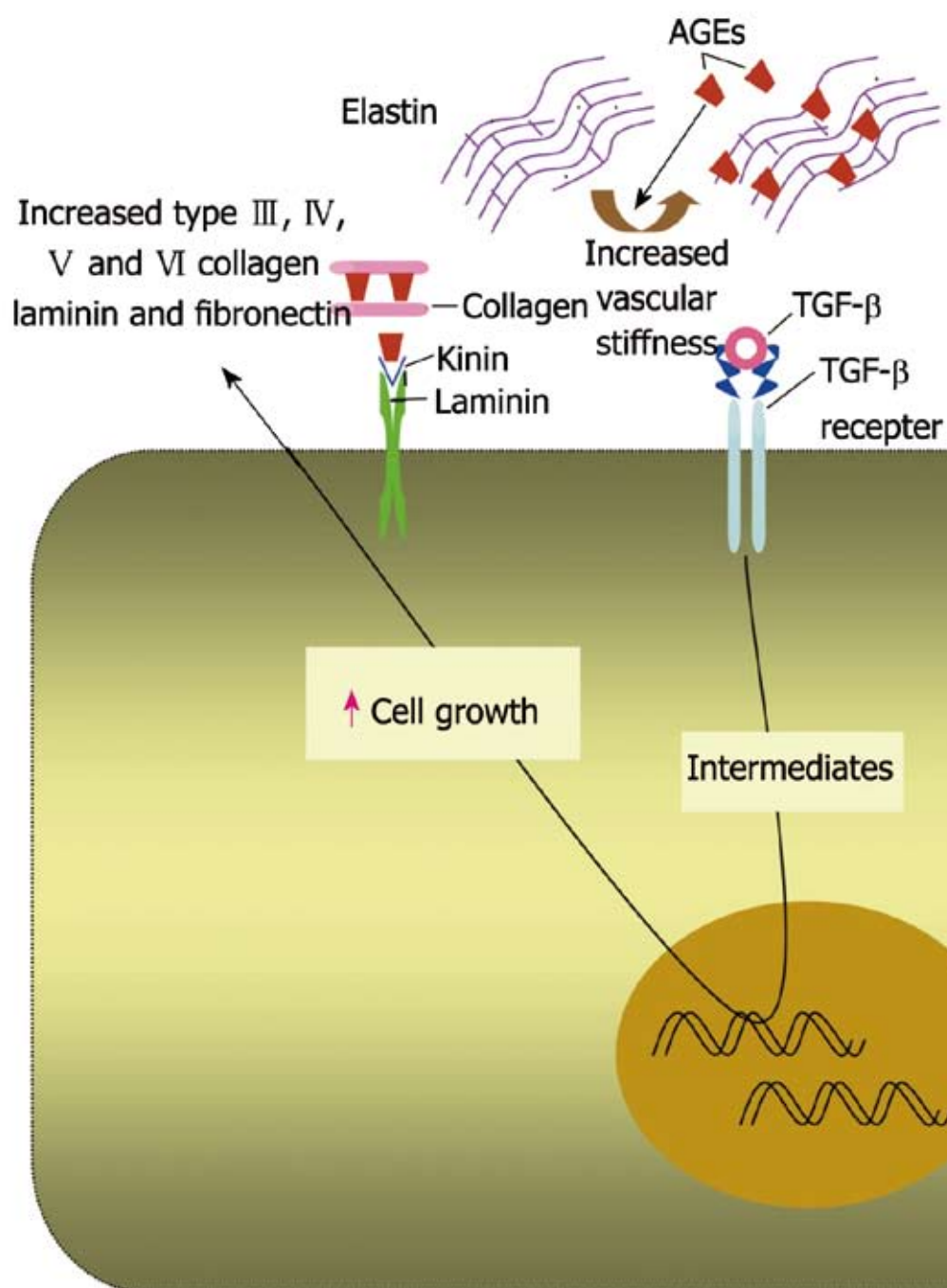


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Role of advanced glycation end products in cardiovascular disease

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Abstract

Advanced glycation end products (AGEs) are produced through the non enzymatic glycation and oxidation of proteins, lipids and nucleic acids. Enhanced formation of AGEs occurs particularly in conditions associated with hyperglycaemia such as diabetes mellitus (DM). AGEs are believed to have a key role in the development and progression of cardiovascular disease in patients with DM through the modification of the structure, function and mechanical properties of tissues through crosslinking intracellular as well as extracellular matrix proteins and through modulating cellular processes through binding to cell surface receptors [receptor for AGEs (RAGE)]. A number of studies have shown a correlation between serum AGE levels and the development and severity of heart failure (HF). Moreover, some studies have suggested that therapies targeted against AGEs may have therapeutic potential in patients with HF. The purpose of this review is to discuss the role of AGEs in cardiovascular disease and in particular in heart failure, focussing on both cellular mechanisms of action as well

as highlighting how targeting AGEs may represent a novel therapeutic strategy in the treatment of HF.

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Key words: Advanced glycation end products; Diabetes; Cardiovascular disease; Atherosclerosis; Heart failure

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INTRODUCTION

Advanced glycation end products (AGEs) are a heterogeneous group of molecules that are generated through non-enzymatic glycation and oxidation of proteins, lipids and nucleic acids^[1]. They alter tissue function and mechanical properties through crosslinking intracellular as well as extracellular matrix proteins^[2-6] and through binding to their cell surface receptor, receptor for AGEs (RAGE), they are capable of modulating multiple cellular processes^[7-9]. Enhanced formation and accumulation of AGEs has been reported to occur in conditions such as diabetes mellitus (DM) as well as in natural aging, renal failure and chronic inflammation^[10-12].

In vivo detectable AGEs include three main groups:

(1) Fluorescent cross-linking AGEs such as pentosidine

and crossline^[13]; (2) Non-fluorescent cross-linking AGEs such as imidazolium dilysine cross-links named either glyoxal lysine dimer or methylglyoxal lysine dimer result from reactions taking place between glyoxal derivatives and lysine residues^[14]; (3) Non-cross-linking AGEs such as N-carboxymethyllysine (CML)^[15].

In patients with diabetes, cardiovascular complications are the principal cause of morbidity and mortality and account for up to 65% of diabetic fatalities^[16]. It has been reported that 33% of diabetic patients on insulin therapy will have died from cardiovascular disease by the age of 50 years^[17]. It is thought that AGEs have a central role in the pathophysiological processes that lead to the development of such cardiovascular complications observed in diabetes. This review highlights how AGEs are formed, summarises the evidence for the role of AGEs in the development of cardiovascular complications in diabetic patients, as well as their underlying mechanisms of action and finally we review the potential of anti-AGE therapies for their use in clinical practice.

MAILLARD REACTION AND AGE SYNTHESIS

AGE are a spectrum of heterogeneous compounds that are derived from proteins, lipids and nucleic acids that are glycosylated or oxidized non-enzymatically in a process termed the “Maillard reaction”^[18]. D-glucose plays a primary role in glycation of proteins *in vivo* due to its high concentration in human plasma^[19]. The Maillard reaction starts as a reaction between the carbonyl group of a reducing sugar such as glucose and the amino acid of proteins, lipids or nucleic acids leading to the production of an unstable compound known as a “Schiff base”. This step is reversible and usually takes a few hours to occur. Over weeks the Schiff base turns into a more stable compound called the “Amadori” product through various molecular rearrangements. Over months and years, the Amadori products undergo further structural changes through a series of reactions such as oxidation, dehydration and degradation to finally yield highly stable AGE compounds^[20,21] (Figure 1).

Highly reactive dicarbonyl compounds are generated during the conversion of Amadori products to AGEs. Methylglyoxal and 3-deoxyglucosone are the best known AGE dicarbonyl precursors^[22-24]. *In vivo*, CML is the most abundant form of AGEs and is characterized by its highly antigenic nature^[25,26].

It has been reported that non-enzymatic glycation of proteins and formation of AGEs affects the protein physiological functions and is capable of inducing enzyme inactivation^[27]. The influence of such modifications on protein structure has been far less investigated. Recently, using nuclear magnetic resonance (NMR), Howard *et al.*^[28] have showed that glycation of a model helical peptide from human serum albumin (HSA) by glucose caused distortion of the helical structure of the protein at the point of glycation. Another protein struc-

tural study for the changes induced by non-enzymatic glycation in the secondary and tertiary protein structure of HSA showed that the in general protein structure was unaltered. Instead the change was only limited to local regions after glycation. This was revealed using fluorescence-dependant methods^[29].

AGES AND CARDIOVASCULAR DISEASE

AGEs are produced normally in the body and they accumulate by age and are considered not only as biomarkers of senescence but they correlate inversely with left ventricular ejection fraction (EF) and can predict the outcome of cardiac surgery in elderly patients. A direct linear correlation between CML levels in the pericardial fluid and the age of the patients was shown where mean CML level of 260.8 ± 19.7 ng/mL was detected in patients with mean age 52.2 ± 1.3 years, mean CML level of 293.4 ± 18.8 ng/mL was identified in patients with mean age 65.8 ± 0.6 years and mean CML level of 357.0 ± 28.3 ng/mL was recorded at mean age 75.1 ± 0.6 years^[30].

In addition, AGEs accumulate at a much higher rate in diabetics than in normal population. AGEs serum levels are much higher in diabetic patients when compared to normal non diabetic population. AGE serum levels have been reported in a number of clinical studies involving diabetic patients compared to healthy individuals. AGE levels were recorded as 7.4 U/mL in diabetic patients *vs* 4.2 U/mL in normal population, whereas CML levels reached 15.6 U/mL in diabetics *vs* 8.6 U/mL in nondiabetics. Serum AGEs were found to be significantly elevated in diabetic patients with coronary heart disease (CHD) (8.1 U/mL) *vs* diabetics without CHD (7.1 U/mL)^[31]. In another study concerned with AGE tissue levels and the severity of diabetic nephropathy, the average AGE content in arterial wall collagen of diabetics was significantly higher than that of samples obtained from nondiabetic patients (14.5 ± 5.2 U/mg *vs* 3.6 ± 1.5 AGE U/mg). Furthermore, it was revealed that AGE content in renal tissues obtained from diabetic patients with end-stage renal disease is as twice as AGE content in tissue of diabetic patients without renal disease (21.3 ± 2.8 U/mg *vs* 11.5 ± 1.9 AGE U/mg)^[32]. Serum levels of pentosidine were found to be significantly higher in patients with diabetes than in nondiabetic normal controls (64.4 ± 21.0 µg/L *vs* 22.8 ± 7.0 µg/L). Moreover, serum pentosidine levels were significantly higher in diabetic patients with cardiovascular disease than in those without (72.3 ± 23.7 µg/L *vs* 62.3 ± 19.8 µg/L) and they were found to correlate with increased arterial wall stiffness in diabetic patients^[33].

AGES AND CARDIOVASCULAR COMPLICATIONS OF DIABETES

As mentioned above, several studies have shown a positive association between serum and tissue AGEs and macro and microvascular complications of diabetes^[31,34-39].

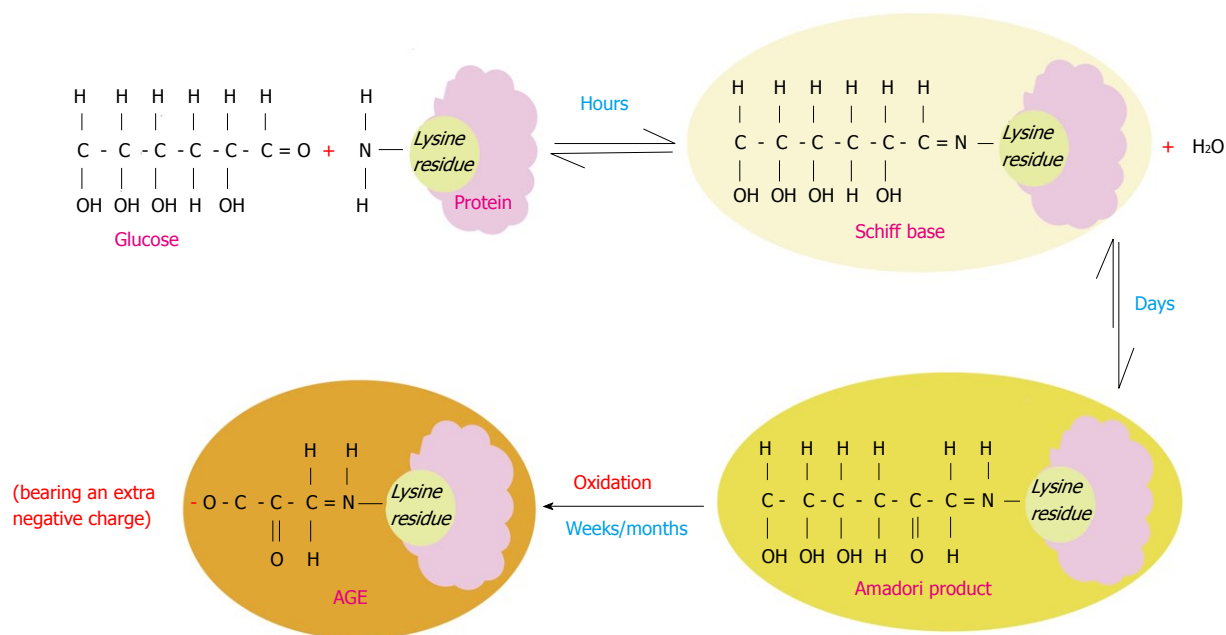


Figure 1 Maillard reaction. Schematic illustration of the Maillard process that starts by a non-enzymatic reaction of a protein lysine residue (as an example of the most common residues that get glycosylated) and glucose with consequent loss of a water molecule. This is a reversible reaction that takes place over a few hours leading to the formation of an unstable compound (Schiff base). The latter undergoes molecular rearrangements over a period of days yielding a more stable compound known as (the Amadori product). Over months/years, the Amadori product turns to a very stable compound known as advanced glycation end product (AGE) through a series of reactions such as oxidation. Therefore AGE molecules acquire more negative charges. AGEs are irreversible once they are formed. The Maillard reaction leads to denaturation and browning of the modified proteins.

The following sections overview how serum AGE levels correlate with the development and the progression of several cardiovascular complications of diabetes.

AGEs, coronary heart disease and diabetic heart failure

Elevated serum levels of AGEs such as CML have been documented in type 2 diabetic patients with coronary heart disease^[31]. AGEs have been detected in atherosclerotic lesions in coronary arteries of diabetic patients, suggesting a role of AGEs in the accelerated development of atherosclerosis reported in diabetics^[40]. Moreover, serum AGE levels have been shown to be a biomarker for the severity of coronary artery atherosclerosis in type 2 diabetic patients^[27] independent from other well known risk factors such as hypertension, hyperlipidaemia and smoking. Higher serum AGE levels were detected in type 2 diabetic patients with obstructive coronary artery disease in comparison to diabetics with non-obstructive coronary disease and AGE serum levels were found to correlate with the degree of the coronary atherosclerosis in those with obstructive coronary disease^[41]. AGE levels have also been reported to influence the success rate of coronary artery revascularization in patients with diabetes. Elevated serum AGE levels in patients undergoing percutaneous coronary intervention has been shown to be an independent risk factor for restenosis in diabetic patients^[42]. Following cardiac surgery, serum AGE levels also inversely correlate with left ventricular ejection fraction and are associated with prolonged ventilation time and prolonged stays on the Intensive Care Unit^[43,44].

Other studies have demonstrated that elevated serum

AGE levels have been shown to predict mortality due to coronary heart disease in female patients with type 2 diabetes followed up for 18 years^[31]. Similarly, increased serum AGE levels in type 1 diabetes have been shown to correlate with incident fatal as well as nonfatal cardiovascular events independent from other known cardiovascular risk factors such as age, body mass index, smoking, hypertension and hyperlipidaemia^[45].

The risk of development of cardiovascular disease is increased by a factor of 2-4 fold in diabetic patients^[46]. DM is considered to be an independent risk factor for incident heart failure (HF)^[47-49]. In the Framingham study (between the ages 45-74), the risk of developing HF was higher in diabetic males (2.4:1) and diabetic females (5:1) independent of age, obesity, hypertension, hyperlipidaemia and coronary artery disease^[50].

Elevated serum levels of AGEs in patients with diabetes accelerate the development and progression of heart failure both indirectly through their vascular effects (coronary dysfunction, atherosclerosis and thrombosis) and directly through direct actions on the myocardium. In the former, AGEs binding to their cell surface receptor (RAGE) on endothelial cells, smooth muscle cells and monocytes thereby inducing a wide range of signaling pathways that trigger inflammation, atherogenesis and vasoconstriction leading to coronary dysfunction, atherosclerosis and thrombosis^[14]. On the other hand, AGEs have been reported to have a direct effect on the myocardium independent of effects on the vascular tree, mediated in part *via* cross linking of extracellular cardiac proteins and through actions mediated by AGE

receptors expressed on the myocardium^[5,6,51]. AGEs have been implicated in the development of both systolic and diastolic cardiac dysfunction in diabetics which may explain the increased prevalence of heart failure in diabetic patients^[14,52]. It was shown by Steine *et al.*^[53] that serum AGE levels and duration of diabetes can predict systolic strain (as evaluated by doppler tissue imaging) in patients of type 1 diabetes. Moreover, Kilhovd *et al.*^[51] showed that parameters of left ventricular diastolic dysfunction, e.g., delayed isovolumetric relaxation time and reduced LV end-diastolic diameter correlate with elevated plasma AGE levels in type 2 diabetic patients. Similarly, Willemssen *et al.*^[54] showed that increased tissue levels of AGEs (as detected by increased skin autofluorescence) in diabetic heart failure patients are independently associated with diastolic dysfunction and consequently reduced exercise capacity in those patients in comparison to non-diabetic heart failure patients.

Serum AGE levels have been demonstrated as independent predictors of both the severity and prognosis in heart failure patients^[14,55]. Plasma pentosidine levels, one of the crosslinking AGEs, has been shown to be an independent predictor of both re-hospitalization and mortality in heart failure patients independent from other known risk factors such as brain natriuretic peptide (BNP), age, renal function and New York Heart Association (NYHA) functional class^[55]. Similarly, plasma levels of N-CML, one of the most prevalent antigenic AGEs in sera of diabetic patients, have been shown to correlate with NYHA functional class and predict outcomes in patients with systolic heart failure^[14].

Another study conducted by Neeper *et al.*^[56] showed that serum levels of soluble RAGE (sRAGE) are markers of the development and the progression of heart failure in diabetic and non-diabetic patients. The term sRAGE includes both cleaved RAGE (cRAGE) and endogenously secreted RAGE (esRAGE). The former is cleaved RAGE from cell surface by action of metalloproteinases that are increased in HF. This form lacks the V-domain and is therefore unable to neutralize AGEs. The latter is an endogenously secreted RAGE that helps to neutralize serum AGEs. Both higher serum levels of cRAGE and lower serum levels of esRAGE correlate with the severity of cardiac dysfunction, severity of symptoms and clinical outcomes in patients with heart failure^[56]. Similar findings have been recorded in a number of other HF studies. For instance, Koyama *et al.*^[57] have shown that serum levels of sRAGE correlate with NYHA functional class and that they are particularly higher in HF patients with preserved EF suggesting that they have a role in diastolic dysfunction. Furthermore, Koyama *et al.*^[57] reported that sRAGE levels are independent prognostic factors in HF^[57]. Similarly, Raposeiras-Roubín *et al.*^[58] also demonstrated that sRAGE is a highly sensitive and specific marker of prognosis of HF patients.

Other studies have yielded conflicting observations about the role of AGEs in the development of heart failure whether directly or indirectly. For instance, in

another study, the authors demonstrated that increased serum sRAGE levels are associated with increased severity of HF particularly in patients with an ischemic cause of heart failure although this correlation was shown to be independent of AGE serum levels^[59]. Similarly, in the study of Campbell *et al.*^[60], left ventricular biopsies were taken from pre-diabetic, type 2 diabetic and control subjects undergoing coronary heart bypass surgery to assess myocardial fibrosis and myocardial expression of the AGE N-CML and the RAGE. All the patients had similar degrees of coronary disease with no previous history of myocardial infarction or heart failure although diabetic patients exhibited diastolic dysfunction on echocardiography. The study demonstrated no significant differences in either myocardial AGE or RAGE expression between patient groups or the control group suggesting that myocardial AGE/RAGE expression was not an important factor in diastolic dysfunction development in diabetes. In a similar study in which endomyocardial biopsies of failing hearts of diabetic patients were studied, no increase in myocardial fibrosis or myocardial CML expression was observed in cases with preserved left ventricular ejection fraction although both myocardial fibrosis and CML expression were elevated in cases with significant systolic dysfunction^[60].

AGEs and other forms of macrovascular diseases

Serum levels of AGEs were also shown to correlate with the presence of other forms of macrovascular pathology as carotid stenosis and peripheral artery occlusive disease. Serum levels of the esRAGE that can neutralize circulating AGEs were found to be inversely proportionate to carotid artery intima-media thickness in type 1 diabetic patients^[61]. The same was reported in type 2 diabetic patients as well as non-diabetic cases^[62]. Higher expression of the RAGE was detected in carotid artery plaques and was shown to be associated with enhanced inflammatory reactions^[63].

