcations or branch points.

Leukocyte-endothelial cell adhesion.

Capillary blood flow.

Effect of red cell concentration on oxygen transport.

Regulation of blood flow in the microcirculation (local regulation, nervous regulation, humoral and biochemical regulation).

Capillary-lymphatic dynamics, transport and exchange.

References

Fagrell B, Intaglietta M. Microcirculation: its significance in clinical and molecular medicine. *J Intern Med* 1997;241:349-362.

This article, written by experts in microcirculation, analyzes the significance of microcirculation in clinical and molecular medicine. The physiology and pathophysiology of this system are reviewed and future directions in the study of microcirculation are outlined.

Usami S. Development of hemorheology: perspective in instrumentation development. *Clin Hemorheol Microcirc* 2000;23:77-83.

In this article, recent instrumentation developments for the study of hemorheology and molecular biology are reviewed. New viscometers for blood viscometry, improved intravital microscope, fluorescence microscopy, digitized video microscopic techniques as well as laser confocal microscopy are presented in terms of recent developments and applications.

Koenig W, Ernst E. The possible role of hemorheology in atherothrombogenesis. *Atherosclerosis* 1992;94:93-107.

This article reviews the involvement of hemorheological and hemostatic mechanisms in thromboatherogenesis and explores the interactions between these factors and the traditional risk factors for atherosclerosis. elucidation of these mechanisms might lead to new preventive strategies as well as to therapeutic procedures in the management of atherosclerosis and associated thrombotic events.

Stoltz JF, Donner M. New trends in clinical hemorheology: an introduction to the concept of the hemorheological profile. Schweiz Med Wochenschr Suppl 1991;43:41-49.

Blood behaves like a non-Newtonian fluid exhibiting specific features with the probable existence of a plasticity threshold, a viscosity that varies as a function of shear rate and a non-homogeneous nature of the medium during flow. This paper discusses factors affecting blood viscosity and reviews hyperviscosity syndromes ensuing from disorders of these factors.

Carpentier PH. New techniques for clinical assessment of the peripheral microcirculation. Drugs 1999;59:17-22.

This article reviews current methods for clinical investigation of the cutaneous microcirculation. These methods are based mainly on laser Doppler and capillary microscopy and, combined with systems for digital image analysis, they allow quantification of the structure of the microvascular bed (quantitative appraisal of microangiopathies) and function (capillary haemodynamics and exchange).

21. DRUGS IN VASCULAR DISEASE

Anticoagulants (mechanism of action, clinical use, complications, monitoring of the anticoagulant effect).

Heparin (unfractionated and low molecular weight).

Heparinoids (danaparoid).

Warfarin.

Hirudin.

Ancrod.

Thrombolytic agents (source, mechanism of action, complications, monitoring of the fibrinolytic effect).

First-generation agents (streptokinase and urokinase).

Second-generation agents (recombinant tissue plasminogen activator and antistreplase).

Third-generation agents (reteplase).

Antiplatelet medications (mechanism of action, complications).

Aspirin.

Dipyridamole

Ticlopidine.

Clopidogrel.

Abciximab.

IV Claudication drugs (mechanism of action, clinical use, complications).

Pentoxifylline.

Dextran.

L-carnitine, L-propionylcarnitine.

Cilostazol.

Serotonergic agents (mechanism of action, clinical use, complications).

Vasodilator drugs (mechanism of action, clinical use, complications).

Direct acting drugs (papaverine, isoxuprine, cyclandelate).

α -adrenergic blockers (guanethidine, phenoxybenzamine, prazosin, tolazoline, phentolamine).

Prostaglandins (PGE, PGI).

β -stimulating drugs (nylidrin).

Calcium channel blockers (nifedipine, verapamil, diltiazem, amlodipine, felodipine, isradipine, nicardipine, nimodipine).

Nitrates (nitroprusside).

References

Frangos SG, Chen AH, Sumpio B. Vascular drugs in the new millennium. J Am Coll Surg 2000;191:76-92.

This review discusses pharmacologic therapy of cardiovascular disorders including antiplatelet agents, anticoagulants, thrombolytics, and claudication-alleviating drugs. Each drug category is introduced with a brief review of the current "gold standard" medication, with emphasis on the limitations and weaknesses that the newer agents have been designed to overcome.

Ginsberg JA, Crowther MA, White RH, Ortel TL. Anticoagulation therapy. Hematology (Am Soc Hematol Educ Program) 2001;:339-57.

A broad spectrum of issues related to anticoagulation therapy is presented in this article, including initiation and control of anticoagulation therapy, a comparison between unfractionated and low molecular weight heparin, and the management of the "problem patient" who requires anticoagulants.

Doggrell SA. Pharmacotherapy of intermittent claudication. Expert Opin Pharmacother 2001;2:1725-1736.

Several drugs are currently used for patients with intermittent claudication: pentoxifylline, cilostazol, naftidrofuryl, inhibitors of platelet aggregation (including nitric oxide from L-arginine or glyceryl trinitrate), anticoagulants (low molecular weight heparin, defibrotide) and intravenous or oral prostaglandins. The evidence supporting the use of these drugs is summarized by the author and new approaches to the treatment of intermittent claudication, including propionyl-L-carnitine and basic fibroblast growth factor, are outlined.

Jaff MR. Pharmacotherapy for peripheral arterial disease: emerging therapeutic options. Angiology 2002;53:627-633.

An overview of pharmacotherapy for peripheral arterial disease is provided by the author of this article. The properties of pentoxifylline and cilostazol are reviewed and new therapeutic opportunities offered by angiogenic growth factors are presented.

Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001;344:1608-1621.

This review focuses on risk-factor modification and antiplatelet therapies, as well as strategies for symptomatic relief in patients with peripheral arterial disease. Evaluation of patients with suspected peripheral arterial disease as well as evaluation and treatment of patients with proven peripheral arterial disease are also summarized.

22. SCIENTIFIC BASIS FOR BALLOON EMBOLECTOMY.

Mechanics of balloon embolectomy

Lateral wall pressure.

Balloon pressure versus lateral wall pressure.

Balloon-artery shear forces.

Histologic effects of embolectomy.

Determinants of lateral wall pressure and shear forces

Catheter size.

Brands of catheters.

Balloon eccentricity.

Fluid-filled versus gas-filled balloons.

Syringe size.

Velocity of catheter motion.

Blood in the vessel lumen.

Inflating balloons at rest and during catheter motion.

Balloon embolectomy induced injuries

References

Dobrin PB. Mechanisms and prevention of arterial injuries caused by balloon embolectomy. *Surgery* 1989;106:457-466.

