

Anesthesia and Surgical Precautions

Updated: 08/26/2004

ABSTRACTS

[Neuroprotective effect of sodium channel blockers in ischemia: the pathomechanism of early ischemic dysfunction].

Adam-Vizi V.

Orv Hetil. 2000 Jun 4; 141(23):1279-86.

Increase in the intracellular Na⁺ concentration ([Na⁺]_i) plays a key role in the cell damage induced by ischemia/reperfusion. In addition to imposing an energy demand on cells due to stimulation of the plasmalemmal Na, K-ATPase, it contributes to an impairment of Ca²⁺ homeostasis by driving Ca²⁺ into the cells via the Na(+)-Ca²⁺ exchanger, and to the development of other acute dysfunctions such as acidosis, cytotoxic oedema and glutamate excitotoxicity. Rise in [Na⁺]_i induced by ischemia further worsens during reperfusion when reactive oxygen species are generated, and oxidative stress occurs. As activation of voltage-dependent Na⁺ channels has a crucial role in mediating a sustained Na⁺ entry during ischemia, blocking of these channels is expected to exert neuroprotection. Indeed, a wide range of compounds able to block Na⁺ channels proved to be beneficial in experimental ischemia. Among these are local anaesthetics, Ca²⁺ channel blockers, anticonvulsants and the neuroprotective drug, vinpocetine

Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr-1) expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations.

Aljada A, Ghanim H, Mohanty P, et al.

J Clin Endocrinol Metab. 2002 Mar; 87(3):1419-22.

We have recently demonstrated that an infusion of a low dose of insulin reduces the intranuclear NF-kappa B (a pro-inflammatory transcription factor) content in MNC while also reducing the plasma concentration of NF-kappa B dependent pro-inflammatory cytokines and adhesion molecules. We have now tested the effect of insulin on the pro-inflammatory transcription factor, early growth response-1 (Egr-1) and plasma concentration of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1), two major proteins whose expression is modulated by Egr-1. Insulin was infused at the rate of 2 IU/h in 5% dextrose (100 mL/h) and KCl (8 mmol/h) for 4 h in the fasting state in ten obese subjects. Blood samples were obtained at 0, 2, 4 and 6 h. MNC were isolated and their total homogenates and nuclear fractions were prepared and Egr-1 was measured by electrophoretic mobility shift assay (EMSA). Plasma TF and PAI-1 were assayed by ELISA. There was a significant fall in Egr-1 at 2 (66 +/- 14% of basal level) and 4 h (47 +/- 17% of the basal level; P<0.01). PAI-1 levels (basal = "100%") decreased significantly after insulin infusion at 2 h (57 +/- 6.7% of the basal level) and at 4 h (58 +/- 8.3% of the basal level; P<0.001). Plasma TF levels (basal = "100%") decreased to 76 +/- 7.7% of the basal level at 2 h and to 85 +/- 10.4% of the basal level at 4 h (P<0.05). Thus, insulin reduces intranuclear Egr-1 and the expression of TF and PAI-1. These data provide further evidence that insulin has an anti-inflammatory effect including the inhibition of TF and PAI-1 expression. These effects suggest a potential beneficial effect of insulin in thrombin formation and fibrinolysis in atherothrombosis

Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial.

Arthur HM, Daniels C, McKelvie R, et al.

Ann Intern Med. 2000 Aug 15; 133(4):253-62.

BACKGROUND: In publicly funded health care systems, a waiting period for such services as coronary artery bypass graft surgery (CABG) is common. The possibility of using the waiting period to improve patient outcomes should be investigated. **OBJECTIVE:** To examine the effect of a multidimensional preoperative intervention on presurgery and postsurgery outcomes in low-risk patients awaiting elective CABG. **DESIGN:** Randomized, controlled trial. **SETTING:** A regional cardiovascular surgery center in a tertiary care hospital, southwestern Ontario, Canada. **PATIENTS:** 249 patients on a waiting list for elective CABG whose surgeries were scheduled for a minimum of 10 weeks from the time of study recruitment. **INTERVENTION:** During the

waiting period, the treatment group received exercise training twice per week, education and reinforcement, and monthly nurse-initiated telephone calls. After surgery, participation in a cardiac rehabilitation program was offered to all patients.

MEASUREMENTS: Postoperative length of stay was the primary outcome. Secondary outcomes were exercise performance, general health-related quality of life, social support, anxiety, and utilization of health care services. **RESULTS:** Length of stay differed significantly between groups. Patients who received the preoperative intervention spent 1 less day [95% CI, 0.0 to 1.0 day] in the hospital overall ($P = 0.002$) and less time in the intensive care unit (median, 2.1 hours [CI, -1.2 to 16 hours]; $P = 0.001$). During the waiting period, patients in the intervention group had a better quality of life than controls. Improved quality of life continued up to 6 months after surgery. Mortality rates did not differ. **CONCLUSION:** The waiting period for elective procedures, such as CABG, may be used to enhance in-hospital and early-phase recovery, improving patients' functional abilities and quality of life while reducing their hospital stay

Antioxidant properties of carvedilol and metoprolol in heart failure: a double-blind randomized controlled trial.

Arumanayagam M, Chan S, Tong S, et al.

J Cardiovasc Pharmacol. 2001 Jan; 37(1):48-54.

Animal and human studies have shown that carvedilol has significant antioxidant properties compared with other beta-blockers. The objective of this study was to determine if these antioxidant effects are detectable in patients with heart failure and to compare carvedilol with the selective beta-blocker metoprolol. Twenty-four patients with chronic heart failure were randomly assigned to receive either carvedilol or metoprolol in a double-blind control trial for 12 weeks in a University teaching hospital clinic. Blood pressure, heart rate, exercise tolerance, left ventricular ejection fraction, plasma total antioxidant status, erythrocyte superoxide dismutase, and glutathione peroxidase activities were determined at baseline and every 4 weeks up to 12 weeks. The results showed that erythrocyte superoxide dismutase and glutathione peroxidase were significantly reduced in carvedilol treated patients after 12 weeks of therapy, whereas metoprolol had no significant effect, although the clinical improvement over the short-term was similar with both drugs. Thus carvedilol, in addition to improving symptoms in heart failure, also possesses significant antioxidant properties. Whether this additional action influences long-term outcome is at present unknown

The effect of chronic hydergine treatment on the plasticity of synaptic junctions in the dentate gyrus of aged rats.

Bertoni-Freddari C, Giuli C, Pieri C, et al.

J Gerontol. 1987 Sep; 42(5):482-6.

The number of synapses (N_v), the surface density of contact zones (S_v) as well as the average size (S) of E-PTA stained synapses in the supragranular layer of the dentate gyrus from adult (12 months), old (30 month), and Hydergine-treated old (30 months) rats were measured by using quantitative morphometric techniques. In old animals, N_v and S_v were significantly reduced, whereas S was significantly increased as compared with the values in adult rats. Hydergine (Codergocrine mesylate) treatment of old animals (3 mg/Kg/day for 4 weeks) influenced these three parameters, differentially. The S_v in aged animals receiving Hydergine, relative to that in untreated old rats, was significantly increased; the number and size of synapses in the treated old rats were significantly higher and smaller, respectively, than that in old controls. We interpret the present findings to indicate a modulating effect of Hydergine on the morphological plasticity of synaptic junctions in the dentate gyrus of aged rats

Glial cell survival is enhanced during melatonin-induced neuroprotection against cerebral ischemia.

Borlongan CV, Yamamoto M, Takei N, et al.

FASEB J. 2000 Jul; 14(10):1307-17.

