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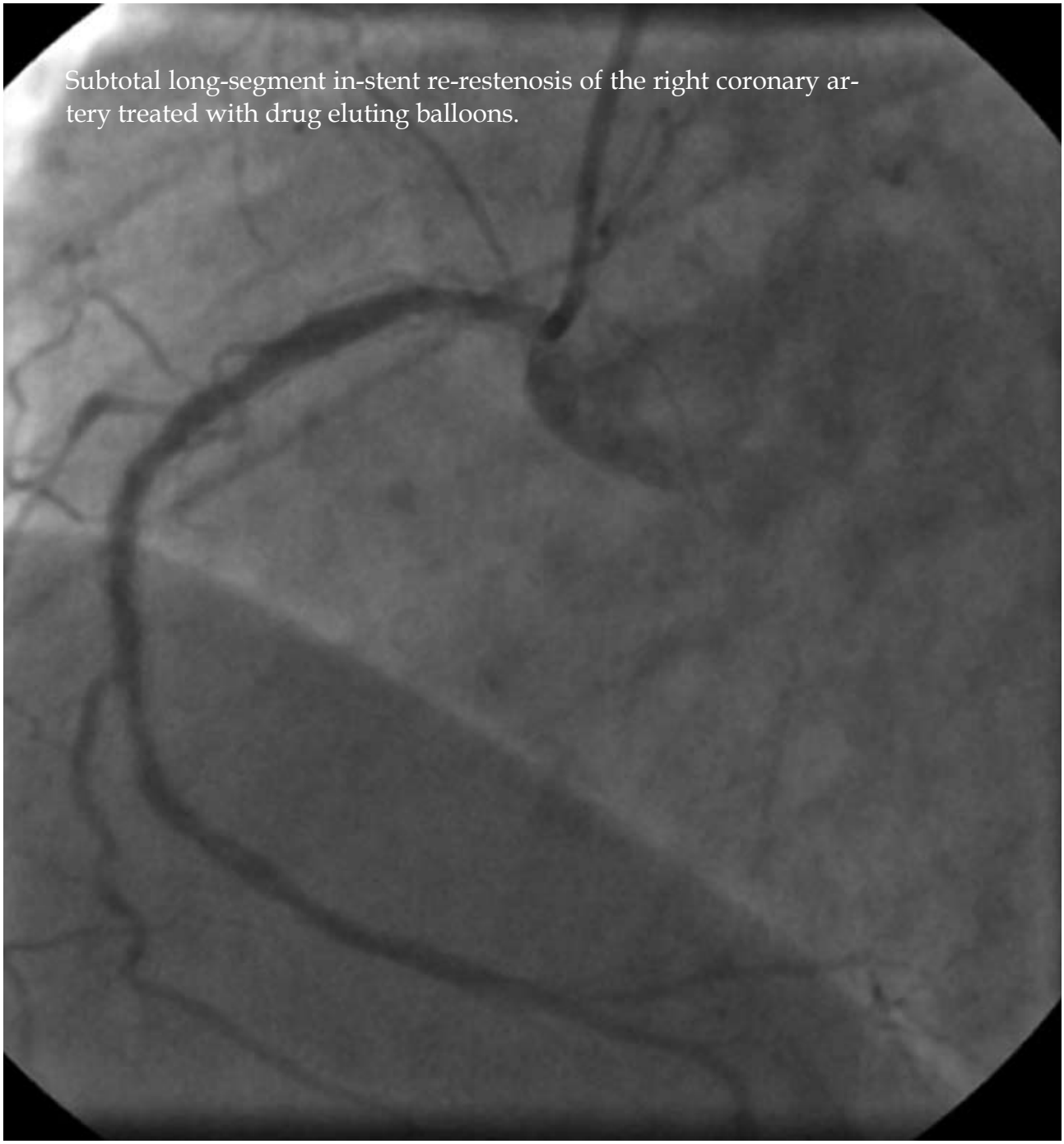

Subtotal long-segment in-stent re-restenosis of the right coronary artery treated with drug eluting balloons.

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EDITORIAL

Drug eluting balloons for the treatment of coronary artery disease: What can we expect?

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Abstract

Drug-eluting balloons (DEBs) represent an enhancement of the therapeutic repertoire for the interventional cardiologist. The therapeutic concept of DEBs is promising, notably on the basis of initial studies in patients with diffuse in-stent restenosis (ISR). At present, however, a number of questions regarding long-term efficacy and safety remain, specifically in indications other than diffuse ISR. The results of the evaluation of different substances, balloon systems and clinical indications will determine the long-term success of DEBs.

Key words: Coronary artery disease; Coronary balloon angioplasty; Drug delivery systems; Vascular graft restenosis

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INTRODUCTION

Ever since the broad clinical introduction of angioplasty and subsequentially coronary stent implantation in the 1990s, in-stent restenosis (ISR) has become and remains one of the major limitations of this treatment modality. In the era of "plain old balloon angioplasty (POBA)", restenosis occurred as a result of elastic recoil and negative vascular remodeling. However, other factors such as neointima proliferation may contribute to the POBA-induced restenosis to some extent. These processes have been reduced using coronary stents during percutaneous coronary intervention (PCI). However, the proliferation and migration of vascular smooth muscle cells and myofibroblasts, together with the production of extracellular matrix, resulted in a new form of restenosis: ISR.

The development of drug-eluting stents (DES) markedly reduced the rate of ISR both in randomized clinical trials and so called "all-comer" evaluations. As compared to bare metal stent (BMS) usage, the implantation of DES, however, is associated with late stent-thrombosis and the need of a long-term dual antiplatelet therapy (DAPT), which in the majority of cases comprises acetylsalicylic acid and clopidogrel. Although the incidence of ISR has declined as a result of increased usage of DES worldwide, the issue of ISR will continue to be notable because of the increasing numbers of patients treated with PCIs. As over 3 million PCIs and consecutive implantation of one or more stents are performed worldwide every year, a clinically relevant rate of restenosis of 5%-10% in these patients may lead to at least 150 000 to 300 000 recurrent interventions per year.

Current treatment alternatives for ISR include plain angioplasty using conventional or cutting balloons, reimplantation of BMS or DES, rotablation, atherectomy or brachytherapy. The latter ones, however, have not proven to be more effective than balloon angioplasty alone. The implantation of DES, clearly, has become a common treatment modality, specifically in long restenotic lesions. The recurrent ISR-restenosis rate ("re-restenosis"), however, remains above 20%[1-3].

DRUG-ELUTING BALLOONS: A NEW CONCEPT

Balloon-based concepts for prevention and effective therapy of ISR are attractive for a number of reasons. Possible advantages include: (1) homogeneous drug absorption into the vessel tissue; (2) the highest concentration of the drug at the time of intervention and therefore at the beginning of the neointimal proliferation; (3) the absence of polymers, with a consequent reduction in chronic inflammation and the risk of late stent thrombosis; (4) the preservation of the original coronary anatomy particularly in small vessels and bifurcation lesions; (5) a reduction in the duration of DAPT; and (6) drug application in special situations where stent implantation is not allowed or wanted[4]. Paclitaxel plays an exceptional role in the context of local drug therapy because of its lipophilic properties, short absorption time after contact with the artery wall and prolonged duration of antiproliferative effects of up to several days[5]. Sound preclinical data specifically exist regarding the application of paclitaxel using the radio-contrast agent Iobromid[6]. This kind of application has been used for Paccocath® technology in the first-in-man study[7] within the PEPCAD-trial program.

REPRESENTATIVE CASES

Case 1

A 73-year-old woman with coronary 3-vessel-disease, insulin-dependent diabetes mellitus and hypercholesterolemia underwent PCI for multiple right coronary artery stenoses with implantation of 3 zotarolimus-eluting stents (total stent length 60 mm). One year later, she was readmitted with non-ST segment myocardial infarction as a result of long segment ISR which was treated percutaneous transluminal coronary angioplasty (PTCA), including dilatation with cutting balloons. Six months later the patient again presented with unstable angina. Control angiography revealed a subtotal long segment ISR (Figure 1A). Recanalization was performed by wire passage and PTCA using a low-diameter low-profile balloon (Figure 1B). Postdilatation was performed by means of a 3 mm cutting-balloon followed by 2 paclitaxel-eluting balloons (SeQuent® Please, 3.0 mm × 30 mm). Six months after drug-eluting balloon (DEB) treatment, control angiography showed only moderate recurrent neointimal proliferation (Figure 1C).

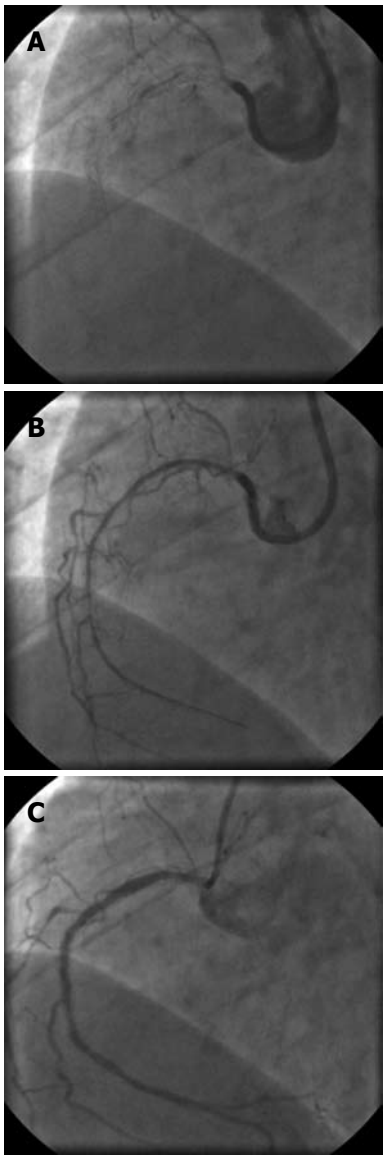

Figure 1 Subtotal long-segment in-stent re-restenosis of the right coronary artery treated with drug eluting balloons. A: Pre-percutaneous coronary intervention; B: After recanalization; C: Angiographic 6-mo follow-up.