Type 2 diabetic patients with peripheral artery disease exhibited higher levels of serum AGEs *vs* the non-diabetic subjects^[59]. A tight link has been shown between AGE plasma levels and pulse pressure in type 1 diabetic patients as was reported in the EURODIAB Prospective Complications Study^[64].

AGEs and microangiopathy

Serum and tissue levels of AGEs are predictors of the development of microvascular complications in diabetes. For example in type 1 diabetes control and complications trial, increased AGE levels in skin biopsies predict the development of diabetic microvascular complications, e.g., retinopathy and nephropathy^[13,65]. AGE/RAGE interaction has been suggested as a possible mechanism coupling microangiopathy with diabetic nephropathy, retinopathy and neuropathy^[43].

Diabetic nephropathy: Correlation between the levels of skin collagen AGEs particularly CML and the devel-

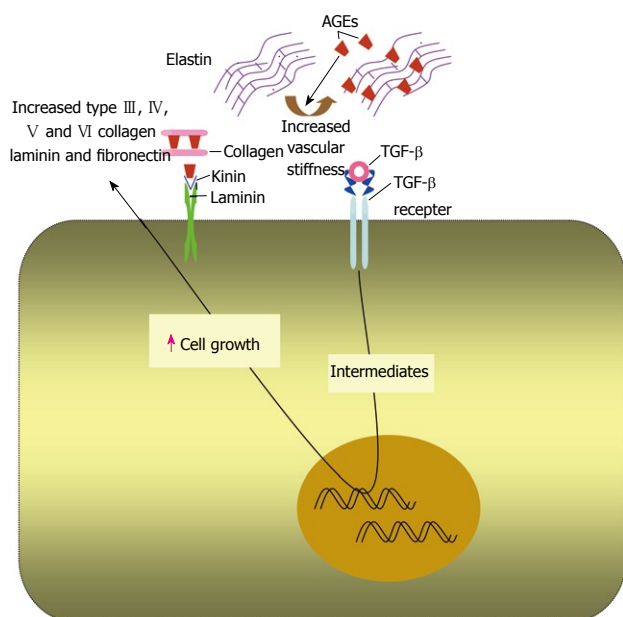


Figure 2 Effects of advanced glycation end products on extracellular matrix proteins. In extracellular matrix, advanced glycation end products (AGEs) form on different molecules as collagen, laminin and elastin. This alters the physiological properties of the matrix and increases its stiffness. AGEs upregulate transforming growth factor (TGF)- β that increases the production of extracellular matrix components by binding to its receptor.

opment and worsening of microvascular complications including nephropathy in type 1 diabetic patients was initially reported by Genuth *et al.*^[65]. Similarly, in type 2 diabetes skin AGEs (skin autofluorescence) were shown to be potent independent predictors of evolution of microvascular complications including nephropathy^[66]. In diabetes, the kidney is an important site for AGE accumulation but also contributes to the increased levels of AGEs in the serum of diabetic patients since the kidney is the main site for AGE clearance^[67]. Diabetic animal models exhibit higher levels of AGE deposition in their kidneys^[68] which has been linked to renal structural alterations reported in diabetic nephropathy such as glomerular basement membrane thickening, glomerulosclerosis, mesangial expansion and tubulointerstitial fibrosis. Similar histological findings have also been also documented in murine models injected with AGE-albumin^[69].

Diabetic retinopathy: Accumulation of AGEs especially CML in retinal blood vessels of type 2 diabetic patients has been reported. It has been also documented that the levels of AGEs correlated with the severity of the retinopathy^[70,71]. Infusion of AGE-albumin in non-diabetic animals has shown that AGEs localize both inside and around the pericytes co-localizing with the AGE receptor causing thickening of the basement membrane and destruction of the blood retinal barrier^[72,73]. *In vitro* exposure of retinal cells to AGEs induced upregulation of vascular endothelial growth factor (VEGF) that may contribute to retinal neovascularisation reported in diabetic retinopathy^[74].

Diabetic neuropathy: Both peripheral and autonomic neuropathies have been shown to correlate with AGE levels even before neuropathy becomes clinically evident^[75]. Skin autofluorescence reflecting AGE bound collagen levels has been reported to have a tight link with the degree of diabetic neuropathic foot ulceration^[76]. AGEs have been shown to accumulate in peripheral nerves of diabetic patients and they were shown to co-localize with RAGE receptor in endoneurial, perineurial and epineurial blood vessels^[77].

MECHANISMS OF ACTIONS OF AGES

AGEs mediate their tissue effects through three main mechanisms: (1) Cross linking extracellular (matrix) proteins thereby affecting tissue mechanical properties^[51]; (2) Cross linking intracellular proteins thus altering their physiological functions^[5,6]; and (3) Binding to their cell surface receptor RAGE to inducing multiple intracellular signalling cascades^[56]. In the following sections these mechanisms will be discussed.

Crosslinking tissue proteins

Cross linking extracellular matrix proteins: AGE formation is a process of chronicity usually affecting long-lived proteins. Extracellular matrix proteins especially collagen type IV that is involved in basement membrane structure, are more prone to advanced glycation due to their long turnover^[20,78]. Advanced glycation and crosslinking of other extracellular matrix proteins, e.g., collagen I and elastin render them stiffer and less susceptible to proteolytic digestion^[51] (Figure 2). This may contribute to the observed increase in vascular stiffness reported in diabetes and old age^[20,51,79]. In addition, cross linking myocardial collagen with AGEs has been suggested to cause myocardial stiffness and diastolic dysfunction in diabetic patients^[51,80].

AGEs alter the structure of low density lipoproteins (LDL) through glycation therefore preventing their clearance from the circulation *via* the normal elimination route, i.e., uptake by the endothelial cells. Instead they are uptaken by the blood monocytes leading to foam cells that contribute to the pathogenesis of atherosclerosis^[81,82].

Cross linking intracellular proteins: AGEs have been shown to be implicated in crosslinking of intracellular proteins and hence altering their physiological properties and functions. For instance AGEs were shown to cross link the domains of both the Ryanodine receptor^[5] and SERCA2a^[6] in cardiomyocytes leading to alterations in calcium homeostasis reported in diabetic cardiomyopathy^[83,84].

RAGE dependant effects of AGEs

RAGE receptor: RAGE belongs to the immunoglobulin superfamily of receptors^[56]. It has been reported that RAGE gene is located on chromosome 6 in humans between genes coding for class II and class III major histocompatibility complexes^[85]. The RAGE promoter

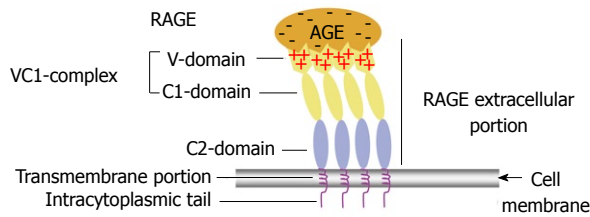


Figure 3 Receptor for advanced glycation end product (i.e., colon) receptor structure and its functional implication in binding different advanced glycation end products. A diagrammatic illustration of the structure of the receptor for advanced glycation end product (RAGE) showing that it is composed of an extracellular portion, a transmembrane portion and an intracytoplasmic tail. The extracellular portion comprises three domain V, C1 and C2. The first two are believed to work together as a single functional complex (VC1) whereas the C2 domain remains attached to the VC1 complex but works independently from it. The diagram also illustrates how multiple RAGE receptors polymerise within the cell membrane to facilitate high affinity binding of the positively charged V domain with the negatively charged advanced glycation end products (AGEs) independent of their chemical structure. That is why RAGE is considered one of the pattern recognition receptors.

has been shown to possess nuclear factor kappa B (NF- κ B) binding sites, hence linking RAGE expression to the inflammatory cascade^[86].

RAGE is a multiligand receptor with advanced glycation end products being identified as its first known ligands. Hereafter, multiple other RAGE ligands have been revealed including; high mobility group protein box-1^[21], some members of the S100 protein family^[87] amyloid β ^[88,89] and fibrillar protein aggregates^[90,91]. Therefore, RAGE has an important role in the pathogenesis of the diseases induced by such ligands, e.g., inflammation, tumours, neurodegeneration and amyloidosis^[21,88,92,93].

RAGE structure: Full length RAGE comprises three domains, an extracellular domain of 332-amino acids arranged as a single “V”-type immunoglobulin-like (variable) domain with subsequent two “C”-type (constant) domains^[89,94]. Modern biochemical techniques have revealed evidence suggesting that both the V and C1 domains of RAGE function together as an incorporated single structural unit for the binding of some ligands. In contrast, C2 RAGE domain is suggested to function completely independent from the VC1 complex while remaining attached to it through a flexible hinge (Figure 3). It has been deduced from experimental work that different RAGE ligands interact with one or more of its domains^[19].

RAGE has a single transmembrane domain and a highly charged cytosolic tail formed of 43 amino acids (Figure 3). The cytosolic tail is vital for RAGE ligands to activate intracellular signalling cascades. RAGE isoforms in which the cytosolic tail was absent, bind AGEs but fail to elicit intracellular signaling on ligand binding^[95]. It has recently been shown that for some RAGE actions, its tail binds directly to a cytoplasmic molecule known as the mammalian diaphanous-1 which is essential for eliciting phosphorylation/activation steps needed for initiation of the signalling cascade^[96].

Despite the wide variation in their chemical structure,

AGEs bind to the V domain of the RAGE receptor^[94]. The fact that RAGE recognizes a class of biochemically heterogeneous ligands such as AGEs categorizes RAGE as one of the pattern recognition receptors^[97-99] that identifies common features or patterns rather than a specific ligand. Though AGEs exhibit diverse chemical structure, however, they have some common general characteristics. First, all AGE modified proteins demonstrate a net negative charge that accumulates during their formation by glycation and oxidation^[100,101]. The second main feature is that modifications of proteins by AGEs lead to creation of multiple covalent cross-links resulting in higher molecular mass molecules (multimers). This ligand geometry is thought to be important for RAGE activation^[100].

Recent molecular structure revealing technologies including X-ray crystallographic, NMR together with conventional biochemical data have illustrated that the unusual ability of the RAGE receptor to bind different AGEs lies in its extracellular portion (VC1 ectodomain) where it has been suggested that the ligand binding is triggered mainly by electrostatic interactions between the positively charged surface of this subunit and negatively charged ligands (Figure 3)^[102]. The V domain has been shown by NMR to exhibit three distinct areas for mediating AGE-V domain interactions. Such areas are situated in the positively charged regions of the V domain. The first interaction surface includes strand C and loop CC', the second interaction surface comprises strand C', strand F and loop FG, and the third interaction one consists of strand A' and loop EF^[101].

The second main point to be considered here is that studies based on using a fluorescence-labelled receptor demonstrated that RAGE does not float as one molecule in the plasma membrane but instead multiple RAGE receptors aggregate to form receptor assemblies^[19,101]. Therefore, RAGE exists in constitutive multimers that usually includes four molecules or more within the plasma membrane^[101,103]. RAGE multimers are thought to display a parallel orientation with VC1 subunits exhibiting side to side contacts (Figure 3) as revealed in protein crystals. Therefore it has been speculated that the general multimeric structure adopted by AGE modified proteins together with numerous AGE-modified side chains are essential requirements for preserving the receptor assemblies' stability needed for activation of the receptor^[100] probably in a similar way to that previously described for the receptor tyrosine kinases where the intracellular domains of the receptor that possess intrinsic kinase activity must come very close together in a particular orientation that facilitates cross-phosphorylation of the domains and hence commencement of the signalling cascade^[104].

RAGE isoforms: Despite the presence of a single gene coding for RAGE, there are several splice variants of this gene with three main RAGE isoforms having been identified: full length RAGE, dominant-negative RAGE (DN-

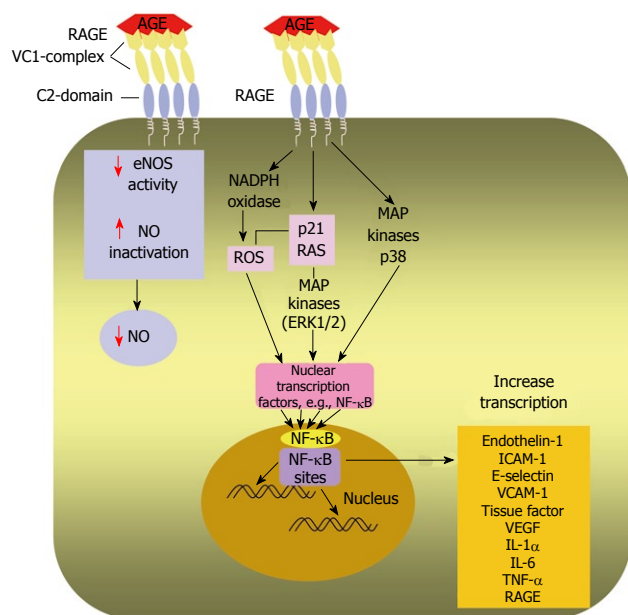


Figure 4 Intracellular effects of AGEs after AGE/RAGE binding. Diagrammatic representation of AGE/RAGE interaction on the surface of an endothelial cell leads to transduction of a signalling cascade; activates nicotinamide adenine dinucleotide phosphate oxidase and enhances ROS production and phosphorylate p21 RAS and MAPKs. Moreover, the AGE/RAGE interaction induces signalling through activation of p38 MAPK. A main step in AGE/RAGE signalling is activation of NF- κ B and its translocation to the nucleus, where it enhances transcription of target genes as endothelin-1, ICAM-1, E-selectin and tissue factor. Hence, AGE/RAGE binding triggers an inflammatory cascade. AGE may decrease NO availability by reducing eNOS activity and by inactivating NO. AGE: Advanced glycation end-product; RAGE: Receptor for advanced glycation end products; ROS: Reactive oxygen species; MAPKs: Mitogen-activated protein kinases; ERK1/2: Extracellular signal-regulated kinase 1/2; NF- κ B: Nuclear factor kappa B; ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular endothelial growth factor; IL-1 α : Interleukin-1 α ; IL-6: Interleukin-6; TNF- α : Tumor necrosis factor- α ; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide.

RAGE) and endogenous soluble RAGE (es-RAGE)^[105]. Full length RAGE is composed of the whole three domains; extracellular, trans-membrane and intracellular domains. DN-RAGE has extracellular and transmembrane domains, but no cytosolic tail. Endogenous soluble RAGE possesses the extracellular domain only so it is found free in the circulation. The only RAGE isoform that is capable of eliciting intracellular signalling upon interacting with its ligands is the full length RAGE as this is induced through its cytosolic tail. However, the other two isoforms; DN-RAGE and esRAGE help in clearance and neutralisation of circulating AGEs by competing with full length RAGE in binding them^[56,105].

RAGE tissue distribution: RAGE expression has been detected in a number of cells including endothelial cells, smooth muscle cells, monocytes/macrophages, T lymphocytes, cardiomyocytes, glomerular podocytes, dendritic cells, neurons of the central and peripheral nervous systems and transformed cells^[106]. Generally, there is a low expression of RAGE in tissues. However, it becomes up-regulated in an environment rich with its

ligands as in the case of diabetes or aging. RAGE expression was higher in endothelial cells, monocytes and smooth muscles in diabetic vascular tissue^[107].

INTRACELLULAR EFFECTS OF AGE-RAGE BINDING ON CARDIOVASCULAR SYSTEM

RAGE activation by high serum and tissue levels of AGEs induces multiple intracellular signalling pathways (Figure 4) that have been implicated in pathogenesis of serious diabetic complications such as enhanced atherosclerosis, cardiovascular disease, nephropathy and chronic inflammation^[9,10,108-110]. It has been documented that circulating AGEs bind with endothelial RAGE resulting in endothelial dysfunction *via* activation of a number of signaling pathways, e.g., activation of nicotinamide adenine dinucleotide phosphate oxidase that enhances the production of reactive oxygen species (ROS)^[108]. ROS have been shown to play a pivotal role in causing major cardiovascular damage in diabetes through modifying the structure of cellular proteins, lipids and nucleic acids and therefore altering their physiological roles^[111].

In addition, it has been reported as well that AGE-RAGE engagement increases phosphorylation of p21ras, the mitogen-activated protein kinases, extracellular signal-regulated kinase 1/2 and p38, and activates GTPases Cdc42 and Rac, ultimately inducing activation and translocation of NF- κ B from cytoplasm to the nucleus where it starts transcribing its target set of genes^[112]. The latter include, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, VEGF, endothelin-1, tissue factor, E-selectin, thrombomodulin and proinflammatory cytokines, including interleukin (IL)-1 α , IL-6 and tumor necrosis factor- α ^[113,114]. The above mentioned cytokines and adhesion molecules have central roles in both inflammation and atherosclerosis^[108,115].

ANTI-AGE THERAPIES

Therapies that target AGEs can be classified into two main categories, the ones that prevent the formation of AGEs and others that breakdown the already formed AGEs.

Prevention of AGEs formation

Aminoguanidine (AG), is a hydrazine compound that inhibits AGE formation *via* trapping of carbonyl intermediates (early active glycation products) and hence preventing modification of nucleophilic residues in proteins^[116,117]. In a placebo-controlled, randomized trial involving type 1 diabetes patients, the use of aminoguanidine hindered reduction in glomerular filtration rate, reduced 24-h urinary proteinuria and prevented the deterioration of retinopathy. However, it did not influence time-to-doubling of serum creatinine^[118]. Being an NOS inhibitor, which is an essential renovasodilator, this may offset some of AG benefits as an AGE inhibitor^[119].

Pyridoxamine, (form of vitamin B6 that naturally exists) and benfotiamine (a lipid-soluble derivative of thiamine), are known to inhibit AGE formation. In phase 2 trials using pyridoxamine in diabetic patients suffering from obvious diabetic nephropathy, a significant decline in the serum levels of creatinine from baseline was observed although this was not accompanied by a corresponding change in urinary albumin excretion^[120]. Using benfotiamine in type 2 diabetic patients prevented both macro- and microvascular endothelial dysfunction and oxidative stress induced by an AGE rich meal^[121]. Moreover, the combined use of benfotiamine and alpha-lipoic acid normalized elevated AGE levels and blocked the enhancement hexosamine-modified protein formation in monocytes in type 1 diabetic patients^[122].

AGE degradation (AGE cross link breaker, ALT-711)

Cross link breakers such as ALT-711 contain a thiazolium structure that is capable of breaking α -carbonyl compounds by cleaving the carbon-carbon bond between carbonyls. *In vitro*, incubation of AGE crosslinked collagen with ALT-711 promotes collagen digestibility by metalloproteinases (MMP), a phenomenon used as a key sign of an effective cross link-breaker effect^[123].

ALT-711 has been used in a number of small clinical studies to investigate the effects of targeting AGE on cardiovascular complications. A phase II clinical trial demonstrated that ALT-711 (210 mg/d, 8 wk) reduced the arterial pulse pressure and improved the compliance of large arteries in older patients (> 50 years) who exhibited age-dependent stiffening of their large arteries secondary to isolated systolic hypertension^[124].

Two more phase 2b clinical trial trials currently being undertaken to assess the safety as well as the efficacy of ALT-711 use in the treatment of isolated systolic hypertension with or without left ventricular hypertrophy (LVH) in elderly patients (> 50 years), termed systolic and pulse pressure hemodynamic improvement by restoring elasticity (SAPPHIRE) and systolic hypertension interaction with left ventricular remodeling (SILVER). SAPPHIRE is designed to use multiple doses (four) of ALT-711 over a period of 6 mo in patients with systolic hypertension without LVH whilst the control group will be treated with placebo. The SILVER study is being conducted on patients with systolic hypertension and LVH, including both diabetics and non-diabetics treated with a single dose of ALT-711 and a placebo group for 6 mo. The primary endpoints of both studies are alterations in both systolic blood pressure and pulse pressure. Secondary endpoints involve extra measurements of arterial blood pressure and modifications in definite urological parameters. The results of both trials are still not yet available^[125].

In addition, two small and open label clinical trials suggested an important role of AGEs in the development of cardiac dysfunction and HF. In both trials HF patients were treated with an AGE cross-link breaker Alagebrium (ALT-711). In the Distensibility Improvement

and Remodeling in Diastolic Heart Failure (DIAMOND) trial, 23 patients with stable diastolic HF received ALT-711 for 16 wk after which patients were assessed by magnetic resonance imaging and tissue doppler which revealed both a reduction of left ventricular mass and an improvement of left ventricular diastolic function^[126]. The Patients with Impaired Ejection Fraction and Diastolic Dysfunction: Efficacy and Safety Trial of Alagebrium trial was conducted on 22 patients suffering from systolic HF and diastolic dysfunction who were treated by ALT-711 (35-420 mg). The results of this trial were in line with those of the DIAMOND trial. Doppler assessment showed improvement in isovolumetric relaxation time and consequently reduction in the left atrial pressure. Furthermore, reduced left ventricular mass and left ventricular end-diastolic volume was also reported in some patients^[127].