This article reviews the spectrum of clinical injuries produced by balloon embolectomy. The concepts of lateral wall pressure and balloon-artery shear force are presented, and the histologic reactions to passage of embolectomy catheters are described. On the basis of the results of experimental investigations, technical recommendations are made regarding the performance of embolectomy in patients.

Jorgensen RA, Dobrin PB. Balloon embolectomy catheters in small arteries. IV. Correlation of shear forces with histologic injury. *Surgery* 1983;93:798-808.

The aim of this experimental study was to evaluate the character and time course of arterial injury caused by balloon embolectomy catheters. Shear forces of up to 30 gm caused no injury, while shear forces of 60-120 gm caused stripping of the endothelium which was completely repaired by myointimal proliferation within 6 months. Two hundred gram initial force caused intimal injury and fracturing of the internal elastic lamina, with the latter injury persisting even after 6 months.

Dobrin PB, Jorgensen RA. Balloon embolectomy catheters in small arteries. III. Surgical significance of eccentric balloons. *Surgery* 1983;93:402-408.

This study was undertaken to compare balloon eccentricity in air with that which occurs in arteries, to determine the influence of balloon eccentricity on shear force, and to estimate the injury potential of eccentric balloons. The presented data suggest that

balloon eccentricity in air is an accurate indicator of balloon eccentricity within arteries, that moderately eccentric balloons are acceptable for clinical use, but that extremely eccentric balloons may cause severe injury and should not be used in the operating room.

Dobrin PB. Balloon embolectomy catheters in small arteries. II. Comparison of fluid-filled and gas-filled balloons. *Surgery* 1982;91:671-679.

Balloon embolectomy catheters were studied in canine common carotid arteries (2 to 3 mm) in vitro to evaluate a technique of preventing excessive shear forces and to examine the effect of blood within the lumen. From these studies it is recommended that during embolectomy in patients the balloons be distended during the first half centimeter or centimeter of catheter withdrawal to prevent excessive shear forces and that residual blood in the vessel lumen proximal to the point of embolic obstruction be accepted without concern, provided adequate heparinization has been achieved.

Dobrin PB. Balloon embolectomy catheters in small arteries. I. Lateral wall pressures and shear forces. *Surgery* 1981;90:177-185.

This article presents data from balloon embolectomy experiments in 2 to 3 mm canine arteries in vitro. These data suggest that every effort should be made to achieve the low LWP since this strongly influences shear force; the smallest effective catheter should be used and that negligible benefit may be gained if catheters are withdrawn at moderate velocities.

23. BASIC PRINCIPLES UNDERLYING THE FUNCTION OF ENDOVASCULAR DEVICES.

Transluminal balloon angioplasty

Forces of transluminal vascular dilatation.

Mechanism of transluminal dilatation.

Characteristics of balloon construction (catheter pushability, trackability, crossability, balloon compliance).

Characteristics of catheter design.

Pathophysiology of the complications of transluminal dilation.

Endoluminal stents

Characteristics of balloon expandable stents.

Characteristics of self-expanding stents.

Coated stents.

Drug-eluting stents.

Parameters of proper stent deployment.

Complications of stent deployment.

Atherectomy

Characteristics of the Kensey catheter.

Characteristics of the Auth rotoblator.

Characteristics of the Simpson atherectomy catheter.

Characteristics of the transluminal extraction catheter.

Laser angioplasty

Laser physics.

Principles of dosimetry.

Characteristics of optical fibers.

Laser effects on target tissue (photothermal, photochemical, photoacoustic, nonlinear).

Specific laser systems (Nd:YAG laser, argon laser, excimer laser, CO₂ laser).

Intravascular ultrasound

Basic properties of sound.

Instrumentation of intravascular ultrasound.

Practical application of ultrasound.

Angioscopy

Principles of light transmission.

The angioscopic system.

References

Moore WS, Ahn SS (eds). Endovascular surgery (3rd edition). Philadelphia: WS Saunders Co: 2001, pp 48-86, 149-171.

Basic principles underlying the function of endovascular devices are discussed in these sections, including guidewires, catheters and sheaths, balloon angioplasty, peripheral atherectomy, vascular stents, thrombectomy catheters, endovascular grafting, angiосcopy and intravascular ultrasonography.

Haji-Aghaii M, Fogarty TJ. Balloon angioplasty, stenting, and role of atherectomy. *Surg Clin North Am* 1998;78:593-616.

An overview of endovascular interventions for the treatment of lower-extremity atherosclerotic disease is presented in this article. The indications, and results of balloon angioplasty, endoluminal stenting and transluminal atherectomy are discussed.

Ahn SS, Concepcion B. Current status of atherectomy for peripheral arterial occlusive disease. *World J Surg* 1996;20:635-643.

This article presents the unique features of four atherectomy devices: Simpson AtheroCath, Transluminal Extraction Catheter (TEC), Trac-Wright Catheter, and Auth Rotablator. The results, complications, and limitations reported by clinical investigators are discussed critically and realistically.

Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. *Circulation* 2001;103:604-616.

This review describes the rationale, technique, and interpretation of IVUS imaging in diagnostic and therapeutic applications. Special emphasis is placed on the impact of ultrasound in understanding atherosclerotic coronary disease and its management.

White JV, Eid I. Diagnostic and interventional angiосcopy. *Surg Clin North Am* 1998;78:539-559.

The diagnostic and therapeutic applications (angiосcopically guided luminal intervention) of angiосcopy are reviewed in this article, including advantages, indications and technical considerations.

24. VASCULAR GRAFTS

Vascular graft interfacial histology

Protein absorption.

Platelet adhesion.

Neutrophil infiltration.

Monocyte recruitment.

Endothelial cell and smooth muscle cell ingrowth.

Mechanisms of vascular graft healing

The role of platelets.

The role of macrophages.

The role of endothelial cells and smooth muscle cells.

Characteristics of grafts

Composition.

Porosity.

Durability.

Flexibility.

Compliance.

Modes of graft failure

Thrombogenicity.

Anastomotic pseudointimal hyperplasia.

Current vascular grafts

Aortic grafts (knitted Dacron grafts coated with albumin, gelatin or collagen, ePTFE grafts: characteristics, advantages, disadvantages).

Femoral-popliteal/tibial grafts (autogenous saphenous vein, ePTFE grafts, Dacron grafts, glutaraldehyde-stabilized human umbilical vein graft, homologous vein: characteristics, advantages, disadvantages).

Experimental biohybrid prostheses

Synthetic materials impregnated with antimicrobial agents.

Anticoagulant substances affixed to synthetic graft surfaces.

Synthetic grafts impregnated with growth factors.

Bioresorbable synthetic grafts

Bioresorbable grafts (polyglycolic acid, polyglactin 910, polydioxanone grafts).