Case 2

An 81-year-old man with known coronary artery disease, who underwent coronary artery bypass graft surgery 10 years previously, and had permanent atrial fibrillation (continuous warfarin therapy) and a history of peptic gastric ulcer as a result of former acetylsalicylic acid therapy was admitted to our hospital with unstable angina. Coronary angiography revealed open bypasses to the left anterior descending artery, first obtuse marginal and right coronary artery, and a proximal stenosis of the native left circumflex coronary artery (LCX) with a reference vessel diameter of 2.5 mm (Figure 2A). The LCX lesion was predilated with a 2 mm balloon followed by angioplasty using a paclitaxel-eluting balloon (SeQuent® Please, 2.5 mm × 20 mm). Postinterventional angiography showed a slight residual stenosis and a circumscript dissection without flow limitation (Figure 2B). DAPT with acetylsalicylic acid and clopidogrel was given for a period of 4 wk accompanied by continuation of warfarin (with a target international normalized ratio (INR) of 2 dur-

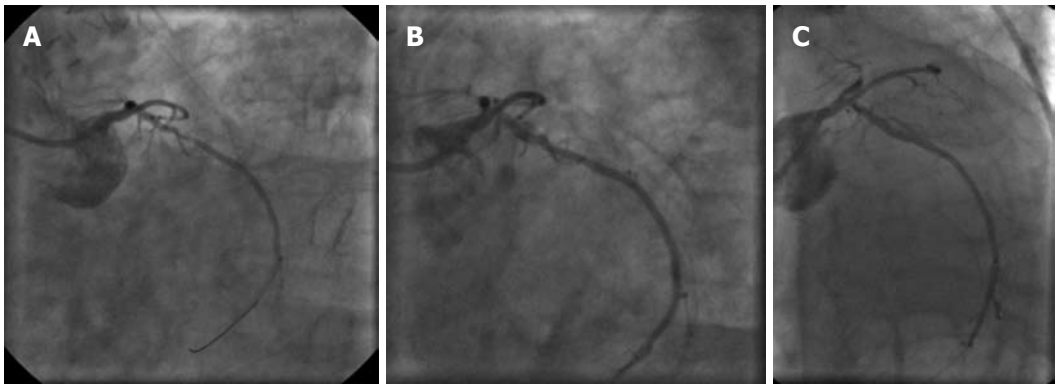

Figure 2 Proximal *de novo* stenosis of the native left circumflex coronary artery treated with "plain old balloon angioplasty" using a drug eluting balloon. A: Pre-percutaneous coronary intervention (PCI); B: Immediately after PCI; C: Angiographic 6-mo follow-up.

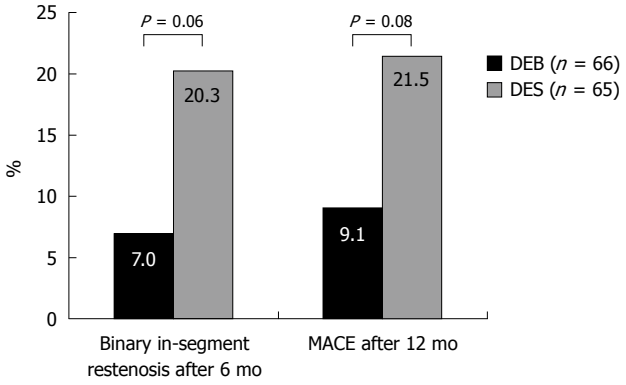

Figure 3 Treatment of in-stent-restenosis using a drug eluting balloon (paclitaxel-releasing balloon) *vs* a drug-eluting stent (paclitaxel-eluting stent). Left columns: Rate of binary in-segment restenosis (%) after 6 mo; Right columns: Major adverse cardiac events (MACE, including target lesion revascularization, myocardial infarction, stent thrombosis, or death) (%) after 12 mo[9]. DEB: Drug-eluting balloon; DES: Drug-eluting stents.

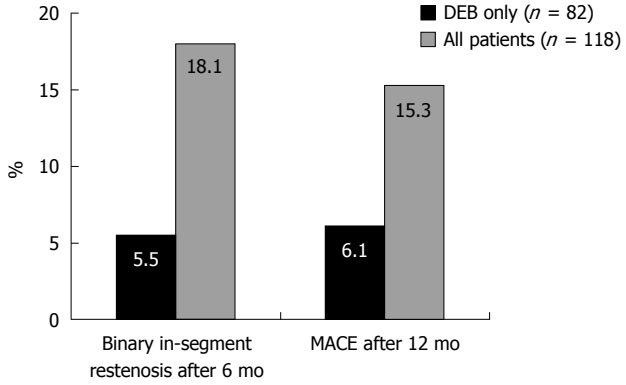

Figure 4 Treatment of small vessels (diameter < 2.8 mm) using a drug eluting balloon (paclitaxel-eluting balloon). Left columns: Rate of binary in-segment restenosis (%) after 6 mo; Right columns: Major adverse cardiac events (MACE) (%) after 12 mo[10]. DEB: Drug-eluting balloon.

ing the 4 wk of "triple therapy", and a target INR of 3 thereafter). Because of the patient's history of aspirin-associated ulcer, the proton pump inhibitor pantoprazol was administered along with DAPT. After PCI, the patient continued to be free of symptoms, and angiography after 6 mo showed a fair interventional result with no restenosis of LCX (Figure 2C).

CLINICAL EVIDENCE

These case examples provide further information regarding potential indications for this new technique. Few data, however, have been published thus far regarding the efficacy of DEBs, particularly concerning the long-term efficacy and safety issues. Initial clinical trials have been performed using the Paccocath® technique. The Paccocath® ISR- I and ISR-Ⅱ trials were designed as randomized, multicenter trials evaluating the efficacy of a DEB in comparison to an uncoated balloon in 108 patients with ISR. The use of the DEB reduced the late lumen loss, the rate of binary restenosis and the frequency of major adverse cardiac events[7,8]. The PEPCAD-Ⅱ-trial, in contrast, evaluated the efficacy of the Paccocath® technique using a DEB (SeQuent® Please) in a randomized comparison with a paclitaxel-eluting stent (Taxus Liberté®) for the treatment of ISR in 131 patients[9]. The utilization of the DEB was associated with a lower rate of restenosis and a lower frequency of target lesion revascularization (Figure 3).

The efficacy of the SeQuent® Please DEB was also evaluated in 118 patients with *de novo* coronary stenosis < 2.8 mm in a non-randomized study[10]. The aim was to evaluate outcomes using a "DEB only" strategy and avoidance of any further stent implantation. Additional stents were only permitted in cases of dissection or acute recoil. The rate of binary restenosis was significantly lower in patients who were treated only with the DEB in comparison to patients who had to receive additional stents (Figure 4).

Bifurcation lesions are associated with a high risk of restenosis and thus represent a potential indication for DEBs. A non-randomized trial including 20 patients was able to document successful interventions of bifurcation lesions with promising mid-term results[11]. The largest randomized trial so far which evaluated the application of DEB in combination with BMS was the recently published PEPCAD-Ⅲ trial. In this trial, the efficacy of treatment of *de novo* lesions in coronary arteries with a pre-crimped BMS on a DEB system (Coroflex® DEBlue) was compared to

a sirolimus-eluting stent (Cypher®) in 637 patients. The results clearly showed that treatment with a "BMS on DEB" system was effective, but revealed less favorable results regarding the endpoint late lumen loss and frequency of target lesion revascularization than in the DES arm of the study[12]. At present, several ongoing trials are evaluating the application of DEB, e.g. in patients with diabetes mellitus, or for the treatment of chronic coronary occlusions, or for PCI of an ISR in DES. In addition to the treatment of coronary lesions, 2 randomized trials in 87 and 154 patients using DEBs for treatment of stenoses or occlusions of the femoropopliteal arteries in comparison to BMS or the addition of paclitaxel to the contrast media showed superior results for the DEB technology[13,14].

CURRENT LIMITATIONS

The concept of local drug delivery has been experimentally and clinically investigated for more than a decade[5]. The limitations of the currently used polymer-based DES (prolonged DAPT, late stent thrombosis) shifted the focus to DEB. At first glance, the DEB is apparently able to integrate several favorable characteristics. Preclinical *in vivo* data are only available for 2 systems[6,15,16]. The successful delivery of paclitaxel from the balloon into the vessel tissue and prolonged residence in the tissue was proven in experimental pig models. Other DEB systems currently used in the clinical context lack sound preclinical data. At present, however, it is also unclear what kind of drug coating on the balloon (e.g. hydrophilic Iopromid coating, microporous balloon surface, special balloon folding) or elution in the vessel tissue produces the most favorable safety-efficacy ratio. Regarding the clinical evaluation of DES, the last years clearly showed that a reliable assessment of safety and efficacy depends on major randomized trials and consecutive registry data with sufficient long-term follow-up periods (years rather than months). This approach should also be maintained in the context of DEBs as late adverse effects (e.g. as a result of delayed healing) may occur. At the moment, published data are only available for one balloon system (Paccocath®, Sequent® Please) regarding one indication (ISR) in comparison to lone dilatation or DES (Taxus®)[7,9]. The largest trial in the context of DEB in 637 patients with *de novo* lesions, the PEPCAD-Ⅲ study, compared the combined usage of DEB and BMS to the sirolimus-eluting Cypher® stent and demonstrated better results for the DES concept[12].