The role of glial cells in neuronal death has become a major research interest. Glial cell activation has been demonstrated to accompany cerebral ischemia. However, there is disagreement whether such gliosis is a cell death or a neuroprotective response. In the present study, we examined alterations in glial cell responses to the reported neuroprotective action of the free radical scavenger, melatonin, against cerebral ischemia. Adult male Wistar rats were given oral injections of either melatonin (26 micromol/rat) or saline just prior to 1 h occlusion of the middle cerebral artery (MCA), then once daily for 11 or 19 consecutive days. At 11 and 19 days after reperfusion of the MCA, randomly selected animals were killed and their brains removed for immunohistochemical assays. Melatonin significantly enhanced survival of glial cells (as revealed by glial cell specific markers, glial fibrillary acidic protein and aquaporin-4 immunostaining) at both time periods postischemia, and the preservation of these glial cells in the ischemic penumbra corresponded with a markedly reduced area of infarction (detected by immunoglobulin G and hematoxylin-eosin staining), as well as increased neuronal survival. The ischemia-induced locomotor deficits were partially ameliorated in melatonin-treated animals. In vitro replications of ischemia by serum deprivation or by exposure to free radical-producing toxins (sodium nitroprusside and 3-nitropropionic acid) revealed that melatonin (10 microg/ml or 100 microM)

treatment of pure astrocytic cultures significantly reduced astrocytic cell death. These results suggest a potential strategy directed at enhancing glial cell survival as an alternative protective approach against ischemic damage

[Prevention of perioperative myocardial ischemia--an update].

Böttiger BW, Martin E.

Anaesthesist. 2000 Mar; 49(3):174-86.

Perioperative cardiac morbidity and mortality are a major health care challenge with important individual as well as economic aspects. Up to 30% of all perioperative complications and up to 50% of all postoperative deaths are related to cardiac causes. Perioperative myocardial ischemia, which occurs in more than 40% of patients with or at risk for coronary artery disease and undergoing noncardiac surgery, represents a dynamic predictor of postoperative cardiac complications. Long-duration myocardial ischemia and ischemic episodes associated with myocardial cell damage are particularly of prognostic relevance. In patients suffering from this type of ischemia, the incidence of adverse cardiac outcome is increased up to 20-fold. Reducing the incidence of perioperative myocardial ischemia is associated with a decrease in adverse cardiac outcome. Important issues related to perioperative myocardial ischemia are hematocrit level, body temperature, and hemodynamic variables. In contrast, the choice of anesthetic agents and techniques appears to be less important. Perioperative administration of anti-ischemic drugs in patients at risk, however, leads to a further decrease in the incidence of myocardial ischemia and to an improvement in patient outcome. Recent studies suggest that alpha 2-agonists and particularly beta-adrenoreceptor blocking agents are effective anti-ischemic drugs in the perioperative setting. Perioperative administration of beta-adrenoreceptor blocking agents in coronary risk patients undergoing noncardiac surgery is associated with a reduced rate of postoperative cardiac complications and an improvement in long-term outcome. This is particularly relevant in high risk patients with preoperative stress-induced ischemic episodes. In clinical practice, therefore, chronically administered anti-ischemic drugs should also be administered on the day of surgery and during the postoperative period. In untreated patients with or at risk for coronary artery disease and who have to undergo urgent surgical procedures without the opportunity of preoperative anti-ischemic intervention, perioperative administration of beta-adrenoreceptor blocking agents is mandatory

Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview.

Capes SE, Hunt D, Malmberg K, et al.

Lancet. 2000 Mar 4; 355(9206):773-8.

BACKGROUND: High blood glucose concentration may increase risk of death and poor outcome after acute myocardial infarction. We did a systematic review and meta-analysis to assess the risk of in-hospital mortality or congestive heart failure after myocardial infarction in patients with and without diabetes who had stress hyperglycaemia on admission. **METHODS:** We did two searches of MEDLINE for English-language articles published from 1966 to October, 1998, a computerised search of Science Citation Index from 1980 to September, 1998, and manual searches of bibliographies. Two searchers identified all cohort studies or clinical trials reporting in-hospital mortality or rates of congestive heart failure after myocardial infarction in relation to glucose concentration on admission. We compared the relative risks of in-hospital mortality and congestive heart failure in hyperglycaemic and normoglycaemic patients with and without diabetes. **FINDINGS:** 14 articles describing 15 studies were identified. Patients without diabetes who had glucose concentrations more than or equal to range 6.1-8.0 mmol/L had a 3.9-fold (95% CI 2.9-5.4) higher risk of death than patients without diabetes who had lower glucose concentrations. Glucose concentrations higher than values in the range of 8.0-10.0 mmol/L on admission were associated with increased risk of congestive heart failure or cardiogenic shock in patients without diabetes. In patients with diabetes who had glucose concentrations more than or equal to range 10.0-11.0 mmol/L the risk of death was moderately increased (relative risk 1.7 [1.2-2.4]). **INTERPRETATION:** Stress hyperglycaemia with myocardial infarction is associated with an increased risk of in-hospital mortality in patients with and without diabetes; the risk of congestive heart failure or cardiogenic shock is also increased in patients without diabetes

Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview.

Capes SE, Hunt D, Malmberg K, et al.

Stroke. 2001 Oct; 32(10):2426-32.

BACKGROUND AND PURPOSE: "Stress" hyperglycemia may be associated with increased mortality and poor recovery in diabetic and nondiabetic patients after stroke. A systematic review and meta-analysis of the literature relating acute poststroke glucose levels to the subsequent course were done to summarize and quantify this relationship. **METHODS:** A comprehensive literature search was done for cohort studies reporting mortality and/or functional recovery after stroke in relation to admission

glucose level. Relative risks in hyperglycemic compared with normoglycemic patients with and without diabetes were calculated and meta-analyzed when possible. RESULTS: Thirty-two studies were identified; relative risks for prespecified outcomes were reported or could be calculated in 26 studies. After stroke of either subtype (ischemic or hemorrhagic), the unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose level >6 to 8 mmol/L (108 to 144 mg/dL) was 3.07 (95% CI, 2.50 to 3.79) in nondiabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients. After ischemic stroke, admission glucose level >6.1 to 7.0 mmol/L (110 to 126 mg/dL) was associated with increased risk of in-hospital or 30-day mortality in nondiabetic patients only (relative risk=3.28; 95% CI, 2.32 to 4.64). After hemorrhagic stroke, admission hyperglycemia was not associated with higher mortality in either diabetic or nondiabetic patients. Nondiabetic stroke survivors whose admission glucose level was >6.7 to 8 mmol/L (121 to 144 mg/dL) also had a greater risk of poor functional recovery (relative risk=1.41; 95% CI, 1.16 to 1.73). CONCLUSIONS: Acute hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke in nondiabetic patients and increased risk of poor functional recovery in nondiabetic stroke survivors

Reduction of oxidative stress by carvedilol: role in maintenance of ischaemic myocardium viability.

Cargnoni A, Ceconi C, Bernocchi P, et al.

Cardiovasc Res. 2000 Aug 18; 47(3):556-66.

OBJECTIVES: To differentiate the impact of the beta-blocking and the anti-oxidant activity of carvedilol in maintaining myocardium viability. METHODS: Isolated rabbit hearts, subjected to aerobic perfusion, or low-flow ischaemia followed by reperfusion, were treated with two doses of carvedilol, one dose (2.0 microM) with marked negative inotropic effect due to beta-blockage and the other (0.1 microM) with no beta-blockage nor negative inotropism. Carvedilol was compared with two doses of propranolol, 1.0 - without - and 5.0 microM - with negative inotropic effect. Anti-oxidant activity was measured as the capacity to counteract the occurrence of oxidative stress and myocardium viability as recovery of left ventricular function on reperfusion, membrane damage and energetic status. RESULTS: Carvedilol counteracted the ischemia and reperfusion induced oxidative stress: myocardial content of reduced glutathione, protein and non-protein sulfhydryl groups after ischaemia and particularly after reperfusion, was higher in hearts treated with carvedilol, while the myocardial content of oxidised glutathione was significantly reduced (0.30+/-0.03 and 0.21+/-0.02 vs. 0.39+/-0.03 nmol/mg prot, both P<0.01, in 0.1 and 2.0 microM). At the same time, carvedilol improved myocardium viability independently from its beta-blocking effect. On the contrary, propranolol maintained viability only at the higher dose, although to a lesser extent than carvedilol. This suggests that the effects of propranolol are dependent on energy saving due to negative inotropism. The extra-protection observed with carvedilol at both doses is likely due to its anti-oxidant effect. CONCLUSIONS: Our data show that the anti-oxidant activity of carvedilol is relevant for the maintenance of myocardium viability

Iron and liver diseases.

Fargion S, Mattioli M, Fracanzani AL, et al.

Can J Gastroenterol. 2000 Nov; 14 Suppl D:89D-92D.