However, a more recent clinical trial BENEFICIAL, a prospective, randomized, double-blind, phase II, placebo controlled trial on the effects of the AGE-breaker alagebrium on exercise capacity and diastolic function in 102 patients with systolic HF did not support the findings of the earlier trials. In BENEFICIAL study, patients were assessed after receiving 200 mg alagebrium twice daily or placebo treatment for a period of 36 wk. No improvement was reported in exercise capacity or systolic function of those patients. In addition, no significant change was detectable in a number of other parameters including diastolic dysfunction, NYHA functional class, NT pro-BNP levels and AGE levels (skin autofluorescence). However, the authors highlighted some important points that may explain their findings. Firstly, inclusion into this study did not mandate the presence of diastolic dysfunction as an entry criterion into the trial, and it is this sub group with diastolic dysfunction that may have shown a better response to alagebrium treatment. Secondly, tissue AGE levels were relatively low in the patient cohort, especially since only (18%) of the patients included into this study were diabetic. Finally, the duration of treatment might be too short for alagebrium to produce a therapeutic effect^[128].

Anti-RAGE receptor therapies

Recently, therapies targeting the RAGE receptor, e.g., sRAGE have been used in experimental studies and proved to be effective in reducing atherosclerosis in diabetic mice^[129,130] as well as microvascular complications of diabetes as diabetic retinopathy^[131], nephropathy^[132] and neuropathy^[133]. The use of the latter in the clinical setting has not yet been approved.

CONCLUSION

Cardiovascular diseases are one of the leading causes of morbidity and mortality in the western world particularly amongst patients with diabetes. AGEs accumulate rapidly in the hyperglycaemic milieu of diabetes and have an important role in the development of the macro and

microvascular complications of diabetes.

Several clinical and experimental studies support the view that AGEs might have a significant role in pathogenesis of heart failure by contributing to its development and progression either *via* indirect mechanisms mediated through enhancing coronary artery disease or directly by inducing myocardial damage independent of vascular effects. AGEs adverse effects on cellular and tissue function arise from their potential to cross link intracellular and extracellular proteins thus altering their function and through binding to their cell surface receptor RAGE activating multiple signalling cascades in many different cells within the cardiovascular system. Preliminary data suggests that targeting AGEs therapeutically may represent a novel treatment strategy in the management of DM and its cardiovascular complications.

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Investigation of cardiomyopathy using cardiac magnetic resonance imaging part 1: Common phenotypes

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Abstract

Cardiac magnetic resonance imaging (CMRI) has emerged as a useful tertiary imaging tool in the investigation of patients suspected of many different types of cardiomyopathies. CMRI sequences are now of a sufficiently robust quality to enable high spatial and temporal resolution image acquisition. This has led to CMRI becoming an effective non-invasive imaging gold standard for many cardiomyopathies. In this 2-part review, we outline the typical sequences used to image cardiomyopathy, and present the imaging spectrum of cardiomyopathy. Part 1 focuses on the current classification of cardiomyopathy, basic CMRI sequences used in evaluating cardiomyopathy and the imaging spectrum of common phenotypes.

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Key words: Cardiac magnetic resonance imaging; Cardiomyopathies

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INTRODUCTION

A cardiomyopathy has been described as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality, with the exception of ischemic cardiomyopathy (Table 1)^[1]. Cardiomyopathy follows myocardial infarction as the commonest cause of sudden cardiac death^[2].

Cardiac magnetic resonance imaging (CMRI) has emerged as a useful non-invasive imaging modality capable of producing high-resolution images of the heart in any desired image plane and without ionizing radiation. As a result, it has become a primary imaging modality for many cardiomyopathies^[3,4]. There are many different sequences that can be performed in various combinations, although a basic generic set of sequences is common to most protocols^[5].

CLASSIFICATION OF CARDIOMYOPATHY

A recent statement from the European Society of Cardiology working group on myocardial and pericardial diseases^[1] has grouped cardiomyopathies into specific mor-

Table 1 Examples of common and rare cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene	Familial, unknown gene	Familial, unknown gene	Familial, unknown gene	Familial, unknown gene
	Sarcomeric protein mutations	Sarcomeric protein mutations (see HCM)	Intercalated disc protein mutations	Sarcomeric protein mutations	Left ventricular Non-compaction
	β myosin heavy chain	Z-band	Plakoglobin	Troponin I (RCM +/- HCM)	Barth syndrome
	Cardiac myosin binding protein C	Muscle LIM protein	Desmoplakin	Essential light chain of myosin	Lamin A/C
	Cardiac troponin 1	TCAP	Plakophilin 2	Familial amyloidosis	ZASP
	Troponin T	Cytoskeletal genes	Desmoglein 2	Transthyretin (RCM + neuropathy)	α -dystrophin
	α -tropomyosin	Dystrophin	Desmocollin 2	Apolipoprotein (RCM + neuropathy)	
	Essential myosin light chain	Desmin	Cardiac RyR2	Desminopathy	
	Regulatory myosin light chain	Metavinculin	TGF β 3	Pseuxanthoma elasticum	
	Cardiac actin	Sarcoglycan complex		Haemochromatosis	
	α -myosin heavy chain	CRYAB		Anderson-Fabry disease	
	Titin	Epicardin		Glycogen storage disease	
	Troponin C	Nuclear membrane			
	Muscle LIM protein	Lamin A/C			
	Glycogen storage disease (e.g., Pompe; PRKAG2, Forbes', Danon)	Emerin			
	Lysosomal storage disease (e.g., Anderson-Fabry, Hurler's)	Mildly dilated cardiomyopathy			
	Disorders of fatty metabolism	Intercalated disc protein mutations (see ARVC)			
	Carnitine deficiency	Mitochondrial myopathy			
	Phosphorylase B kinase deficiency	Dystrophies			
	Mitochondrial cytopathies				
	Syndromic HCM				
	Noonan syndrome				
	LEOPARD syndrome				
	Friedreich's ataxia				
	Beckwith-Wiedemann syndrome				
	Swyer's syndrome				
	Other				
	Phospholamban promotor				
	Familial amyloid				
Non familial	Obesity	Myocarditis (infective/toxic/autoimmune)	Inflammation?	Amyloid (AL/prealbumin)	Tako Tsubo cardiomyopathy
	Infants of diabetic mothers	Kawasaki disease		Scleroderma	
	Athletic training	Eosinophilic (Churg Strauss syndrome)		Endomyocardial fibrosis	
	Amyloid (AL/prealbumin)	Viral persistence		Hypereosinophilic syndrome	
		Drugs		Idiopathic	
		Pregnancy		Chromosomal cause	
		Endocrine		Drugs (serotonin, methysergide, ergotamine)	
		Nutritional - thiamine, carnitine, selenium, hypophosphatemia, hypocalcemia			
		Alcohol			
		Tachycardiomyopathy		Carcinoid heart disease	
				Metastatic cancers	
				Radiation	
				Drugs (anthracyclines)	

HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; ARVC: Arrhythmogenic right ventricular dysplasia; RCM: Restricted cardiomyopathy; RyR2: Ryanodine receptor; TGF: Transforming growth factor.

phological and functional phenotypes; each phenotype is then sub-classified into familial and non-familial forms. Familial refers to the occurrence, in more than one family member, of either the same disorder or a phenotype that is (or could be) caused by the same genetic muta-

tion and not from acquired cardiac or systemic diseases in which the clinical phenotype is influenced by genetic polymorphism. Most familial cardiomyopathies are monogenic disorders. Non-familial cardiomyopathies are subdivided into idiopathic and acquired cardiomyopa-

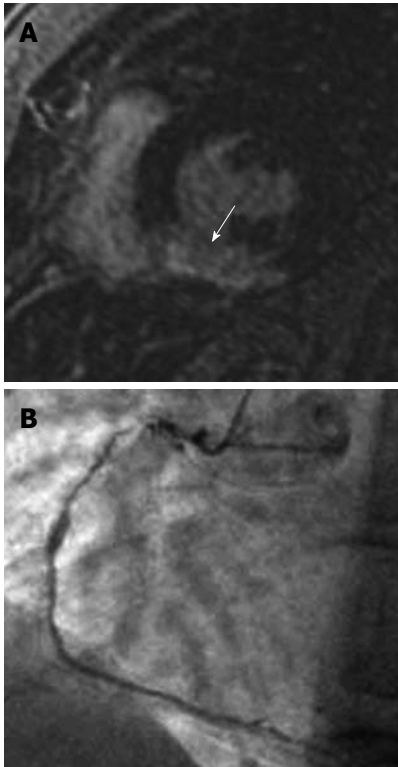


Figure 1 A 42-year-old female who presented with acute chest pain to the emergency department. She had no risk factors for coronary artery disease and the clinical suspicion was of myocarditis. A: Late-enhancement short axis sequence shows a transmural area (arrow) of high signal involving the inferior segment consistent with an acute myocardial infarction involving the right coronary artery territory. Note that it is an acute rather than chronic infarct, because there is no wall thinning; B: An invasive angiogram confirmed diffuse coronary artery disease throughout the right coronary artery. Note that the likelihood of recovery of this segment with revascularization is extremely low because it is a transmural infarct.

thies in which ventricular dysfunction is a complication of the disorder rather than an intrinsic feature of the disease. Left ventricular (LV) dysfunction secondary to coronary artery occlusion, hypertension, valve disease, and congenital heart disease are excluded because the diagnosis and treatment of these disorders are quite different from those encountered in most cardiomyopathies. The division of cardiomyopathies into familial and non-familial forms is useful as it raises awareness of genetic disease as a cause of heart muscle dysfunction.

BASIC CMRI PROTOCOLS FOR CARDIOMYOPATHY ASSESSMENT

The CMRI protocol used in imaging cardiomyopathy should be tailored specifically to the suspected type of cardiomyopathy. There are many different sequences, but all follow a basic generic protocol^[5,6]: (1) scouting images - axial, coronal and sagittal; (2) stacking of axial slices of the thorax [half-fourier acquisition single-shot turbo spin-echo or steady-state free precession (SSFP)]; (3) vertical long-axis or 2-chamber steady-state free precession (SSFP) - this imaging plane typically depicts the left atrium and ventricle. If the right ventricle is the

chamber of interest, the plane can be placed along the right ventricle; (4) horizontal long-axis or 4-chamber SSFP - depicts all 4 cardiac chambers; (5) short-axis SSFP - from the annulus to the apex. These are used to allow quantification of ventricular volumes and function; (6) T2-weighted typically short-axis sequence - to assess for acute myocardial edema; and (7) late gadolinium enhancement (LGE) - appears as high signal enhancement within the myocardium following a double-inversion fast spin echo sequence. Images are typically acquired 10 to 30 min after contrast injection. Many studies have now shown that myocardial enhancement using this sequence enables the detection of myocardial infarction, inflammation, infiltration or fibrosis. Late gadolinium enhancement sequences have added a tremendous additional dimension to CMRI in detecting, localizing and quantifying myocardial disease^[7].

Specific additional sequences may be added depending on the particular cardiomyopathy being investigated^[5]. When describing the location of myocardial pathology it is important to use standardized nomenclature^[8]. Typically, the ventricle is divided into 3 levels (basal, mid and apical) and each level can be divided into 6 (basal), 6 (mid) and 4 (apical) segments with the 17th segment being represented by the apex. Note that there is normally a thin apical thin point, and it is important not to confuse this normal appearance with an apical aneurysm^[9].

Ischemic cardiomyopathy

In ischemic disease, myocardial ischemia may result in 3 functionally altered states commonly referred to as stunning, hibernation, and true infarction^[10]. The stunned myocardium typically occurs in the setting of an acute ischemic insult and results in reversible contractile dysfunction whereas hibernation is the term used to describe chronic contractile impairment secondary to obstructive coronary stenosis (Figure 1). CMRI allows the detection, location and quantification of the extent of acute and chronic myocardial infarction. Chronic myocardial infarction is defined as new pathological Q waves with or without symptoms, imaging evidence of a loss of myocardial viability with wall thinning that fails to contract, in the absence of a non-ischemic cause or pathological findings of a healed or healing myocardial infarction^[11]. Cardiac MRI has become the clinical non-invasive gold standard for the assessment of myocardial viability. It has superseded cardiac positron emission tomography and single photon emission computed tomography scanning for the detection of subendocardial infarction^[12]. Revascularization of viable tissue should lead to an improvement in myocardial contractility, as long as the myocardium is non-transmurally infarcted^[13]. In full-thickness infarcted (scarred) tissue revascularization does not improve myocardial function^[14]. Despite the small size of such infarcts, detection is critical, as even patients with small infarcts have a relatively poor prognosis compared to non-infarcted patients^[15]. More recently, T2-weighted sequences (sensitive to myocardial edema) have shown the area-at-risk. This shows an area

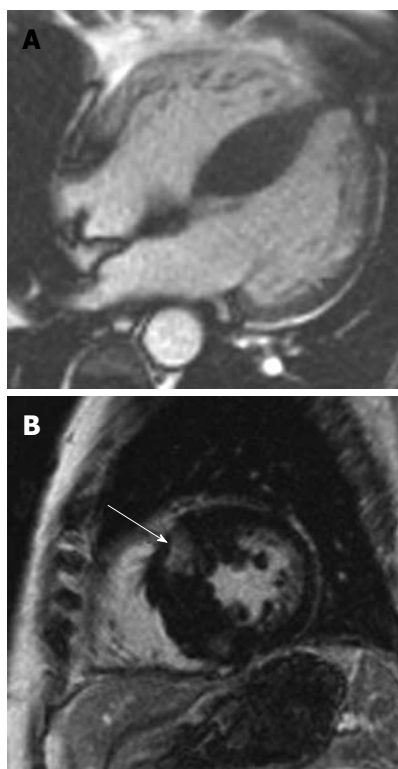


Figure 2 Hypertrophic cardiomyopathy. A: 28-year-old man who presented with progressive heart failure and palpitations. The horizontal long-axis steady-state free precession sequence demonstrates a hypertrophic interventricular septum measuring 23 mm (normal ≤ 11 mm) consistent with hypertrophic cardiomyopathy (HCM); B: Late-enhancement short-axis image shows late-enhancement in the hypertrophied septum (arrow). Note that there are 2 abnormal areas of enhancement corresponding to the right superior and inferior ventricular insertion points. This is a characteristic pattern in HCM. Such late-enhancement has prognostic implications for patients with HCM, being associated with an increased prevalence of heart failure admissions, deterioration to New York Heart Association functional class III or IV, or heart failure-related death.

of higher signal, larger than the actual infarcted ‘dead-zone’ of the myocardium, and thus indicates the area at risk of further ischemia^[16]. Regional wall motion abnormalities are detected on CMRI in the areas of abnormal enhancement.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by ventricular muscle hypertrophy and impaired diastolic function associated with a non-dilated cavity, in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy^[17,18]. It is the commonest cause of sudden cardiac death in young people. It is genetically transmitted in an autosomal dominant pattern with variable penetrance and expression^[19]. Symptoms are variable but can include dyspnea, orthopnea, paroxysmal nocturnal dyspnea and sudden death. Patients may also be asymptomatic. CMRI is the gold-standard non-invasive imaging modality for estimating LV volumetrics, ventricular mass and systolic function. As such, it has become a valuable imaging tool in patients suspected of HCM (Figure 2). The role of CMRI in providing prognostic information in HCM is evolving.

An important initial study found LGE in the majority of patients with HCM^[20]. The enhancement typically occurred in the hypertrophied regions, predominantly involving the middle third of the wall in a patchy, multifocal distribution. Moon *et al*^[21] found that the extent of LGE was strongly associated with other risk factors for sudden death in HCM. Another study showed that even in mild HCM or asymptomatic HCM, the presence of LGE was associated with ventricular tachycardia^[22]. More recently, O’Hanlon *et al*^[23] demonstrated that in 217 patients with HCM followed for 3.1 years, the risk of unplanned heart failure admissions, deterioration to New York Heart Association functional class III or IV, or heart failure-related death was greater in the fibrosis group on CMRI [hazard ratio (HR): 2.5, $P = 0.021$], and this risk increased as the extent of fibrosis increased (HR: 1.16; 5% increase, $P = 0.017$). Thus, the presence and extent of late-enhancement on CMRI appears to hold prognostic information in patients with HCM.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by dilation of the cardiac chambers coupled with impaired contraction of the ventricles. The ventricular chambers exhibit increased diastolic and systolic volumes and a low ejection fraction $<45\%$ ^[24]. Although 50% of cases remain idiopathic^[25], DCM may be a common end-pathway in many disease processes, such as chronic myocarditis and burnt-out HCM^[26]. Several studies have shown that endomyocardial biopsy of a subgroup of patients with idiopathic dilated cardiomyopathy (IDC) reveals a viral genome or HCM genotype^[27]. The presenting symptoms and signs are progressive dyspnea and orthopnea in the majority of patients. Arrhythmias and sudden death may also occur.

Chamber enlargement and decreased function are hallmarks of the pathological process in DCM (Figure 3). CMRI is the gold-standard non-invasive imaging modality for detecting such changes^[28,29]. In addition, late contrast enhancement has been reported, most frequently in the mid-interventricular septum, indicating myocardial fibrosis. The presence of LGE has prognostic implications for patients with DCM^[30]. Those patients with macroscopically detectable fibrosis on CMRI have a higher rate of repeat hospitalizations with cardiac failure, worsening symptoms, ventricular arrhythmias and cardiac related death. Thus, CMRI offers a useful non-invasive diagnostic method of diagnosing IDC whilst excluding many other potential causes of DCM, including ischemia^[29]. CMRI offers the most accurate non-invasive method for assessing LV ejection fraction, can provide baseline volumetric measurements in order to monitor response to therapy and provides prognostic information.

Cardiac sarcoid

Cardiac abnormalities are caused by myocardial infiltration by sarcoid granulomas^[31]. The classical clinical presentation is heart block; however, other clinical features of sarcoid heart disease include congestive heart failure,

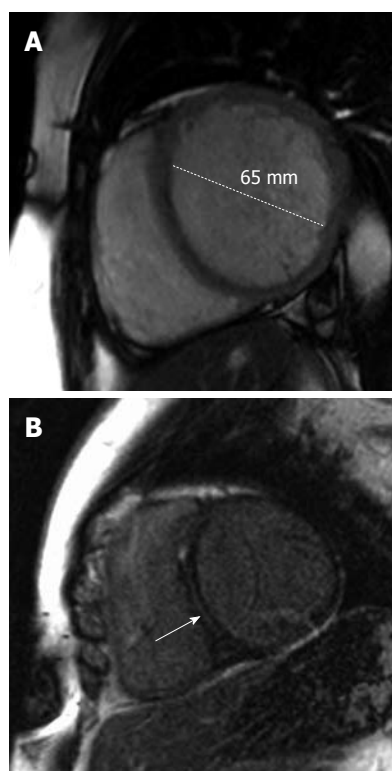


Figure 3 Dilated cardiomyopathy. A: A 48-year-old man with progressive shortness of breath. The short-axis steady-state free precession sequence demonstrates a dilated left ventricle with a thin wall characteristic of dilated cardiomyopathy (DCM); B: Late-enhancement short-axis image shows late-enhancement in the interventricular septum (arrow). This is a characteristic location for fibrosis detection in idiopathic DCM and effectively excludes an ischemic etiology. Such late-enhancement has prognostic implications for patients with idiopathic DCM, being associated with an increased prevalence of all-cause death, hospitalization, sudden cardiac death and ventricular tachycardia.

cor pulmonale, supraventricular and ventricular arrhythmias, conductive disturbances, ventricular aneurysms, pericardial effusion, and sudden death. About 7% of patients with sarcoidosis develop cardiac symptoms but postmortem studies have revealed cardiac involvement in 20%-50% of patients^[32].