CHALLENGES

The DEB represents an excellent therapeutic concept. However, this technique carries a number of unanswered questions and is being further evaluated in different clinical settings. Regarding product development, it is unclear which method of drug retention and elution and which drug is most favorable. It has to be proven in the clinical context whether use of DEBs beyond the indication in ISR (< 10% of our patients) compares favorably with current standard therapy. Furthermore, reliable data regarding the implantation of BMS for clinical reasons (e.g. for a dissection) after a DEB-dilatation are lacking. A thorough analysis of the PEPCAD-Ⅲ study may give the answers (DEB-stent "mismatch"). Currently, additional stent implantation seems to improve the acute procedural outcome, but worsens the long-term outcome. In addition, long-term results when treating ISR in DES are uncertain. Taken together, expectations should not be too high regarding the broad application of DEB in the near future. At our center, we are also using the DEB primarily for the treatment of recurrent diffuse restenosis of BMS and, in some cases, of DES. The results of ongoing preclinical development and clinical evaluation of various DEB, however, will determine the long-term success of the concept of DEB. As a result of the rapid development in the field of stent technologies (e.g. degradable drug-eluting polymers, complete stent degradation, polymer-free eluting systems) and concomitant pharmacologic therapy, it is unclear whether DEBs will be used for more than niche indications in the long-term.

CONCLUSION

The DEB enhances the therapeutic repertoire of interventional cardiologists. The use of DEB especially for the treatment of ISR can prevent the implantation of further stents. First results from trials evaluating small vessels and bifurcation lesions may give rise to more indications for this technique, but results of randomized trials regarding these issues are still required. The use of DEBs in selected patients in combination with BMS may be considered as an alternative to BMS, mainly because of the possible reduction in the duration of DAPT. Regarding the broad utilization of DEBs, in terms of efficacy and especially safety, data from larger clinical trials and registries should be awaited.

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EDITORIAL

Cutaneous markers of coronary artery disease

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Abstract

Coronary artery disease (CAD) is rapidly increasing in prevalence across the world and particularly in south Asians at a relatively younger age. As atherosclerosis starts in early childhood, the process of risk evaluation must start quite early. The present review addresses the issue of cutaneous markers associated with atherosclerosis, and the strengths and weaknesses of the markers in identifying early coronary atherosclerosis. A diligent search for such clinical markers, namely xanthelasma, xanthoma, arcus juvenilis, acanthosis nigricans, skin tags, ear lobe crease, nicotine stains, premature graying in smokers, hyperpigmented hands in betel quid sellers, central obesity, and signs of peripheral vascular disease may prove to be a rewarding exercise in identifying asymptomatic CAD in high risk individuals.

Key words: Cutaneous markers; Coronary artery disease; Xanthoma; Arcus juvenilis; Acanthosis nigricans; Nicotine

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INTRODUCTION

Coronary artery disease (CAD) is rapidly increasing in prevalence across the world and particularly in south Asians at a relatively younger age, with severe and diffuse forms of lesions. The subject of CAD in Indians (referred to as immigrants or Asian Indians, or south Asians when outside India) has become an interesting and challenging issue for research worldwide[1,2]. The prevalence of CAD has progressively increased in India during the latter half of the last century[3]. The risk of CAD in Indians is considered to be 3-4 times higher than in white Americans, 6 times higher than in the Chinese, and 20 times higher than in the Japanese[1,4]. Indians as a community are prone to CAD at a much younger age[5,6]. As atherosclerosis starts in early childhood, the process of risk evaluation must start quite early. Identifying subtle cutaneous clinical markers suggesting atherosclerosis at a young age may prove to be helpful in early diagnosis and prevention of CAD. It costs little to look for various cutaneous signs which may suggest subclinical or obvious atherosclerosis and/or other vascular diseases, such as diabetes, hypertension, peripheral arterial diseases *etc*. Judicious appraisal of various cutaneous markers linked to CAD would help clinicians to suspect disease in the subclinical phase, and thus make it easier to decide who is likely to need further detailed cardiovascular investigation. A diligent search for the following cutaneous markers relevant to CAD may prove to be a rewarding exercise in identifying asymptomatic CAD in high risk individuals (Table 1).

XANTHELASMA/XANTHOMA

The term xanthelasma is derived from the Greek *xanthos* (yellow) and *elasma* (beaten metal plate). These are yellow

Table 1 Clinical markers of atherosclerosis[7]

1	Xanthelasma, xanthoma/giant gluteal xanthoma
2	Arcus juvenilis
3	Acanthosis nigricans
4	Skin tags
5	Premature graying and balding in smokers
6	Ear lobe crease
7	Nicotine stains
8	Betel quid seller syndrome
9	Central obesity-flabs and folds
10	Signs of peripheral vascular disease
11	Gouty arthritis
12	Rheumatoid arthritis
13	Psoriasis

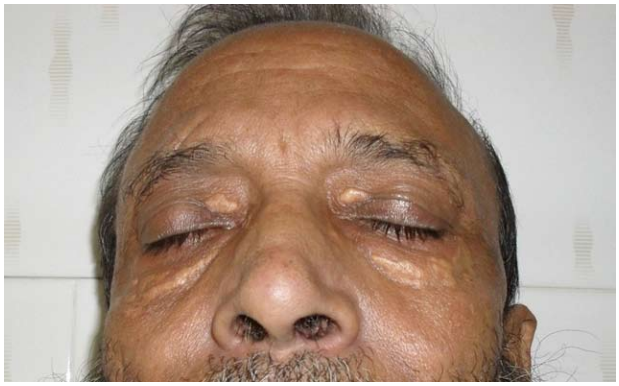

Figure 1 Symmetrical xanthelasma in all four lids.

plaques that occur most commonly near the inner canthus of the eyelid, more often on the upper lid than the lower lid. Xanthelasma palpebrarum is the most common cutaneous xanthoma. Xanthelasma can be soft, semisolid, or calcareous. Frequently, they are symmetrical; often, all four lids are involved (Figure 1). Xanthelasma have a tendency to progress, coalesce, and become permanent.

Pathophysiology

Xanthomas usually are associated with a disturbance of lipid metabolism[8]. The mechanism of accumulation of lipids in skin lesions is similar to the development of atheroma, especially when considering the role of modified low density lipoprotein (LDL) and the method of accumulation of lipids in macrophages. One half of these lesions are associated with elevated plasma lipid levels. Some occur with altered lipoprotein composition or structure, such as low high density lipoprotein (HDL) levels. They frequently occur in patients with type Ⅱ and type Ⅳ hyperlipidemia. In some cases, xanthoma may be seen in many members of the same family with pleomorphic presentation in individual members. We came across a 40-year-old female presenting with acute coronary syndrome and peripheral vascular disease (PVD) and having manifest bilateral xanthelasma. Both her parents had suffered CAD and one of her three brothers had a past history of a cerebrovascular accident. Interestingly both parents and two siblings had some form of xanthoma.

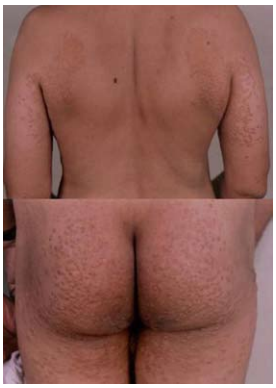

Figure 2 Xanthomas spread over the back and gluteal region.

The elder brother who had suffered a stroke was found to have both xanthelasma palpebrarum and extensive xanthomas spread over the back of his shoulders and gluteal region as well as dyslipidemia (Figure 2).

Types and causes

Xanthomas are of many types including xanthelasma palpebrum, tuberous xanthomas, tendinous xanthomas, eruptive xanthomas, plane xanthomas, diffuse plane xanthomatosis, xanthoma disseminatum and giant gluteal xanthoma. Tuberous and tendinous xanthomas are typical of familial hypercholesterolemia and are common symptoms of homozygous familial hypercholesterolemia.

Small and quickly developing eruptive xanthomas are typical of mixed hyperlipoproteinemia. Eruptive xanthomas can be seen in primary and secondary causes of hyperlipidemia. Examples of primary genetic causes include familial dyslipoproteinemia, familial hypertriglyceridemia, and familial lipoprotein lipase deficiency. Uncontrolled diabetes is a common cause of secondary hyperlipidemia. However, most xanthelasmas occur in normolipemic persons who may have low HDL cholesterol levels or other lipoprotein abnormalities.

Gluteal xanthomas warrant special mention because of their peculiar location in the gluteal region and are likely to be missed completely if not looked for diligently. In a recent case report[9], it was found that a 27-year-old male who was being investigated for a possible diagnosis of familial hypercholesterolemia (total cholesterol: 480 mg/dL; LDL: 440 mg/dL; HDL: 25 mg/dL and triglyceride: 76 mg/dL on treatment) had acute myocardial infarction and extensive triple vessel disease at age 24 years. He was found to have extensive tendon and gluteal xanthomas. There were 13 xanthomatous swellings of various sizes measuring 14 cm × 8 cm to 2 cm × 2 cm in the gluteal region alone. Besides gluteal xanthomas, there were xanthomatous lesions in bilateral elbows, knees, and Achilles tendons. On family screening, all his family members (i.e. parents and three siblings) were found to have CAD. Notably neither the patient nor any of his family members were smokers or diabetic, but all had clinical clues to suggest dyslipidemia.