Grafts of compound yarns containing both resorbable (polyglycolic acid, polyglactin 910, polydioxanone) and a nonresorbable (Dacron or polypropylene) material.

References

Pasquinelli G, Freyrie A, Preda P, Curti T, D'Addato M, Laschi R. Healing of prosthetic arterial grafts. *Scanning Microsc* 1990;4:351-362.

The healing of prosthetic arterial grafts in animals and in humans is described in this paper. New strategies and approaches, such as endothelial cell seeding, that have recently been attempted to improve the patency of synthetic vascular grafts are also outlined.

Greenwald SE, Berry CL. Improving vascular grafts: the importance of mechanical and haemodynamic properties. *J Pathol* 2000;190:292-299.

The importance of mechanical and hemodynamic factors for the development of intimal hyperplasia at the graft anastomotic site is analyzed in this article. Disturbed flow at the anastomosis leading to fluctuations in shear stress at the endothelium (a known cause of intimal hyperplasia in normal arteries), injury due to suturing and stress concentration at the anastomosis are explained in detail with equations, graphs and schematic representations.

Bos GW, Poot AA, Beugeling T, van Aken WG, Feijen J. Small-diameter vascular graft prostheses: current status. *Arch Physiol Biochem* 1998;106:100-115.

In this overview article, the strategies used to improve the patency of these small-diameter grafts, the current status in clinical trials, and further perspectives in the field of artificial vascular graft development are reviewed. It is concluded that, in view of recent developments in tissue engineering approaches, the future of small-diameter vascular prostheses looks promising.

Liu SQ. Biomechanical basis of vascular tissue engineering. *Crit Rev Biomed Eng* 1999;27:75-148.

Biomechanical engineering approaches can be used to reduce tensile stress and strain due to exposure to arterial blood pressure and to prevent eddy blood flow in vein grafts. In this article, the background, principles, clinical potentials, as well as the limitations of vascular biomechanical engineering are discussed.

Teebken OE, Haverich A. Tissue engineering of small diameter vascular grafts. *Eur J Vasc Endovasc Surg* 2002;23:475-485.

Tissue engineering, using either polymer or biological based scaffolds, represents the newest approach to overcoming limitations of small diameter prosthetic vascular grafts. This current review represents an overview about previous and contemporary studies in the field of artificial vascular conduits development regarding arterial and venous autografts, allografts, xenografts, alloplastic prostheses, and tissue engineering.

25. STATISTICS FOR THE VASCULAR SURGEON

Fundamental concepts

Sample versus population.

Random sampling.

Descriptive versus inferential.

Descriptive statistics

Data collection (nominal scale, ordinal scale, interval scale, ratio scale).

Frequency distribution, histogram, frequency polygon.

Location: measures of central tendency (arithmetic mean, median, mode), quartiles, deciles and percentiles.

Measures of variability and spread (minimum and maximum and range, variance, standard deviation).

Distribution curves (normal distribution, bimodal distribution), Kurtosis, outlier, skewness.

Inferential statistics

Standard error of mean, confidence intervals.

Significance tests, hypothesis testing, error of hypothesis testing, statistical power and sample size, p value, one-tail versus two-tail test).

Inference on means (student's t-test, comparison of means in paired and unpaired samples).

Inference on proportions (chi-square test, Fisher's exact test)

Regression and correlation

Nonparametric methods or distribution-free methods

Signed rank test (Wilcoxon).

Wilcoxon rank sum test.

Mann-Whitney U test.

Kruskal-Wallis test.

Life-table analysis

Kaplan-Meier curve.

Log rank test or Mantel-Haenszel test.

Meta-analysis (goals, pitfalls).

Evaluation of a new diagnostic test

Reliability.

Sensitivity, specificity, positive predictive value, negative predictive value, overall accuracy.

Receiver operating characteristic curve.

References

MacNeill IB, Umphrey GJ. Biostatistics. Kluwer Academic Publishers, 1987.
Lewis AE. Biostatistics. New York: Van Nostrand Reinhold, 1984.
R.H. Riffenburgh. Statistics in medicine. San Diego: Academic Press, 1999.
Khachatryan A and Linardakis N. Biostatistics and epidemiology. New York: McGraw-Hill, 1998.
Indrayan A, Sarmukaddam SB. Medical biostatistics. New York: Marcel Dekker, 2001.

26. ANEURYSMAL DISEASE OF THE ABDOMINAL AORTA

Histological changes

Extracellular matrix (collagen, elastin).

Cellular components – inflammatory infiltrates.

Genetics

Experimental models

Spontaneous animal models.

Pharmacologic models.

Dietary models.

Surgical models.

Causes of aneurysms

The role of proteases (elastases, collagenases, plasmin, matrix metalloproteinases) and proteases inhibitors (α -1 antitrypsin, tissue inhibitor of metalloproteinases).

The role of inflammation.

The role of autoimmunity.

The role of atherosclerosis.

The role of hemodynamics.

V. Potential for intervention based on pathophysiology.

References

van Vlijmen-van Keulen CJ, Pals G, Rauwerda JA. Familial abdominal aortic aneurysm: a systematic review of a genetic background. *Eur J Vasc Endovasc Surg* 2002;24:105-116.

This article gives an overview of research data on the genetic background of AAA. Based on the familial clustering of the AAA, reported in 11-19% of AAA patients, a gene mutation in one of the structural proteins of the connective tissue is expected. However, no specific genetic factor responsible for familial AAA has been identified yet.

Carrell TW, Smith A, Burnand KG. Experimental techniques and models in the study of the development and treatment of abdominal aortic aneurysm. *Br J Surg* 1999;86:305-312.

This article discusses animal models and experimental techniques that have been described in the investigation of the pathophysiology of AAA and in the development of improved endovascular surgical and pharmacological therapies. The advantages of these models and some of the problems encountered in extrapolating experimental findings to the human condition are also discussed.

Rehm JP, Grange JJ, Baxter BT. The formation of aneurysms. *Semin Vasc Surg* 1998;11:193-202.

Recent progress in our understanding of the pathogenesis of aneurysmal disease is summarized in this article. The role of immunology, biochemistry, cell biology, and genetic issues is reviewed with special emphasis on the role of the local inflammatory infiltrates and the destructive proteolytic enzymes.

Grange JJ, Davis V, Baxter BT. Pathogenesis of abdominal aortic aneurysm: an update and look toward the future. *Cardiovasc Surg* 1997;5:256-265.

This article reviews current knowledge on the pathogenesis of abdominal aortic aneurysm. The role of atherosclerosis, inflammation, matrix changes and proteolysis is specifically addressed.