The CMRI appearances of cardiac sarcoidosis depend on the acuteness of the process (Figure 4). In cases of acute inflammation, enhancement is typically in a subepicardial or mid-myocardial pattern^[33]. In the chronic setting, granulomas cause focal areas of myocardial thinning resulting from scar formation. Late contrast enhancement can be seen in areas of granulomatous infiltration and is frequently patchy and nodular^[34]. One study found that cardiac sarcoidosis predominantly affects the basal myocardium and the subepicardial layer^[35]. They also found that hyperenhancement may be related to LV dysfunction^[35]. CMRI provides an accurate estimation of the extent of cardiac involvement and may reveal signs of early infiltration that are not detected by standard echocardiographic assessment^[36]. In a study of 81 consecutive patients with biopsy-proven extra-cardiac sarcoidosis, patients underwent CMRI and Japanese Ministry of Health (JMH) assessment^[37]. Patients were

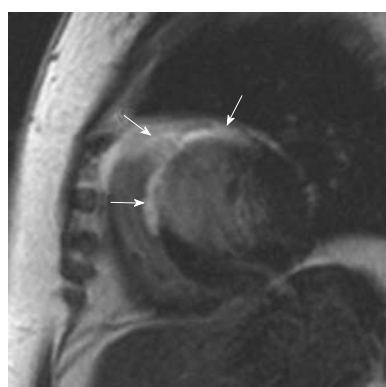


Figure 4 Cardiac sarcoidosis. A 54-year-old woman who presented with recurring palpitations and progressive shortness of breath for several months before suddenly collapsing. Cardiac magnetic resonance imaging demonstrates extensive scarring throughout the anterior and anteroseptal segments of the left ventricle (arrows). However, the involvement of the anterior segment of the right ventricle is unusual for ischemia and suggests another cause for the images. An endomyocardial biopsy revealed cardiac sarcoidosis. There was no previous history of lung or mediastinal sarcoid.

followed for 21 ± 8 mo for major adverse events (death, defibrillator shock, or pacemaker requirement). Late gadolinium enhancement on CMRI identified cardiac involvement in 21 patients (26%) and JMH criteria in 10 (12%, 8 overlapping), a 2-fold higher rate for delayed enhancement-CMRI ($P < 0.005$). Pathology evaluation in 15 patients (19%) identified 4 with cardiac sarcoidosis and all 4 were positive by LGE, whereas 2 were JMH positive. On follow-up, 8 had adverse events, including 5 cardiac deaths. Patients with myocardial damage and LGE had a 9-fold higher rate of adverse events and an 11.5-fold higher rate of cardiac death than patients without enhancement.

Cardiac amyloidosis

Cardiac amyloidosis describes amyloid deposition in the heart, which may occur as part of systemic amyloidosis or as a localized process.

Systemic amyloidosis is a complication of chronic inflammatory conditions with renal disease being the predominant feature, presenting with proteinuria and renal failure. Cardiac involvement is rare^[38]. Systemic amyloidosis is the most commonly diagnosed form of clinical amyloid. Multiorgan involvement is common and the heart is affected approximately 90% of the time. Diastolic heart failure with right heart failure is the most common mode of presentation^[38]. Hereditary systemic amyloidosis is due to deposition of amyloid fibrils derived from transthyretin, lysosome or apolipoprotein A-1. Clinical syndromes include cardiomyopathy, nephropathy or neuropathy. Senile systemic amyloidosis is caused by deposition of amyloid fibrils derived from normal wild-type transthyretin and presents as a slowly progressive infiltrative amyloid cardiomyopathy^[38].

Cardiac amyloid typically demonstrates a diffuse decrease in signal intensity on T1-weighted fast spin echo images^[39,40]. It generally causes diffuse hypertrophy of

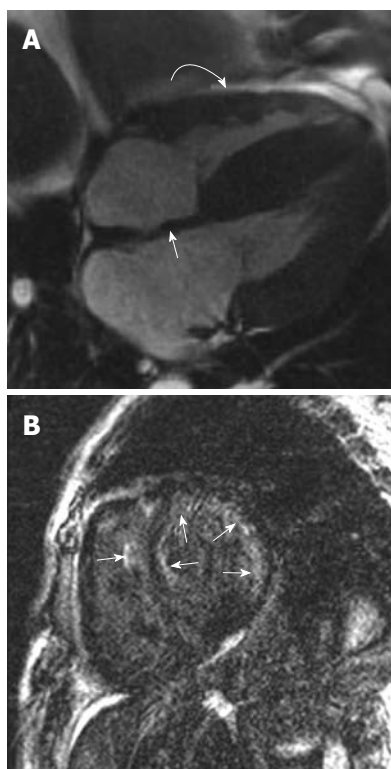


Figure 5 Right ventricular endomyocardial biopsy showed cardiac amyloid. A: Horizontal long axis steady-state free precession sequence showing hypertrophy of the basal segments of the left ventricle (straight arrow), and bi-atrial enlargement and thickening of the interatrial septum (curved arrow). Note the small pericardial effusion; B: Late-enhanced sequence shows a circumferential subendocardial high signal. Note the high signal on the right ventricular side of the interventricular septum resulting in the tram track sign (arrow). Note also the small pericardial effusion.

both the left and right ventricles, in contrast to HCM, which typically causes more focal hypertrophy (Figure 5). Thickening of the interatrial septum and posterior right atrial wall > 6 mm is also seen in cardiac amyloidosis^[41]. Late gadolinium enhancement is another hallmark of cardiac amyloidosis on CMRI. In a study by Vogelsberg *et al*^[42], LGE was demonstrated in 79% of patients with cardiac amyloidosis. Several different patterns of LGE were seen; LGE of the entire subendocardial circumference extending in various degrees into neighboring myocardium, circumferentially in the left ventricle with sparing of the subepicardial myocardium, and in the papillary muscles. Ejection fractions, LV end-diastolic volume and myocardial mass were not significantly different between the cardiac amyloid group and the other group of patients with various cardiac disorders. The average interventricular septum was 17 ± 4 mm in the amyloid group compared with 13 ± 3 mm in the non-amyloid group^[42]. A more recent study by Syed *et al*^[43] of CMRI in 120 patients with cardiac amyloidosis demonstrated LGE in 97% of patients and increased LV wall thickness in 91%. Global transmural or subendocardial LGE was the most common pattern seen in 83% of patients and this was associated with greater interstitial amyloid deposition.

Iron overload cardiomyopathy

Iron overload occurs either due to excess gastrointestinal absorption or secondary to repeated blood transfusion. Iron overload cardiomyopathy (IOC) is the leading cause of death in patients receiving chronic blood transfusion therapy^[44]. IOC is reversible, if chelation is started in time, but the diagnosis is often delayed due to the late appearance of symptoms and the absence of echocardiographic abnormalities^[45]. IOC has been defined as the presence of systolic or diastolic cardiac dysfunction secondary to increased deposition of iron in the heart independent of other concomitant processes^[46]. Serum ferritin or liver iron may be normal in the context of extensive myocardial iron overload. Similarly, echocardiography may be normal until extensive myocyte iron deposition has occurred.

The T2* sequence is the optimal sequence for detecting increased iron overload in the myocardium. Iron works as a paramagnetic substance, decreasing the T2* relaxation time of precessing protons in the x-y image plane. This reduces the signal from these protons, and thus leads to a darker appearance of the myocardium on grey-scale imaging (Figure 6). The decay in T2 signal can be semi-quantitatively graphed. In patients with moderate-to-severe iron deposition T2* values are substantially reduced - from the normal value of approximately 50 ms or greater to less than 20 ms. When T2* is less than 20 ms, LV systolic function is seen to decline progressively, accompanied by an increase in LV end-systolic volume index and LV mass^[47]. In order to assist with clinically grading the severity of IOC, patients at risk of IOC may be divided into 3 categories based on cardiac T2* values^[48]: (1) those with T2* > 20 ms (green zone) are at low risk for the imminent development of congestive heart failure; (2) those with T2* between 10 and 20 ms (yellow zone) in whom cardiac deposition has probably occurred are at intermediate risk of cardiac decompensation; and (3) those with T2* < 10 ms (red zone) are in the high-risk category of cardiac decompensation and need intensification of chelation therapy.

Metastatic disease

Metastatic disease to the heart and pericardium is uncommon but far more frequent than primary cardiac tumors^[49]. Cardiac metastases are associated with a poor prognosis. The most common tumors to metastasize to the cardiac structures are lung, lymphoma, breast, renal and melanoma^[50,51]. Bronchogenic carcinoma is the most common malignancy to spread to the cardiac structures and adenocarcinoma is the most common histological type^[51]. Metastatic disease from bronchogenic carcinoma to the heart may be *via* direct spread, lymphatic or hematogenous spread^[52]. Involvement of the heart and pericardium is usually a late manifestation of lymphoma, occurring in approximately 18% of cases. Primary cardiac lymphoma is diagnosed when there is no identifiable disease outside of the heart^[53]. Metastases typically have the appearance of multiple focal nodules within the myo-

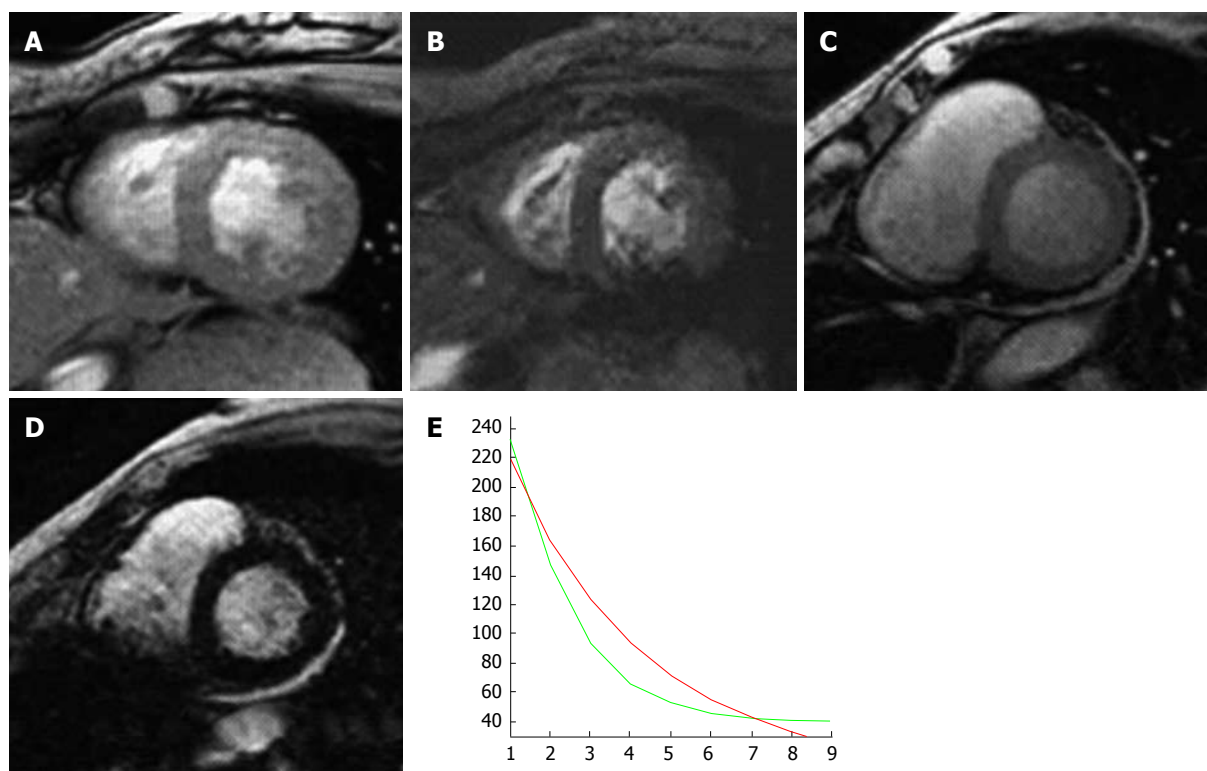


Figure 6 A 79-year-old woman with myelodysplasia treated with blood transfusions over many years. A (echo time 10 ms) and B (echo time 20 ms) are two short axis T2star sequences from a normal patient with no evidence of myocardial iron overload; C (echo time 10 ms) and D (echo time 20 ms) are from the patient with myelodysplasia showing a progressive loss of signal with increasing T2 echo time indicating shortened T1 relation secondary to iron infiltration; E: Graph of decreasing T1 relaxation times (green line) compared with a normal patient (red line).

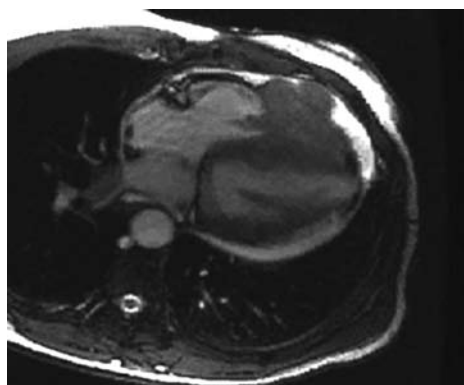


Figure 7 A 72-year-old woman with metastatic breast cancer to the heart. Note the location of the metastatic nodules in the right heart chambers, the infiltration through the right ventricular free wall, the pericardial effusion and the pericardial metastasis. Any infiltrative appearing cardiac mass involving the right heart chambers in the presence of a pericardial effusion should be considered suspicious for malignancy.

cardium, and can also be found in the pericardium^[54]. An interesting sub-type of cardiac metastases is “charcoal heart”, which has been described in melanoma spreading to the heart, and is related to the excessive pigment visualized in these metastases^[55]. Breast cancer may spread *via* direct invasion (usually *via* the internal mammary lymph node chain) or hematogenous dissemination. Generally, metastases have irregular borders, are bulky, infiltrative, more commonly involve the right heart chambers and may be associated with a pericardial effusion^[6].

Most cardiac metastases are low signal intensity on T1 sequences and brighter on T2 sequences^[56] with the exception of melanoma which appears as a high signal on T1 and T2 weighted sequences due to the paramagnetic properties of melanin. Malignant disease typically enhances post contrast administration (Figure 7). An issue that is a common problem on CMRI is the blood-pool artifact on immediate post-gadolinium T1 weighted sequences. An adaption of a double-inversion fast spin echo sequence using a tissue nulling time of 600 ms is a useful additional sequence to confirm a tumor and exclude a thrombus^[57]. Osteogenic sarcoma involving the heart is rare but merits mention as the metastasis contains bone. These calcific areas of increased opacity may be visible on a chest X-ray but are better characterized on computed tomography. Calcification is shown as a low signal on CMRI.

CONCLUSION

CMRI has established itself as an important diagnostic investigation tool for assessing the morphological and functional characteristics of cardiomyopathy. Particular strengths of CMRI are the ability to overcome anatomical limitations, suboptimal acoustic windows, a multi-sequencing approach to uniquely characterize the myocardium, and the absence of ionizing radiation. The use of LGE sequences has had an important impact on the ability to characterize the myocardium, and also aids in improving

clinical risk stratification for many cardiomyopathies.

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Regional variations in cardiovascular risk factors in India: India heart watch

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Abstract

Cardiovascular disease (CVD) is an important cause of mortality and morbidity in India. Mortality statistics and morbidity surveys indicate substantial regional variations in CVD prevalence and mortality rates. Data from the Registrar General of India reported greater age-adjusted cardiovascular mortality in southern and eastern states of the country. Coronary heart disease (CHD) mortality is greater in south India while stroke is more common in the eastern Indian states. CHD prevalence is higher in urban Indian populations while stroke mortality is similar in urban and rural regions. Case-control studies in India have identified that the common major risk factors account for more than 90% of incident myocardial infarctions and stroke. The case-control INTERHEART and INTERSTROKE studies reported that

hypertension, lipid abnormalities, smoking, obesity, diabetes, sedentary lifestyle, low fruit and vegetable intake, and psychosocial stress are as important in India as in other populations of the world. Individual studies have reported that there are substantial regional variations in risk factors in India. At a macro-level these regional variations in risk factors explain some of the regional differences in CVD mortality. However, there is need to study the prevalence of multiple cardiovascular risk factors in different regions of India and to correlate them with variations in CVD mortality using a uniform protocol. There is also a need to determine the "causes of the causes" or fundamental determinants of these risk factors. The India Heart Watch study has been designed to study socioeconomic, anthropometric and biochemical risk factors in urban populations in different regions of the country in order to identify regional differences.

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Key words: Cardiovascular disease; Risk factors; Socioeconomics; Epidemiology; Hypertension; Obesity; Lipids

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INTRODUCTION

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is the largest cause of mortal-

ity in the world, and the majority of deaths occur in low- and middle-income countries such as India and China^[1]. These diseases are epidemic in urban locations of these countries and are rapidly increasing in rural areas as well^[2]. With demographic shifts, epidemiological transition and increasing urbanization associated with increase in CVD risk factors (smoking, sedentary lifestyle, obesity, hypertension and hypercholesterolemia), and a lack of policy directives aimed at chronic disease control, CVDs are poised to accelerate further^[3]. This review summarizes the current information on CVD mortality in India with a focus on CHD. It evaluates studies that reported regional variations in CVD prevalence and mortality. The article also focuses on studies of risk factor prevalence, and highlights the urban-rural differences and regional variations in these risk factors. Finally, we identify gaps in existing knowledge regarding epidemiology of CVD in India and suggest the way forward for research to curb the CVD epidemic currently sweeping India. This article also sets the background for the India Heart Watch study, a cross-sectional and prospective epidemiological study, that is designed to study multiple socioeconomic and biological cardiovascular risk factors in different regions of the country.

CARDIOVASCULAR DISEASES IN INDIA

There are no detailed reports on CVD mortality by the Indian government. The World Health Organization (WHO) periodically reports on the proportion of deaths from CVD in India but trends are not reported due to lack of specific data. Prior to 1998, the Indian mortality data were obtained from predominantly rural populations where vital registration varied from 5% to 15%. Accordingly, the Registrar General of India reported that from the 1990s the proportion of mortality attributed to CVD or circulatory system diseases remained almost static at 15%-17%^[4]. However, these rates were based on limited data, mainly rural, and the only significant information on CVD mortality in urban subjects was from Maharashtra. We previously discussed the shortcomings of these reports^[4]. However, it was reported that there were significant regional variations, with high CVD mortality in Goa, Tamil Nadu, Andhra Pradesh and Punjab, and low mortality in the central Indian states of Uttar Pradesh, Madhya Pradesh and Rajasthan^[4].

Since 2001, the Registrar General of India and Million Death Study investigators have systematically collected mortality statistics from all Indian states using the country-wide Sample Registration System^[5]. In the first phase of this study from 2001-2003, causes of deaths in more than 113 000 subjects from 1.1 million homes were retrospectively analyzed using a validated verbal autopsy instrument^[5]. CVD was the largest cause of deaths in males (20.3%) as well as females (16.9%) and led to about 2 million deaths annually. Mortality data from CVD in India are also reported by the WHO. The Global Status on Non-Communicable Diseases Report

(2011)^[1] has reported that there were more than 2.5 million deaths from CVD in India in 2008, two-thirds due to CHD and one-third to stroke. These estimates are significantly greater than those reported by the Registrar General of India, and shows that CVD mortality is increasing rapidly in the country.

There are national differences in cardiovascular mortality across the world. The report on CVD in low income countries by the United States Institute of Medicine^[2] shows that there are substantial national variations. The highest age-adjusted mortality is observed in countries of central Asia, east and central Europe, some countries in Africa, while the lowest rates are observed in west European and north American countries. There are within-country variations also, and the report presents data on significant differences in regions and locations within countries and in many large nations such as the United States, Russia and China.

In India, CVD is the largest cause of mortality in all regions of the country. Table 1 shows the top 5 causes of deaths in different populations (rural *vs* urban, economically backward *vs* developed states, men *vs* women, and at all-ages *vs* middle aged individuals). CVD is the largest cause of mortality in each of these groups. There are large regional differences in cardiovascular mortality in India among both men and women^[6]. The mortality is highest in south Indian states, eastern and north-eastern states and Punjab in both men and women, while mortality is the lowest in the central Indian states of Rajasthan, Uttar Pradesh and Bihar. Sub-analysis of the mortality trends shows that CHD mortality is higher in the south Indian states while stroke mortality is higher in the eastern Indian states^[6]. There is no currently available information on trends in CVD mortality in India or different regions and states. The prospective phase of the ongoing Million Deaths Study^[7] from 2004-2013 shall provide robust data on regional variations and trends in CVD mortality in India.

Morbidity

WHO has predicted that from years 2000 to 2020 disability-adjusted life years lost (DALYs) from CHD in India shall double in both men and women from 7.7 and 5.5 million, respectively^[8]. It has also been reported that cerebrovascular diseases will account for more DALYs than CHD. These data do not report on regional variations within a large country such as India and more region-specific data are needed.

In the last 50 years there have been multiple cardiovascular epidemiological studies in India that have defined prevalence of CHD and stroke and identified the burden of disease^[8]. Prevalence studies have diagnosed CHD using history and electrocardiographic changes (Q-wave, ST-T changes). A meta-analysis of these studies reported that prevalence rates have more than trebled in the Indian population^[9]. The increase in CHD is largely an urban phenomenon and only recently a rapid rise in rural populations has been reported. Studies in the

Table 1 Top five causes of deaths in India classified according to areas of residence and gender

Rank	India (all age groups)	Economically backward states	Economically advanced states	Rural populations	Urban populations	Men	Women	Middle-age (25-69 yr)
1	Cardiovascular	Cardiovascular	Cardiovascular	Cardiovascular	Cardiovascular	Cardiovascular	Cardiovascular	Cardiovascular
2	COPD, asthma	Diarrhea	COPD, asthma	COPD, asthma	Cancers	COPD, asthma	Diarrhea	COPD, asthma
3	Diarrhea	Respiratory infections	Cancers	Diarrhea	COPD, asthma	Tuberculosis	COPD, asthma	Tuberculosis
4	Perinatal	COPD, asthma	Senility	Perinatal	Tuberculosis	Diarrhea	Respiratory infections	Cancers
5	Respiratory infections	Perinatal	Diarrheas	Respiratory infections	Senility	Perinatal	Senility	Ill-defined

Adapted from Registrar General of India Report^[5]. COPD: Chronic obstructive pulmonary disease.

