Sweet Heartaches

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Heart and Pancreas: a pulsating handshake

Pulse pressure (PP) (the difference between systolic and diastolic blood pressure), Cardiovascular disease (CVD) and type 1 diabetes- the connections are clear. A large cross-sectional, case-control study of almost 3000 diabetic patients was conducted in Finland recently to compare the age-related blood pressure changes in type 1 diabetic patients with those in non-diabetic individuals.[1] Pulse pressure, an important predictor of cardiovascular disease and possibly the most powerful blood pressure index in predicting CVD endpoints in older patients, was found to be higher and more rapidly increasing in diabetic individuals as compared to controls. This critical new finding suggests that blood pressure patterns differ markedly in diabetic and non-diabetic subjects. The premature rise in PP is strongly associated with the time of onset of diabetes and to the development of diabetic renal dysfunction. Although previous studies[2] have shown that the prevalence of essential hypertension in type 1 diabetics without renal dysfunction is similar to that in the general population, this study provides new evidence that type 1 diabetes is associated with a deleterious blood pressure pattern, even in the absence of diabetic kidney disease. The authors further explain that the premature rise in PP observed in their sample could be an explanation for the increased risk of CVD in type 1 diabetic patients without kidney disease. In view of the fact that antihypertensive treatment greatly lowers the risk of CVD (and this reduction is more pronounced in diabetic patients), the authors emphasize their finding that isolated systolic hypertension is observed in younger middle-aged patients with type 1 diabetes (15-20 years younger than non-diabetic controls) without any signs of diabetic nephropathy.

1. Ronnback. Altered age-related blood pressure pattern in type 1 diabetes. Circulation 2004;110:1076-82.
2. Norgaard. Prevalence of hypertension in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1990;33:407-10.

ACE-ing Albuminuria

This Italian double-blind randomized placebo-controlled multi-centre trial was conducted to assess whether ACE inhibitors and non-dihydropyridine calcium channel blockers, alone or in combination, prevent microalbuminuria in type 2 diabetic patients with high blood pressure and normal urinary albumin secretion.[1] The study was critically important because renal dysfunction affects one-third of patients with diabetes and the first clinical sign of renal dysfunction in these patients is generally microalbuminuria. Approximately 1200 subjects were randomized in the study and followed for over 3.5 years. Trandolapril plus verapamil significantly reduced the incidence of microalbuminuria and normal urinary albumin secretion, as compared with placebo. The physiological significance of this result is renal and possibly cardio-protection. Recent clinical trials have shown that inhibition of the renin-angiotensin system may actually prevent nephropathy. The authors also suggest that in type 2 diabetic patients, with hypertension and normal renal function, ACE inhibitors may be the medication of choice in controlling blood pressure. The conclusion: 'The apparent advantage of ACE inhibitors over other agents includes a protective effect on the kidney against the development of microalbuminuria, which is a major risk factor for cardiovascular events and death in this population.'

1. Ruggenenti P. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941-51.

Imidazole links diabetes and hypertension

The effects of clonidine, an alpha-2 receptor antagonist anti-hypertensive agent, are blocked by imidazoles. This led to the hypothesis that there are imidazole receptors (IR) in the brain. Imidazole-4-acetic acid (IAA) is a GABA-A receptor agonist and produces CNS effects such as analgesia, sedation, hypnosis, aggression and hypotension. Although IAA was originally thought not to exist in the brain, it was recently shown to be synthesized in mammalian brain from histidine. It exists as an active ribotide, which can be cleaved by 5'-nucleotidases to an inactive riboside form. Prell et al. demonstrate the central and peripheral physiological roles of IAA.[1] They show that IAA-ribotide functions as a neurotransmitter in the brain. Antibodies against the ribotide form of IAA strongly stained the rostroventrolateral medulla (RVLM) neurons. RVLM is an important brainstem region where imidadole-derived antihypertensive drugs act. However, microinjection of IAA-ribotide in the rat ventricular system resulted in hypertension instead of hypotension. The authors show that blood pressure (BP) control by IAA is mediated through two types of receptors - the high affinity type 3 receptors which increase BP and low affinity type 1 recep-

that blood pressure (BP) control by IAA is mediated through two types of receptors - the high affinity type 3 receptors which increase BP and low affinity type 1 receptors, which lower BP. Type 3 IRs are present in pancreatic islet cells as well. IAA-ribotide was shown to be highly potent at causing insulin release however its high concentrations were inhibitory. The authors postulate that at low concentrations IAA-ribotide may be acting at type 3 IRs whereas at high doses it may act at alpha 2-receptors to decrease insulin release. Thus, in high doses IAA, as a neurotransmitter may overstimulate brainstem IRs leading to hypertension and as a hormone in the periphery may lead to diabetes.

1. Prell GD. Imidazoleacetic acid-ribotide: an endogenous ligand that stimulates imidazol(in)e receptors. Proc Natl Acad Sci 2004;10:13677-82.