Thompson RW, Parks WC. Role of matrix metalloproteinases in abdominal aortic aneurysms. *Ann N Y Acad Sci* 1996;800:157-174.

The finding that elastolytic MMPs, particularly MMP-9 and MMP-2, are expressed and produced in increased amounts in human aneurysm tissue, has led to the possibility that these enzymes might serve as rational targets for pharmacotherapy in this disease. The role of matrix metalloproteinases in abdominal aortic aneurysm disease as well as the therapeutic implications of this role are outlined in this review.

27. CEREBRAL BLOOD FLOW

Regulation of cerebral blood flow

Mechanical effects on cerebral blood flow.

Neurogenic coupling mechanisms in cerebral blood flow.

Local effects on cerebral blood flow.

Methods for evaluating cerebral blood flow

Experimental methods (pial artery diameter, hydrogen diffusion, radioactive microspheres, laser Doppler).

Clinical methods (Duplex ultrasound, transcranial ultrasound, xenon clearance, single photon emission cerebral tomography, magnetic resonance angiography, magnetic resonance spectroscopy, perfusion/diffusion MRI, positron emission tomography).

Clinical research areas in cerebral blood flow

Pharmacologic effects on cerebral blood flow.

Effects of anesthesia on autoregulation.

Neonatal cerebral blood flow.

Cerebral blood flow in altitude sickness.

Cerebral blood flow following cardiac arrest.

Head trauma and cerebral blood flow.

Hemodynamics of atherosclerotic cerebrovascular disease.

References

Wahl M, Schilling L. Regulation of cerebral blood flow--a brief review. *Acta Neurochir Suppl* (Wien) 1993;59:3-10.

Cerebral blood flow is largely independent of perfusion pressure when autoregulation is intact. The mechanisms of cerebral autoregulation are reviewed in this paper, including the role of local-chemical factors, endothelial factors, autacoids, and transmitters from perivascular nerves.

Griffiths PD, Hoggard N, Dannels WR, Wilkinson ID. In vivo measurement of cerebral blood flow: a review of methods and applications. *Vasc Med* 2001;6:51-60.

This article reviews the concepts of cerebral blood flow for the clinician involved in the management of patients with carotid stenosis and/or ischaemic stroke. Methods of assessing cerebral blood flow in vivo using nuclear medicine, magnetic resonance and X-ray computed tomography are described. Applications of magnetic resonance and X-ray computed tomographic methods are reviewed and illustrated by examples from the authors' radiological practice.

Young WL, Prohovnik I, Correll JW, Ostapkovich N, Ornstein E, Quest DO. A comparison of cerebral blood flow reactivity to CO₂ during halothane versus isoflurane anesthesia for carotid endarterectomy. *Anesth Analg* 1991;73:416-421.

The effects of isoflurane or halothane on cerebral blood flow (CBF) reactivity to changes in arterial carbon dioxide tension during carotid endarterectomy were compared using the intravenous method of ¹³³Xe-CBF determination. It is concluded that there is no significant difference between halothane and isoflurane in their effects on CO₂ reactivity in the mildly hypocapnic to normocapnic range.

Golding EM. Sequelae following traumatic brain injury. The cerebrovascular perspective. *Brain Res Brain Res Rev* 2002;38:377-388.

Although vascular damage is a key event, it remains a somewhat neglected component to the underlying degenerative processes that evolve following injury to the brain. The present review integrates the current knowledge of the vascular events proceeding injury to the brain, with an emphasis on how this impacts the control of vascular function and thus cerebral blood flow.

Derdeyn CP, Grubb RL Jr, Powers WJ. Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. *Neurology* 1999;53:251-259.

This article reviews the responses of the cerebral vasculature to reduced perfusion pressure, examines their association with stroke risk, presents various methods of hemodynamic assessment and discusses their clinical applications.

28. BASIC SCIENCE OF RENOVASCULAR HYPERTENSION

1. Anatomy of the renal vasculature

Arterial anatomy.
Venous anatomy.

2. Physiology of the renin-angiotensin system

Angiotensin peptides and the nephron.
Angiotensin peptides and the cardiovascular system.
Angiotensin peptides and the central nervous system.
Angiotensin peptides and the adrenals.

3. Mechanisms of renal autoregulation

The myogenic mechanism and angiotensin peptides.
Tubuloglomerular feedback and angiotensin peptides.
Vascular endothelial substances.
Renal nerves and function regulation.

4. Pathologic considerations

Atherosclerosis (etiology, pathology, pathophysiology).
Fibromuscular dysplasia (etiology, pathology, pathophysiology).
Developmental lesions (etiology, pathology).

5. Diagnostic studies (performance, diagnostic criteria, application and limitations, accuracy).

Screening studies for renovascular occlusive disease (rapid sequence excretory pyelogram, peripheral plasma renin assays, renal Duplex ultrasonography, renal arteriography).
Functional studies (isotope renography, renal vein renin assays, split renal function studies).

References

Welch WJ. The pathophysiology of renin release in renovascular hypertension. *Semin Nephrol* 2000;20:394-401.

This article reviews the pathophysiology of renin release in renovascular hypertension, including stimuli and mechanisms of release as well as factors modifying renin release.

Palmer BF. Impaired renal autoregulation: implications for the genesis of hypertension and hypertension-induced renal injury. *Am J Med Sci* 2001;321:388-400.

Autoregulation of the renal vasculature provides a mechanism by which renal function is maintained relatively constant despite variations in systemic blood pressure. Alterations in the autoregulatory response can have clinical consequences such as hypertension, hypertension-induced renal injury and increase in the serum creatinine concentration. The consequences of impaired renal autoregulation are discussed in this review.

Begelman SM, Olin JW. Fibromuscular dysplasia. *Curr Opin Rheumatol* 2000;12:41-47.

Fibromuscular dysplasia is an important cause of renovascular hypertension in young, predominantly female patients. This article presents the main characteristics of fibromuscular dysplasia, including pathologic classification, etiology, clinical manifestations, differential diagnosis and treatment.

Mitty HA, Shapiro RS, Parsons RB, Silberzweig JE. Renovascular hypertension. *Radiol Clin North Am* 1996;34:1017-1036.

This paper presents diagnostic imaging modalities of renovascular hypertension including captopril scintigraphy, angiography, Doppler sonography and MR angiography. The indications, advantages and disadvantages of each technique are discussed.

Bloch MJ. An evidence-based approach to diagnosing renovascular hypertension. *Curr Cardiol Rep* 2001;3:477-484.

Available tests for the diagnosis of renovascular hypertension can be divided into those that identify the functional consequences of a renal artery obstruction (angiotensin-converting enzyme inhibitor-augmented renography) and those that identify the anatomic presence of stenosis (duplex ultrasonography, magnetic resonance angiography, and contrast tomography angiography). After reviewing current evidence regarding the use of these techniques, the authors present a potential treatment algorithm.