Xanthomas and xanthelasmas are also indicators of other complicating diseases such as development of acute pancreatitis during a hyperlipoproteinemic crisis, aggrava-

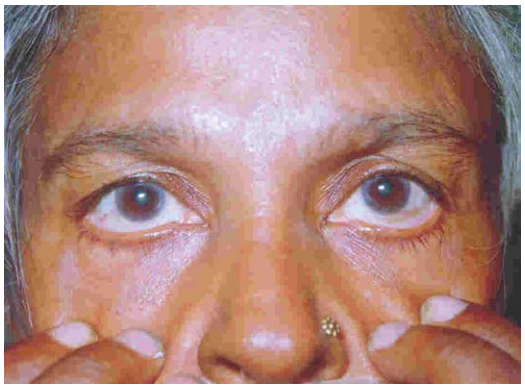

Figure 3 A female smoker with manifest arcus senilis and early graying.

Figure 4 A 25-year-old male showing acanthosis nigricans over the nose bridge.

tion of insulin resistance, and decompensation of type 2 diabetes mellitus, in addition to atherosclerotic coronary diseases[10].

Treatment

Therapy focuses on adjustment of diet (elimination of dietary fat and concentrated saccharides); in the long run patients have to strictly observe their dietary regime based on the type of hyperlipoproteinemia. As regards drug therapy, fibrates and atorvastatin are the drugs of choice. It is very important not to focus on symptoms, i.e. xanthoma or xanthelasma, but to correct the associated dyslipidemia or the disease that underlies hyperlipoproteinemia (e.g. type 2 diabetes mellitus or metabolic syndrome). Unfortunately, it is still the practice for dermatologists, ophthalmologists or plastic surgeons to remove extensive xanthelasmas, while the underlying cause such as diabetes, CAD and dyslipidemia is not investigated diagnostically or adequately addressed.

ARCUS JUVENILIS

A corneal arcus is a lipid-rich and predominantly extracellular deposit that forms at the corneoscleral limbus (Figure 3). It represents the most common peripheral corneal opacity and is not associated with tissue breakdown but rather with the deposition of lipids. Rudolf Virchow, who is credited with the hypothesis that atherosclerosis reflects insudation of pathogenic agents into tissue, also noted, in 1852, the association of corneal arcus with atherosclerosis, and hypothesized a similar mechanism for its formation[11]. However, the attempt to correlate corneal lipid deposits and vascular lipid deposits has been and remains controversial, despite continued interest[12,13]. It has been associated with hypercholesterolemia, xanthelasmas, alcohol, blood pressure, cigarette smoking, diabetes, age, and coronary heart disease (CHD)[14].

In a cross-sectional study by Zech *et al*[15] of 17 patients homozygous for familial hypercholesterolemia presented to the Clinical Center of the National Institutes of Health; plasma lipoproteins, circumferential extent of the corneal arcus and thoracic aorta, coronary calcific atherosclerosis score, and Achilles tendon width were measured. Corneal arcus and Achilles tendon width were strongly correlated and predictive of each other. Although the corneal arcus was correlated with calcific atherosclerosis ($r = 0.67$, $P = 0.004$), it was not as highly correlated as was the Achilles tendon width ($r = 0.855$, $P < 0.001$). Thus it was concluded that the corneal arcus reflects widespread tissue lipid deposition and is correlated with both calcific atherosclerosis and xanthomatosis in these patients. Patients with a more severe arcus tend to have more severe calcific atherosclerosis.

In a systematic review to examine the relationship of a corneal arcus and CHD to determine if a corneal arcus is an independent CHD risk factor, it was concluded that there was no consensus that a corneal arcus is an independent risk factor, but the presence of a corneal arcus in a young person should prompt a search for lipid abnormalities[12]. Also, because a corneal arcus represents physical evidence of early lipid deposition, its presence suggests the need for aggressive lipid therapy[12].

ACANTHOSIS NIGRICANS

Acanthosis nigricans (AN) is a skin disorder characterized by darkening (hyperpigmentation) and thickening (hyperkeratosis) of the skin, occurring mainly in the folds of the skin, back of the neck, the axilla and/or groin. Rarely it may be observed in some regions of the face (Figure 4). AN is not a skin disease *per se* but is a cutaneous sign indicating insulin resistance, diabetes, metabolic syndrome, Cushing's syndrome, internal malignancy, polycystic ovarian syndrome, *etc*.

The cause of AN is still not clearly defined but it appears to be related to insulin resistance. It has been associated with various benign and malignant conditions. Based on the pre-disposing conditions, AN has been divided into seven subtypes (Table 2).

In the cross-sectional study by Kumar *et al*[16] to determine the prevalence of AN in a south Indian population and to evaluate its correlations with diabetes, obesity, insulin levels and other factors, it was shown that 16.1% of the population had AN and it was significantly higher among females (19.6%) than males (11.4%). The prevalence of

Table 2 Types of acanthosis nigricans

Type	Characteristics
Obesity-associated AN	Most common type of AN May occur at any age but more common in adulthood Obesity often caused by insulin resistance
Syndromic AN	Defined as AN that is associated with a syndrome, e.g. hyperinsulinemia, Cushing's syndrome, polycystic ovary syndrome, total lipodystrophy
Benign AN	Also referred to as acral acanthotic anomaly Thick velvety lesion most prominent over the upper surface of hands and feet in patients who are in otherwise good health Most common in dark-skinned people, especially those of African American descent
Drug-induced AN	Uncommon, but AN may be induced by several medications, including nicotinic acid, insulin, systemic corticosteroids and hormone treatments
Hereditary benign AN	AN inherited as an autosomal dominant trait Lesions may manifest at any age, infancy, childhood or adulthood
Malignant AN	AN associated with internal malignancy Most common underlying cancer is tumor of the gut (90%) especially stomach cancer In 25%-50% of cases, lesions are present in the mouth on the tongue and lips
Mixed-type AN	Patients with one type of AN who also develop new lesions of a different type, e.g. overweight patient with obesity-associated AN who then develops malignant AN

AN: Acanthosis nigricans.

AN was highest in the 30-40 years age group and it decreased with the age. The prevalence of AN correlated positively with female gender, obesity, high triglyceride levels and presence of diabetes. The presence of AN was significantly associated with higher fasting insulin levels. Males with AN had significantly higher insulin levels than females with AN. The authors concluded that AN has stronger clinical relevance among males than females and it can be used as a marker of insulin resistance in the south Indian population especially if obesity and a family history of diabetes are also present. It is therefore suggested that patients with AN should be evaluated for underlying insulin resistance and CAD.

SKIN TAGS

Skin tags are thought to be relatively common skin lesions. However it has been reported that they might reflect insulin resistance states[17,18]. In a large study of patients with skin tags, over 25% of individuals had diabetes mellitus and a further 8% had impaired glucose tolerance, although there was no association with the number or localization of the skin tags in that study[19]. There are reports describing an association between skin tags and an atherogenic lipid profile. This lipid profile is thought to be strongly associated with atherosclerosis and cardiovascular disease[20].

In a study by Erdoğan *et al*[21], comprising 36 patients with skin tags and 22 healthy controls, it was found that the mean body mass index (BMI), homeostasis model assessment of insulin resistance, and total cholesterol were significantly higher in patients showing skin tags than in controls. It was concluded that skin tags may not be innocent tumoral proliferations; instead, follow-up of such patients with regard to the development of diseases associated with atherosclerosis may be beneficial. Furthermore, skin tags associated with AN carry more sinister significance than skin tags alone.

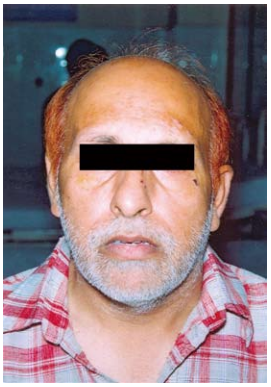

Figure 5 A male, who had a stroke at 27 years of age, continued to smoke, and developed an acute myocardial infarction at 44 years old. Note premature graying and balding.

PREMATURE GRAYING AND BALDING

Smoking has been considered to be the most important preventable risk factor responsible for premature CAD[22]. Coupled with this fact, it has been observed that young CAD patients who are heavy smokers develop premature graying and balding (Figure 5). Thus, the presence of premature graying in chronic smokers indicates higher-than-normal risk for CAD[7]. Also, early-onset androgenic alopecia, in particular, is somehow related to CAD. Besides premature graying, premature balding has also been suspected to be associated with CAD in smokers.

In a review of 24 articles by Rebora[23], it was concluded that baldness did not coincide with androgenic alopecia. However, it was observed that subjects who developed baldness before their 30s may have a higher risk for CAD than other men, and they may be the individuals with early-onset androgenic alopecia who also present with particularly elevated dihydrotestosterone:testosterone ratios. Based on this, it is suggested that the baldness theory should be included as a secondary hypothesis in large epidemiological studies of CAD.

A case-control study[24] examined the association of dermatological signs, such as baldness, thoracic hairiness,

hair graying, and diagonal ear lobe crease (ELC), with the risk of myocardial infarction in male subjects younger than 60 years, and concluded that baldness, thoracic hairiness and diagonal earlobe crease indicate an additional risk of myocardial infarction in men under the age of 60 years, independent of age and other established coronary risk factors.

In a report by Matilainen *et al*[25], the presence of insulin resistance that increases coronary disease risk has been shown to be associated with an early onset of male-pattern baldness or alopecia. This may represent a common pathogenetic mechanism for baldness and coronary atherosclerosis.