A mild to moderate iron excess is found in patients with liver diseases apparently unrelated to genetic hemochromatosis. Iron appears to affect the natural history of hepatitis C virus-related chronic liver diseases, alcoholic liver disease and nonalcoholic steatohepatitis by leading to a more severe fibrosis and thus aiding the evolution to cirrhosis. A higher frequency of mutations of the HFE gene, the gene responsible for hereditary hemochromatosis, is found in patients with liver diseases and increased liver iron than in normal patients. Patients with excess iron are potentially at a higher risk of developing hepatocellular carcinoma. Iron depletion therapy could interfere with fibrosis development and possibly reduce the risk of liver cancer occurrence

Calcium antagonists in patients with aneurysmal subarachnoid hemorrhage: a systematic review.

Feigin VL, Rinkel GJ, Algra A, et al.

Neurology. 1998 Apr; 50(4):876-83.

BACKGROUND AND PURPOSE: It has been reported that nimodipine reduces the frequency of secondary ischemia and improves outcome after aneurysmal SAH, but definitive evidence concerning all available calcium antagonists is lacking. METHODS: Systematic overview of randomized trials that were completed by January 1996 compared calcium antagonists with control and started treatment within 10 days after onset of subarachnoid hemorrhage (SAH) was performed. All calcium antagonists studied thus far (nimodipine, nicardipine, and AT877) were included. RESULTS: We analyzed 10 trials totaling 2756 patients. The relative risk (RR) reduction of poor outcome (death or dependency) was 16% (95% CI, 6 to 27%) and that of case fatality was 10% (95% CI, -6 to 25%). To prevent one poor outcome, 19 (12 to 59) patients need to be treated. Calcium antagonists give a 33% (95% CI 25 to 41) RR reduction in the frequency of ischemic neurologic deficit and a 20% (95% CI, 11 to 28) RR reduction in the frequency of CT-scan documented cerebral infarction. Eight (6 to 11) patients need to be treated to

prevent one ischemic neurologic deficit. In the analyses for nimodipine only, treatment was associated with a 24% RR reduction of poor outcome (95% CI, 12 to 38). To prevent one poor outcome, 13 (8 to 30) patients need to be treated with nimodipine. The RR reduction of angiographically detected cerebral vasospasm was statistically significant for AT877 (38%; 95% CI, 17 to 54%) and nicardipine (21%; 95% CI, 6 to 34%) but not for nimodipine (9%; 95% CI, -2 to 19%). CONCLUSION: Calcium antagonists reduce the proportion of ischemic neurologic deficits and nimodipine improves overall outcome within 3 months of aneurysmal SAH; evidence for a reduction of poor outcome from all causes by nicardipine and AT877 is inconclusive. The intermediate factors by which nimodipine exerts its beneficial effect remain uncertain

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Diazepam promotes ATP recovery and prevents cytochrome c release in hippocampal slices after in vitro ischemia.

Galeffi F, Sinnar S, Schwartz-Bloom RD.

J Neurochem. 2000 Sep; 75(3):1242-9.

Benzodiazepines protect hippocampal neurons when administered within the first few hours after transient cerebral ischemia. Here, we examined the ability of diazepam to prevent early signals of cell injury (before cell death) after in vitro ischemia. Ischemia in vitro or in vivo causes a rapid depletion of ATP and the generation of cell death signals, such as the release of cytochrome c from mitochondria. Hippocampal slices from adult rats were subjected to 7 min of oxygen-glucose deprivation (OGD) and assessed histologically 3 h after reoxygenation. At this time, area CA1 neurons appeared viable, although slight abnormalities in structure were evident. Immediately following OGD, ATP levels in hippocampus were decreased by 70%, and they recovered partially over the next 3 h of reoxygenation. When diazepam was included in the reoxygenation buffer, ATP levels recovered completely by 3 h after OGD. The effects of diazepam were blocked by picrotoxin, indicating that the protection was mediated by an influx of Cl⁻ through the GABA(A) receptor. It is interesting that the benzodiazepine antagonist flumazenil did not prevent the action of diazepam, as has been shown in other studies using the hippocampus. Two hours after OGD, the partial recovery of ATP levels occurred simultaneously with an increase of cytochrome c (approximately 400%) in the cytosol. When diazepam was included in the reoxygenation buffer, it completely prevented the increase in cytosolic cytochrome c. Thus, complete recovery of ATP and prevention of cytochrome c release from mitochondria can be achieved when diazepam is given after the loss of ATP induced by OGD

Neuroprotection by estradiol.

Garcia-Segura LM, Azcoitia I, DonCarlos LL.

Prog Neurobiol. 2001 Jan; 63(1):29-60.

This review highlights recent evidence from clinical and basic science studies supporting a role for estrogen in neuroprotection. Accumulated clinical evidence suggests that estrogen exposure decreases the risk and delays the onset and progression of Alzheimer's disease and schizophrenia, and may also enhance recovery from traumatic neurological injury such as stroke.

Recent basic science studies show that not only does exogenous estradiol decrease the response to various forms of insult, but the brain itself upregulates both estrogen synthesis and estrogen receptor expression at sites of injury. Thus, our view of the role of estrogen in neural function must be broadened to include not only its function in neuroendocrine regulation and reproductive behaviors, but also to include a direct protective role in response to degenerative disease or injury. Estrogen may play this protective role through several routes. Key among these are estrogen dependent alterations in cell survival, axonal sprouting, regenerative responses, enhanced synaptic transmission and enhanced neurogenesis. Some of the mechanisms underlying these effects are independent of the classically defined nuclear estrogen receptors and involve unidentified membrane receptors, direct modulation of neurotransmitter receptor function, or the known anti-oxidant activities of estrogen. Other neuroprotective effects of estrogen do depend on the classical nuclear estrogen receptor, through which estrogen alters expression of estrogen responsive genes that play a role in apoptosis, axonal regeneration, or general trophic support. Yet another possibility is that estrogen receptors in the membrane or cytoplasm alter phosphorylation cascades through direct interactions with protein kinases or that estrogen receptor signaling may converge with signaling by other trophic molecules to confer resistance to injury. Although there is clear evidence that estradiol exposure can be deleterious to some neuronal populations, the potential clinical benefits of estrogen treatment for enhancing cognitive function may outweigh the associated central and peripheral risks. Exciting and important avenues for future investigation into the protective effects of estrogen include the optimal ligand and doses that can be used clinically to confer benefit without undue risk, modulation of neurotrophin and neurotrophin receptor expression, interaction of estrogen with regulated cofactors and coactivators that couple estrogen receptors to basal transcriptional machinery, interactions of estrogen with other survival and regeneration promoting factors, potential estrogenic effects on neuronal replenishment, and modulation of phenotypic choices by neural stem cells

Harvey Stanley Hecht, MD: a conversation with the editor.

Hecht HS.

Am J Cardiol. 2000 Nov 1; 86(9):989-97.

Kinin-mediated activation of endothelial NO formation: possible role during myocardial ischemia.

Hecker M, Fleming I, Busse R.

Agents Actions Suppl. 1995; 45:119-27.

Endothelial cells produce a variety of factors involved in the control of vascular tone, platelet activation and cell growth, one of the most important being nitric oxide (NO). Although continuously produced in response to fluid shear stress, the release of NO from these cells can be enhanced further by humoral stimuli, such as bradykinin. This is the result of a chain of complex intracellular events involving changes in Ca²⁺, pH and protein phosphorylation. Endothelial cells are also capable of synthesizing bradykinin from an endogenous source, the release of which is markedly enhanced under hypoxic conditions. The finding that ACE inhibitors promote the local accumulation of the peptide and increase its efficacy at the receptor level may partly explain the potent anti-ischemic and cardioprotective effects of these drugs

Estrogen as a neuroprotectant in stroke.

Hurn PD, Macrae IM.

J Cereb Blood Flow Metab. 2000 Apr; 20(4):631-52.