29. BASIC MECHANISMS IN MESENTERIC ISCHEMIA

Anatomy

Normal arterial and venous anatomy of the mesenteric circulation.

Collateral circulation.

More frequently encountered anatomic variations.

Regulation of mesenteric blood flow

Intrinsic control of the mesenteric circulation (metabolic theory, myogenic theory).

Reactive and postprandial hyperemia.

Extrinsic control of the mesenteric circulation (neural mechanisms, hormonal mechanisms).

Intestinal ischemia

Histologic injury.

Biochemical – metabolic events.

Reperfusion injury

Formation of reactive oxygen species (redox reactions, enzyme-substrate reactions, activation/degranulation of inflammatory cells).

Mechanisms of reactive oxygen species cell and tissue injury.

Polymorphonuclear leukocytes in reperfusion injury.

V. New approaches to diagnosis and treatment of mesenteric ischemia/reperfusion.

1. Recent laboratory efforts in quantifying the effects of mesenteric ischemia-reperfusion (ICAM-1, ELAM-1, alkaline phosphatase).

2. New approaches to treatment of mesenteric ischemia/reperfusion (changes in the nature of the reperfusate, alterations in the adherence or activation of polymorphonuclear cells and the administration of pharmacologic scavengers of reactive oxygen species).

References

Rosenblum JD, Boyle CM, Schwartz LB. The mesenteric circulation. Anatomy and physiology. Surg Clin North Am 1997;77:289-306.

This article reviews the angiographic appearance of the major visceral arteries, the more common variants, their embryologic origins, and some of the most common sources of collateral flow. A brief review of the physiology of the mesenteric circulation is also provided, including a discussion of the intrinsic and extrinsic mechanisms of splanchnic blood flow control.

Matheson PJ, Wilson MA, Garrison RN. Regulation of intestinal blood flow. J Surg Res 2000;93:182-196.

This review summarizes the current understanding regarding the regulatory mechanisms of intestinal blood flow in fasted and fed conditions and during pathological stress. The role of absorbed nutrients, enteric nervous system effects and reflexes, gastrointestinal

hormones and peptides and local nonmetabolic and metabolic vasoactive mediators is discussed. Alterations of intestinal blood flow in pathologic conditions, including septic shock, hemorrhagic shock, cardiogenic shock and portal hypertension are also described.

Patel A, Kaleya RN, Sammartano RJ. Pathophysiology of mesenteric ischemia. Surg Clin North Am 1992;72:31-41.

Intestinal ischemia can result from a host of pathophysiologic disturbances and, in turn, may produce a variety of adverse local and systemic consequences. Mechanisms of ischemic injury and the central role of vasoconstriction are discussed.

Haglund U, Bergqvist D. Intestinal ischemia - the basics. Langenbecks Arch Surg 1999;384:233-238.

In this review the physiology of the intestinal circulation is briefly outlined, followed by a discussion of nonocclusive intestinal ischemia and reperfusion injury. The clinical causes, diagnostic process and therapeutic options of intestinal ischemia are also outlined.

Kurland B, Brandt LJ, Delany HM. Diagnostic tests for intestinal ischemia. Surg Clin North Am 1992;72:85-105.

The various diagnostic tests for intestinal ischemia are presented in this study. These include serum biochemical markers, peritoneal fluid analysis, tonometry, radionuclide imaging, laparoscopy, and endoscopic techniques. Newer techniques, including radionuclide-labeled antibodies, tonometry, and reflectance spectrophotometry, are also discussed.

30. HEMODYNAMIC BASIS OF PORTAL HYPERTENSION

Anatomy

Anatomy of the liver.

Anatomy of the portal circulation.

Anatomy of the hepatic arterial circulation.

Anatomy of the collateral circulation.

Regulation of hepatic blood flow

Regulation of the portal circulation.

Regulation of the hepatic arterial blood flow (intrinsic, extrinsic).

Hepatic artery:portal vein interactions.

Pathophysiology of portal hypertension

Increased intrahepatic resistance (pathology, pathophysiologic sequels).

Hyperdynamic circulation (definition, mechanisms, pathophysiologic sequels).

the role of increased circulating vasodilators (glucagon, prostacyclin, NO).

the role of reduced response to endogenous vasoconstrictors.

The role of the sympathetic nervous system.

The role of plasma volume.

Extrahepatic responses to portal hypertension

Cardiac and systemic hemodynamics.

Gastrointestinal effects.

References

Ekataksin W, Kaneda K. Liver microvascular architecture: an insight into the pathophysiology of portal hypertension. *Semin Liver Dis* 1999;19:359-382.

The liver microvascular architecture is described in detail in this paper. The implications of the microvascular structure for hepatic hemodynamics and portal hypertension are also discussed.

Rockey DC. Cellular pathophysiology of portal hypertension and prospects for management with gene therapy. *Clin Liver Dis* 2001;5:851-865.

The structural, cellular, and humoral factors involved in the regulation of sinusoidal blood flow in normal and injured liver are reviewed in this article. The role of the stellate cells and the modulation of their function by the endothelin and NO systems is discussed. These systems represent potential targets for gene therapy.

Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. *Pharmacol Ther* 2001;89:221-231.

This article presents an overview of the hyperdynamic circulation in cirrhosis. Based on the available data, the authors propose a two-phase pathogenesis of the hyperdynamic circulation of cirrhosis. Initially, passive vascular relaxation, and the resulting hyperdynamics, appear to be secondary to blood volume expansion. In the second, much more complex phase, active vasodilatation, associated with hyporesponsiveness to vasoconstrictors, especially in the splanchnic bed, increased portosystemic shunting, and the development of new vessels by angiogenesis likely are part of the explanation.

Thuluvath PJ, Yoo HY. Portal Hypertensive gastropathy. Am J Gastroenterol 2002;97:2973-2978.

An overview of portal hypertensive gastropathy is provided in this article, including its pathogenesis, diagnosis, clinical presentation and treatment.

Moller S, Bendtsen F, Henriksen JH. Splanchnic and systemic hemodynamic derangement in decompensated cirrhosis. Can J Gastroenterol 2001;15:94-106.

Patients with cirrhosis and portal hypertension exhibit characteristic hemodynamic changes with hyperkinetic systemic circulation, abnormal distribution of blood volume and neurohumoral dysregulation. The pathophysiologic aspects of these disorders are discussed in this article.

31. ANATOMY AND PHYSIOLOGY OF NORMAL ERECTION

Anatomy

Arterial anatomy.