EAR LOBE CREASE

The ear lobes of children and young adults are normally smooth. The presence of an ELC and its association with CAD was first described in 1973[26]. Blodgett *et al*[27] found that 75% of CAD cases had an ELC as compared to 35% of the controls (age and gender matched). Afterwards, many studies presented ELC as a marker for CAD[28,29].

In addition, a diagonal ELC has also been suggested as a marker of vascular disease in a population with diabetes (population with increased risk of microangiopathy); but only limited data are available[30]. The Fremantle Diabetes Study reported the prevalence of ELC to be 55% in the western Australian population[30]. In an Indian study, data suggested that the ELC was present in 59.7% of the diabetic population > 40 years in the urban south Indian population[31]. The above study showed that the subjects in the ELC group were older, had longer duration of diabetes and had poor glycemic control. These observations were in agreement with the Fremantle study[30]. Subjects with ELC had a higher socioeconomic status as compared to the group without ELC; this could be an indirect measure of the population at a greater risk of CAD.

With regard to the association between ELC and diabetic retinopathy, the Indian study noted that increasing age, poor glycemic control and increasing duration of diabetes were significant variables in both univariate and multivariate models[30]. Similar observations were made in other population-based studies on diabetic retinopathy[32,33]. However some other studies have found no such associations and have concluded that the prevalence of earlobe creases probably increases with age, as does heart diseases[34,35].

Taking into consideration the above points, it appears prudent to examine the earlobes in a suspected case of CAD as additional indirect evidence.

NICOTINE STAINING

Nicotine is a naturally-occurring alkaloid found primarily in tobacco. It is most commonly absorbed from cigarette smoke, with each puff containing approximately 50 μg of nicotine. The adverse effects of smoking on the cardiovascular system are known to all.

There are certain cutaneous markers which indicate that a person is a smoker, thus indirectly pointing towards a cardiovascular risk. The most evident and enduring signs of smoking are the tar and nicotine stains found on hands, fingers, lips and on the skin in addition to the teeth. The discolorations more often than not develop on the lips and on the nails of the fingers. Black stained nails, dark brownish crusts below the fingernails, blackened lips, dark gums and stained enamel of the teeth point towards chronic heavy smoking and the likely possibility of coexisting CAD and/or other smoking-associated diseases[36].

BETEL QUID SELLER SYNDROME

This syndrome, first described by Dwivedi *et al*[37] is characterized by central obesity, brick-brownish lips and palms of the hands and denuded skin over the tips of the fingers, as observed in betel quid sellers in south Asian countries, primarily India, Pakistan, Bangladesh and Nepal. People who sell betel quid in south Asia also sell smokeless, non-perishable and dried tobacco preparations like 'gutkha' and 'pan masala' and over the years they develop a characteristic body habitus comprising central obesity because of long hours of sitting, and have discolored tips and palms of the hands as they are constantly exposed to betel quid, containing resinous extract of *Acacia catechu*, baked shell lime, betel nut (*Areca catechu* containing arecoline) and tobacco[37]. In the process of preparing quid they apply baked lime and liquefied *Acacia catechu* paste to the betel leaf, varying from 100 to 1000 times a day. The overlying skin surface that comes into direct contact with the shell lime and *Areca catechu* becomes roughened, denuded and brick-red colored. It is speculated that the denuded epithelium may be the source of absorption of nicotine and arecoline in the betel quid sellers. They are also prone to consume betel quid, gutkha and paan masala containing betel nut and sweetening agents[38]. The sedentary nature of their occupation combined with their daily intake of tobacco and betel nut leads to early development of diabetes, hypertension and dyslipidemia[39-41]. In addition, keeping quid in the space between the buccal mucosa and lower teeth results in the coloring of saliva due to interaction of *Acacia catechu* with alkaline shell lime, and damage to teeth. It is considered that features of 'betel quid seller syndrome' are a harbinger of diabetes, hypertension and/or CAD.

Interestingly, people who consume surti, a form of saltless tobacco (SLT) much used in south Asia, develop a patch of white discoloration on their palm due to constant rubbing of liquefied calcium carbonate and meshed tobacco leaves before putting it in oral cavity (Figure 6). This may provide evidence of SLT being associated with an increased risk of CAD.

CENTRAL OBESITY - FLABS AND FOLDS

Obesity is defined as a state of excessive adipose tissue mass. Although not a direct measure of adiposity, the most widely used method to gauge obesity is the BMI, which is equal to weight/height^2 in kg/m^2 with BMI > 25 taken as obesity in South Asian countries[42]. The vast majority of urban people currently have excess abdomi-

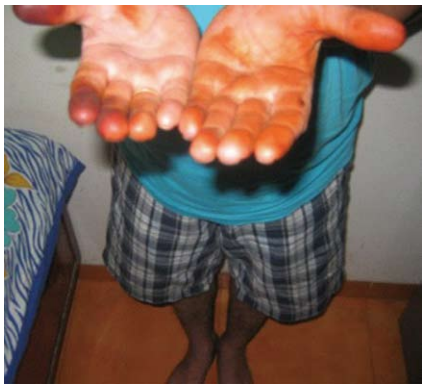

Figure 6 Betel Quid Seller Syndrome[37].

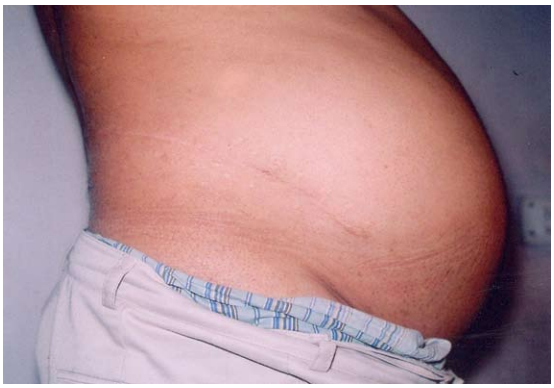

Figure 7 A beer belly in a patient with coronary artery disease.

nal fat. The excess belly fat is not just an esthetic issue alone, but is also a risk factor to health. There is a large amount of convincing scientific data which confirms it is unhealthy in general to have excess body fat throughout the body, particularly so in the abdomen. A large belly objectively measured as waist circumference is clinically known as central obesity (Figure 7). This is due to an increased amount of visceral fat. Visceral fat lies deeper in the abdomen beneath the muscles and the surrounding organs. Visceral fat also plays a role in giving certain men that "beer belly" appearance where their abdomen protrudes excessively but at the same time, also feels hard if prodded. Excessive visceral fat is more dangerous than subcutaneous fat. Central obesity increases the risk of developing diabetes, heart disease, high blood pressure, stroke, sleep apnea, various forms of cancer, and other degenerative diseases[43]. Thus excessive fat and flabs, particularly abdominal obesity, can indicate underlying CHD. According to the current guidelines a waist circumference of > 90 cm in south Asian men and > 80 cm in south Asian women are indicative of central obesity[42].

SIGNS OF PVD

PVD, also known as arteriosclerosis obliterans, is primarily the result of atherosclerosis. The atheroma consists of a core of cholesterol attached to proteins with a fibrous intravascular covering. The atherosclerotic process may gradually progress to complete occlusion of medium and large arteries. Cutaneous signs of PVD are the classic "5 P's" namely pulselessness, paralysis, paresthesia, pain and pallor. The disease typically is segmental, with significant variation from patient to patient. Other maladies that often coexist with PVD are CAD, myocardial infarction, atrial fibrillation, transient ischemic attack, stroke, and renal disease. Studies have suggested that even asymptomatic peripheral arterial disease is associated with increased CAD mortality[44]. Features of PVD are thus helpful in predicting potential CAD.

GOUT AND SIGNS OF ARTHRITIS

Gout is a metabolic disease marked by acute arthritis and inflammation of the joints, usually beginning in the knee or foot and clinically characterized by acute mono or poly arthritis often involving the metatarso-phalangeal joint of the first toe, bursitis, tendonitis, enthesitis, tophaceous deposits, or synovial osteochondromatosis. It is caused by hyperuricemia. Gout often accompanies both risk factors for heart disease and heart disease itself. It is found in higher rates in people with obesity, high blood pressure, CAD, and congestive heart failure.

The relationship between gout, not associated with the use of diuretics, and the development of CAD was examined in 5209 subjects originally enrolled in the Framingham Study[45]. Based on 32 years of follow-up, it was concluded that gout, unrelated to the intake of diuretics, imparts an additional risk of CAD in men, unexplained by clinically measured risk factors, but in women there were no significant associations between gout and CAD. Therefore, looking for gouty inflamed joints can be a useful tool for the physicians to predict underlying heart disease.

PERIPHERAL AND CUTANEOUS SIGNS OF RHEUMATOID ARTHRITIS

Atherosclerosis is now considered as inflammatory disease[46]. As rheumatoid arthritis (RA) is considered a quintessential systemic disease that can manifest in most major organ systems, it also spreads to extra-articular sites, such as mid-size arteries and capillaries, and predisposes patients to accelerated atherosclerosis and CAD[47]. Several studies have documented an increased risk of atherosclerosis and myocardial infarction in patients with RA[48,49]. Therefore, it is prudent to look for CAD if a patient presents with chest pain and has evidence of peripheral/cutaneous signs of RA.