Heart-Kidney ballet

Outcome of acute myocardial infarction (AMI) is significantly influenced by coexisting morbidities. Renal dysfunction is associated with one of the highest risks for adverse events post-AMI. The VALIANT trial (valsartan) compared two groups of about 15 thousand patients of AMI based on GFR.[1] They estimated GFR using 'Modification of Diet in Renal Disease' (MDRD) equation, which states that GFR=186xserum creatinine-1.154 (mg/dl) x age$^{-0.203}$ (years). This has been shown to be a very accurate estimate of GFR. The study shows that as GFR decreases adverse cardiovascular outcomes increase. Below 81.0 ml/ min/1.73m^2, each reduction in GFR of 10 units was associated with a 10% increase in relative risk of death or nonfatal cardiovascular complications. Thus, even mild renal dysfunction should be considered a major risk factor for cardiovascular complications post-AMI and GFR instead of serum creatinine should be used as a measure to assess renal function.

1. Anavekar NS et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285-95.

Is diet enough?

Patients with diet-controlled diabetes are generally less thoroughly managed and studied by clinical and research groups respectively. A large UK-based cross-sectional study of about 8000 patients with type 2 diabetes was recently conducted with the specific aim of determining the proportion of patients with diet-controlled diabetes and of comparing level of complications and quality of care compared with patients on hypoglycemic medications.[1] Patients on diet-controlled diabetes were less thoroughly monitored in general. Even routine tests (e.g. HbA1C) were infrequently done on these patients. Although some patients with type 2 diabetes may be managed adequately with diet alone, more thorough monitoring (especially if blood sugar levels, blood pressure and cholesterol levels are not optimum) is required along with greater consistency in clinical practice regarding the decision to start medications. The study provides strong evidence to reinforce that diabetics treated by diet only need to be managed more thoroughly within general practice.

1. Hippisley-Cox J, Pringle M. Prevalence, care, and outcomes for patients with diet-controlled diabetes in general practice: cross sectional survey. Lancet. 2004;364:423-8.

Magic touch for Vertigo

Dizziness is one of the commonest complaints of patients presenting to the Emergency Department (ER). Vertigo, a cause of dizziness, is defined as an illusion of motion and results from Benign Positional Vertigo (BPV).

The Epley maneuver is a simple bedside maneuver which provides a vertiginous patient with immediate relief, without the need for an intravenous line, medications, imaging studies or lab work. First described in 1992, it remains unknown to most ER physicians.

In point form, the maneuver is as follows:

1. Turn patient's head 45 degrees to one side
2. Guide patient to supine position, with head hanging over the edge of the bed
3. Turn patient's head 90 degrees to the other side
4. Ask patient to roll over onto one side with head rotated so that head faces downward
5. Raise patient to sitting position and move head 45 degrees forward

Each position should be held for at least 30 seconds, or till nystagamus and/or resolution of vertigo occurs. Total time to perform this maneuver is about 2-3 minutes. A recent American trial showed that the Epley maneuver was significantly more efficacious than a placebo maneuver in the treatment of Acute BPV in patients presenting to the ER.[1]

1. Chang AK, Schoeman G, Hill M. A randomized clinical trial to assess the efficacy of the epley maneuver in the treatment of acute benign positional vertigo. Acad Emerg Med. 2004;11:918-24.

Lung development

The Children's Health Study[1] is a notable research effort that began in the early 1990's aiming to determine the extent of harm air pollution may have on children. The

the extent of harm air pollution may have on children. The authors designed a large, rigorous prospective study which monitored lung function of school children from the ages of 10 to 18 years in 12 southern California communities with a relatively wide range of air pollutants. This is perhaps the first study ever to follow children for such a long duration of time and to study lung development along with other parameters of lung function. Lung development was significantly affected by a correlated set of pollutants that included fine particulate matter, nitrogen dioxide, acid vapour and elemental carbon. The primary source of these pollutants is motor vehicles. The strength of this study, coupled with the importance of lung function as a determinant of morbidity and mortality in adulthood, warrant continued and greater emphasis on the reduction of air pollution. Of note is the fact that air pollution has been implicated beyond doubt with pulmonary and cardiovascular disease.

1. Gauderman WJ et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med. 2004;351:1057-67.

Heart Attacks

Potential external triggers for myocardial infarction (MI) include strenuous exercise, anger, cocaine and marijuana use. Particulate matter from air pollution has been added to this list recently. It had previously been shown that residents of areas close to major roads and highways were at significantly increased risk of death due to cardiopulmonary causes than those who lived far away.[1] Peters et al. investigated the association between the onset of MI and exposure to traffic.[2] Exposure to traffic was more frequent on the day of MI (~6%) compared to previous 3 days (~5%). Being in traffic an hour before onset of MI, increased its risk 3 times. Travel by car was the most common source of exposure to traffic. Cyclists had a slightly reduced risk compared to car-commuters perhaps because they may be able to leave congested situations (e.g. traffic jams) more quickly than people in cars or buses. The biological plausibility of this finding and stresses on the need for improved city planning and air quality is warranted.[3]

1. Hoek G. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet. 2002;360:1203-9.

2. Peters A. Exposure to traffic and the onset of myocardial infarction. N Engl J Med. 2004;351:1721-30.

3. Stone PH. Triggering myocardial infarction. N Engl J Med 2004;351:1716-18.