Venous drainage.

Penile innervation.

Hemodynamics of normal erection

Causes of impotence

Cavernosal malfunction.

Venous or cavernosal leakage.

Arteriogenic impotence.

Diagnostic methods

Noninvasive sequence (penile brachial blood pressure index, penile plethysmographic pulse recording, pudental-evoked potentials, bulbo-cavernosal reflex time).

Artificial erection.

Dynamic infusion cavernosometry and cavernosography.

Ultrasonography.

Nocturnal penile tumescence.

Treatment of vasculogenic impotence

Drug therapy.

Small vessel reconstruction.

Venous interruption.

Prosthetics.

References

Simonsen U, Garcia-Sacristan A, Prieto D. Penile arteries and erection. *J Vasc Res* 2002;39:283-303.

The anatomy of the penile vasculature and the physiology of erection are reviewed in this paper. Risk factors for vasculogenic erectile dysfunction are also briefly discussed.

Moreland RB. Pathophysiology of erectile dysfunction: the contributions of trabecular structure to function and the role of functional antagonism. *Int J Impot Res* 2000;12 Suppl 4:S39-46.

At present, there are two major views regarding the pathophysiology of erectile dysfunction. In the first hypothesis, the oxygen tension-dependent changes in the penis during erection are proposed to impact corpus cavernosum structure by altering smooth muscle metabolism and connective tissue synthesis. The alternate hypothesis proposes that ED is the result of a metabolic imbalance between relaxatory and contractile processes within the trabecular smooth muscle such that contractile processes

predominate. In this review of the pathophysiology of ED, each hypothesis is examined and a synthesis devised incorporating both views.

Maggi M, Filippi S, Ledda F, Magini A, Forti G. Erectile dysfunction: from biochemical pharmacology to advances in medical therapy. *Eur J Endocrinol* 2000;143:143-154.

This article focuses on the main biochemical events leading to penile erection and detumescence as well as on the potential manipulation of these events for therapeutic purposes. The role of nitric oxide, cGMP, cAMP and phosphodiesterases is analyzed and potential pharmacologic interventions including papaverine, sildenafil and yohimbine are discussed.

Broderick GA. Evidence based assessment of erectile dysfunction. *Int J Impot Res* 1998;10 Suppl 2:S64-73; discussion S77-9.

The most commonly utilized diagnostic tests for erectile dysfunction are outlined in this monograph. These tests include nocturnal penile tumescence studies, somatosensory evoked potentials, bulbocavernosus reflex latency, corporal cavernosal smooth muscle electrical activity, penile plethysmography, penile blood pressures, penile brachial index, selective internal pudendal pharmacoangiography, Doppler sonography, dynamic infusion cavernosometry/cavernosography, nuclear washout radiography, and color duplex Doppler ultrasound.

DePalma RG. Vascular surgery for impotence: a review. *Int J Impot Res* 1997;9:61-67.

This review considers current and past results of vascular surgery in men with impotence failing to respond to medical treatment. Guidelines for case selection for vascular interventions as well as reporting criteria are suggested.

32. SKELETAL MUSCLE ISCHEMIA AND REPERFUSION: MECHANISMS OF INJURY AND INTERVENTION

Skeletal muscle energy metabolism

Normal skeletal muscle energy metabolism.

Skeletal muscle energy metabolism during ischemia.

Skeletal muscle energy metabolism during reperfusion.

Tissue injury in skeletal muscle ischemia/reperfusion

Histology.

Methods of assessment.

Pathophysiology of skeletal muscle ischemia/reperfusion

Endogenous free radical production by postischemic endothelial cells.

Recruitment and activation of neutrophils wielding free radicals and lytic enzymes (including the role of complement, arachidonic acid metabolites, platelet activating factor, cytokines, cell adhesion molecules).

Occlusion of microvascular beds secondary to endothelial cell swelling, perivascular tissue edema, failed endothelium-dependent vessel relaxation, adherence of activated neutrophils and microvascular thrombosis).

Interventional outline

Metabolic salvage.

Inhibition of free radical production during reperfusion.

Graded reoxygenation during reperfusion.

Leukopenic reperfusion.

Hypothermia during reperfusion.

Fibrinolysis, anticoagulation.

References

Defraigne JO, Pincemail J. Local and systemic consequences of severe ischemia and reperfusion of the skeletal muscle. *Physiopathology and prevention. Acta Chir Belg* 1998;98:176-186.

This article analyzes the local and systemic consequences of severe ischemia and reperfusion of the skeletal muscle. The mechanisms responsible for reperfusion injury as well as methods of prevention and treatment are also discussed.

Duran WN, Takenaka H, Hobson RW 2nd. Microvascular pathophysiology of skeletal muscle ischemia-reperfusion. *Semin Vasc Surg* 1998;11:203-214.

This article reviews the pivotal role of endothelium-leukocyte interactions and of cytokines in the genesis of postischemic damage in muscle. Clinical considerations and future directions based on research and practice are presented.

Gute DC, Ishida T, Yarimizu K, Korthuis RJ. Inflammatory responses to ischemia and reperfusion in skeletal muscle. *Mol Cell Biochem* 1998;179:169-187.

This article describes the cytologic and biochemical responses of skeletal muscle to ischemia and reperfusion injury. It is also discussed how an endogenous protective mechanism, ischemic preconditioning, may be exploited to limit postischemic skeletal muscle injury.

Rubin BB, Romaschin A, Walker PM, Gute DC, Korthuis RJ. Mechanisms of postischemic injury in skeletal muscle: intervention strategies. *J Appl Physiol* 1996;80:369-387.

This article reviews the mechanisms involved in the pathogenesis of skeletal muscle ischemia-reperfusion injury including oxidant generation, elaboration of proinflammatory mediators, infiltration of leukocytes, Ca^{2+} overload, phospholipid peroxidation and depletion, impaired nitric oxide metabolism, and reduced ATP production. Based on these mechanisms, rational intervention strategies may be proposed and implemented as potential treatments for skeletal muscle dysfunction associated with ischemia-reperfusion.

Pang CY, Forrest CR, Mounsey R. Pharmacologic intervention in ischemia-induced reperfusion injury in the skeletal muscle. *Microsurgery* 1993;14:176-182.

This article provides a concise review on the potential causes of ischemia-induced reperfusion injury and pharmacologic intervention in the skeletal muscle. The mechanism of ischemic preconditioning and its clinical applications for augmentation of skeletal muscle tolerance to prolonged ischemic insult are also discussed.