Table 2 Population attributable risks (%) of various cardiovascular risk factors for coronary heart disease and stroke in [11,12]

Risk factor	INTERHEART (acute myocardial infarction)	INTERSTROKE (thrombotic or hemorrhagic strokes)
Apolipoprotein A/B ratio	49.2	24.9
Hypertension	17.9 (history)	34.6
Smoking	35.7	18.9
Diabetes history	9.9	5.0
High waist-hip ratio	20.1	26.5
Psychosocial stress	32.5	9.8
Regular physical activity	12.2	28.5
Diet/ diet score	13.7	18.8
Lack of alcohol intake	6.7	3.8
Cardiac causes	-	6.7

middle of the last century reported a low prevalence of 1%-2% in urban locations and 0.5%-1% in rural locations with very little urban-rural difference. In the intervening years the CHD prevalence in urban areas increased to 10%-12% while it increased to only 4%-5% in rural adults^[8]. Stroke prevalence studies report a substantial burden of stroke in urban and rural subjects^[8]. Stroke is also increasing in India and incidence registries using population-based surveillance have reported that the annual incidence of stroke varies from 100-150/100 000 population in urban locations with greater incidence in rural regions^[10]. However, these studies provide only limited information and there is a need for properly designed prospective studies to correctly identify trends. Regional variations in the burden of CVD using a uniform protocol have not been studied and there is a need to conduct such studies.

CARDIOVASCULAR RISK FACTORS

There are no prospective cardiovascular epidemiological studies that have identified risk factors of importance in India. Multiple case-control studies exist. The largest of these case-control studies is the INTERHEART study^[11]. This study was performed in 27 000 cases of acute myocardial infarction and controls in 52 countries of the world and assessed multiple cardiovascular psychosocial and biological risk factors in both the groups. Of these subjects more than 2000 cases and controls

were from South Asian regions^[11]. This study reported that standard risk factors such as smoking, abnormal lipids, hypertension, diabetes, high waist-hip ratio, sedentary lifestyle, psychosocial stress, and a lack of consumption of fruit and vegetables explained more than 90% of acute CHD events in South Asians. Similar conclusions were reached in smaller case-control studies^[8].

The INTERSTROKE study^[12] reported 10 common risk factors explained more than 90% of incident hemorrhagic and thrombotic strokes. The risk factors were similar to the INTERHEART study (hypertension, smoking, dyslipidemia, diabetes, high waist-hip ratio, sedentary lifestyle, psychosocial stress, poor quality diet, and cardiac causes), but the population-attributable risks were different with greater importance of hypertension and lesser importance of diabetes and lipids (Table 2).

Reviews of epidemiological studies suggest that all the major cardiovascular risk factors are increasing in India (Figure 1). Tobacco production and consumption has increased significantly. Smoking is increasing among young subjects (20-35 years), according to second and third National Family Health Surveys (NFHS)^[6]. In urban populations, smoking is increasing among the low educational status subjects^[13]. The prevalence of hypertension has increased in both urban and rural subjects and presently is 25%-40% in urban adults and 10%-15% among rural adults (Table 3)^[14]. Lipids levels are increasing and serial studies from a north Indian city reported increasing mean levels of total, low density lipoprotein and non-high density lipoprotein (HDL) cholesterol and triglycerides, and decreasing HDL cholesterol^[15]. Although there are large regional variations in the prevalence of diabetes it has more than quadrupled in the last 20 years from < 1%-3% to 10%-15% in urban areas and 3%-5% in rural areas (Figure 1)^[16]. Studies have reported increasing obesity as well as truncal obesity due to sedentary lifestyles, and psychosocial stress in the country^[8].

Regional variations

In India there has been no national study that used uniform methodologies to assess regional variations in the prevalence of multiple cardiovascular risk factors. A study in the 1940s by Chopra *et al*^[17] assessed the difference in mean blood pressure (BP) levels among army recruits belonging to different states in India, and reported

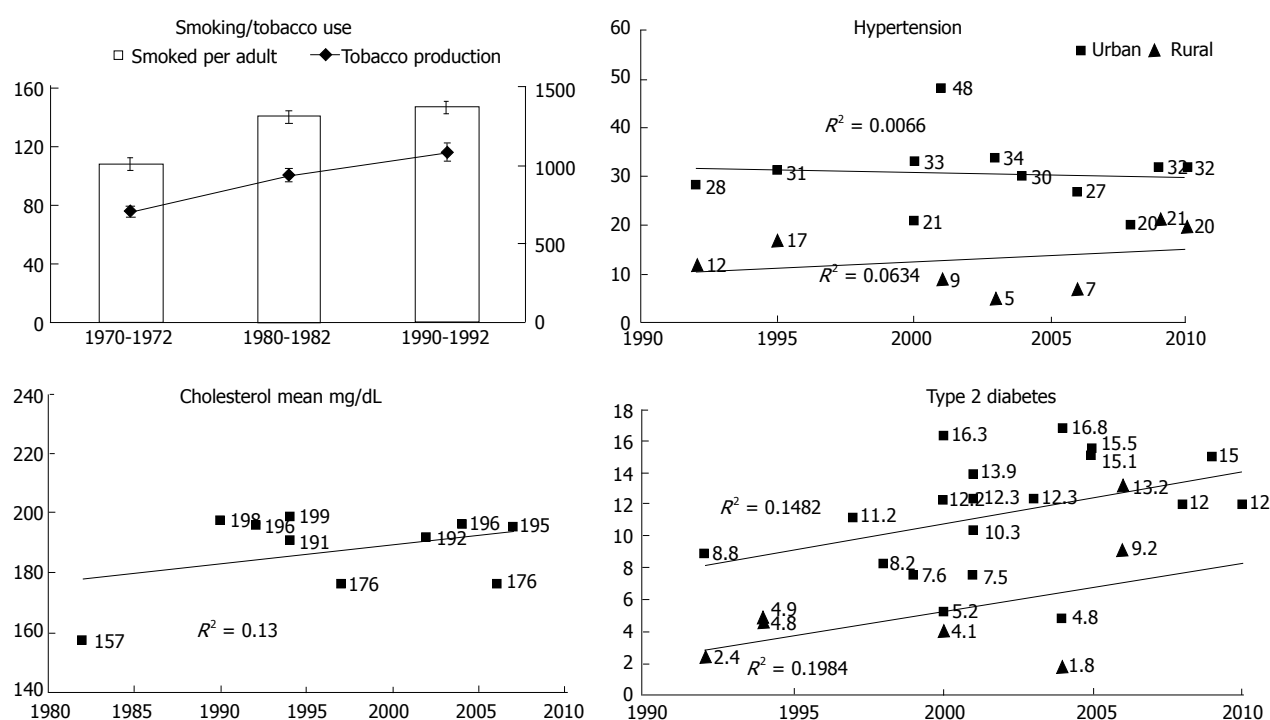


Figure 1 Secular trends in prevalence of major coronary risk factors in India. There is increasing prevalence of smoking, hypercholesterolemia and diabetes while hypertension prevalence has stabilised in urban (squares) and increasing in rural locations (triangles).

Table 3 Recent studies of hypertension prevalence in India

First author	Year	Place	Age (yr)	Sample size	Prevalence (%)
Urban Populations					
Gupta R	1995	Jaipur	≥ 20	2212	30.9
Anand MP	2000	Mumbai	30-60	1662	34.0
Gupta R	2002	Jaipur	≥ 20	1123	33.4
Shanthirani CS	2003	Chennai	≥ 20	1262	21.1
Gupta PC	2004	Mumbai	≥ 35	88 653	47.9
Prabhakaran D	2005	Delhi	20-59	2935	30.0
Reddy KS	2006	National	20-69	19 973	27.2
Mohan V	2007	Chennai	≥ 20	2350	20.0
Kaur P	2007	Chennai	18-69	2262	27.2
Yadav S	2008	Lucknow	≥ 30	1746	32.2
Rural Populations					
Gupta R	1994	Rajasthan	≥ 20	3148	16.9
Kusuma Y	2004	Andhra	≥ 20	1316	21.0
Hazarika NC	2004	Assam	≥ 30	3180	33.3
Krishnan A	2008	Haryana	15-64	2828	9.3
Todkar SS	2009	Maharashtra	≥ 20	1297	7.2
Bhardwaj R	2010	Himachal	≥ 18	1092	35.9
By Y	2010	Karnataka	≥ 18	1900	18.3
Kinra S	2010	National	20-69	1983	20.0

higher mean levels in those from north Indian states as compared to the south. Malhotra^[18] performed a study among railway employees in the 1960s to investigate variations in dietary habits and cardiovascular mortality in different regions of India. Greater cardiovascular mortality was observed among north Indian railway men, which was related to greater consumption of calories and fats. The multisite Prevalence of Diabetes in India Study^[19] focused on the epidemiology of diabetes prevalence in the country and performed studies in all

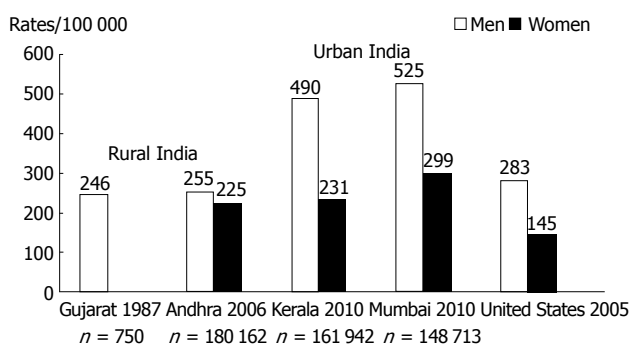
large Indian states, but did not report on regional variations. The multi-city Diabetes Epidemiology Study in India reported on differences in prevalence of diabetes in 8 urban locations^[20]. A higher prevalence of diabetes was reported in south India compared with other regions. NFHS-3^[21] investigated the prevalence of self-reported diabetes and reported a low prevalence of this condition, which precluded further analyses for regional differences.

A few studies evaluated the prevalence of multiple cardiovascular risk factors in 2 or more cities in India using uniform methodology. An Indian Council of Medical Research (ICMR) study in the 1990s evaluated risk factors in Delhi in north India and Vellore in south India and reported a significantly greater prevalence of risk factors in north India^[22]. A multisite Indian Industrial Population Surveillance Study (8 sites) reported variable prevalence of risk factors among industrial workers^[23]. A multisite study involving 5 rural and 4 urban sites in middle-aged women reported the prevalence of cardiovascular risk factors in different regions of India^[24]. The results focused on assessment of urban-rural differences and not on regional variations. An ICMR surveillance study evaluated the differences in self-reported prevalence of behavioral and anthropometric cardiovascular risk factors in different Indian states in rural and urban populations (Table 4)^[25]. Epidemiological studies were performed in urban and rural populations in states of south India (Kerala, Tamilnadu, Andhra Pradesh), west India (Maharashtra), central India (Madhya Pradesh), east India (Mizoram) and north India (Uttarakhand). The prevalence of smoking was highest in Mizoram

Table 4 Risk factor prevalence (%) among men and women (15-64 years) in 8 Indian states in Indian Council of Medical Research Noncommunicable Disease Risk Factor Surveillance Study^[25]

Risk factor	Andhra Pradesh		Madhya Pradesh		Maharashtra		Mizoram		Kerala		Tamilnadu		Uttarakhand	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Numbers	2719	3499	2857	2996	3084	3007	2297	2198	1710	3128	2077	3028	2147	3286
Current smoking	31.5	4.0	41.2	0.9	15.9	2.5	67	18.8	27.3	0.2	27.4	0.0	35.2	5.0
Smokeless tobacco use	13.6	4.5	53.8	22.6	40.7	23.6	46.5	55.4	7.0	3.4	13.6	8.4	21.0	2.2
Low physical activity	55.9	79.7	33.5	52.0	75.4	87.7	60.9	82.4	64.7	86.2	57.3	74.2	64.6	69.7
Obese, BMI ≥ 25 kg/m ²	19.4		8.2		13.1		10.3		27.1		22.6		14.5	
Hypertension	16.6		21.1		20.1		19.4		18.0		17.7		18.8	
Diabetes history	2.7	1.7	0.6	0.6	0.9	1.0	0.7	0.5	6.5	5.3	3.4	2.6	1.2	1.1

BMI: Body mass index.

**Figure 2 Prospective studies of cardiovascular mortality in urban and rural Indian populations^[29-32]. Age-adjusted cardiovascular disease mortality in urban India is almost twice that of the United States^[2].**

and overweight/obesity, hypertension and self-reported diabetes highest in the south Indian states of Kerala and Tamilnadu. The study focused on limited lifestyle and anthropometric risk factors and no data were obtained for more important risk factors such as lipid abnormalities and hyperglycemia. The INTERHEART study reported that these biochemical risk factors explained more than 50% of cardiovascular events among South Asians^[11].

On the other hand, reviews of CVD risk factor epidemiological studies from India showed significant regional variations in the prevalence of the important CVD risk factors of smoking, obesity, hypertension, diabetes and lipid abnormalities. The second and third NFHS reported the prevalence of smoking and tobacco use in populations of all Indian states^[6]. There were significant state-level and regional variations in smoking^[6,21]. The smoking rates were the highest in eastern Indian states and the lowest in Punjab^[26]. The second and third NFHS also reported on differences in prevalence of overweight and obesity among men and women in different Indian states^[21]. Prevalence of overweight and obesity was the highest in southern and northern Indian states and the lowest in central Indian states^[27].

Regional variations in other cardiovascular risk factors are not well reported within a single study using uniform methodology. A review of epidemiological hypertension studies reported that the prevalence of hy-

pertension was significantly higher in urban populations in India compared with rural populations^[14]. However, no consistent trends were observed for regional variations. In rural populations the prevalence of hypertension was higher in Rajasthan while in urban studies prevalence rates were not significantly different in different regions^[14]. The prevalence of hypertension was highest in metropolitan cities such as Mumbai and lower in less populated cities (Table 3)^[28]. An important finding of the current studies is that the prevalence of hypertension in rural populations is now approaching the rates in urban subjects (Figure 1).

Urban-rural differences

CVD is epidemic in urban regions of low income countries such as India^[8]. Cardiovascular mortality data from India has reported large regional variations with annual mortality rates greater than 250/100 000 in southern and eastern regions of the country and less than 100/100 000 in central India^[6]. There are large urban-rural differences in cardiovascular mortality also, with rates of less than 200/100 000 in rural areas and 450-500/100 000 in metropolitan urban locations. Only a few prospective studies of cardiovascular mortality are available in India. A small study in rural Gujarat^[29], and a larger study in rural Andhra Pradesh^[30], reported age-adjusted annual mortality rates of 200-250/100 000 while studies in urbanized Kerala^[31] and Mumbai^[32] have reported very high cardiovascular mortality with age-adjusted rates approaching 500/100 000 for men and 250/100 000 for women. These rates are almost twice that of United States^[1] (Figure 2).

The causes for these urban-rural differences in CVD mortality have not been systematically evaluated, but previous studies from India have reported that there are significant urban-rural differences in cardiovascular risk factors^[8]. The prevalence of smoking is greater in rural men, while all other risk factors such as sedentary lifestyle, obesity, central obesity, hypercholesterolemia, diabetes and metabolic syndrome are more prevalent in urban men and women^[33]. A recent nationwide study among women has reported a greater prevalence of multiple CVD risk factors in urban women (Table 5)^[24]. This is similar to previous studies on urban-rural differences in cardiovascular risk factors using uniform protocols

Table 5 Greater prevalence of cardiovascular risk factors among urban women in India^[24]

Variable	Urban (n = 2008)	Rural (n = 2616)	Age-adjusted urban-rural relative risk (95% CI)
Smoking/tobacco use			
Current users	326 (19.6)	871 (41.6)	0.35 (0.18-0.65) ¹
Smoking	14 (0.7)	276 (10.6)	0.09 (0.01-0.70)
Non-smoked tobacco use	325 (16.2)	607 (23.2)	0.64 (0.31-1.30)
Sedentary lifestyle PALs < 1.55 units	1406 (71.0)	1558 (60.1)	1.63 (0.90-2.94)
Overweight/obesity			
BMI 23.0-24.99 kg/m ²	355 (11.6)	324 (12.5)	0.91 (0.40-2.11)
BMI 25.0-29.99 kg/m ²	640 (31.7)	451 (16.8)	2.30 (1.12-3.47) ¹
BMI ≥ 30.0 kg/m ²	288 (13.9)	152 (5.7)	2.55 (1.61-3.49) ¹
Truncal obesity			
WHR > 0.9	880 (44.3)	318 (13.03)	5.26 (2.61-10.63) ¹
Waist circumference > 90 cm	638 (31.4)	226 (8.4)	5.17 (2.24-11.94) ¹
Hypertension	925 (48.2)	746 (31.6)	1.96 (1.10-3.49) ¹
Hypercholesterolemia ≥ 200 mg/dL	552 (27.7)	322 (13.5)	2.39 (1.17-4.88) ¹
Diabetes (history or fasting glucose ≥ 126 mg/dL)	292 (15.1)	98 (4.3)	4.24 (1.35-13.26) ¹

¹Significant. PAL: Physical activity levels; WHR: Waist-hip ratio; BMI: Body mass index.

and have been reported from Haryana, Delhi, Rajasthan and Tamilnadu^[8].

The higher prevalence of cardiovascular risk factors in urban areas in India is in contrast to high income countries where the CVD risk factors are equal in urban and rural areas^[34]. This is due to advancing disease and epidemiological transition and it is likely that the prevalence of risk factors will change in India with socio-economic development of rural areas. There is recent evidence that, in more developed states of India such as Kerala, the rural-urban differences in cardiometabolic risk factors have largely disappeared and the risk factors are equal or slightly greater in rural subjects^[35]. Whether a similar situation emerges in other Indian states is a matter for future studies. Recent studies in certain states have reported a high prevalence of diabetes (Figure 1) and hypertension (Table 3) in some rural locations in south and west India.

Trends in risk factors

An important focus of recent studies is the changing trends in cardiovascular risk factors. Reviews show that all major risk factors are increasing in India (Figure 1)^[36]. In the last 30 years, the prevalence of hypertension and hypercholesterolemia has doubled while that of diabetes has trebled. However, there are almost no studies that have evaluated risk factors using a prospective cohort design. The Jaipur Heart Watch studies in India evaluated multiple cardiovascular risk factors in urban middle-class subjects using a multiple cross-sectional study design over a 20-year period from 1991 to 2010^[37]. Over this period in these urban subjects, the prevalence of smoking declined, hypertension did not change significantly (due to increased awareness and treatment), while all other risk factors such as obesity, truncal obesity, hypercholesterolemia, diabetes and metabolic syndrome increased significantly^[37]. No similar studies that have evaluated multiple cardiovascular risk factors are available from India.

The Global Burden of Diseases Chronic Disease Risk Factors Collaborating Group has reported 35-year (1980-2005) trends in mean levels of body mass index (BMI), systolic BP and cholesterol in 199 high-income, middle-income and low-income countries^[38]. These studies evaluated trends in these risk factors using data from local and regional population-based epidemiological studies. A trend for increasing BMI was observed in all 3 regions, with greatest increase in high-income countries and a lesser increase in low-income countries^[38]. Mean systolic BP declined in high- and middle-income countries but increased in low-income countries and is now more than in high-income countries^[38]. Mean cholesterol levels have also declined in high- and middle-income countries but have increased in low-income countries^[38]. The India specific data are similar to the overall trends in low-income countries.

GAPS IN KNOWLEDGE

There are significant gaps in the knowledge of the epidemiology of CVD and associated risk factors in countries of the South Asian region, such as India. The mortality data have been inadequately collected and collated and there is little information on regional variations in CVD incidence and mortality. There are no national studies that have evaluated the disease incidence and prevalence. Studies in similar densely populated regions in Europe^[39], North America^[40] and China^[41] have reported significant regional variations in CVD mortality, CVD prevalence and incidence, and major cardiovascular risk factors. CVD mortality is greater in north European countries than in south Europe^[39]. This is associated with greater prevalence of hypertension, hypercholesterolemia and diabetes in the northern European countries. CVD mortality is greater in the north of England than in the south, and is related to socioeconomic factors as well as a higher prevalence of smoking, obesity and lipid abnormalities^[42]. CVD mortality, especially stroke, is higher in

the south-west of the United States^[40] associated with a greater prevalence of abnormal lifestyles, obesity and hypertension. In China, CVD, especially stroke mortality, is greater in the north-east^[41], and this is due to a greater prevalence of obesity and hypertension.

In India, regional variations in cardiovascular risk factors such as smoking, obesity, hypertension, diabetes and lipid abnormalities have not been systematically studied. The government of India sponsored the National Sample Survey Organization surveys and the NFHS have been conducted for many years, but these have not focused on non-communicable diseases and risk factors. Only in the recent NFHS-2 and NFHS-3 has there been an attempt to quantify smoking and tobacco use and adult body weight^[21,26]. Other risk factors have not been studied. There have been a number of *ad hoc* population-based surveys for estimation of CVD risk factor prevalence in India as reported above^[8]. All these studies have been performed by local investigators using different age groups, variable sample sizes, non-uniform methodology, improper statistical techniques, and reported results inconsistently. There are no prospective studies in India that have evaluated either the incidence of CVD or risk factor associations. The Prospective Urban Rural Epidemiological (PURE) study is the only large study which is prospectively identifying the risk factor-CVD association^[43]. Finally, due to lack of national data there are no national efforts to initiate policy change for controlling the CVD epidemic^[3]. There are no initiatives to change the population-wide distribution of risk factors or to evaluate the efficacy of high-risk approach for risk factor control and disease management.