SIGNS OF PSORIASIS

Recently, much emphasis has being laid on a link between CAD and psoriasis in the medical literature[50,51]. Reports suggest that psoriasis increases the chance of acute coronary episodes and also psoriasis appears to play a bigger role in heart disease in young people[52]. It was reported that a 30-year-old with severe psoriasis is approximately three times (300%) more likely to suffer a heart attack

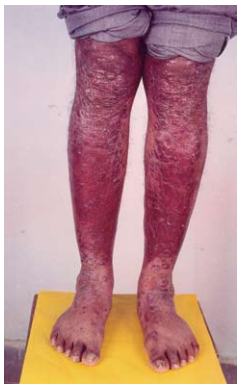

Figure 8 A patient with psoriasis and coronary artery disease.

than a 30-year-old from the general population, but a 60-year-old with severe psoriasis has only a 36% higher risk than his age-matched peers[52]. The above findings emphasize the need for psoriasis patients to monitor their cardiovascular health at an earlier age and to take measures to lessen their risks for heart attack, heart failure and other cardiovascular problems (Figure 8).

CONCLUSION

Judicious appraisal of the above cutaneous markers linked to CAD would help clinicians to recognize disease in the subclinical phase and thus make it easier to decide who is likely to need further detailed cardiovascular investigation. A diligent search for these cutaneous markers relevant to CAD may prove to be a rewarding exercise in unraveling asymptomatic CAD in high risk individuals at no extra cost.

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Neoplastic pericardial disease: Old and current strategies for diagnosis and management

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Abstract

The prevalence of neoplastic pericardial diseases has changed over time and varies according to diagnostic methods. The diagnostic factor is usually the detection of neoplastic cells within the pericardial fluid or in specimens of pericardium, but the diagnosis may be difficult. Accurate sampling and cytopreparatory techniques, together with ancillary studies, including immunohistochemical tests and neoplastic marker dosage, are essential to obtain a reliable diagnosis. The goals of treatment may be simply to relieve symptoms (cardiac tamponade or dyspnea), to prevent recurrent effusion for a long-term symptomatic benefit, or to treat the local neoplastic disease with the aim of prolonging survival. Immediate relief of symptoms may be obtained with percutaneous drainage or with a surgical approach. For long term prevention of recurrences, various approaches have been proposed: extended drainage, pericardial window (surgical or percutaneous balloon pericardiostomy), sclerosing local therapy, local and/or systemic chemotherapy or radiation therapy (RT) (external or with intrapericardial radionuclides). The outcomes of various therapeutic approaches vary for different tumor types. Lymphoma and leukemias can be successfully treated with systemic chemotherapy; for solid tumors, percutaneous drainage and the use of systemic and/or local sclerosing and antineoplastic therapy seems to offer the best chance of success. The use of "pure" sclerosing agents has been replaced by agents with both sclerosing and antineoplastic activity (bleomycin or thiotepa), which seems to be quite effective in breast cancer, at least when associated with systemic chemotherapy. Local chemotherapy with platinum, mitoxantrone and other agents may lead to good local control of the disease, but the addition of systemic chemotherapy is probably relevant in order to prolong survival. The surgical approach (creation of a pericardial window, even with the mini-invasive method of balloon pericardiostomy) and RT may be useful in recurring effusions or in cases that are refractory to other therapeutic approaches.

Key words: Neoplastic pericarditis; Neoplastic pericardial disease; Diagnosis; Therapy

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INTRODUCTION

The reported prevalence of neoplastic pericardial diseases has changed over time and has varied according to diagnostic methods. In an autopsy series, it has been found in 2%-4% of the general population, in 7%-12% of cancer

patients and, among these, in 19%-40% of patients dying of lung cancer, 10%-28% dying of breast cancer and in 9%-28% with leukemia or lymphoma, apparently with a trend toward increasing frequency among lung cancer patients in more recent years and a decrease in haematologic malignancies. This trend can only be observed in the very long term, however. In a necropsy study between 1974 and 1987, the prevalence of primary tumors showed little variation over time[1-8]. Autopsy studies overestimate the clinical problem because they include mostly terminally ill patients and identify even microscopic metastases or small effusions without clinical relevance. In two studies comparing clinical and pathologic features of pericardial metastases, 60%-70% were clinically non significant[9,10]. In fact, in a study on 2700 breast cancer patients, seen from 1987 to 1997, symptomatic neoplastic pericardial effusion was only diagnosed in 19 (0.7%)[11]. This finding was confirmed by a retrospective study on 1600 patients with leukemia who had one or more echocardiographic examinations during their illness. A pericardial effusion was detected in 325 (20%) cases, but was very mild in 70% of the cases. It was moderate to large in < 9% of the cases and only 10 (3%) patients required pericardiocentesis (4 of them had leukemic blasts in the pericardial fluid). Approximately 75% of the patients with pericardial effusion had concomitant pleural effusion, and the presence of pericardial effusion did not have any impact on survival. In this study, the incidence of neoplastic effusion appeared to be treasurable[12]. Among lymphoma patients, a particular subgroup is the one with primary effusion lymphoma, which usually affects human immunodeficiency virus-infected patients, but has been described occasionally in immunocompetent patients, and is characterized by a clinical appearance of pleural, pericardial and/or peritoneal effusion without solid masses or lymph node involvement[13,14]. This particular type of lymphoma generally has a poorer prognosis compared to other non-Hodgkin's lymphomas (NHL). It has peculiar behaviour characteristics and can be treated, not only with chemotherapeutic agents, but also with antiretroviral therapy[15,16]. Among symptomatic effusion, on the other hand, cancer was the principal cause in the past, but its prevalence has decreased over time. In a retrospective analysis on 1127 pericardiocenteses performed at Mayo Clinic on 977 patients over 21 years, malignant effusion accounted for 50% of the procedures in years 1979 to 1986, 45% in years 1986 to 1993 and 25% between 1993 and 2000[17]. According to the authors, this change was due to an increase in other causes of pericardial effusion (mainly postoperative or perforation from invasive procedures) rather than to a decrease of malignant pericarditis cases, which actually increased from 91 to 159 from the first to the second period mentioned above. Nevertheless, in the third period (1993-2000) there were only 125 cases of neoplastic pericarditis. This inversion of the trend might be due both to an improvement in the treatment of cancer and to the increasing use of routine computed tomography (CT), magnetic resonance imaging, echocardiography and positron emission tomography that leads to an early detection and therapy of small effusions, which then prevents the need for pericardiocentesis. The decrease in neoplastic etiology among large pericardial effusions in the past years seems to be confirmed by a Spanish study and an Italian study covering the years 1998-2002 and 1996-2003, respectively, with results showing a prevalence of 13% and 7.3%, respectively[18,19]. Since the relative proportion of neoplastic pericarditis depends also on the prevalence of other causes of effusion, it may vary widely in particular populations. In a Turkish report, 15/50 patients (30%) had neoplastic pericarditis, but there were no cases of post-surgical pericardial effusion in this group. However, in a larger study from Turkey, there were only 46/368 cases of neoplastic pericarditis (13%) in a population with high prevalence of uraemic pericardits[20,21]. On the other hand, in a report from Brigham and Women's Hospital of Boston, 40% of the patients undergoing pericardiocentesis had malignant effusions (27.4% definite and 12.3% likely), with only 0.9% with infectious causes in the same cohort[22]. A South Korea study reported 61/116 (53%) of the cases as "malignant effusions", but this diagnosis was confirmed by cytology in only 27 cases (44% of the cancer subgroup, 27% of the entire cohort)[23]. Among neoplastic pericardial disease diagnosed *in vivo*, as in autopsy studies, lung and breast carcinoma are the more frequent primary tumors[24]. In lung cancer, the metastatic pathway to the pericardium is almost always lymphatic (usually from the dorsal side). This finding explains why pericardial effusion is often large, and why neoplastic cells may be found in the pericardial fluid even if absent in pericardial biopsies[25,26].

DIAGNOSIS

As mentioned above, pericardial effusion in patients is not always due to malignancy; other causes of pericardial effusion are radiotherapy, lymphatic drainage impairment and hypoalbuminemia. The diagnostic clue is usually the detection of neoplastic cells within the pericardial fluid or in specimens of pericardium. But the diagnosis is not always simple, and sometimes impossible. Reactive lymphocytes may be morphologically indistinguishable from malignant cells in NHL. On the other hand, in Hodgkin's disease, effusion cytology is often non diagnostic. Accurate sampling and cytopreparatory techniques, together with ancillary studies (immunocytochemistry, flow cytometry, morphometry and cytogenetics) may help in the diagnosis, which usually requires a definition of the lymphoma subtype as well[27]. In solid tumors, on the other hand, effusion cytology may be extremely difficult because mesothelial cells exhibit a spectrum of cytomorphologic features, sometimes mimicking carcinoma[28,29]. In the case of mesothelioma, the cytologic diagnosis is even more difficult because hyperplastic or reactive mesothelial cells may mimic malignant mesothelioma. Differentiation from metastatic adenocarcinoma may be challenging and, on the other hand, effusion may have no cytologic evidence;

the sensitivity has been reported to be 38%-50%[30,31]. Some problems may arise in cytological evaluation due to the storage of effusion fluid. When the amount of neoplastic cells is relatively low, the probability to detect them is obviously higher when examining the entire drained fluid rather than a few milliliters[32]. Moreover, benign cells may degenerate during storage and, for this reason, effusion specimens should be received in the cytopathology laboratory immediately after drainage in the fresh state or refrigerated, and should be stored at 2-8℃ (best at 4℃)[33,34]. A number of immunohistochemical markers have been selected to improve the sensitivity and specificity of the diagnosis; for optimal use, cell block preparations, in addition to smears, are required[35-39].