33. SPINAL CORD ISCHEMIA ASSOCIATED WITH HIGH AORTIC CLAMPING: METHODS OF PROTECTION

1. Anatomy of the blood supply to the spinal cord
2. Pathophysiology of spinal cord ischemia and reperfusion
 - Hemodynamic changes.
 - Ischemic injury.
 - Reperfusion injury.
 - Delayed onset paraplegia.
3. Methods of protection
 - Experimental results of spinal cord protection (including the role of cerebrospinal fluid drainage, systemic hypothermia, hypothermic perfusion, regional cooling, barbiturates, superoxide dismutase, calcium channel blockers, prostaglandins, papaverine, MK-801, monoclonal antibodies, flusol-DA, opiate antagonists, aminosteroids).
 - Clinical results of spinal cord protection (including the role of aortic cross-clamp time, reimplantation of intercostals arteries, bypass or shunt, evoked potentials, spinal fluid drainage, hypothermia).

References

Huynh TT, Miller CC 3rd, Safi HJ. Delayed onset of neurologic deficit: significance and management. *Semin Vasc Surg* 2000;13:340-4.

This review discusses the significance and management of delayed-onset neurologic deficit. The pathophysiology of delayed-onset neurologic deficit after thoracoabdominal aortic aneurysm repair, the various factors known to increase the risk of spinal cord ischemia, as well as the different intraoperative adjuncts to improve spinal cord protection are presented.

Cambria RP, Davison JK. Regional hypothermia with epidural cooling for spinal cord protection during thoracoabdominal aneurysm repair. *Semin Vasc Surg* 2000;13:315-324.

The authors present a method for providing regional cord hypothermia with epidural cooling during TAA repair. Technical considerations with epidural cooling and the clinical results obtained in their experience are discussed.

Coselli JS, LeMaire SA, Schmittling ZC, Koksoy C. Cerebrospinal fluid drainage in thoracoabdominal aortic surgery. *Semin Vasc Surg* 2000;13:308-314.

The purpose of this randomized clinical trial was to evaluate the impact of cerebrospinal fluid drainage (CSFD) on the incidence of spinal cord injury after extensive thoracoabdominal aortic aneurysm (TAAA) repair. Overall, CSFD resulted in an 80% reduction in the relative risk of postoperative deficits. The authors conclude that perioperative CSFD reduces the rate of paraplegia after repair of extent I and II TAAAs.

de Haan P, Kalkman CJ, Jacobs MJ. Pharmacologic neuroprotection in experimental spinal cord ischemia: a systematic review. *J Neurosurg Anesthesiol* 2001;13:3-12.

In this article, the literature on pharmacological neuroprotection in experimental SCI is systematically reviewed to assess the neuroprotective efficacy of the various agents. The results suggest that numerous agents may protect the spinal cord from transient ischemia. However, poor temperature management and lack of statistical power severely weakened the evidence. The authors conclude that clinical evaluation of pharmacological neuroprotection in surgical procedures that carry a risk of ischemic spinal cord damage is not justified on the basis of this analysis.

Robertazzi RR, Cunningham JN Jr. Intraoperative adjuncts of spinal cord protection. *Semin Thorac Cardiovasc Surg* 1998;10:29-34.

After a brief discussion of the etiology of spinal cord ischemia, the authors present several intraoperative interventions and strategies, which address the multifactorial nature of cord injury. The role of adequate distal aortic perfusion, cerebrospinal fluid drainage, pharmacological agents such as papaverine and steroids, as well as the role of circulatory arrest and profound hypothermia are analyzed.

34. ARTERIOVENOUS HEMODIALYSIS ACCESS

Anatomy

Snuff-box fistula.

Brescia-Cimino fistula.

Radial artery to antecubital vein (straight graft).

Radial artery to basilic vein-above elbow (straight graft).

Brachial artery-below elbow to antecubital vein (loop graft).

Brachial artery-below elbow to basilic vein-above elbow (loop graft).

Brachial artery-above elbow to axillary vein (C-shaped graft).

Basilic transposition.

Physiology

Resistance.

Velocity and volume.

Flow patterns.

Energy changes.

Pathophysiology

Local hemodynamics/pathophysiology (hemodynamic and structural changes in the proximal artery, the distal artery, the proximal vein and the distal vein).

Systemic hemodynamics/pathophysiology (determinants and consequences of the drop in total peripheral resistance).

Pathogenesis of complications

Thrombosis.

Infection.

Steal syndrome.

Pseudoaneurysm formation.

Venous hypertension.

References

Roy-Chaudhury P, Kelly BS, Narayana A, Desai P, Melhem M, Munda R, Duncan H, Heffelfinger SC. Hemodialysis vascular access dysfunction from basic biology to clinical intervention. *Adv Ren Replace Ther* 2002;9:74-84.

Venous stenosis and thrombosis as a result of venous neointimal hyperplasia are the major causes of hemodialysis vascular access dysfunction. This review describes the lesion of venous neointimal hyperplasia in human samples and in a pig model and suggests possible future directions for the development of effective local therapies for this condition.

Dikow R, Schwenger V, Zeier M, Ritz E. Do AV fistulas contribute to cardiac mortality in hemodialysis patients? *Semin Dial* 2002;15:14-17.

Potential fistula-related problems which may impact on patient survival include high fistula flow with hyperkinetic circulation and cardiac failure, low fistula flow with the risks of underdialysis and fistula thrombosis, vascular access infection with local or systemic manifestations, and possibly induction and maintenance of a microinflammatory state. All of these problems are briefly reviewed in this article.

Lavigne JE, Messina LM, Golding MR, Kerr JC, Hobson RW 2nd, Swan KG. Fistula size and hemodynamic events within and about canine femoral arteriovenous fistulas. *J Thorac Cardiovasc Surg* 1977;74:551-556.

The effects of diameters of canine femoral arteriovenous fistulas upon regional and central hemodynamics were determined to correlate fistula size with fistula flow, as well as changes in cardiac output, reversal of distal arterial flow, and distal venous hypertension. The study shows that there is a direct correlation between fistula size and cardiac output, a direct correlation between fistula size and venous hypertension and an inverse relation between fistula size and distal femoral artery flow and pressure.

Joseph S, Adler S. Vascular access problems in dialysis patients: pathogenesis and strategies for management. *Heart Dis* 2001;3:242-247.

This article describes the means of accessing the circulation for hemodialysis, the pathogenesis of access failure through progressive stenosis followed by thrombosis, methods of detecting access dysfunction before thrombosis, and therapeutic options. Although angiographic or surgical intervention remain the mainstays of management, medical treatments to decrease stenosis and delay thrombosis are currently under investigation.

Anderson CB, Allen BT, Sicard GA. Physiology and hemodynamics of vascular access. In Sommer BG, Henry ML, editors. *Vascular access for hemodialysis*. W.L. Gore & Associates, Inc. Pluribus Press, Inc. 1989;17-31.