There is an obvious need to perform multisite and multicity studies for identification of cardiovascular risk factor prevalence and their trends in different regions of India using uniform methodology. Such studies have been reported from Europe and North America. The United States National Health and Nutrition Evaluation Surveys^[44] have periodically assessed risk factors in the country and have reported continuing greater prevalence of hypertension and metabolic risk factors in the south-eastern states. The British Regional Heart Study^[45] and many studies in Europe have reported variable prevalence of risk factors in different regions of these countries. Studies in Europe have reported greater prevalence of cardiovascular metabolic risk factors in the North and East European countries as compared to the southern countries^[39]. The CARMELA study in 7 Latin American cities in Argentina, Chile, Colombia, Ecuador, Mexico, Peru and Venezuela reported a high prevalence of smoking, hypertension, hypercholesterolemia and diabetes in these cities^[45]. The study reported a high prevalence of all these risk factors in urban communities in these countries. Regional studies in China^[41] have reported greater hypertension and hypercholesterolemia prevalence in the north-east regions as compared to others.

INDIA HEART WATCH

An investigator-initiated study to identify regional differences of CVD risk factors in India has been organized. Funding has been obtained from South Asian Society of Atherosclerosis and Thrombosis, Bangalore and Minneapolis (United States). The protocol was devised and the study was approved by the institutional ethics committee of the national coordinating center. The proforma focused on demographic characteristics, family history of CHD, stroke, hypertension and diabetes and self-reported details of smoking, alcohol intake, hypertension, diabetes, lipid abnormalities, CVD, physical activity and dietary fat and fruit intake. The proforma is similar to previous studies performed by this group^[13,15,37]. Measurements focus on height, weight, sitting BP, waist and hip dimensions, using methodologies prescribed by WHO^[46]. Biochemical measurements in fasting blood samples are performed, with uniform sample collection and methods at a national laboratory (Thyrocare Technologies Ltd, Mumbai, India, www.thyrocare.com).

The study has been planned according to the regional variations in cardiovascular mortality reported above^[4-6]. Medium-sized cities were identified in each of the large states of India and investigators who had a track record of research in CVD or diabetes epidemiology were invited to participate in the study. A total of 20 investigators were invited from large states of India and 15 agreed to participate in the study. The cities were in northern India (Jammu, Chandigarh, Karnal, Bikaner), western India (Ahmedabad, Jaipur), eastern India (Lucknow, Patna, Dibrugarh), southern India (Madurai, Hyderabad, Belgaum) and central India (Jaipur, Indore, Lucknow). The study used simple cluster sampling at each study site. A middle-class location was identified in each city. This depended upon the municipal classification which is based on municipal reserve land prices and is periodically revised by local government and municipal agencies for taxation purpose. This is based on the cost of land, type of housing, public facilities (roads, water supply, electricity supply and gas), and educational and medical facilities. A sample size of about 250 men and 250 women ($n = 500$) at each site is considered adequate by WHO to identify a 20% difference in the mean level of biophysical and biochemical risk factors^[46]. About 800-1000 subjects in each location were invited to participate in the study, to ensure participation of at least 500 subjects at each site. This number was based on our earlier surveys in urban areas where the response rate for participation in such surveys has been about 60%-70%^[13,15,37]. The surveys were preceded by meetings with community leaders to ensure good participation. The subjects were invited to a community center within each locality either twice or thrice a week depending upon the investigator's schedule. Measurements focused on demographic history, socioeconomic status, educational status, type of family, any major previous illnesses, history of known hyperten-

sion, diabetes, lipid abnormalities and CVD. Details of lifestyle risk factors such as smoking, intake of alcohol, dietary fat, fruit and vegetables, physical activity, psychosocial factors and depression were inquired using the validated INTERHEART study questionnaire^[47]. Physical examination emphasized the measurement of height, weight, waist and hip, and proper BP measurement. A fasting blood sample was obtained from all individuals after at least 8 h fasting. The study is powered to assess prevalence of various CVD risk factors in urban locations in India, identification of regional differences^[6], assessment of influence of social development index^[48] on risk factors, and lifestyle determinants of various risk factors. This study is not comparable to the Indian arm of the PURE study^[49]. PURE is a prospective study localised to five urban and five rural locations, three in south (Bangalore, Chennai, Trivandrum) and two (Jaipur, Chandigarh) in north India while India Heart Watch has centres all over the country. The PURE study has recruited more than 28 000 subjects from these centres and is larger than the India Heart Watch. It also has a prospective design with proposed follow-up of these individuals for 15 years and is unlike the India Heart Watch study which essentially is a study with cross sectional design and limited follow-up.

CONCLUSION

In conclusion, this review shows that there are wide regional variations in cardiovascular disease mortality and burden in India. Apart from the well known gender based differences, there are variations in mortality in different states and in urban and rural regions and among different socioeconomic groups within states. Although no nationwide study of risk factors exists, review suggests that there are significant state-level and rural-urban differences in major cardiovascular risk factors of smoking, obesity, central obesity, hypertension, hypercholesterolemia and diabetes. However, there is need to perform nationwide studies for determining cardiovascular risk factors using uniform protocols to assess regional differences. There is also a need to determine the “causes of the causes” or primordial determinants of these risk factors. The India Heart Watch study shall be able to provide some of these answers.

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Continuous respiratory monitoring for sleep apnea screening by ambulatory hemodynamic monitor

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In addition to AHI, an expert over-reader annotated individual breaths, snores and SDB breathing events to which the automated algorithms were compared.

RESULTS: The test set consisted of data from 85 patients (age: 50.5 ± 12.4 years). Of these, 57 had a positive PSG defined as $AHI \geq 5.0$ (mean: 30.0 ± 29.8 , negative group mean: 1.5 ± 1.2). The sensitivity and specificity of the SDBSS compared to AHI was 57.9% and 89.3%, respectively. The correlation of snoring rate by CPAM compared to the expert over-reader was $r = 0.58$ (mean error: 1.52 snores/min), while the automated respiration rate had a correlation of $r = 0.90$ (mean error: 0.70 breaths/min).

CONCLUSION: This performance assessment shows that CPAM can be a useful portable monitor for screening and follow-up of subjects for SDB.

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Key words: Portable monitor; Sleep-disordered breathing; Polysomnography; Sleep apnea; Hemodynamic monitor

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Abstract

AIM: To validate the sleep-disordered breathing components of a portable electrocardiography and hemodynamic monitor to be used for sleep apnea screening.

METHODS: Sleep-disordered breathing (SDB) is associated with cardiovascular disease. Patients with existing cardiovascular disease may have unrecognized SDB or may develop SDB while under the care of a cardiologist. A screening device for SDB, easy to use and appealing to cardiologists, would assist in referral of appropriate patients for full polysomnography (PSG). A cardiac and respiratory monitor (CPAM) was attached to patients undergoing PSG and an apnea/hypopnea index (AHI) generated. The CPAM device produced respiration rate, snoring rate, individual apnea/hypopnea events and an SDB severity score (SDBSS).

INTRODUCTION

As recognized by the American College of Cardiology in 2008, sleep-disordered breathing (SDB) is associated

with cardiovascular disease including heart failure, hypertension and increased arrhythmias^[1]. Central sleep apnea is a common comorbidity of heart failure and may contribute to readmission, poor response to treatment and heart failure progression. Effective treatment exists for SDB that may improve or reverse the cardiovascular consequences, making accurate diagnosis important. The prevalence of SDB ranges from 24% of men in a random sample of middle-aged adults^[2] to 73% in patients with stable heart failure^[3]. In addition, it has been estimated that 80%-90% of patients with obstructive sleep apnea (OSA) are undiagnosed^[4]. SDB is typically diagnosed during overnight polysomnography (PSG), with technicians attending to both the patient and the equipment. These extensive studies are the accepted gold standard for diagnosis of sleep disorders. In 2007, the American Academy of Sleep Medicine (AASM) provided guidelines on the use of portable monitors to assess moderate to severe sleep apnea^[5] for screening. In certain populations, such as those with heart failure, repeat studies are beneficial to evaluate the effectiveness of treatment, and a portable monitor for at-home studies would facilitate that process, especially if information concerning cardiac function was also available.

Standard PSG techniques have been adapted to portable monitors including electro-encephalography (EEG), electro-oculography (EOG), thoracic and abdominal effort, and oximetry. Novel technologies have been developed including one device that measures peripheral artery tone from a finger sensor to estimate changes in vascular flow^[6] during apnea, whereas another incorporates actigraphy as a marker of sleep and wakefulness^[7]. The performance of portable monitors compared to PSG has been reported and varies greatly^[8]. To date, there have been no monitors available to assess both hemodynamic function and SDB simultaneously.

Targeting the patient population with cardiovascular disease, we report the performance of the respiratory components of a new portable monitor capable of recording 48-h electrocardiography (ECG), heart sounds, snoring, body position and respiration [Cardiopulmonary Ambulatory Monitor (CPAM), Inovise Medical, Inc., Beaverton, OR, United States]. In addition to full Holter-type ECG analysis and heart rate variability, this device incorporates automated algorithms for quantification of diastolic heart sounds and systolic time intervals previously validated and shown to correlate with independent hemodynamic measurements of left ventricular (LV) function^[9,10]. Parameters produced by CPAM include those to assess systolic and diastolic function^[11]. For systolic function, the presence of a third heart sound has been shown to be associated with increased LV filling pressures and electromechanical activation time (Q-wave onset to S1 interval) correlating with reduced ejection fraction. For diastolic function the presence of a fourth heart sound (S4) has been shown to be associated with increased LV stiffness^[12]. Moreover, we have previously shown that additional use of portable acoustic cardiog-

raphy can improve cardiovascular diagnosis^[13].

To test this device for SDB screening, we compared the results obtained with CPAM against standard PSG AHI and over-read of sound and respiration signals by trained personnel for snoring and respiration rate.

MATERIALS AND METHODS

Ambulatory cardiorespiratory monitoring equipment

The cardiorespiratory monitor records three leads of ECG (leads I, II and a modified V4-RA) and two heart sound signals (V3 and V4 locations) (Figure 1); body position, snoring, and respiration. Body position and respiration are determined from a triaxial accelerometer within the main recorder unit. A wireless connection to a computer allows a preview of ECG and heart sound traces to confirm data quality. A removable micro SD card can store up to 48 h of data. The data are downloaded to a Windows PC application with automated algorithms for detection of respiration, including SDB events, snoring, body position, and activity level. The monitor uses previously validated automated algorithms for heart sound parameters and systolic time intervals^[14] that were not part of this study.

The main recorder unit is secured in a holster that is placed on the upper chest wall and attached with two standard ECG snap-type electrodes. The triaxial accelerometer signals undergo several signal processing steps to create a pseudo-respiration signal. This signal is used to detect breaths for calculation of respiration rate and also to detect individual SDB events. The SDB, respiration and snoring algorithms were developed on learn portions of large datasets from apparently healthy subjects and from the learn set of data from this and other PSG studies. The algorithms were developed strictly on learning set data and tested infrequently on the separate testing datasets. The test data in this study were over-read and annotated by trained experts for individual breaths, snores and individual episodes of SDB. The data collected on patients during PSG studies had the additional independent results for apnea/hypopnea index (AHI).

Study design, patient recruitment and assessment

The patients participating in this study were prospectively enrolled at Luzerner Kantonsspital for PSG at the Center of Sleep Disorders. The main inclusion criterion was suspicion of sleep apnea. Exclusion criteria were: age < 18 years, decompensated heart failure, myocardial infarction within the last 6 mo, and significant chronic obstructive pulmonary disease. The study protocol was approved by the local medical ethics committee and all patients gave written informed consent. The anthropometric parameters of all patients were determined, and a brief medical history and all current medications were recorded. The ambulatory monitor was placed on the subject by research team members independent of the sleep study team not involved in the data analysis. Patients were fitted with the PSG equipment and the AU-

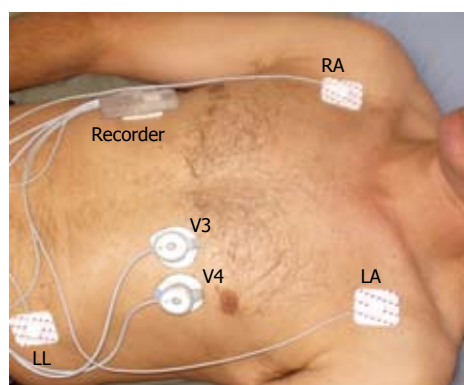


Figure 1 Placement of the recorder unit and the electrocardiography/sound sensors. Regular electrocardiography (ECG) monitoring electrodes are placed on the right arm (RA), left arm (LA) and left leg (LL) locations for ECG monitoring. Combined ECG/sound sensors are placed in the precordial V3 and V4 positions. The recorder unit is placed on the right upper chest wall.

DICOR CPAM device between 20:00 and 22:00 h. The patients followed their personal routine and retired between 22:30 and midnight and were awakened between 05:00 and 07:00 h next morning. The PSG equipment was fully disconnected while the ambulatory monitor continued to record until the research team removed the device later in the morning. The ambulatory monitor data were downloaded and sent to one individual for automated analysis while PSG analysis was performed in the sleep laboratory according to usual standards by separate personnel.

PSG

PSG was performed in accordance with AASM 2007 standards^[15] by trained and certified technicians. The following parameters were monitored: EEG (Fp1/Fp2, C3/C4, O1/O2 *vs* M1/M2, rate 500-2000 Hz), EOG, chin, submental and leg electromyograms, and ECG. Respiration was monitored with thoracic and abdominal effort (induction plethysmography) while airflow was monitored by nasal cannula (flow pressure transducer). A microphone was placed near the head of the bed and sound recorded for later snoring analysis. The body position was recorded using a position sensor and the patient monitored by an infrared camera. Oxygen saturation was monitored by a pulse oximeter applied to the finger. All these parameters were computerized using the Embla™ Recording System S7000 or N7000 (ResMed Embla™, ResMed Corp., San Diego, CA, United States). CO₂ was measured using a transcutaneous partial pressure of CO₂ (tcpCO₂) sensor (TOSCA 500, Radiometer GmbH, Switzerland).

SDB scoring

PSG: The PSG data were scored using AASM 2007 standards^[15] by a certified Swiss sleep technician and physician certified by the Swiss Board of Sleep Medicine. Apnea was categorized into central, obstructive and mixed using the thermistor recordings or hypopnea (unclassified) using the cannula recordings. The criteria of hypopnea were 30% reduction of airflow and 4% oxy-

Table 1 Demographics and clinical characteristics (mean \pm SD)

Parameter	All (<i>n</i> = 85)	Negative SDB (AHI < 5, <i>n</i> = 28)	Positive SDB (AHI \geq 5, <i>n</i> = 57)
Age (yr)	50.5 \pm 12.4	47.2 \pm 12.3	52.1 \pm 12.2
Sex (% male)	83.50%	78.60%	91.60%
Weight (kg)	88.1 \pm 18.9	82.1 \pm 17.1	91.1 \pm 19.2 ^a
BMI (kg/m ²)	28.9 \pm 5.5	26.9 \pm 4.8	29.9 \pm 5.6 ^a
History of hypertension (%)	34%	39%	21%
History of MI (%)	6%	11%	2%
History of CAD (%)	9%	18%	3%
AHI (events/h)	20.6 \pm 27.8	1.5 \pm 1.2	30.0 \pm 29.8 ^a
Obstructive apnea (<i>n</i>)	34.8 \pm 89.3	0.9 \pm 1.8	51.5 \pm 105.3 ^a
Central apnea (<i>n</i>)	5.7 \pm 22.3	1.6 \pm 4.8	7.7 \pm 26.9 ^a
Mean % SaO ₂ (%)	93.1 \pm 2.7	93.9 \pm 2.5	92.7 \pm 2.7 ^a
Oxygen desaturation index	12.5 \pm 19.6	1.1 \pm 1.2	17.5 \pm 21.8 ^a
Desaturation > 4% (<i>n</i>)	70.1 \pm 120.3	6.2 \pm 7.0	98.4 \pm 135.7 ^a
Apnea arousal (<i>n</i>)	31.6 \pm 79.3	1.8 \pm 4.9	46.2 \pm 93.6 ^a
Total arousals (<i>n</i>)	200.0 \pm 137.8	166.1 \pm 74.3	216.6 \pm 158.0 ^a
Awakening > 1 min (<i>n</i>)	17.4 \pm 32.7	11.0 \pm 17.2	20.6 \pm 37.9
SDBSS	9.3 \pm 15.3	1.4 \pm 3.7	13.2 \pm 17.2 ^a

^a*P* < 0.05 *vs* negative SDB; AHI: Apnea/hypopnea index; MI: Myocardial infarction; CAD: Coronary artery disease; SDB: Sleep-disordered breathing; SDBSS: Sleep-disordered breathing severity score; BMI: Body mass index.

gen desaturation or 50% airflow reduction and arousal. Sleep, arousal, periodic limb movements and respiration were analyzed using 30-s epochs with assistance from REMlogic software (Embla Systems, Thornton, CO, United States).

AUDICOR CPAM: Using the PSG report, the beginning and end of sleep were input to the software ignoring periods of intermittent wakefulness. The data were analyzed using the automated algorithms for snoring, respiration, individual timing and duration of SDB events and an SDB severity score. The timing and durations of the individual SDB events are used to create an SDB severity score (SDBSS). Apnea and hypopnea > 10 s in duration that met certain physiological timing constraints and occurred during quiescent periods were considered SDB events and were totaled and divided by the total sleep time. This score was developed by the manufacturer of the device on a learn set of data collected using AUDICOR CPAM from patients undergoing PSG, and was intended to correlate with the PSG AHI.

RESULTS

Population

The test set of this study consisted of 85 patients (71 men) whose mean age was 50.5 \pm 12.4 years (range: 22-81 years). There were 57 patients with a positive PSG (AHI \geq 5.0), and the others, while negative for SDB, had other sleep disorders such as restless legs syndrome, periodic limb movements, narcolepsy or cataplexy syndrome. The positive SDB group had a mean AHI of

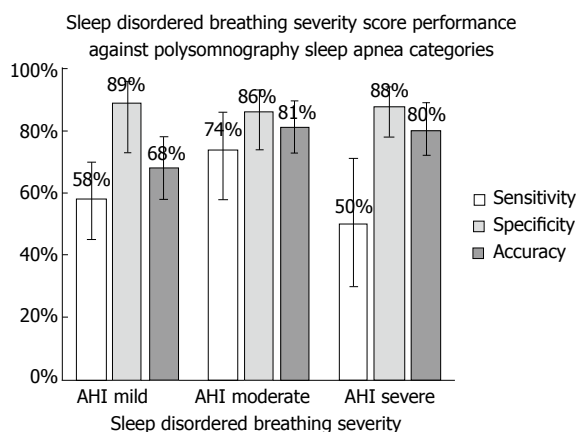


Figure 2 Performance of sleep-disordered breathing severity score against polysomnography apnea/hypopnea index for categorizing subjects into mild, moderate or severe sleep apnea on test set data. Error bars show 95% confidence intervals. AHI: Apnea/hypopnea index.

Table 2 Per minute sleep-disordered breathing results

		Expert	
		Negative	Positive
Algorithm	Negative	9782	413
	Positive	398	1381

30.0 ± 29.8 events/h, whereas the negative SDB group had a mean AHI of 1.5 ± 1.2 events/h. Age was not significantly different, but body mass index was significantly higher in the positive SDB group (Table 1). Mean percent oxygen saturation, oxygen desaturation index, number of desaturations > 4%, apnea arousals, total arousals, and the SDBSS were all significantly different in the positive SDB group (AHI ≥ 5) compared to the negative SDB group (AHI < 5).

SDB detection

Expert over-readers annotated individual episodes of SDB for a total of 16 071 min in the test set. The product provided the clinician with a time-based graph of SDB events as well as duration of each event. The per-minute performance metrics represented the ability of the product to represent correctly these individual events. Performance metrics are presented in Tables 2 and 3 on a per-minute basis comparing the automated SDB detection algorithm to the expert over-reader. For the expert over-reader, a positive minute had at least one annotation of SDB > 10 s in length.