In cytology-negative samples, or whenever the diagnosis is equivocal, the dosage of tumor markers, such as carcinoembryonic antigen (CEA), serum cytocheratin 19 fragments (CYFRA 21-1), neuron-specific enolase (NSE) and carbohydrate antigens CA 125, CA 15-3 and CA 19-9, in the effusion may be helpful in the setting of solid tumors[40-44]. These markers must be used cautiously because the cut-off values have not been well defined. Different tumors may be identified by different markers and the sensitivity of every marker could be rather low. Nevertheless, specificity is high for some markers and tumors (among carcinomas: 80%-100% for CEA, 80%-97% for NSE and 70%-100% for CYFRA), and the combination of two or more tumour markers leads to a higher diagnostic value[45]. Paganuzzi found that a high value of CYFRA 21-1 with low CEA in the pleural fluid can identify patients with mesothelioma, while Dejmek used a combination of CEA, epithelial membrane antigen, BerEp4 and hyaluronan in this setting, with a sensitivity of 79% and a specificity of 100%[44,46]. A meta-analysis of published data showed good performance with both CEA and CYFRA 21-1 in the differential diagnosis of pleural effusions. The majority of these studies was focused on pleural effusions (which are much more common and easily drained) but similar results have been obtained in pericardial effusions[47,48]. More recently, Her-2/neu has been added to the panel of possible markers in lung carcinoma effusions, but CEA is still the most accurate single diagnostic marker, followed by CYFRA 21-1, and the combination of a CEA > 6 ng/mL and CYFRA 21-1 > 60 ng/mL resulted in a sensitivity of 97.6% and a specificity of 91.4% in the most recent report[49]. After drainage of the pericardial fluid, samples of fluid are sent both to microbiology and pathology laboratories for culture, chemical tests and neoplastic marker dosages. The remaining fluid should be sent immediately to the pathology laboratory for centrifugation and cytological diagnosis, or refrigerated at 4℃.

Pericardioscopy has been suggested to further define the etiology of pericardial effusions, in general allowing mirate biopsies, and has been reported to significantly raise the probability of obtaining a diagnosis, compared to effusion cytology and fluoroscopy-guided biopsy, in the neoplastic setting[50-54]. In the diagnostic algorithm suggested by the European Society of Cardiology, pericardioscopy has been included among the optional procedures if other tests (ECG, blood analysis and effusion fluid analysis) are inconclusive (indication class Ⅱa)[55].

TREATMENT

The goals of treatment may be simply to relieve symptoms (cardiac tamponade or dyspnea), to prevent recurrent effusion for a long-term symptomatic benefit, or to treat the local neoplastic disease with the aim of prolonging survival. Immediate relief of symptoms may be obtained with percutaneous drainage or with a surgical approach. For the long term prevention of recurrences, various approaches have been proposed: extended drainage, pericardial window (surgical or percutaneous balloon pericardiostomy), sclerosing local therapy, local and/or systemic chemotherapy, radiation therapy (RT) (external or with intrapericardial radionuclides). It is hard to compare the efficacy of these methods on the basis of the many reports on the topic, because the diagnosis is often not well defined (large pericardial effusion in a patient with cancer classified as "malignant" even without cytology or neoplastic marker confirmation, as discussed above). The efficacy criteria, which are necessarily arbitrary, change in different reports and few prospective randomized studies have been published. Moreover, most of the older reports consider an intervention successful if the patient survived for 30 d without recurrence of symptoms or tamponade[56,57]. This approach has two main defects: first, the fixed time of observation (a patient dying for non-cardiac causes without pericardial disease would be considered as "unsuccessfully treated", while one with relapsing tamponade after 32 d would be considered successfully treated); and second, cardiac tamponade depends not only on the entity of pericardial effusion but also on many variables, such as blood volume, right and left ventricular wall thickness and rate of accumulation of pericardial fluid. Moreover, one of the main signs (pulsus paradoxus) may be absent with atrial septal defect, left ventricular dysfunction or regional tamponade[58-60]. These limitations (particularly in cancer patients that can have a variety of concomitant problems, such as pleural effusion, intrathoracic masses, anaemia, low blood proteins, which can mimic signs and/or symptoms of cardiac tamponade or heart failure) have been thoughtfully addressed by Vaitkus *et al*[61] in a 1994 review in which several treatment approaches were compared. In this review, the authors considered an intervention "successful" if the patient survived the procedure, the symptoms did not recur, and no other interventions directed at the pericardium were required, regardless of the length of survival". This definition still has two limitations: first, there are the above mentioned problems in assessing symptoms, and second, the decision to undertake subsequent interventions may depend on the attitudes of both the physician and patient. The outcome would be better evaluated with objective outcomes, such as a complete response, partial response, stable disease and progression, as usual with solid tumors.

However, effusions are considered "not measurable" in oncologic staging[62]. Nevertheless, a semiquantitative assessment of pericardial effusion is possible by measuring the daily drained fluid from the catheter or by echocardiography, as done usually in the more recent reports[63,64].

Percutaneous drainage

In large pericardial effusions, percutaneous drainage using the Seldinger technique is useful to prevent or rapidly relieve symptoms of tamponade. Echocardiographic guidance reduces the risk of cardiac puncture or other complications, and is the presently accepted routine method[65]. Without any additional treatment, the rate of recurrence is high (up to 40%) and by extending the drainage for several days, the rate of recurrence is reduced[66]. Systemic CT without further local interventions has been reported to be effective in lymphomas and in some cases of solid tumors (mostly breast and ovarian)[67-72].

Surgical treatment

The most commonly used surgical approach is pericardiotomy or the creation of a pericardial window connected to a drainage tube or draining into the pleural or peritoneal space (using the subxiphoid approach, a left thoracotomy or a ballon catheter). The efficacy of this approach may be due, not only to the creation of a persistent communication through which fluid is drained, but to the inflammatory process that promotes adhesion between parietal and visceral pericardium, as confirmed by a small autopsy study[73]. In a prospective study from Duke University, surgical subxiphoid pericardiotomy was done under local anesthesia in 77% of 57 patients with various diseases, with general anesthesia required in the others. Effusion recurred in 8 patients in 2 mo and in 9 (16%) in the first year. In the subgroup of neoplastic pericardial effusion (n = 13), the mortality was 54% at 2 mo and 92% at 12 mo follow-up[74]. In a report of 67 patients (26 with cancer, 14 with neoplastic pericardial involvement) treated with subxiphoid pericardial drainage, the overall success rate was 82%, but the median survival was 393 d in cancer patients with negative cytology *vs* 122 d for those with malignant pericardial involvement. No data on concomitant antineoplastic therapies were reported[75]. In a larger study by Becit *et al*[21], 368 patients had subxiphoid surgical pericardiostomy connected to an external drainage tube. General anesthesia was used in 6% (mostly children), while local anesthesia with sedation (ketamine) was used in 94%. Within 1 mo, 37 patients (most with tuberculous and uremic pericarditis) had relapsing pericardial effusion and had a pleuropericardial window made, without any recurrence thereafter. Eleven patients (3%), all in the bacterial pericarditis group, developed constrictive pericarditis requiring pericardiectomy. In a retrospective study, the risks and efficacy of subxiphoid pericardiostomy *vs* percutaneous pericardial drainage was compared in 117 patients[76]. The authors reported a significantly higher mortality (1/23, 4% *vs* 0/94) and complication rate (4/23, 17% *vs* 1/94, 1.1%) in the pericardial drainage group. It should be noted, however, that pericardiostomy was the first choice method of treatment, and percutaneous drainage was limited to patients "considered too hemodynamically unstable to undergo surgical subxiphoid pericardiostomy, even under local anesthesia". The patients with underlying malignancy were 64/117, and this subgroup had a median survival of 2.2 mo and a 1-year actual survival rate of only 13.8%, regardless of drainage technique. On the other hand, a more recent retrospective analysis of 60 neoplastic pericardial effusions treated either with percutaneous (n = 10) or surgical pericardiostomy (n = 50) did not report any death and did not observed any difference in time to recurrence in either group. The median overall survival was 6.1 mo, and was higher (7.9 mo) in patients with adenocarcinoma than in other cytologic types (1.25 mo, P < 0.01). Gross, describing the outcome of 43 solid cancer patients treated with different surgical approaches (21 subxiphoid pericardial window, 14 pleuropericardial window and 8 pericardiodesis with thiotepa), reported 2.1% mortality (myocardial rupture during finger exploration of the pericardial space), and 6.4% morbidity. Most of the patients had concomitant chemo- or RT and the median overall survival was 5.2 mo in patients with breast cancer and 3.2 mo in the others[77]. In the early 1990s, the use of percutaneous balloon pericardiotomy was suggested as an alternative, less invasive intervention. The method appeared to be safe, with short-term success in preventing tamponade, but the long-term outcome was poor in the large subgroup of neoplastic patients, with a mean survival of 3.3 mo[78]. In the following years, the technique was modified with the use of an Inoue balloon catheter and a double-balloon. The inflation of two adjacent balloons might have some advantages over a single large balloon: stronger tension and more secure location in the pericardial space. In a retrospective analysis of 50 patients with cancer, Wang reported a 90% success rate (prevention of recurring effusion) using this method, but a median survival rate of 4 mo overall, with a significantly shorter survival in the cytology positive subgroup[79]. Complications were fever (30%) and pneumothorax (20%). More recently, the outcome of 43 patients, with various cancers, treated with primary single balloon pericardiostomy has been reported[80]. In this report, pain was a common side effect and required opioids before and during the procedure; 7.4% of patients had reaccumulation of fluid requiring reintervention, and the median survival was only 56 d. The authors suggested this technique as the management of choice for malignant pericardial effusion, but an editorial comment suggested to consider this approach as a second choice after percutaneous catheter pericardial drainage[81].