Recent evidence suggests that reproductive steroids are important players in shaping stroke outcome and cerebrovascular pathophysiologic features. Although women are at lower risk for stroke than men, this native protection is lost in the postmenopausal years. Therefore, aging women sustain a large burden for stroke, contrary to a popular misconception that cancer is the main killer of women. Further, the value of hormone replacement therapy in stroke prevention or in improving outcome remains controversial. Estrogen has been the best studied of the sex steroids in both laboratory and clinical settings and is considered increasingly to be an endogenous neuroprotective agent. A growing number of studies demonstrate that exogenous estradiol reduces tissue damage resulting from experimental ischemic stroke in both sexes. This new concept suggests that dissecting interactions between estrogen and cerebral ischemia will yield novel insights into generalized cellular mechanisms of injury. Less is known about estrogen's undesirable effects in brain, for example, the potential for increasing seizure susceptibility and migraine. This review summarizes gender-specific aspects of clinical and experimental stroke and results of estrogen treatment on outcome in animal models of cerebral ischemia, and briefly discusses potential vascular and parenchymal mechanisms by which estrogen salvages brain

Protection of hearts from reperfusion injury by propofol is associated with inhibition of the mitochondrial permeability transition.

Cardiovasc Res. 2000 Jan 14; 45(2):360-9.

OBJECTIVE: Diminishing oxidative stress may protect the heart against ischaemia-reperfusion injury by preventing opening of the mitochondrial permeability transition (MPT) pore. The general anaesthetic agent propofol, a free radical scavenger, has been investigated for its effect on the MPT and its cardioprotective action following global and cardioplegic ischaemic arrest.

METHOD: Isolated perfused Wistar rat hearts were subjected to either warm global ischaemia (Langendorff) or cold St. Thomas' cardioplegia (working heart mode) in the presence or absence of propofol. MPT pore opening was determined using [3H]-2-deoxyglucose-6-phosphate ([3H]-DOG-6P) entrapment. The respiratory function of isolated mitochondria was also determined for evidence of oxidative stress. **RESULTS:** Propofol (2 micrograms/ml) significantly improved the functional recovery of Langendorff hearts on reperfusion (left ventricular developed pressure from 28.4 +/- 6.2 to 53.3 +/- 7.3 mmHg and left ventricular end diastolic pressure from 52.9 +/- 4.3 to 37.5 +/- 3.9 mmHg). Recovery was also improved in propofol (4 micrograms/ml) treated working hearts following cold cardioplegic arrest. External cardiac work on reperfusion improved from 0.42 +/- 0.05 to 0.60 +/- 0.03 J/s, representing 45-64% of baseline values, when compared to controls ($P < 0.05$). Propofol inhibited MPT pore opening during reperfusion, [3H]-DOG-6P entrapment being 16.7 vs. 22.5 ratio units in controls ($P < 0.05$). Mitochondria isolated from non-ischaemic, propofol-treated hearts exhibited increased respiratory chain activity and were less sensitive to calcium-induced MPT pore opening. **CONCLUSION:** Propofol confers significant protection against global normothermic ischaemia and during cold cardioplegic arrest. This effect is associated with less opening of mitochondrial MPT pores, probably as a result of diminished oxidative stress. Propofol may be a useful adjunct to cardioplegic solutions in heart surgery

Disturbed memory and amnesia related to intensive care.

Jones C, Griffiths RD, Humphris G.

Memory. 2000 Mar; 8(2):79-94.

Patients, when admitted to an intensive care unit (ICU), have one thing in common: their illness is life-threatening. Patients may remain on ICU in a critical condition, needing support with their breathing, circulation, and/or kidneys for varying lengths of time, from days to weeks. During that time the patients will receive sedative and analgesic drugs to ensure compliance with artificial ventilation. Patients recovering from critical illness frequently have little or no recall of their period in ICU, or remember nightmare, hallucinations, or paranoid delusions. The nature, extent and reason for these difficulties, have been under-reported and consequently our purpose was to conduct a review of memory problems experienced by ICU patients. A systematic literature review of computer databases (Medline, PsycLit, and CINAHL) identified 25 relevant papers. In addition, other relevant articles were obtained, citation lists and associated articles retrieved. Due to lack of research on processes underlying memory problems in ICU patients all articles that introduced an insight into possible mechanisms were included in the review. There seem to be two possible processes contributing to memory problems in ICU patients. First the illness and treatment may have a general dampening effect on memory. Delirium and sleep disturbance are both common in ICU patients. Delirium can result in a profound amnesia for the period of confusion. Sleep deprivation exacerbates the confusional state. Slow wave sleep is important for the consolidation of episodic memories. Treatment administered to patients in ICU can have effects on memory. Opiates, benzodiazepines, sedative drugs such as propofol, adrenaline, and corticosteroids can all influence memory. In addition, the withdrawal of drugs, such as benzodiazepines, can cause profound withdrawal reactions, which may contribute to delirium. Second, we hypothesise that there is a process that affects memory negatively for external events but enhances memory for internal events. The physical constraints and social isolation experienced by ICU patients and the life-threatening nature of the illness may increase the experience of hypnagogic hallucinations. Attentional shift during hypnagogic images from external stimuli to internally generated images would explain why ICU patients have such poor recall of external ICU events, but can clearly remember hallucinations and nightmares. Patients describe these memories as being very vivid and this is explored in terms of flashbulb memory formation. The absence of memories for real events on ICU can result in ICU patients remembering paranoid delusions of staff trying to kill them, with little information to reject these vivid memories as unreal. This has implications for patients' future psychological health

Fentanyl protects the heart against ischaemic injury via opioid receptors, adenosine A1 receptors and KATP channel linked mechanisms in rats.

Kato R, Ross S, Foex P.

Br J Anaesth. 2000 Feb; 84(2):204-14.

We have investigated if fentanyl protects against myocardial ischaemic injury and if so, if the mechanism of this protection is mediated via opioid and adenosine A1 receptors, and KATP channels. Langendorff rat hearts were subjected to global ischaemia (30 min) and reperfusion (60 min). The drugs were administered before induction of ischaemia and maintained throughout the experiment. Treatment with fentanyl 740 nmol litre⁻¹ improved post-ischaemic mechanical function, assessed as developed

pressure, +dP/dtmax and -dP/dtmin, compared with controls after 60 min of reperfusion. These effects were abolished by naloxone 1 $\mu\text{mol litre}^{-1}$, DPCPX 10 $\mu\text{mol litre}^{-1}$, a selective adenosine A1 antagonist and sodium 5-hydroxydecanoate 100 $\mu\text{mol litre}^{-1}$, a K⁺ATP channel blocker. We conclude that fentanyl protected the heart against post-ischaemic injury by a mechanism which was blocked by an opioid and an adenosine A1 receptor antagonist and also by a KATP channel antagonist

[Gamma-hydroxybutyric acid--significance for anesthesia and intensive care medicine?].

Kleinschmidt S, Mertzlufft F.

Anesthesiol Intensivmed Notfallmed Schmerzther. 1995 Nov; 30(7):393-402.

Gamma-hydroxybutyric acid (GHB) as a natural component of the mammalian brain was first introduced in clinical anaesthetic practice more than 30 years ago. Although GHB induced a reliable state of sedation and anaesthesia without depressing either respiratory or cardiocirculatory parameters or liver and kidney function, the drug was nearly displaced from clinical practice because of its prolonged duration of action. The results of recent clinical studies indicate a re-evaluation of GHB in emergency and critical care medicine. GHB is regarded as a natural neuronal transmitter with circuits which synthesise, accumulate and release GHB. Specific binding sites have also been demonstrated and identified. GHB is completely metabolized in the liver to the natural substrates carbon dioxide and water without accumulation in central or peripheral tissues. The reduction of energy metabolism and its possible properties as an "oxygen radical scavenger" may be of therapeutic benefit if tissues are exposed to hypoxia or reperfusion. Therefore, the application of GHB seems to be of advantage in states of traumatic brain injury with cerebral oedema or ischaemic lesions of brain or extraneural tissues. In hypovolaemic states or in patients with impaired cardiovascular function, the pressure effects of GHB may be beneficial for the prevention of tissue damage and may improve survival in the case of cardiocirculatory resuscitation. In the intensive care unit, GHB might be a favourable alternative to established sedative agents. Occurrence of side effects such as tolerance and withdrawal syndromes after the application of sedative drugs, an impaired metabolism with the accumulation of metabolites in the case of liver or kidney dysfunction as well as an insufficient regulation of natural sleep may be diminished by the application of GHB. The results of various clinical studies also suggest that GHB may be useful in the treatment of alcohol and opiate withdrawal syndrome. However, further studies are necessary to specify the proposed indications of GHB in anaesthesiology and critical care medicine

The prevention and treatment of cerebral ischemia.

