The new cardiovascular continuum

The cardiovascular continuum

The cardiovascular continuum was first proposed by Dzau and Braunwald[1] in 1991 as a new paradigm for cardiovascular diseases (Fig). It arose from the realisation that cardiovascular events such as heart failure and myocardial infarction are really late complications in a chain of events that starts with a number of cardiovascular risk factors and continues as a progressive pathogenic process lasting for decades. Atherosclerosis, myocardial necrosis, and heart failure cannot be reversed easily, if at all, so addressing the early components of the continuum—such as hypertension, diabetes, hyperlipidaemia, and smoking—offers a chance of arresting the progression of cardiovascular disease at an early stage. These cardiovascular risk factors are rarely immediately life-threatening, but because they are asymptomatic, much effort has been devoted to screen for them and to modify them by lifestyle changes and drug treatment.[2]

Antihypertensive drugs and statins demonstrate the clinical utility of the cardiovascular continuum concept, namely, that the correction of cardiovascular risk factors prevents escalation of cardiovascular disease and downstream complications including myocardial infarction, stroke, and ultimately, death.[2,3] Angiotensin-converting enzyme inhibitors, for example, address different parts of the continuum, including hypertension, diabetes, left ventricular hypertrophy, remodelling, and heart failure.[1] Research into cardiovascular risk factors suggests that 80% of cardiovascular events can be prevented, using either existing drugs or the "polypill".[4] Can we do better by preventing cardiovascular disease itself?

Obesity and the metabolic syndrome

Hypertension, diabetes, and hyperlipidaemia are all related to obesity as part of the metabolic syndrome, which was first identified by Reaven[5] nearly two decades ago. In fact, type 2 diabetes, hyperlipidaemia, and hypertension all respond to diet and weight control.[2,6] Conventionally, the body mass index (BMI) is used to quantify obesity, and in Asia, a BMI of 23 is already associated with a much increased cardiovascular risk. However, waist circumference is more closely associated with cardiovascular risk than BMI.[7] Abdominal obesity results in insulin resistance and the metabolic syndrome through multiple and complex mechanisms, such as the active role adipose tissues play in energy homeostasis and the secretion of hormones, including leptin, adiponectin, resistin, and acylation-stimulating protein, that regulate appetite and insulin sensitivity.[8] Thus, abdominal or central obesity (which is more common in men than women) is clearly a target for intervention.

Obesity and inflammation

In adipose tissues, fat-laden adipocytes attract macrophages and initiate a vicious cycle of inflammation.[9] Plasma C-reactive protein (CRP), an inflammatory marker, increases with obesity, even in children[10]; losing weight reduces it. Elevated CRP levels are predictive of future development of diabetes and cardiovascular events.[11]

Adipocytes also secrete tumour necrosis factor alpha and plasminogen activator inhibitor-1.[8] Inflammation in adipose tissues is, therefore, an early event in the cardiovascular continuum, preceding the development of diabetes, endothelial dysfunction, and atherosclerotic disease. An increase in pro-inflammatory cytokines and a decrease in adiponectin may lead to endothelial dysfunction and facilitate the development of hypertension and atherosclerosis.

Diet and obesity

Obesity is caused by calorie intake in excess of energy requirements. In modern, urban society, automation and the ready availability and commercial promotion of foods with high energy content all contribute to weight gain. Exercise reduces body weight and reverses endothelial dysfunction,[12] but the amount of exercise recommended in the latest WHO directive[13] (at least 30 minutes each day) is often not feasible without profound changes in lifestyle, such as fewer social engagements, and less television viewing and internet use. Publications in leading journals suggest that the current recommendation of a low-fat high-carbohydrate diet may be wrong: a low carbohydrate diet is more effective than a low-fat diet in inducing weight loss.[14] Dr Atkins was right: one can eat steaks and lose weight effectively. Surprisingly, a low carbohydrate diet will significantly raise high density lipoprotein–cholesterol but not low density lipoprotein–cholesterol, and will reduce plasma triglycerides and CRP.[15]

Not all carbohydrates are equally bad. The concept of the glycaemic index is useful and is directly relevant to diabetes and the metabolic syndrome. Foods with high glycaemic indices are undesirable because a high blood glucose peak stimulates insulin secretion, causing hunger a few hours later.[16] Foods with low glycaemic indices release glucose more gradually. In a study in laboratory animals comparing diets of low and high glycaemic indices with the same total calories, rats and mice weighed the same in both groups, but the animals fed the high glycaemic index diet had twice as much body fat and a lower lean body mass.[17]

Polished rice, the staple food in much of Asia, is low in fibre with a high glycaemic index ranging from 50 to 94, depending on the variety of rice and how it is cooked. Congee, popularly believed to be a healthy food item, can