Performance of the SDBSS

The AHI threshold recommended by AASM is 5 events/h (AHI ≥ 5). On this test set, the sensitivity and specificity of the SDBSS compared to positive PSG (AHI ≥ 5) was 57.9% and 89.3%, respectively (Figure 2 and Table 4). The performance was not significantly different between those patients with a final diagnosis of OSA (sensitivity 50.0%, specificity 89.3%) or central/mixed sleep apnea

Table 3 Per minute sleep-disordered breathing algorithm performance statistics (%)

	Mean	95% CI
Accuracy	93.2	92.8-93.7
Sensitivity	77.0	75.0-78.9
Specificity	96.1	95.7-96.4
Positive predictive value	77.6	75.7-79.6
Negative predictive value	95.9	95.6-96.3

Table 4 Sleep-disordered breathing severity score performance statistics against apnea/hypopnea index ≥ 5 (%)

	Mean	95% CI
Accuracy	68.2	58.3-78.1
Sensitivity	57.9	45.0-69.8
Specificity	89.3	72.8-96.3
Positive predictive value	91.7	82.6-100
Negative predictive value	51.0	37.0-65.0

Table 5 Sleep-disordered breathing severity score performance statistics against mild, moderate and severe apnea/hypopnea index categories (%)

	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
Mild	57.9	89.3	68.2
5 ≤ AHI < 15	(45.0-69.8)	(72.8-96.3)	(58.3-78.1)
Moderate	74.3	86.0	81.2
15 ≤ AHI < 30	(57.9-85.8)	(73.8-93.0)	(72.9-89.5)
Severe	50.0	88.1	80.0
AHI ≥ 30	(29.0-71.0)	(78.2-93.8)	(71.5-88.5)

AHI: Apnea/hypopnea index.

(sensitivity 69.6%, specificity 89.3%).

The standard thresholds defined by the AASM on AHI for classification into mild, moderate and severe sleep apnea were: (1) mild, 5 ≤ AHI < 15; (2) moderate, 15 ≤ AHI < 30; and (3) severe, AHI ≥ 30. In Table 5, these three thresholds for SDBSS were implemented, yielding the performance statistics shown.

We also sought to determine the impact of periodic limb movements on the performance of the CPAM device SDB detections. The SDB detection algorithm was not trained specifically on patients with and without periodic limb movement syndrome (PLMS). Therefore, the full dataset from this study (*n* = 111, 32 patients with final diagnosis of PLMS) was used to determine the impact of PLMS on performance. The sensitivity and specificity of SDB detection on patients with PLMS was 57.9% and 92.3% and those without PLMS was 60.4% and 90.0%, respectively, indicating no substantial performance degradation with PLMS.

Snoring

The automated algorithmic snore detections generated event markers on the main AUDICOR CPAM summary

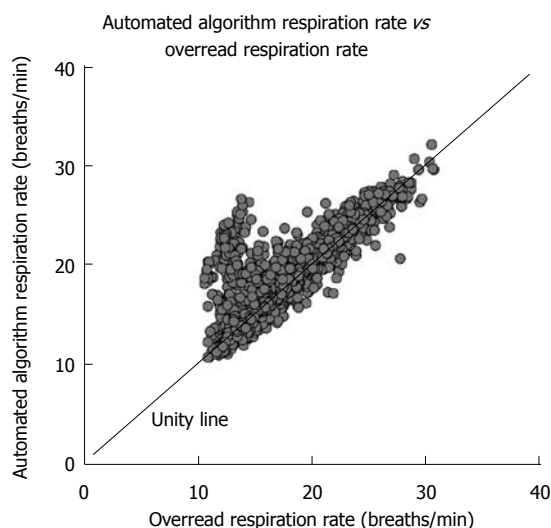


Figure 3 Relationship of the automated respiration rate algorithm to the over-read respiration rate on test set data.

screen and metrics in the physician's report to assist categorization of SDB into obstructive or central by the clinician.

To test the ability of the device to detect snoring, the expert over-readers annotated individual snores visually from the collected sound signal. The automated algorithm of the ambulatory monitor to detect snoring was developed by the manufacturer strictly on learn datasets. On this test set, the correlation of snoring rate by the automated algorithm compared to the expert over-reader snoring rate was $r = 0.58$, mean error of 1.52 snores/min with 74% of the algorithm snoring rates within 10% of the expert over-reader snoring rate.

Respiration rate

The CPAM product generated a trend of respiration rate, and to test this feature, the expert over-readers annotated individual breaths in the test dataset. The CPAM automated algorithm to detect individual breaths and respiration rate was developed strictly on learn datasets. The performance of the respiration rate by the automated algorithm compared to the expert over-reader respiration rate calculated on 4830 5-min intervals in this test dataset is shown in Figure 3 ($r = 0.90$, average error = 0.70 breaths/min). The respiration rate of the ambulatory monitor was within 2 breaths/min of the over-reader respiration rate 93% of the time.

DISCUSSION

Cardiovascular disease and SDB are common comorbidities. An overnight technician-attended sleep study with multi-parameter PSG provides the standard measurement of AHI used to diagnose SDB. However, the desire for a less expensive, more timely and convenient alternative for screening patients and to use for repeat studies has grown and various devices have been developed. There are different classes of portable sleep

monitors based upon the number of channels of data collected and the type of sensors/technology used in the assessment^[16]. A single device capable of assessing SDB and cardiac function such as CPAM is desirable, particularly for cardiologists following the progression of diseases such as heart failure with central sleep apnea, and to understand the efficacy of treatment over time.

Other portable monitors have reported performance of SDB detection with moderate to quite good accuracy^[17], using a variety of thresholds on the PSG AHI, ranging from 5 to 40 events/h. In a study of 75 stable heart failure patients comparing PSG to a home study with a portable monitor, Quintana-Gallego found diagnostic accuracies of 78.6%, 84% and 80% using AHI thresholds of 5, 10 and 15, respectively^[18]. In another study of 37 patients comparing contemporaneous PSG and a multichannel portable monitor to detect correctly the presence of SDB (defined as $AHI \geq 15$), the reported sensitivity was 96% and the specificity was 83%^[19]. The AUDICOR CPAM monitor has similar performance to these devices.

Growing evidence shows that over time SDB contributes to LV dysfunction and the American College of Cardiology has provided guidelines for diagnosis and treatment of SDB in the context of cardiovascular disease^[1]. In heart failure, there is a high prevalence of central sleep apnea, whose effect may lead to further decline of LV function, but since symptoms overlap, underdiagnosis of CSA is common. The German Sleep Society has recommended that a sleep study be performed on every patient with congestive heart failure and LV ejection fraction $< 40\%$, irrespective of the presence of sleep-related symptoms^[20]. Treatment for SDB within the context of heart failure could lead to improved quality of life and better prognosis^[21], especially if repeat sleep study confirms effectiveness of treatment. OSA has been shown to be associated with hypertension, LV dysfunction, arrhythmias and increased sympathetic tone. In one study, LV diastolic function was assessed by echocardiography in 68 OSA patients. Abnormal diastolic relaxation patterns were common in OSA patients and more severe sleep apnea was associated with longer isovolumic relaxation times^[22]. Alchanatis *et al.*^[23] found that OSA patients had lower LV ejection fraction, reduced LV peak emptying rate, lower LV peak filling rate, and delayed time to peak filling rate as compared to controls. The authors conclude that OSA patients without any cardiovascular disease tend to develop both LV systolic and diastolic dysfunction that can be reversed after 6 mo of CPAP.

AUDICOR CPAM has the ability to detect abnormal diastolic heart sounds and assess systolic function through systolic time intervals. Until recently, the ability to do long-duration simultaneous ECG and heart sound recording has not been available. We performed CPAM ambulatory monitoring in 128 asymptomatic subjects^[24] and found the third heart sound was significantly more prevalent in patients aged < 40 years and more pronounced during sleep in this age group. The fourth heart

sound was meanwhile significantly more prevalent in patients aged > 40 years and more pronounced during sleep in this age group, reflecting the change in diastolic filling patterns with increasing age. In addition, time intervals reflecting systolic function showed less circadian variation and less worsening with age in this asymptomatic population. We also performed CPAM ambulatory monitoring on 67 heart failure patients and 63 asymptomatic controls with no history of heart failure^[25]. The heart failure group had significantly greater prevalence of the third heart sound and prolongation of the electromechanical activation time, indicating poorer systolic function and worse prognosis^[26]. Now that the ability of CPAM to detect SDB has been determined, studies can begin to use it to evaluate LV function and assess changes in hemodynamic function in the presence of SDB and over the course of its treatment.

AUDICOR CPAM is able to detect SDB with reasonable accuracy. The ambulatory monitor should assist in screening and follow-up of patients at home and in hospital, and may be particularly appealing to cardiologists who can additionally assess contemporaneous cardiac function. Although the automatically generated SDBSS alone is useful, the device is best used with physician over-read to assess the potential relationships of SDB to its hemodynamic consequences.

The present study was conducted solely in the sleep laboratory and further validation of the device performance is needed in at-home environments. The study population was Caucasian and further study on a more diverse group of patients should be completed. Additional testing of heart failure patients and those with associated respiratory or cardiac conditions is important. Given the high prevalence of known SDB and an estimated 80%-90% being undiagnosed, there is a need for simplified diagnostic devices that do not require special facilities and highly trained personnel. We conclude that AUDICOR CPAM can adequately identify subjects with SDB and may be a useful screening device. In addition, the ambulatory monitor can quantify and detect LV dysfunction, which may be present with SDB, particularly in the setting of heart failure.

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COMMENTS

Background

The relationship between sleep-disordered breathing (SDB) and detrimental altered cardiac dynamics has been demonstrated. There exists a need for a portable ambulatory monitor capable of simultaneously assessing both SDB and cardiac hemodynamics.

Research frontiers

Due to the association between SDB and cardiac consequences, the ability to screen for and prioritize patients for full polysomnography (PSG) would be beneficial. A novel device [cardiac and respiratory monitor (CPAM)] is available that is capable of assessing both cardiac hemodynamics and SDB. In this study, the

authors demonstrated that the CPAM device had adequate performance to be used for screening of SDB.

Innovations and breakthroughs

The CPAM device evaluated in this study is unique in its ability to assess both cardiac hemodynamics and SDB simultaneously. The performance of the cardiac assessment portion of CPAM has been investigated and published previously. This study reports the first evaluation of the SDB assessment components of the device.

Applications

The ability to screen and prioritize patients, particularly those with existing cardiac disease such as heart failure, for full PSG would be beneficial. In addition, follow-up assessments after modifications to either cardiac or SDB treatment could assist in optimizing treatment. The performance reported of the SDB assessment components of the device under study indicates its use for screening is feasible.

Terminology

SDB is a term that describes a group of disorders characterized by abnormal respiratory patterns such as pauses or reduced quantity of ventilation, including obstructive and central sleep apnea.

Peer review

The authors aim to validate a portable monitor incorporating a detection method for heart sounds, holter-ecg analysis and detection of sleep-disordered breathing. The study was designed as a prospective cross-sectional mono-centric trial with 85 persons undergoing polysomnography and ambulatory cardiorespiratory monitoring with the CPAM.

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Eosinophilia: Rare cause of arterial thrombosis and cardioembolic stroke in childhood

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INTRODUCTION

There are diverse causes and risk factors for stroke in childhood. The most common arterial ischemic causes are congenital or acquired heart diseases and sickle cell disease. The other hematological causes associated with stroke include paroxysmal nocturnal hemoglobinuria, polycythemia vera, essential thrombocythemia and various hereditary hypercoagulable states. Eosinophilia is common in childhood but has rarely been reported as a cause of stroke in children. Eosinophilia can lead to cardiac and arterial thrombosis, leading to stroke, which can be the lone initial manifestation of eosinophilia.

CASE REPORT

An 11-year-old boy was admitted with recurrent right sided hemiparesis. He gave a history of right lower limb monoparesis 2 wk before, from which he had complete spontaneous resolution. There was no history of fever, chest pain, palpitations, breathlessness, diarrhea, skin rash, joint pains, bleeding diathesis or viral exanthema. There was no evidence suggestive of congenital or rheumatic heart disease. There was no history suggestive of allergic rhinitis or asthma. The family history was non-contributory. The clinical examination was unremarkable except for right hemiparesis with power of 2/5 in the right upper and lower limbs with right extensor plantar response. Hemography revealed hemoglobin of 12.2 g/dL, total leukocyte count $7.9 \times 10^9/L$, platelet count $156 \times 10^9/L$, the differential count showed polymorphs 26%, lymphocytes 25%, monocytes 1% and eosinophils 48% [absolute eosinophilic count (AEC), $3792/mm^3$]. Renal and liver function tests were normal. The contrast-enhanced computed tomography (CECT) of the brain

Abstract

Eosinophilia has been reported as a very rare cause of stroke in children. The thrombotic event may be either due to cardiac damage induced by eosinophils and their granular protein, that is, the major basic protein, or the systemic hypercoagulable state induced by eosinophilia. We report here a case of eosinophilia whose initial presentation was recurrent strokes and cardiac and arterial thrombosis.

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Key words: Eosinophilia; Cardioembolic stroke; Thrombosis; Low molecular weight heparin; Warfarin

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revealed left lenticular nucleus infarct. High-resolution CT and CECT of the chest were normal. Echocardiography revealed mildly dilated left ventricle, with 60% ejection fraction and multiple friable clots. Color Doppler ultrasound of bilateral lower limb vessels revealed mild occlusion of the right external iliac and right common femoral arteries. Doppler ultrasound of the bilateral carotid vessels was normal. Stool examination for ova and parasites was negative. Autoimmune markers for anti-neutrophil antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and anticardiolipin antibodies (immunoglobulin G and immunoglobulin M) were negative. The lipid profile and serum homocysteine levels were normal. Other laboratory parameters including erythrocyte sedimentation rate, high-sensitivity C-reactive protein and troponin were within normal limits. *Wuchereria* microfilariae were not seen on peripheral smeared blood films. Bone marrow examination revealed increased marrow cellularity with increased eosinophilic component. The endomyocardial biopsy was unremarkable and there was no evidence of granulomatosis or vasculitis. FIP1L1-PDGFR α and FIP1L1-PDGFR β gene rearrangements by nested reverse-transcriptase polymerase chain reaction were not detected. The patient was started on low-molecular-weight heparin (LMWH; enoxaparin 1 mg/kg twice daily) and warfarin 4 mg daily. LMWH was stopped after 5 d when international normalized ratio of 2.5 was achieved with warfarin. Hydroxyurea 500 mg daily was also started. The patient had complete clinical recovery within 10 d. Three months following stroke, the patient is clinically stable with AEC 600/mm³ and is on warfarin and hydroxyurea, with normal echocardiography and color Doppler ultrasound of the lower limbs.

DISCUSSION

The common causes for eosinophilia are parasitic infestations, allergic diseases, drugs, neoplasia and connective tissue diseases^[1]. Patients in whom the underlying cause of eosinophilia is not found and who have AEC > 1500/mm³ for > 6 mo with organ dysfunction are labeled as idiopathic hypereosinophilic syndrome (HES). Eosinophilia has rarely been reported as a cause of stroke in children^[2]. Stroke is the most devastating neurological consequence of eosinophilia in adults with an incidence in HES patients of around 17%^[3,4]. Other than cardiac emboli and direct eosinophil toxicity, there is a hypercoagulable state in eosinophilia which can contribute to strokes in HES^[5]. The characteristic features of stroke in eosinophilia are the occurrence of multiple strokes, in different vascular territories, at different times. The etiology may be due to the direct eosinophilic damage to the endocardium and myocardium or by the release of eosinophilic basic proteins which initiate endomyocardial necrosis. This makes the heart a potential source of these recurrent emboli^[6]. Causes of thrombogenicity are multifactorial including the release of tissue factor from specific granules, inactivation of thrombomodulin by binding to the major basic

protein, endothelial damage or by elevation of fibrinogen levels^[5,7]. Anticoagulation and antiplatelet agents are used in the management of stroke but simultaneously lowering eosinophil count with hydroxyurea or steroids results in a better outcome^[8]. Distinction of HES into myeloproliferative and lymphoproliferative variants helps with further characterization of the disease and has therapeutic and prognostic implications^[9]. Our patient had involvement of the heart and major vessels, with thrombus induced by eosinophilia. Reduction of eosinophils with hydroxyurea and simultaneous anticoagulation led to the resolution of thrombus and complete clinical recovery of the patient.

The American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young does not include eosinophilia as a cause or risk factor for stroke in children^[10]. This case highlights the fact that eosinophilia can be a risk factor for both hypercoagulable state and stroke in children and should be considered as a risk factor for stroke in childhood.

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Progressive deterioration of left ventricular function in a patient with a normal coronary angiogram

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Abstract

Cardiac ischemia with a normal coronary angiogram can be caused by coronary microvascular dysfunction. A favorable prognosis, with excellent long-term clinical outcome, without major acute coronary events, has been consistently reported in these patients. We report a patient with a normal coronary angiogram and 3 episodes of myocardial infarctions, where the formation of a ventricular aneurysm and progressive deterioration of left ventricular function was documented, and hypoperfusion of the myocardium was confirmed by cardiovascular magnetic resonance imaging. This case suggests that myocardial ischemia caused by coronary microvascular dysfunction could have a poor prognosis. Whether this case represents a special clinical condition which is between the cardiac syndrome X and coronary artery disease remains to be investigated.

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Key words: Coronary angiogram; Myocardial ischemia; Myocardial infarction; Microvascular dysfunction; Ventricular aneurysm

INTRODUCTION

It has been demonstrated that myocardial ischemia or infarction is the result of a decrease or interruption in the blood supply to the myocardium due to coronary artery disease. However, in some patients with myocardial ischemia or infarction, the coronary artery angiogram is completely normal, and a favorable prognosis, with an excellent clinical outcome at long-term follow-up, without major acute coronary events, has been reported^[1]. Myocardial infarction with an absolutely normal coronary angiogram is also rarely complicated by ventricular aneurysm^[2]. Here, we report a case of a patient with a normal coronary angiogram and 3 episodes of myocardial infarction (MI), formation of a ventricular aneurysm, and progressive deterioration of the left ventricular function.

CASE REPORT

A 67-year-old woman with 28 years of recurrent chest pain was admitted to hospital after 20 d of shortness of breath.

At the age of 39 years, she was diagnosed of an acute anterior wall MI based on her symptoms, typical evolution of ST-T abnormalities and elevation of cardiac

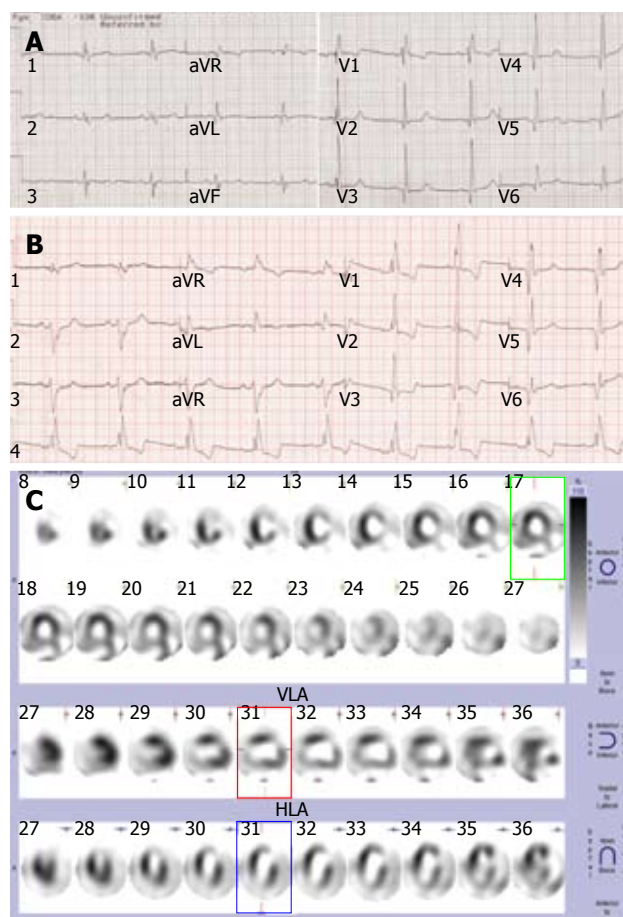


Figure 1 Electrocardiogram and single-photon emission computed tomography. A: Electrocardiogram in 1993; B: Electrocardiogram in 2007; C: Single-photon emission computed tomography myocardial perfusion image scan shows defects in the anterolateral wall and the apex, and hypoperfusion at the inferolateral wall.

enzymes. At that time, chest pain was induced by severe emotional stress, associated with radiation to the left shoulder, and heavy sweating, and was not relieved by nitroglycerin. The patient was hospitalized and treated accordingly. After discharge, she suffered from chest pain once or twice a week, relieved by rest or nitroglycerin. Again, 7 years and 11 years later, the patient had an acute anterior wall MI presenting as severe chest pain during sleep. In the third hospitalization, an echocardiogram revealed an anterior wall ventricular aneurysm. After discharge, chest pain occurred 3-5 times during the day, and occasionally at night. Each episode lasted 10-30 min, and symptoms could be relieved by rest or nitroglycerin. One year after the third MI, at the age of 53, she was hospitalized because of shortness of breath on exertion. An electrocardiogram (ECG) showed an old anterior wall infarction with right bundle branch block (Figure 1A); there was also evidence of mild enlargement of the left ventricle, and an ejection fraction of 50%. Cardiac catheterization was performed for coronary intervention, but the coronary angiogram indicated an absolutely normal coronary artery, and the left ventriculogram showed a left anterior ventricular aneurysm. The left ventricular

end diastolic pressure was normal at 10 mmHg. Since then, she has been stable with intermittent chest pain until 13 years later. Last year, her condition gradually deteriorated, and 20 d after she began to have shortness of breath after light activity, with mild chest pain (relieved by rest) and ankle edema, she was hospitalized again for further treatment.