Lanier WL.

Can J Anaesth. 1999 May; 46(5 Pt 2):R46-R56.

Although the major focus of recent cerebral protection research has been aimed at developing receptor-specific drugs, this effort has currently resulted in few improvements in patient outcome. Until advances in pharmacology translate to improvements in humans, the clinician and his patients will be well served by using more traditional techniques to prevent and treat cerebral ischemic events. This approach will involve interventions to a) identify patients who are experiencing or are at risk for developing cerebral ischemia, and b) alter systemic physiology in an attempt to lessen the duration and severity of any ischemic insults. Initial therapy should include interventions to improve cerebral perfusion and the oxygen carrying capacity of the blood. Once this is accomplished, measures should be taken to control blood glucose concentrations and treat fever. In otherwise stable surgical patients, mild reductions in patient temperature also may be of benefit, provided the temperature reductions do not introduce problems in systemic physiology and the patient is rewarmed prior to awakening from general anesthesia. General anesthetic choice may be of importance in controlling intracranial pressure and seizure activity; however, if direct cerebral protection is desired, the anesthetic of choice should be a barbiturate. Finally, in the patient at risk for cerebral vasospasm, nimodipine treatment should be considered. Collectively, these interventions should increase the patient's chance for optimal neurologic recovery following ischemia

Protective effects of enalaprilat against postischemic renal failure.

Long GW, Misra DC, Juleff R, et al.

J Surg Res. 1993 Mar; 54(3):254-7.

Prolonged intraoperative renal ischemia requires modalities to reduce the incidence of acute tubular necrosis, but there exists no definitive prophylactic regimen. We studied the effects of enalaprilat, an angiotensin-converting enzyme inhibitor, in an attempt to identify such a protective drug. Thirty-four mongrel dogs underwent 90 min of bilateral renal pedicle clamping. Group I was a control of 6 animals. Group II comprised 10 animals who received 12.5 g iv mannitol 15 min prior to clamping and 1 mg/kg iv furosemide immediately after clamp removal. Group III also comprised 10 animals who received enalaprilat 1 mg/kg iv enalaprilat each 15 min prior to clamp placement. Group IV consisted of 8 dogs, each of which received 12.5 g mannitol and 1 mg/kg iv enalaprilat 15 min prior to clamping and 1 mg/kg iv furosemide immediately upon removal of the clamps. Serum blood urea

nitrogen (BUN) and creatinine levels were drawn preoperatively and at 12, 24, 48, and 72 hr postoperatively in each animal. The serum BUN levels in group III were significantly lower than those in group I at all times postoperatively ($P < 0.05$) and were not significantly different from those of group II at any time postoperatively. Similarly, the serum creatinine levels in group III were significantly lower than those of group I ($P < 0.05$) and were not significantly different from those in group II at any time postoperatively. Neither the serum BUN nor the serum creatinine levels in group IV were different from those of group I at any time postoperatively. (ABSTRACT TRUNCATED AT 250 WORDS)

Aspirin and mortality from coronary bypass surgery.

Mangano DT.

N Engl J Med. 2002 Oct 24; 347(17):1309-17.

BACKGROUND: There is no therapy known to reduce the risk of complications or death after coronary bypass surgery. Because platelet activation constitutes a pivotal mechanism for injury in patients with atherosclerosis, we assessed whether early treatment with aspirin could improve survival after coronary bypass surgery. **METHODS:** At 70 centers in 17 countries, we prospectively studied 5065 patients undergoing coronary bypass surgery, of whom 5022 survived the first 48 hours after surgery. We gathered data on 7500 variables per patient and adjudicated outcomes centrally. The primary focus was to discern the relation between early aspirin use and fatal and nonfatal outcomes. **RESULTS:** During hospitalization, 164 patients died (3.2 percent), and 812 others (16.0 percent) had nonfatal cardiac, cerebral, renal, or gastrointestinal ischemic complications. Among patients who received aspirin (up to 650 mg) within 48 hours after revascularization, subsequent mortality was 1.3 percent (40 of 2999 patients), as compared with 4.0 percent among those who did not receive aspirin during this period (81 of 2023, $P < 0.001$). Aspirin therapy was associated with a 48 percent reduction in the incidence of myocardial infarction (2.8 percent vs. 5.4 percent, $P < 0.001$), a 50 percent reduction in the incidence of stroke (1.3 percent vs. 2.6 percent, $P = 0.01$), a 74 percent reduction in the incidence of renal failure (0.9 percent vs. 3.4 percent, $P < 0.001$), and a 62 percent reduction in the incidence of bowel infarction (0.3 percent vs. 0.8 percent, $P = 0.01$). Multivariate analysis showed that no other factor or medication was independently associated with reduced rates of these outcomes and that the risk of hemorrhage, gastritis, infection, or impaired wound healing was not increased with aspirin use (odds ratio for these adverse events, 0.63; 95 percent confidence interval, 0.54 to 0.74). **CONCLUSIONS:** Early use of aspirin after coronary bypass surgery is safe and is associated with a reduced risk of death and ischemic complications involving the heart, brain, kidneys, and gastrointestinal tract

Clonidine and cardiac surgery: haemodynamic and metabolic effects, myocardial ischaemia and recovery.

Myles PS, Hunt JO, Holdgaard HO, et al.

Anaesth Intensive Care. 1999 Apr; 27(2):137-47.

Clonidine may have beneficial effects in patients undergoing major surgery. We enrolled 156 patients having elective CABG surgery in a double-blind, randomized trial. Patients were randomized to receive either two doses of placebo (Group PP) or clonidine 5 micrograms/kg (Group CC). Perioperative measurements included haemodynamics, anaesthetic and analgesic drug usage, creatinine clearance, cortisol excretion, recovery times and quality of life (SF-36) after surgery. Overall, there was no significant difference with time to tracheal extubation (median [10-90 centile]): CC 7.1 (3.4-18) h vs PP 8.0 (4.3-17) h, $P = 0.70$; but there was a higher proportion of patients extubated within four hours: CC 20% vs. PP 8%, $P = 0.038$. Clonidine resulted in a number of significant ($P < 0.05$) haemodynamic changes, particularly pre-CPB: less tachycardia and hypertension, more bradycardia and hypotension. Clonidine was associated with a significant ($P < 0.05$) reduction in anaesthetic drug usage, higher creatinine clearance, lower cortisol excretion and improvement in some aspects of quality of life. This study lends support to consideration of clonidine therapy in patients undergoing CABG surgery

Co-induction of p75NTR and p75NTR-associated death executor in neurons after zinc exposure in cortical culture or transient ischemia in the rat.

Park JA, Lee JY, Sato TA, et al.

J Neurosci. 2000 Dec 15; 20(24):9096-103.

Recently, a 22 kDa protein termed p75(NTR)-associated death executor (NADE) was discovered to be a necessary factor for p75(NTR)-mediated apoptosis in certain cells. However, the possible role for p75(NTR)/NADE in pathological neuronal death has yet been undetermined. In the present study, we have examined this possibility in vivo and in vitro. Exposure of cortical cultures to zinc induced both p75(NTR) and NADE in neurons, whereas exposure to NMDA, ionomycin, iron, or H_2O_2 induced neither. In addition, zinc exposure increased neuronal NGF expression and its release into the medium. A function-blocking antibody of p75(NTR) (REX) inhibited association between p75(NTR) and NADE as well as neuronal death induced by zinc. Conversely, NGF augmented zinc-induced neuronal death. Caspase inhibitors reduced zinc-induced neuronal death, indicating that caspases

were involved. Because reduction of NADE expression with cycloheximide or NADE antisense oligonucleotides attenuated zinc-induced neuronal death, NADE appears to contribute to p75(NTR)-induced cortical neuronal death as shown in other cells. Because zinc neurotoxicity may be a key mechanism of neuronal death after transient forebrain ischemia, we next examined this model. After ischemia, p75(NTR) and NADE were induced in degenerating rat hippocampal CA1 neurons. There was a close correlation between zinc accumulation and p75(NTR)/NADE induction. Suggesting the role of zinc here, injection of a metal chelator, CaEDTA, into the lateral ventricle completely blocked the induction of p75(NTR) and NADE. Our results suggest that co-induction of p75(NTR) and NADE plays a role in zinc-triggered neuronal death in vitro and in vivo

Glutamine metabolism and transport in skeletal muscle and heart and their clinical relevance.