Physiologic and hemodynamic issues related to the construction of a vascular access for hemodialysis are reviewed in this section. These issues provide the basis for the understanding, prevention and treatment of vascular access complications.

35. ARTERIAL AND VASCULAR GRAFT INFECTION

Etiology

Bacterial contamination at the time of graft implantation.

Hematogenic contamination.

Lymphogenic contamination.

Microbiology and immunology

Most commonly involved organisms.

The effect of graft material.

The effect of systemic and local immunosuppression.

Clinical presentation

Depending on the anatomic location.

Depending on the type of graft.

Depending on the infecting organism.

Diagnostic evaluation

Duplex ultrasonography.

Computed tomography.

Magnetic resonance imaging.

Nuclear medicine techniques.

Arteriography.

Endoscopy.

Prevention

Asepsis – antisepsis.

The role of prophylactic antibiotics.

Antibiotics bonded to the vascular graft.

Management

Aortic graft infection.

Femoropopliteal graft infection.

References

Williams GM. Complications of vascular surgery. Surg Clin North Am 1993;73:323-335.

Hemorrhage, early thrombosis of a graft or vessel nerve injury, graft infection, and renal failure are frustrating problems for vascular surgeons. All frequently arise from technical complications. Methods of avoiding these problems are discussed.

Earnshaw JJ. Methicillin-resistant Staphylococcus aureus: vascular surgeons should fight back. Eur J Vasc Endovasc Surg 2002;24:283-286.

This article addresses the problem of methicillin-resistant Staphylococcus aureus (MRSA) which is now the commonest cause of serious vascular wound and graft

infection. Preoperative, intraoperative and postoperative measures against MRSA infections are briefly reviewed.

Valentine RJ. Diagnosis and management of aortic graft infection. *Semin Vasc Surg* 2001;14:292-301.

This report summarizes the currently available methods of diagnosing and treating aortic graft infections. Available imaging techniques and complementary tests are presented, followed by a discussion of the therapeutic options which include graft excision and extra-anatomic revascularization or in situ replacement with autogenous vein, allograft or rifampin-bonded prosthesis.

Seeger JM. Management of patients with prosthetic vascular graft infection. *Am Surg* 2000;66:166-177.

This review discusses diagnosis and treatment of patients with prosthetic vascular graft infection, emphasizing the basic principles necessary for successful management of this complex problem. Basic information about the incidence, etiology, and bacteriology of prosthetic vascular graft infections is also be briefly reviewed.

Bandyk DF. Antibiotics-Why so many and when should we use them? *Semin Vasc Surg* 2002;15:268-274.

This article summarizes the indications and efficacy of antibiotic prophylaxis and treatment in vascular surgery. Well-established indications, as well as new applications for antibiotics in vascular surgery are discussed.

36. NEUROPATHIC AND BIOMECHANICAL ETIOLOGY OF FOOT ULCERATION IN DIABETICS

1. Classification of diabetic neuropathy

Mononeuropathies (isolated and multiple, cranial mononeuropathies).
Polyneuropathies (diabetic sensory polyneuropathy, proximal motor polyneuropathy, autonomic neuropathies).

2. Pathogenesis of diabetic neuropathy

Sorbitol accumulation.
The activated polyol pathway theory.
Changes in perineural and endoneurial vasculature and resultant ischemia of the nerve.
Hyperglycemia-related nonenzymatic glycosylation of the vasoneurosum and the endoneurial matrix.
The role of insulin.

3. Foot changes as they relate to neuropathy

Consequences of sensory dysfunction.
Consequences of motor dysfunction.
Consequences of autonomic dysfunction.

4. Foot biomechanics

Normal gait (stance and swing phases).
Abnormal foot biomechanics.
Charcot deformity.
Biomechanical changes caused by segmental amputations of the foot (hallux amputation, toe amputation, transmetatarsal ray amputations, Lisfranc and Chopart amputations).

5. Pathophysiology of diabetic foot ulceration

The role of the loss of protective sensation.
The role of the structural deformity of the foot.

References

Simmons Z, Feldman EL. Update on diabetic neuropathy. *Curr Opin Neurol* 2002;15:595-603.

The pathogenesis of diabetic neuropathy is multifactorial. There is increasing evidence to link abnormalities in the polyol pathway to the pathogenesis of diabetic neuropathy. In addition, there appear to be abnormalities of nerve regeneration and of sodium and calcium channels. Aldose reductase inhibitors, neurotrophic factors and vascular endothelial growth factor have shown promise for reversing neuropathy. Lamotrigine and bupropion represent new treatments for neuropathic pain. All this new information about the pathogenesis and treatment of diabetic neuropathy is summarized in this article.

Guyton GP, Saltzman CL. The diabetic foot: basic mechanisms of disease. Instr Course Lect 2002;51:169-181.

This article addresses the many synergistic factors that cause both ulceration and neuroarthropathy. These include dramatic alterations in all components of the peripheral nerves, the mechanical characteristics of bones and soft tissues, gait kinematics, the vasculature at both a microscopic and a macroscopic level, the immune system, and the fundamental processes of wound healing.

Cavanagh PR, Ulbrecht JS, Caputo GM. New developments in the biomechanics of the diabetic foot. Diabetes Metab Res Rev 2000;16 Suppl 1:S6-S10.

Biomechanical issues are now widely recognized as being important in the treatment of diabetic foot disease. This article summarizes recent advances in the understanding of the association between foot deformity and plantar pressure, the measurement of shear stress and the importance of neuropathy and callus in the pathogenesis of ulceration. Recent data on the biomechanical evaluation of surgery as well as the efficacy of unloading devices is also presented.

Frykberg RG, Armstrong DG, Giurini J, Edwards A, Kravette M, Kravitz S, Ross C, Stavosky J, Stuck R, Vanore J. Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. J Foot Ankle Surg 2000;39(5 Suppl):S1-60.

The underlying pathophysiology and treatment of diabetic foot ulcers, infections, and the diabetic Charcot foot are thoroughly reviewed. Based on currently available evidence, the authors present a Clinical Practice Guideline for diabetic foot disorders.

Laing P. The development and complications of diabetic foot ulcers. Am J Surg 1998;176(2A Suppl):11S-19S.

Neuropathy and ischemia, two common complications of diabetes mellitus, are the primary underlying risk factors for the development of foot ulcers and their complications. However, an initiating factor, such as physical or mechanical stress, is also required for an ulcer to develop. In addition to increasing the risk of ulceration, diabetes mellitus also increases the risk of infection by impairing the body's ability to eliminate bacteria. The complex processes by which diabetic ulcers develop are reviewed in this article.