She had no history of smoking, diabetes mellitus, hyperlipidemia, hypertension, coagulation disorders, oral contraceptive use, or cocaine abuse.

On physical examination, there was no jugular venous distention. Auscultation revealed a soft first heart sound. No murmur was heard at the cardiac apex. The resting ECG showed sinus rhythm with an old anterior wall MI and right bundle branch block, and more depression of ST segment in V1-3 leads when compared with the previous ECG taken when she was 53 years of age (Figure 1B). Echocardiography revealed a ventricular aneurysm at the apex and anterolateral wall with systolic bulging, mild mitral, aortic, and pulmonary regurgitation, and generalized hypokinetic wall motion. The left ventricular ejection fraction (LVEF) was 27% by echocardiography. Resting single-photon emission computed tomography myocardial perfusion imaging showed fixed defects in the anterolateral wall and the apex, and hypoperfusion at the inferolateral wall (Figure 1C). All laboratory examinations, including biochemical and serological tests, showed no evidence of MI, and pro-brain natriuretic peptide was 943.8 pg/mL.

She was diagnosed with coronary heart disease, unstable angina pectoris, old myocardial infarction complicated with ventricular aneurysm, and congestive heart failure (New York Heart Association class III). For further coronary intervention, cardiac catheterization was performed and showed normal coronary arteries. A left ventriculogram showed aneurysms with systolic bulging in the apex and anterolateral wall and mild mitral regurgitation. LVEF was 22.5% (Figure 2).

For resolution of the clinical dilemma of recurrent MI in the normal coronary artery, cardiovascular magnetic resonance imaging (CMRI) was performed on a 1.5-T Signa Excite HD MR Scanner (GE Healthcare Systems). First-pass perfusion imaging was obtained using a segmented echo-planar imaging pulse sequence with a notched saturation pulse^[3]. All perfusion images were acquired in the short-axis orientation only. The maximum number of slices was limited by heart rate. Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) was delivered at a rate of 4 mL/s using a power injector, with a total volume of 0.1 mmol/kg body weight. Delayed-enhancement images were obtained approximately 10 min after injection of intravenous Gd-DTPA using a segmented inversion recovery prepared fast gradient echo sequence^[4].

Images of the myocardium at peak myocardial enhancement during the first pass of gadolinium showed diffuse hypoperfusion of the myocardium, especially the subendocardium and anterolateral wall (Figure 3A).

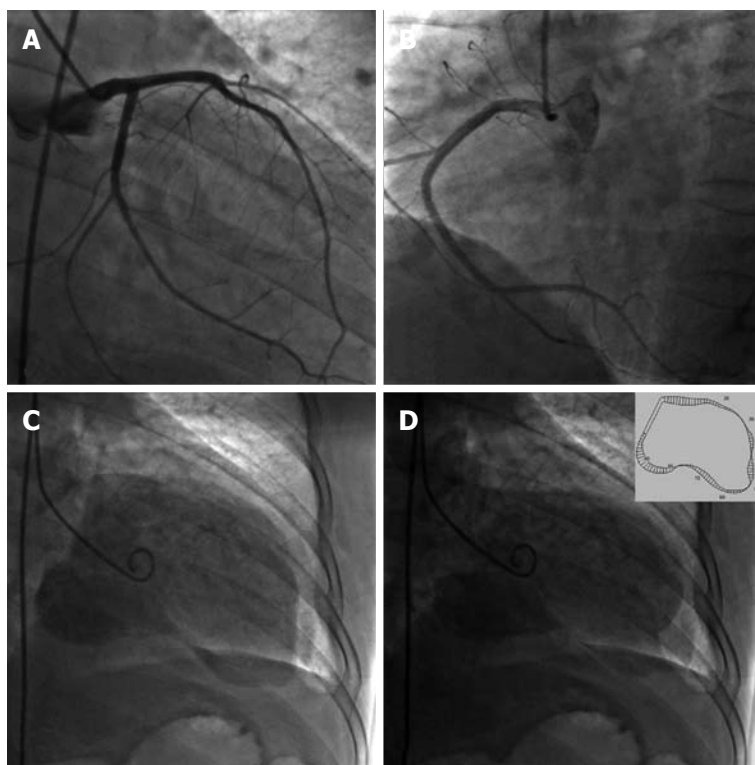


Figure 2 Coronary artery angiogram and left ventriculogram. A: Right anterior oblique (RAO) projection shows normal left anterior descending artery and left circumflex artery; B: Left anterior oblique projection shows normal right coronary artery; C: RAO projection shows the silhouette of the left ventricle at end diastole; D: RAO projection shows the silhouette of the left ventricle at end systole; the wall motion analysis at the top right shows aneurysms with systolic bulging in the apex and anterolateral wall.

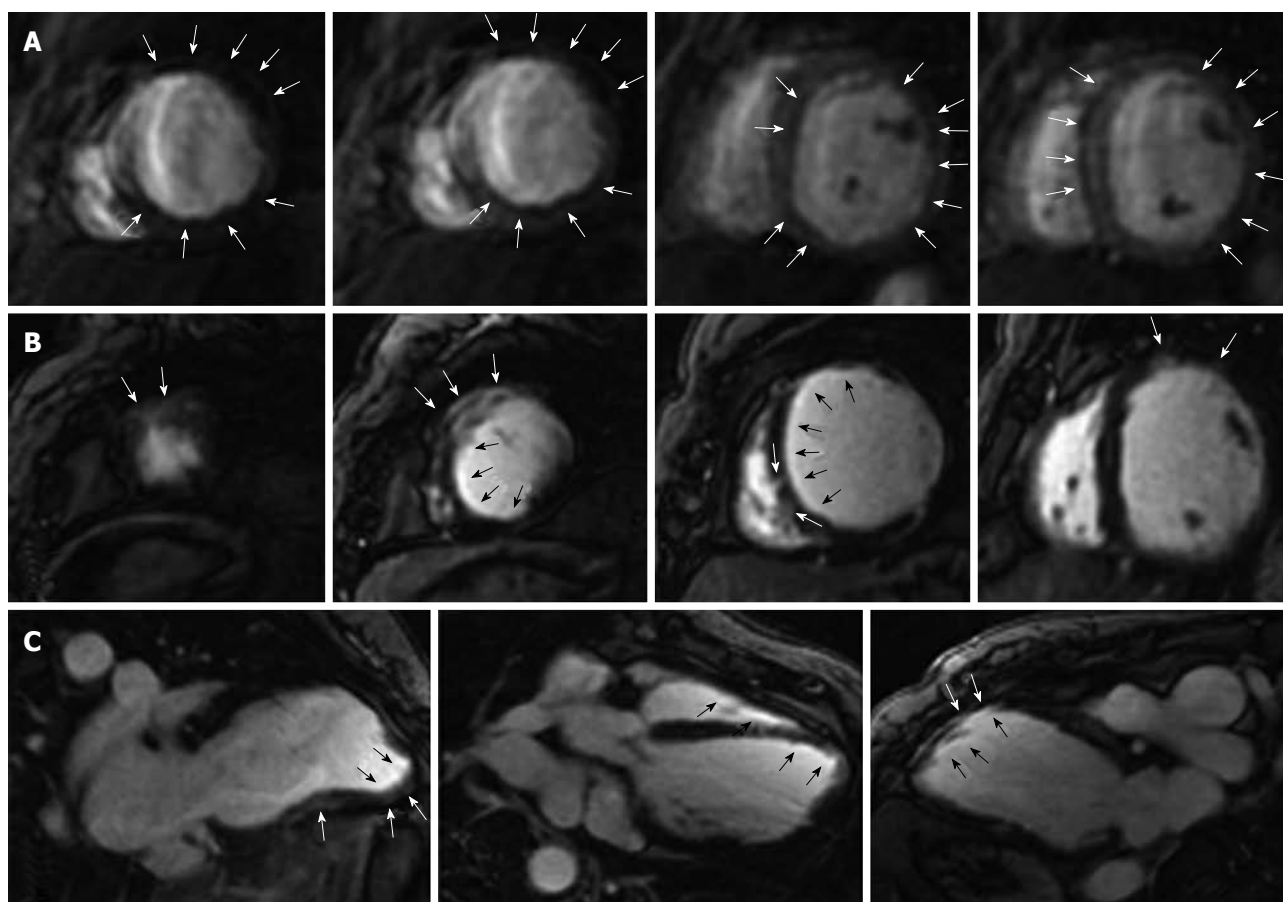


Figure 3 Cardiovascular magnetic resonance imaging. A: Images of the myocardium at peak myocardial enhancement during the first pass of gadolinium shows the perfusion defect (decreased perfusion) in the subendocardium of the mid-inferior wall, posterior-lateral wall, posterior-septal wall and anterolateral wall of the myocardium (white arrows); B, C: Delayed contrast-enhanced images show transmural hyperenhancement in the apical anterior, mid-anterior, mid-septum, basal-anterior wall (white arrows), and mid myocardial hyperenhancement in the inferior wall. The black arrows show delayed contrast enhancement in the subendocardium.

Delayed contrast-enhanced images showed transmural, subendocardial, and intramural enhancement in different segments of the left ventricle, especially in the anterior wall (Figure 3B and C).

DISCUSSION

Ischemia/infarction in patients with a normal coronary artery angiogram

Myocardial ischemia/infarction with a normal coronary angiogram is commonly characterized by coronary microvascular dysfunction, coronary spasm and coronary embolism with subsequent spontaneous clot lysis^[5], retraction, or recanalization^[6]. Only effort angina with a normal coronary artery angiogram and no other cardiac or systemic diseases (for example, hypertension or diabetes) known to influence vascular function was called cardiac syndrome X (CSX), which is believed to be caused by coronary microvascular dysfunction^[7]. Recurrent myocardial ischemia or infarction with a normal coronary angiogram, which constitutes approximately 1% of patients with documented MI^[6], is thought to be caused by coronary spasm, acquired or inherited coagulation disorders, toxic conditions, or embolization^[1]. Myocardial infarction with absolutely normal coronary angiogram usually has a good prognosis^[1,8], and is rarely complicated by left ventricular aneurysm. It was reported that the incidence of left ventricular aneurysm in MI with absolutely normal coronary angiogram was 0.47%^[2]. The present case with 3 episodes of MI associated with left ventricular aneurysm and absolutely normal coronary angiogram has not previously been reported.

Those patients exhibiting MI with a normal coronary angiogram tend to be young and to have relatively few coronary risk factors such as hypertension, hyperlipoproteinemia, or diabetes, except that they often have a history of cigarette smoking. The onset of acute MI in these patients was usually abrupt and without prodromes, and subsequent angina and reinfarction was rare^[1,8]. Coronary spasm was considered as one of the reasons. It has been shown, however, that patients with angina caused by spasm of normal coronary arteries have a distinctive clinical pattern characterized by recurrent, usually nocturnal, attacks of chest pain, with ST segment elevation on the ECG^[9]. The angina in CSX, which is believed to be caused by microvascular dysfunction, is characterized by recurrent, usually exertional, chest pain and ST segment depression in the ECG.

MRI in detection of myocardial ischemia

In recent years, CMRI has been used for the detection of myocardial ischemia or infarction because of its high spatial resolution and diagnostic accuracy. First-pass perfusion CMRI has been used for the assessment of myocardial perfusion. With the first-pass perfusion CMRI technique, some patients with CSX were found to have stress-induced subendocardial perfusion defects on visual inspection^[10,11]. Delayed contrast-enhanced CMRI has

been shown to be a powerful technique to distinguish left ventricular systolic dysfunction related to coronary artery disease (CAD) from other heart diseases^[12-14]. The patients with left ventricular dysfunction resulting from CAD were reported to have subendocardial or transmural enhancement in delayed contrast-enhanced CMRI^[12].

Special findings in this patient

This patient had the first episode of MI at the age of 39 years, without prodromes. Since then, she had recurrent angina and the second and the third MI in the span of 14 years. In the third episode of MI, the left ventricular aneurysm was complicated. Her left ventricular function gradually deteriorated. She had no risk factors. Two coronary angiograms, 1 and 16 years after the third episode of MI showed absolutely normal coronary arteries. However, CMRI revealed a diffuse hypoperfusion of the myocardium. This was different from the normal features of MI with a normal coronary angiogram. Three episodes of anterior wall MI disclosed that each attack of MI did not result in a large area of necrosis of the anterior wall of the myocardium. The intramural and transmural enhancement in different segments of the left ventricle, including the anterior wall, in a delayed contrast-enhanced image of CMRI demonstrated the feature of focal myocardial necrosis. Coronary spasm complicated with embolism and subsequent spontaneous clot lysis was reported to result in MI with a normal coronary angiogram^[5]. This patient had both rest and nocturnal chest pain, which suggest coronary spasm. However, microvascular dysfunction was actually involved in the myocardial ischemia. Though evaluation of endothelial function and sophisticated tests such as intravascular ultrasound and coronary or myocardial flow reserve were not performed in this patient, both the clinical presentation and the results of CMRI suggested that the recurrent myocardial ischemia and infarction were, at least to some extent, attributable to coronary microvascular dysfunction.

Recurrent effort angina, a normal coronary angiogram, microvascular dysfunction, and good prognosis were believed to be features of CSX^[7]. All studies on patients with CSX before the Women's Ischemia Syndrome Evaluation (WISE), reported an excellent clinical outcome at long-term follow-up, with a total absence of major acute coronary events (that is, cardiac death or acute MI)^[15]. However, WISE showed that women with ischemic symptoms and signs but without obstructive CAD were at elevated risk for cardiovascular events compared with asymptomatic community-based women^[16]. This patient was characterized by having a normal coronary angiogram, microvascular dysfunction, recurrent rest angina, infarction, and progressive deterioration of left ventricular function, which supports the results of WISE. Progressive deterioration of left ventricular function in patients with a normal coronary angiogram may be mainly caused by extensive microvascular dysfunction, resulting in poor long-term prognosis because

of many patches of myocardial hibernation, necrosis and left ventricular remodeling; coronary vasospasm might also be involved in the process. Whether this case represents a special clinical condition which resides between CSX and CAD remains to be investigated.

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MEETINGS

Events Calendar 2012

January 18-21, 2012
Ninth Gulf Heart Association
Conference
Muscat, Oman

January 27, 2012
ESC Global Scientific Activities at
the 23rd Annual Conference of the
Saudi Heart Association
Riyadh, Saudi Arabia

January 29-31, 2012
Integrated management of acute and
chronic coronary artery disease
Innsbruck, Austria

January 30, 2012
Webinar on "Best of Euroecho 2011"
Sophia Antipolis, France

February 1-3, 2012
American Heart Association and
American Stroke Association
International Stroke Conference 2012
New Orleans, Louisiana,
United States

February 3-5, 2012
6th Asian-Pacific Congress Of Heart
Failure 2012
Chiang Mai, Thailand

February 9, 2012
4th British Society for Heart Failure
Medical Training Meeting
London, United Kingdom

February 23-25, 2012
Advanced Invasive Cardiac
Electrophysiology
Sophia Antipolis, France

February 24-26, 2012
International Congress of
Cardiology
Hong Kong, China

February 28, 2012
Echocardiography evaluation of
patient with multivalvular disease
Sophia Antipolis, France

February 29-March 3, 2012
Winter ISHNE 2012
Zakopane, Poland

March 8-10, 2012
Cardiac Pacing, ICD and Cardiac
Resynchronisation
Vienna, Austria

March 8-10, 2012
24th Colombian Congress of
Cardiology and Cardiovascular
Surgery
Cali, Colombia

March 10-11, 2012
23rd International Meeting
"Cardiology Today"
Limassol, Cyprus

March 14-18, 2012
Ninth Mediterranean Meeting on
Hypertension and Atherosclerosis
Antalya, Turkey

March 15-17, 2012
e-Cardiology 2012
Osijek, Croatia

March 15-18, 2012
China Interventional Therapeutics
2012-CIT
Beijing, China

March 16-17, 2012
12th Annual Spring Meeting on
Cardiovascular Nursing
Copenhagen, Denmark

March 16-17, 2012
3rd European Meeting: Adult
Congenital Heart Disease
Munich, Germany

March 16-18, 2012
JCS2012 - The 76th Annual Scientific
Meeting
Fukuoka, Japan

March 20-23, 2012
32nd International Symposium
on Intensive Care and Emergency
Medicine
Brussels, Belgium

March 25-29, 2012
16th International Symposium On
Atherosclerosis 2012
Sydney, Australia

March 28-31, 2012
Rome Cardiology Forum 2012
Rome, Italy

March 28-31, 2012
Annual Spring Meeting of the
Finnish Cardiac Society 2012
Helsinki, Finland

March 30-April 1, 2012
Frontiers In CardioVascular Biology

2012
London, United Kingdom

April 5-7, 2012
EAE Teaching Course on New
echocardiographic techniques for
myocardial function imaging
Sofia, Bulgaria

April 12-14, 2012
Cardiovascular Risk Reduction:
Leading The Way In Prevention 2012
National Harbor, MD, USA

April 12-15, 2012
NHAM Annual Scientific Meeting
2012
Kuala Lumpur, Malaysia

April 18-21, 2012
World Congress of Cardiology
Scientific Sessions 2012
Dubai, United Arab Emirates

April 19-21, 2012
Delivering Patient Care in Heart
Failure
Sophia Antipolis, France

April 20-22, 2012
7th Clinical Update on Cardiac MRI
and CT
Cannes, France

April 25-27, 2012
Angioplasty Summit 2012
Seoul, South Korea

April 25-28, 2012
The 61st International Congress
of the European Society of
Cardiovascular and Endovascular
Surgery
Dubrovnik, Croatia

April 28-29, 2012
24th Annual Scientific Meeting of
the SCS
Singapore, Singapore

May 3-5, 2012
EuroPREvent 2012
Dublin, Ireland

May 15-18, 2012
EuroPCR Congress 2012
Paris, France

May 17-20, 2012
2nd International Meeting On
Cardiac Problems In Pregnancy 2012
Berlin, Germany

May 19-22, 2012
Heart Failure 2012
Belgrade, Serbia

May 23-26, 2012
46th Annual meeting of the
Association for European Pediatric
and Congenital Cardiology
Istanbul, Turkey

May 26-27, 2012
Cardiovascular Spring Meeting 2012
Vienna, Austria

June 7-9, 2012
6th Congress of Asian Society of
Cardiovascular Imaging
Bangkok, Thailand

June 7-9, 2012
6th Congress of Asian Society of
Cardiovascular Imaging 2012
Bangkok, Thailand

June 15-17, 2012
13th Annual Cardiology Update
Bhurban, Pakistan

June 21-24, 2012
10th International Pulmonary
Hypertension Conference and
Scientific Sessions 2012
Orlando, Florida, United States

July 19-22, 2012
13th Annual South African Heart
Congress
Sun City, South Africa

August 16-19, 2012
60th annual scientific meeting of
CSANZ
Brisbane, Australia

August 25-29, 2012
ESC Congress 2012
Munich, Germany

September 29-October 4, 2012
International Society of
Hypertension 24th Annual Scientific
Meeting 2012
Sydney, Australia

October 4-6, 2012
Magnetic Resonance in Cardiology
Riva Del Garda, Italy

October 20-23, 2012
Acute Cardiac Care 2012
Istanbul, Turkey

GENERAL INFORMATION

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 362 experts in cardiology from 43 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJC* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJC* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJC* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality ar-

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The major task of *WJC* is to rapidly report the most recent developments in the research by the cardiologists. *WJC* accepts papers on the following aspects related to cardiology: arrhythmias, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, paediatrics, nursing, and health promotion. We also encourage papers that cover all other areas of cardiology as well as basic research.

Columns

The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensus and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

Name of journal

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There are unstructured abstracts (no less than 256 words) and

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An informative, structured abstracts of no less than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/..."; MATERIALS AND METHODS (no less than 140 words); RESULTS (no less than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312194155.htm.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: <http://www.wjgnet.com/1007-9327/13/4520.pdf>; <http://www.wjgnet.com/1007-9327/13/4554.pdf>; <http://www.wjgnet.com/1007-9327/13/4891.pdf>; <http://www.wjgnet.com/1007-9327/13/4986.pdf>; <http://www.wjgnet.com/1007-9327/13/4498.pdf>. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Acknowledgments

Brief acknowledgments of persons who have made genuine con-

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The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability"^[1,2]. If references are cited directly in the text, they should be put together within the text, for example, "From references^[19,22-24], we know that..."

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spicings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *ν* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h,

blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 ± 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantum numbers can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312200347.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, *etc.*

Biology: *H. pylori*, *E. coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/1949-8462/g_info_20100312192220.htm

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