Rennie MJ, Ahmed A, Khogali SE, et al.

J Nutr. 1996 Apr; 126(4 Suppl):1142S-9S.

The glutamine and glutamate transporters in skeletal muscle and heart appear to play a role in control of the steady-state concentration of amino acids in the intracellular space and, in the case of skeletal muscle at least, in the rate of loss of glutamine to the plasma and to other organs and tissues. This article reviews what is currently known about transporter characteristics and mechanisms in skeletal muscle and heart, the alterations in transport activity in pathophysiological conditions and the implications for anabolic processes and cardiac function of altering the availability of glutamine. The possibilities that glutamine pool size is part of an osmotic signaling mechanism to regulate whole body protein metabolism is discussed and evidence is shown from work on cultured muscle cells. The possible uses of glutamine in maintaining cardiac function perioperatively and in promoting glycogen metabolism are discussed

Coenzyme Q10 improves the tolerance of the senescent myocardium to aerobic and ischemic stress: studies in rats and in human atrial tissue.

Rosenfeldt FL, Pepe S, Ou R, et al.

Biofactors. 1999; 9(2-4):291-9.

The inferior recovery of cardiac function after interventional cardiac procedures in elderly patients compared to younger patients suggests that the aged myocardium is more sensitive to stress. We report two studies that demonstrate an age-related deficit in myocardial performance after aerobic and ischemic stress and the capacity of CoQ10 treatment to correct age-specific diminished recovery of function. In Study 1 the functional recovery of young (4 mo) and senescent (35 mo) isolated working rat hearts after aerobic stress produced by rapid electrical pacing was examined. After pacing, the senescent hearts, compared to young, showed reduced recovery of pre-stress work performance. CoQ10 pretreatment (daily intraperitoneal injections of 4 mg/kg CoQ10 for 6 weeks) in senescent hearts improved their recovery to match that of young hearts. Study 2 tested whether the capacity of human atrial trabeculae (obtained during surgery) to recover contractile function, following ischemic stress in vitro (60 min), is decreased with age and whether this decrease can be reversed by CoQ10. Trabeculae from older individuals (> or = 70 yr) showed reduced recovery of developed force after simulated ischemia compared to younger counterparts (or = 70 yr patients). In vitro pretreatment raised trabecular CoQ10 content to similar levels in all groups. We conclude that, compared to younger counterparts, the senescent myocardium of rats and humans has a reduced capacity to tolerate ischemic or aerobic stress and recover pre-stress contractile performance, however, this reduction is attenuated by CoQ10 pretreatment

[Glutamine: effects on the immune system, protein balance and intestinal functions].

Roth E, Spittler A, Oehler R.

Wien Klin Wochenschr. 1996; 108(21):669-76.

Glutamine is the most abundant free amino acid of the human body. In catabolic stress situations such as after operations, trauma and during sepsis the enhanced transport of glutamine to splanchnic organs and to blood cells results in an intracellular depletion of glutamine in skeletal muscle. Glutamine is an important metabolic substrate for cells cultivated under in vitro conditions and is a precursor for purines, pyrimidines and phospholipids. Increasing evidence suggests that glutamine is a crucial substrate for immunocompetent cells. Glutamine depletion in the cultivation medium decreases the mitogen-inducible proliferation of lymphocytes, possibly by arresting the cells in the G0-G1 phase of the cell cycle. Glutamine depletion in lymphocytes prevents the formation of signals necessary for late activation. In monocytes glutamine deprivation downregulates surface antigens responsible for antigen preservation and phagocytosis. Glutamine is a precursor for the synthesis of glutathione and stimulates the formation of heat-shock proteins. Moreover, there are suggestions that glutamine plays a crucial role in osmotic regulation of cell volume and causes phosphorylation of proteins, both of which may stimulate intracellular protein synthesis. Experimental studies revealed that glutamine deficiency causes a necrotising enterocolitis and increases the mortality of animals subjected to bacterial stress. First clinical studies have demonstrated a decrease in the incidence of

infections and a shortening of the hospital stay in patients after bone marrow transplantation by supplementation with glutamine. In critically ill patients parenteral glutamine reduced nitrogen loss and caused a reduction of the mortality rate. In surgical patients glutamine evoked an improvement of several immunological parameters. Moreover, glutamine exerted a trophic effect on the intestinal mucosa, decreased the intestinal permeability and thus may prevent the translocation of bacteria. In conclusion, glutamine is an important metabolic substrate of rapidly proliferating cells, influences the cellular hydration state and has multiple effects on the immune system, on intestinal function and on protein metabolism. In several disease states glutamine may consequently, become an indispensable nutrient, which should be provided exogenously during artificial nutrition

Effects of human growth hormone in men over 60 years old.

Rudman D, Feller AG, Nagraj HS, et al.

N Engl J Med. 1990 Jul 5; 323(1):1-6.

BACKGROUND. The declining activity of the growth hormone--insulin-like growth factor I (IGF-I) axis with advancing age may contribute to the decrease in lean body mass and the increase in mass of adipose tissue that occur with aging. **METHODS.** To test this hypothesis, we studied 21 healthy men from 61 to 81 years old who had plasma IGF-I concentrations of less than 350 U per liter during a six-month base-line period and a six-month treatment period that followed. During the treatment period, 12 men (group 1) received approximately 0.03 mg of biosynthetic human growth hormone per kilogram of body weight subcutaneously three times a week, and 9 men (group 2) received no treatment. Plasma IGF-I levels were measured monthly. At the end of each period we measured lean body mass, the mass of adipose tissue, skin thickness (epidermis plus dermis), and bone density at nine skeletal sites. **RESULTS.** In group 1, the mean plasma IGF-I level rose into the youthful range of 500 to 1500 U per liter during treatment, whereas in group 2 it remained below 350 U per liter. The administration of human growth hormone for six months in group 1 was accompanied by an 8.8 percent increase in lean body mass, a 14.4 percent decrease in adipose-tissue mass, and a 1.6 percent increase in average lumbar vertebral bone density (P less than 0.05 in each instance). Skin thickness increased 7.1 percent (P = 0.07). There was no significant change in the bone density of the radius or proximal femur. In group 2 there was no significant change in lean body mass, the mass of adipose tissue, skin thickness, or bone density during treatment. **CONCLUSIONS.** Diminished secretion of growth hormone is responsible in part for the decrease of lean body mass, the expansion of adipose-tissue mass, and the thinning of the skin that occur in old age

Glutamine supplementation in catabolic patients.

Sacks GS.

Ann Pharmacother. 1999 Mar; 33(3):348-54.

OBJECTIVE: To evaluate the safety and efficacy of parenteral and enteral glutamine supplementation in patients who are catabolic. **DATA SOURCES:** English-language clinical trials and review articles identified by MEDLINE searches (January 1970-December 1997) and from bibliographies of selected articles were considered for possible inclusion. Key words used in the search strategy were glutamine, critical illness, stress, catabolism, injury, enteral nutrition, and parenteral nutrition. **STUDY SELECTION AND DATA EXTRACTION:** Inclusion was restricted to pertinent studies that evaluated the safety of glutamine supplementation, as well as effects of glutamine on amino acid metabolism, immune function, and patient outcome. Data from 18 clinical trials and multiple review articles were compiled into a review format. **DATA SYNTHESIS:** Glutamine is an important metabolic fuel for intestinal enterocytes, lymphocytes and macrophages, and metabolic precursors such as purines and pyrimidines. Although originally considered a nonessential amino acid, experimental work suggests that glutamine is essential for maintaining intestinal function, immune response, and amino acid homeostasis during periods of severe stress. In the past decade, clinical trials conducted in metabolically stressed patients indicate that glutamine improves nitrogen balance, increases cellular proliferation, decreases the incidence of infection, and shortens hospital stay in some catabolic patients. **CONCLUSIONS:** Glutamine has been studied extensively over the past decade for its role during critical illness. Clinical trials conducted in humans demonstrate glutamine to be well tolerated without adverse consequences, even during times of stress. Although glutamine has shown promise in select groups of catabolic patients, additional studies are needed to define which patient populations derive the greatest benefit from supplemental glutamine and the mechanisms by which these effects are exerted

Pretreatment with antioxidants and allopurinol diminishes cardiac onset events in coronary artery bypass grafting.