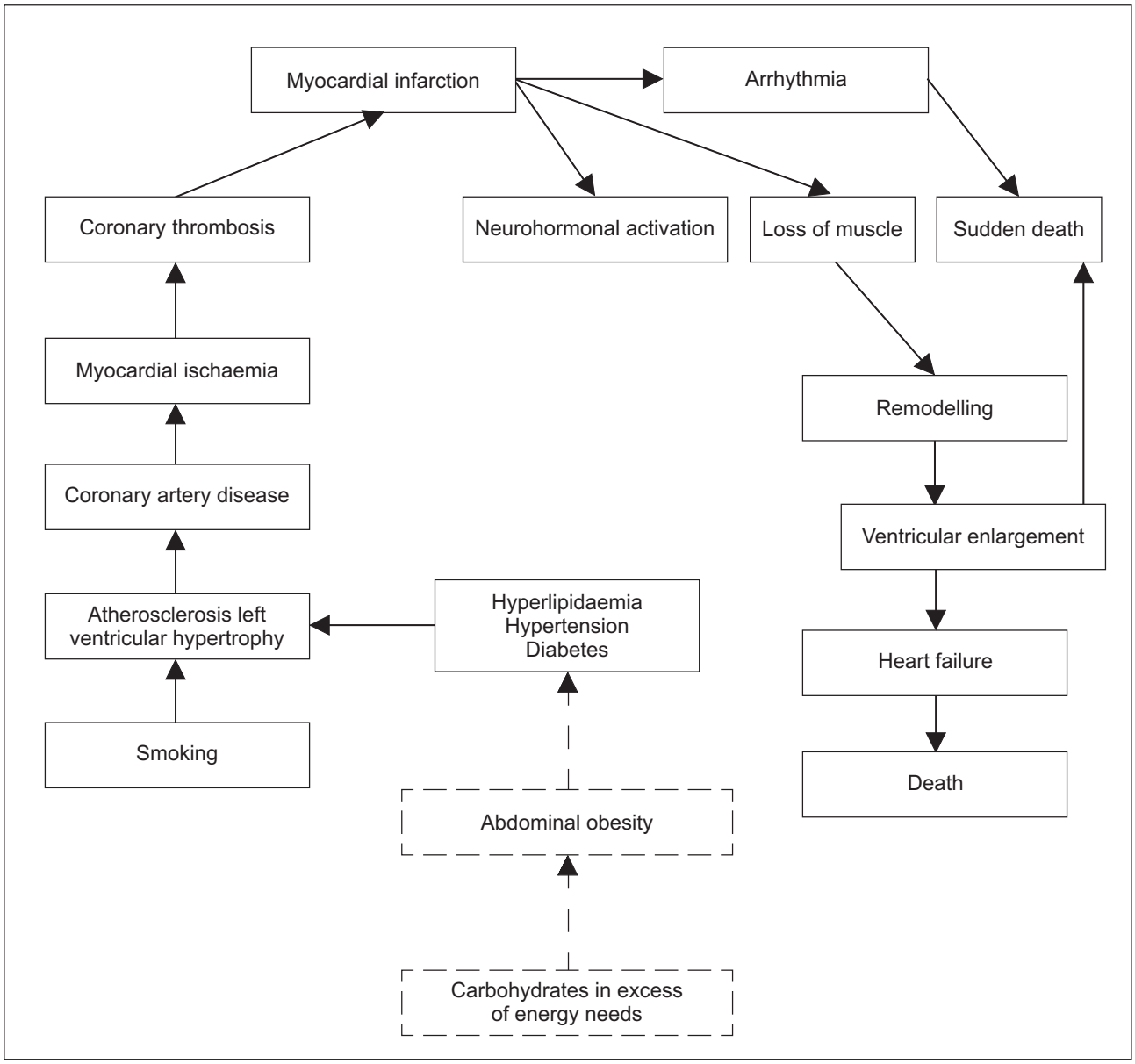

Fig. The cardiovascular continuum
The two boxes in dotted lines at the bottom are hypothetical (adapted from Dzau and Branwald[1])

cause a particularly high peak in plasma glucose. Rice-based meals have a place in rural societies where people walk a lot and perform manual labour. To take a traditional Asian example, Sumo wrestlers have a lot of subcutaneous fat, but have little visceral fat because of heavy exercise. However, the appropriateness of such a diet for an urbanised society is now questionable. The Chinese diet, with low fat content and an abundance of green vegetables and rice, is comparable with the Mediterranean diet in healthiness. Paradoxically, Chinese populations have a very high incidence of impaired glucose tolerance. In the Hong Kong Cardiovascular Risk Factor Prevalence Survey-2 (CRISPS2) cohort,[18] one third of those who were over the age of 65 years had diabetes. A nutritional survey of the same cohort showed that the intake of rice and pasta was higher in diabetics of normal body weight.[19] Thus obesity and insulin resistance in much of Asia are not due to excess fat in the diet, but to carbohydrate intake in excess of energy expenditure requirements (Fig).

A new paradigm

Hypertension, diabetes, dyslipidaemia, and obesity need not be treated in different clinics using different sets of drugs. Obesity is at the centre of the metabolic syndrome and should be treated as seriously as hypertension and diabetes. Treatment of obesity not only reduces body weight, but also waist circumference, blood pressure, plasma glucose, and lipids. In theory, a change in diet should work; lifestyle changes have been shown to prevent

hypertension and diabetes.[6,20] A "polymeal" has been proposed as an alternative to the "polypill" to prevent cardiovascular disease through nutrition rather than drugs.[21] In practice, however, therapeutic lifestyle changes are plagued by poor compliance and high drop-out rates.

There are only five drugs currently approved by US Food and Drug Administration for the treatment of obesity, orlistat and sibutramine being the most widely used. If people cannot change their dietary habits, then drugs are needed to combat excess carbohydrates in the same way statins are used in hypercholesterolaemia. This is an area that urgently requires intensive research, as the epidemic of obesity is happening here and now. We can start by discarding the food pyramid, which, rather like those other pyramids in Egypt, is now of mainly historical interest. The US Department of Agriculture has now replaced the food pyramid with My Pyramid (http://www.mypyramid.gov), which is a step in the right direction to address the problem of obesity and cardiovascular health.

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