Sisto T, Paajanen H, Metsa-Ketela T, et al.

Ann Thorac Surg. 1995 Jun; 59(6):1519-23.

Oxygen-derived free radicals constitute one part of the etiologic factors for cardiac onset harmful events. Allopurinol is able to

reduce the generation of free radicals. Vitamins E and C scavenge radicals after their formation. Eighty-one patients with coronary artery disease were randomized into four study groups: Group 1 (n = 20) patients had stable disease and received oral vitamin E for 4 weeks, and vitamin C and allopurinol 2 days before and 1 day after coronary artery bypass grafting. Group 2 (n = 25) consisted of their controls. Group 3 patients (n = 17) had more unstable disease and received the same medications as group 1, except that vitamin E was given only 2 days before the operation. Group 4 (n = 19) was their controls. Groups 1 and 3 had fewer ischemic electrocardiographic events and required less dopamine perioperatively than corresponding control groups 2 and 4. Group 3 had fewer perioperative infarctions and less creatine kinase-MB release than the respective controls (group 4). Plasma levels of vitamins E and C, urate, and total free radical trapping ability were considered to support the theory about the role of free radicals in reperfusion injury. Especially the unstable patients, but also patients with stable coronary artery disease requiring coronary artery bypass grafting benefit from perioperative allopurinol and vitamin E and C treatment

Essential Neuropharmacology.

Stahl S.

1996;

Evidence that synaptically-released zinc contributes to neuronal injury after traumatic brain injury.

Suh SW, Chen JW, Motamedi M, et al.

Brain Res. 2000 Jan 10; 852(2):268-73.

Prior evidence indicates that synaptically-released zinc enters postsynaptic neurons in toxic excess during ischemia and seizures. In addition, prevention of this zinc translocation has been shown to be neuroprotective in both ischemia and seizures. Here we show evidence that the same translocation of zinc from presynaptic boutons into postsynaptic neurons occurs after mechanical injury to the brain. Specifically, using a rat model of traumatic brain injury, we show that trauma is associated with (i) loss of zinc from presynaptic boutons (ii) appearance of zinc in injured neurons, and (iii) neuroprotection by intraventricular administration of a zinc chelator just prior to brain impact. The possible use of zinc chelators for neuroprotection after head trauma is considered

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The inhibitory effects of carvedilol against arrhythmias induced by coronary reperfusion in anesthetized rats.

Takusagawa M, Komori S, Matsumura K, et al.

J Cardiovasc Pharmacol Ther. 2000 Apr; 5(2):105-12.

BACKGROUND: Previous study has shown the antiarrhythmic effects of carvedilol on isolated rat hearts, but little is known about the mechanism of this protective action. This article examines the inhibitory effect of carvedilol against arrhythmias induced by reperfusion in anesthetized rats. In addition, the results are compared with those with propranolol, superoxide dismutase (SOD) plus catalase, and a combination of both in order to elucidate the mechanism of the protective actions. **METHODS AND MATERIALS:** Ninety percent of the rats in the control group showed lethal ventricular fibrillation (VF). Carvedilol at the doses of 0.03, 0.1, and 0.3 mg/kg significantly reduced the incidence of lethal VF to 0%, 0%, and 10%, respectively ($P < .05$). In contrast, propranolol at the doses of 0.3, 1.0, and 3.0 mg/kg and SOD (35,000 units/kg) plus catalase (400,000 units/kg) did not reduce the incidence of lethal VF (80%, 60%, 70%, and 70%, respectively). However, administration of a combination of propranolol (1.0 mg/kg) and SOD plus catalase completely inhibited the occurrence of lethal VF to 0% ($P < .05$). **CONCLUSION:** These results indicate that carvedilol has the inhibitory effect against reperfusion arrhythmias in rats and suggest

that the mechanism of action of this compound is related to the combined effects of beta-blocking and antioxidant

Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators.

Taylor DW, Barnett HJ, Haynes RB, et al.

Lancet. 1999 Jun 26; 353(9171):2179-84.

BACKGROUND: Endarterectomy benefits certain patients with carotid stenosis, but benefits are lessened by perioperative surgical risk. Acetylsalicylic acid lowers the risk of stroke in patients who have experienced transient ischaemic attack and stroke. We investigated appropriate doses and the role of acetylsalicylic acid in patients undergoing carotid endarterectomy. **METHODS:** In a randomised, double-blind, controlled trial, 2849 patients scheduled for endarterectomy were randomly assigned 81 mg (n=709), 325 mg (n=708), 650 mg (n=715), or 1300 mg (n=717) acetylsalicylic acid daily, started before surgery and continued for 3 months. We recorded occurrences of stroke, myocardial infarction, and death. We compared patients on the two higher doses of acetylsalicylic acid with patients on the two lower doses. **FINDINGS:** Surgery was cancelled in 45 patients, none were lost to follow-up by 30 days, and two were lost by 3 months. The combined rate of stroke, myocardial infarction, and death was lower in the low-dose groups than in the high-dose groups at 30 days (5.4 vs 7.0%, p=0.07) and at 3 months (6.2 vs 8.4%, p=0.03). In an efficacy analysis, which excluded patients taking 650 mg or more acetylsalicylic acid before randomisation, and patients randomised within 1 day of surgery, combined rates were 3.7% and 8.2%, respectively, at 30 days (p=0.002) and 4.2% and 10.0% at 3 months (p=0.0002). **INTERPRETATION:** The risk of stroke, myocardial infarction, and death within 30 days and 3 months of endarterectomy is lower for patients taking 81 mg or 325 mg acetylsalicylic acid daily than for those taking 650 mg or 1300 mg

Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial.

Tepaske R, Velthuis H, Oudemans-van Straaten HM, et al.

Lancet. 2001 Sep 1; 358(9283):696-701.

BACKGROUND: Elderly patients and those with poor ventricular function have increased morbidity and mortality rates when undergoing surgery. We aimed to ascertain whether an oral immune-enhancing nutritional supplement could improve preoperative host defence, and subsequently lower postoperative infections and organ dysfunction in patients undergoing elective cardiac surgery who are at high risk of infection. **METHODS:** In this prospective, randomised, double-blind, placebo-controlled study, we randomly assigned 50 patients who were scheduled to undergo coronary artery bypass to receive either an oral immune-enhancing nutritional supplement containing L-arginine, omega3 polyunsaturated fatty acids, and yeast RNA (n=25), or a control (n=25) for a minimum of 5 days. Patients were included if they were aged 70 years or older, or had an ejection fraction of less than 0.4, or were scheduled to undergo mitral valve replacement. The main outcome was preoperative host defence (delayed-type hypersensitivity response to recall antigens, expression of HLA-DR epitopes on monocytes, and concentration of interleukin 6 in plasma). Analysis was per protocol. **FINDINGS:** Five patients (two in the treatment group) were excluded because they did not take the minimum dose. Preoperative expression of HLA-DR epitopes on monocytes was significantly higher in patients given the study treatment (109% [95% CI 92-128]) than those given the control (69% [58-82]) compared with baseline (100%) (p=0.02, repeated measures ANOVA). However, concentration of interleukin 6 was significantly lower in the treatment group (0.90 pg/L [0.69-1.18]) than in the control group (1.94 pg/L [1.45-2.59]) (p=0.032, repeated measures ANOVA). Additionally, delayed-type hypersensitivity response to recall antigens improved preoperatively and remained better until hospital discharge. **INTERPRETATION:** Intake of an oral immune-enhancing nutritional supplement for a minimum of 5 days before surgery can improve outlook in high-risk patients who are undergoing elective cardiac surgery

Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes.

Umpierrez GE, Isaacs SD, Bazargan N, et al.

J Clin Endocrinol Metab. 2002 Mar; 87(3):978-82.

Admission hyperglycemia has been associated with increased hospital mortality in critically ill patients; however, it is not known whether hyperglycemia in patients admitted to general hospital wards is associated with poor outcome. The aim of this study was to determine the prevalence of in-hospital hyperglycemia and determine the survival and functional outcome of patients with hyperglycemia with and without a history of diabetes. We reviewed the medical records of 2030 consecutive adult patients admitted to Georgia Baptist Medical Center, a community teaching hospital in downtown Atlanta, GA, from July 1, 1998, to October 20, 1998. New hyperglycemia was defined as an admission or in-hospital fasting glucose level of 126 mg/dl (7 mmol/liter) or more or a random blood glucose level of 200 mg/dl (11.1 mmol/liter) or more on 2 or more determinations.

Hyperglycemia was present in 38% of patients admitted to the hospital, of whom 26% had a known history of diabetes, and 12% had no history of diabetes before the admission. Newly discovered hyperglycemia was associated with higher in-hospital mortality rate (16%) compared with those patients with a prior history of diabetes (3%) and subjects with normoglycemia (1.7%; both $P < 0.01$). In addition, new hyperglycemic patients had a longer length of hospital stay, a higher admission rate to an intensive care unit, and were less likely to be discharged to home, frequently requiring transfer to a transitional care unit or nursing home facility. Our results indicate that in-hospital hyperglycemia is a common finding and represents an important marker of poor clinical outcome and mortality in patients with and without a history of diabetes. Patients with newly diagnosed hyperglycemia had a significantly higher mortality rate and a lower functional outcome than patients with a known history of diabetes or normoglycemia

Intensive insulin therapy in the critically ill patients.

Van den BG, Wouters P, Weekers F, et al.

N Engl J Med. 2001 Nov 8; 345(19):1359-67.

BACKGROUND: Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known. **METHODS:** We performed a prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter [4.4 and 6.1 mmol per liter]) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter [11.9 mmol per liter] and maintenance of glucose at a level between 180 and 200 mg per deciliter [10.0 and 11.1 mmol per liter]). **RESULTS:** At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent ($P < 0.04$, with adjustment for sequential analyses). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2 percent with conventional treatment, as compared with 10.6 percent with intensive insulin therapy, $P = 0.005$). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care. **CONCLUSIONS:** Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit

Melatonin protects against ischemia and reperfusion-induced oxidative lipid and DNA damage in fetal rat brain.

Wakatsuki A, Okatani Y, Izumiya C, et al.

J Pineal Res. 1999 Apr; 26(3):147-52.

To investigate whether melatonin reduces the susceptibility of the fetal rat brain to oxidative damage of lipids and DNA, we created a model of fetal ischemia/reperfusion using rats at day 19 of pregnancy. Fetal ischemia was induced by bilateral occlusion of the utero-ovarian artery for 20 min. Reperfusion was achieved by releasing the occlusion and restoring the circulation for 30 min. A sham operation was performed in control rats. Melatonin (10 mg/kg) or vehicle was injected intraperitoneally 60 min prior to the occlusion. We measured the concentration of thiobarbituric acid reactive substances (TBARS) in fetal brain homogenates, as well as levels of deoxyguanosine (dG) and 8-hydroxydeoxyguanosine (8-OHdG) in DNA extracted from those homogenates. Ischemia for 20 min did not significantly alter the levels of dG, 8-OHdG, and TBARS. Subsequent reperfusion, however, led to a significant reduction in the dG level ($P < 0.05$) and to significant increases in the levels of 8-OHdG ($P < 0.05$) and TBARS ($P < 0.05$), and in the 8-OHdG/dG ratio ($P < 0.005$). Melatonin administration prior to ischemia significantly reduced the ischemia/reperfusion-induced increases in the levels of 8-OHdG (14.33 ± 6.52 vs 5.15 ± 3.28 pmol/mg of DNA, $P < 0.001$) and TBARS (11.61 ± 3.85 vs 4.73 ± 3.80 nmol/mg of protein, $P < 0.001$) as well as in the 8-OHdG/dG ratio (7.19 ± 2.49 vs 1.61 ± 0.98 , $P < 0.001$). Furthermore, melatonin significantly increased the dG level (210.19 ± 49.02 vs 299.33 ± 65.08 nmol/mg of DNA, $P < 0.05$). Results indicate that melatonin administration to the pregnant rat may prevent the ischemia/reperfusion-induced oxidative lipid and DNA damage in fetal rat brain

Management of diabetes and hyperglycaemia during myocardial infarction: review of the literature.

Walker EF.

Intensive Crit Care Nurs. 1999 Oct; 15(5):259-65.

For many years now, research has firmly demonstrated the increased mortality in patients with diabetes following myocardial

infarction (MI), a prognosis which has persisted despite major advances in acute coronary care. Research has also shown higher than usual mortality rates in patients without known diabetes presenting with hyperglycaemia during MI. Due to a lack of research evidence, little has been established about how best to manage glycaemic control in these patients during the acute phase of an MI. However, a recent clinical trial has had considerable impact on coronary care practice. It advocates intravenous insulin therapy for all diabetics and patients with hyperglycaemia during acute MI, followed by subcutaneous insulin for three months, regardless of previous treatment. The evidence for mortality benefit is substantial, but the trial has left some questions unanswered. The aim in this literature review is to examine critically the research basis for using insulin during and after MI, and to identify the potential impact of the research on patients and nurses. The author searched the CINAHL and MEDLINE indexes for relevant texts in English from 1975 to 1998, and has recently implemented relevant knowledge from this research into her own work area, a coronary care unit in the north of England

[Indications for hyperbaric oxygen therapy. Organization of the treatment unit. Training of personnel].

Wattel F, Mathieu D, Neviere R.

Bull Acad Natl Med. 1996 May; 180(5):949-63.

Pathophysiologic mechanisms involved in the application of HBO therapy are poorly understood that may limit its clinical use. However, useful indications are well standardized in the setting of critical care medicine, CO poisoning, decompression sickness, gas gangrene and soft tissue anaerobic infections, crush syndrome, burns, sudden deafness... HBO therapy is also indicated in the management of chronic limb ischemia, diabetic foot lesion, osteomyelitis, osteoradionecrosis. These clinical indications have been evaluated in a Consensus Conference on Hyperbaric Medicine that has classified its application according to its efficiency. Indications were classified as strongly recommended (positively affects the patient's survival), recommended (does not influence the patient's survival but is important for the prevention of serious disorders) and optional (regarded as a additional treatment modality). Clinical application of HBO therapy requires specific equipment including a multiplace hyperbaric chamber and specific educational program and training for personnel employed in the clinical hyperbaric center. Lastly, HBO therapy is related to accurate rules defining its indications as well as its evaluation that are minimal prerequisites for safety and clinical results

The mechanisms of coenzyme Q10 as therapy for myocardial ischemia reperfusion injury.

Whitman GJ, Niibori K, Yokoyama H, et al.

Mol Aspects Med. 1997; 18 Suppl:S195-S203.

It has been hypothesized that CoQ10 (CoQ) pretreatment protects myocardium from ischemia reperfusion (I/R) injury by its ability to increase aerobic energy production as well as its activity as an antioxidant. Isolated hearts from rats pretreated with either CoQ 20 mg/kg i.m. and 10 mg/kg i.p. or vehicle 24 and 2 h prior to the experiment, were subjected to 15 min of equilibration (EQ), 25 min of ischemia, and 40 min of reperfusion (RP). Developed pressure, +/-dp/dt, myocardial oxygen consumption, and myocardial aerobic efficiency (DP/MVO₂) were measured. ³¹P NMR spectroscopy was used to determine ATP and PCr concentrations. Lucigenin-enhanced chemiluminescence of the coronary sinus effluent was utilized to determine oxidative stress through the protocol. CoQ pretreatment improved myocardial function after ischemia reperfusion. CoQ pretreatment improved tolerance to myocardial ischemia reperfusion injury by its ability to increase aerobic energy production, and by preserving myocardial aerobic efficiency during reperfusion. Furthermore, the oxidative burst during RP was diminished with CoQ. Similarly it was hypothesized that CoQ protected coronary vascular reactivity after I/R via an antioxidant mechanism. Utilizing a newly developed lyposomal CoQ preparation given i.v. 15 min prior to ischemia, ischemia reperfusion was carried out on Langendorff apparatus as previously described. Just prior to ischemia and after RP, hearts were challenged with bradykinin (BK) and sodium nitroprusside (SNP) and change in coronary flow was measured. CoQ pretreatment protected endothelial-dependent and endothelial-independent vasodilation after I/R. We conclude that CoQ pretreatment protects coronary vascular reactivity after I/R via OH radical scavenger action

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