Sclerosing therapy

The rationale for pericardial sclerosis is to mechanically prevent the reaccumulation of effusion after drainage, promoting adhesion of the visceral and parietal pericardial layers.

"Pure" sclerosing agents: The first agents used for this purpose were antibiotics, such as powdered tetracycline and doxycycline, according to previous favourable experience in pleural effusions. The rationale was to induce irritation, inflammation and subsequent fibrosis, but the exact mechanism of action of these agents is not yet clear. In fact, other irritating agents (such as sodium hydroxide) do not cause pericardial symphysis[82-85]. Actually, a cytostatic activity has been suggested as contributing to the therapeutic effect of tetracycline[86]. The main adverse effects of these agents were pain (reported in 20% of patients in spite of the addition of intrapericardial lidocaine, with occasional severe pain), fever (7%) and paroxysmal atrial fibrillation (8%). Minocycline, a tetracycline derivate, has also been suggested for pericardial sclerosis, but it caused severe pain in the majority of patients (sometimes requiring opiates to be controlled), and the sclerosing effect was found to be independent from the acute irritative effect of the drug[87,88]. The largest study on tetracycline or doxycycline sclerosis reported an outcome of 93 cancer patients (69 with positive and 21 negative cytology, 3 not determined), of whom 85 received sclerosis. The procedure was complicated by pain in 17 (20%), fever in 7 (8%), atrial fibrillation or flutter in 6 (7%) and was effective in 75 (81%). However, 50 patients required > 2 instillations and the median dose used was 1500 mg[84].

Cytotoxic sclerosing agents: Bleomycin (BLM), an anticancer agent with sclerosing properties used in pleural and peritoneal effusion for chemical pleurodesis, has been tested also in pericardial effusions. In one of the first reports, 5 patients (all also receiving systemic CT) had 30-60 mg of BLM intrapericardially, resulting in complete control of effusion in all cases. In 2 cases, an autoptic study was available and residual pericardial tumor implants were still present[89]. In one report, 5/5 patients treated by intrapericardial BLM had a survival rate of 1-29 mo without effusion recurrence (but no mention was made of post-mortem histopathology), and in another study, 5/7 had stable control of effusion[90,91]. In a randomized prospective study on 20 patients, BLM was as effective as doxycycline as a sclerosing agent (82% *vs* 67% without recurring effusion), but with much less morbidity (no pain in the BLM group *vs* 7/10 patients with pain requiring narcotic analgesics in the doxycycline group)[92]. In a prospective randomized study, the outcomes of 79 lung cancer patients with pericardial effusion (58 with positive cytology) treated either with intrapericardial BLM or pericardial drainage alone were compared[93]. There were 9 early deaths within 30 d (5 in the drainage arm and 4 in the BLM arm), 1 case of constrictive pericarditis and 1 of cardiac dysfunction, both in the BLM group. The median effusion failure-free survival was 30 d in the drainage alone arm and 57 d in the BLM arm ($P = 0.03$ by log-rank test), but in the subgroup analysis this advantage was more evident in the cytology negative patients. Moreover, the patients with surgical drainage had a longer effusion failure-free survival compared to those undergoing drainage with a Seldinger technique. Another confounding aspect was that 24 patients received systemic CT. The actual efficacy of sclerosing therapy was not fully evaluable in this heterogeneous group of patients. The immunomodulator OK-432 (a penicillin-treated powder) used in Japan for pleurodesis has also be tested in the pericardium, but it had several, frequent side-effects: fever, pain and rapid reactive reaccumulation of fluid[94,95]. Cytokines (interferon α, β, interleukin-2) have been used in various effusions (mostly pleural) with few side effects but the reported response rate ranged from 10% to 70% in different studies[96-98]. The intrapericardial use of these agents was limited, and is presently not commonly used. Triethylenethiophosphoramide (thiotepa) is another anticancer agent with sclerosing properties used for local therapy with good results and few side effects. A retrospective study on 60 patients (30 only with positive cytology) were treated either with intrapericardial sclerosis with thiotepa or surgery (pericardial window or partial pericardiectomy). This study showed no advantage of this procedure over another in preventing effusion recurrence, but pericardiocentesis was more cost-effective[99]. In this study, the morbidity and recurrence was higher using a surgical approach rather than pericardiocentesis. The overall median survival was 97 d, however, considering different tumors, patients with breast cancer had a median survival of 407 d and those with lymphoma or leukemia had a median survival of 138 d. On the other hand, there was no difference in survival with respect to the type of drainage procedure performed; no subgroup analysis was associated with systemic CT. In a study by Bishiniotis *et al*[64] on 19 women with breast cancer and cytology positive pericardial effusion treated with intrapericardial thiotepa (9 with systemic CT in addition), 15 had complete control of effusion at 6 mo follow-up and 4 had only mild (< 0.5 cm) recurrent or residual pericardial effusion. The median survival in these patients was 330 d. Thiotepa was used by Martinoni *et al*[100] in 33 patients (16 breast cancer, 15 lung cancer, 4 different tumors) with cytology positive effusions, without recurrence in 30 patients at a follow-up of 22 to 1108 d (median 115 d). All patients also received systemic CT, and the overall survival was longer in the breast cancer subgroup compared to the lung cancer group (median 272 d *vs* 85 d). The better outcome of breast cancer compared to other solid tumors has been reported by other authors[101].

Local chemotherapy

The rationale of local chemotherapy is to obtain a higher local concentration of the antineoplastic drug. There have been very few pharmacokinetic studies performed on intrapericardial chemotherapy, but all confirm this hypothesis. Intrapericardial instillation of teniposide (VM 26) in 3 patients resulted in very high concentrations of the intrapericardial drug (peak > 190 μg/mL) lasting up to 3 d (area under the curve of > 2600 μg/mL per hour), with very low plasma concentrations (< 1.7 μg/mL), while with intravenous infusion, the peak intrapericardial concentration was only < 5 μg/mL[102]. 5-fluorouracil had similar phar-

macokinetics[103]. The pharmacokinetics of carboplatinum (300 mg given intrapericardially and removed after 40 min) were studied by Moriya *et al*[63] in 7/10 patients with lung adenocarcinoma, obtaining similar results. In this study, there was one non responder and one recurrence after 89 d, which responded to repeated local carboplatinum. The survival was 29 to 176 d (median 69 d). The pharmacokinetics studies using various intrapleural or intraperitoneal chemotherapic drugs (doxorubicin, docetaxel, liposomal paclitaxel) always showed much higher local concentrations of the drug, compared to plasma concentrations, and a much longer persistence of the drug in the cavity, while the reabsorbed drug was quickly cleared from plasma[104-106]. The use of intrapericardial cis-platinum (DDP) was first reported in 1985 in a single case treated with 10 mg over 5 continuous days[107]. The same schedule was used by others in a small series of mostly lung cancer patients, obtaining good results[108-110]. In a study on 9 patients with various tumors, Tomkowski *et al*[111] had 2 long-lasting responses in lung adenocarcinoma also treated with systemic CT, but most of the patients died of cancer within 3 mo, and in all of the 7 patients who had an autopsy, neoplastic pericardial involvement was found even without pericardial effusion. Maisch *et al*[112] used 30 mg/sm of DDP in a single administration (removing the drug after 24 h) in 42 patients with various tumors also undergoing systemic CT, and observed a relapse in 3/8 (37.5%) breast cancer cases, 1/22 lung cancer cases, 1/2 Hodgkin's cases and in the only mesothelioma patient; the mean survival was 2.8 ± 1.3 mo. Bischiniotis *et al*[113] used 10 mg of DDP over 3 continuous days in 25 cases of lung adenocarcinoma, obtaining complete disappearance of effusion in 13 cases and residual small (< 0.5 cm) effusion in 9 cases; a surgical approach was necessary in 1 case of DDP failure and in 1 case of tumor encasement of the heart. In a recent study, 7 patients with esophageal cancer were treated with local DDP (10 mg 2-5 times), obtaining complete remission in all cases. The 4 patients who received local CT only survived 61-104 d, while those who were treated with systemic CT as well survived 126-268 d[114]. Other chemotherapeutic agents have been used intrapericardially; e.g. nitrogen mustard, mitomycin C, mitoxantrone, 5-fluorouracil, but only case reports or small series have been published, making it impossible to judge the response rates[57,115-117]. Musch *et al*[118] in 2003, reported 12 complete remissions and 3 partial remissions (small pericardial effusion) among 16 patients (8 bronchial, 7 breast, 1 stomach carcinoma) treated with 10-20 mg of mitoxantrone left in the pericardium for 24 h; the follow-up lasted 28-730 d (mean 6 mo). In a multicenter series of various tumors, the mean effusion-free period of the patients treated with local chemotherapy (various agents) was 372 d (median 223 d); at 1, 2, 6 and 12 mo, 58%, 52%, 33% and 16%, respectively, were completely effusion-free. In the subgroup of 88 lung cancer patients, the mean effusion-free period was 271 d (median 215 d) and the percentages for completely effusion-free at 1, 2, 6 and 12 mo were 65%, 57%, 35% and 18%, respectively[119].

Radiotherapy

External beam radiotherapy has been used for radiosensitive tumors, such as lymphomas, acute and chronic leukemias and breast cancer[120]. The intrapericardial instillation of radioactive agents, such as ^{32}P colloid, has been used with a success rate of > 90%; a single dose of 5 mCi ^{32}P colloid would result in a total irradiation dose of > 100 Gy[121,122]. The mechanism is probably a combination of cytotoxic effect and post-inflammatory adhesion. Although this therapy is apparently well tolerated, it has not become very popular, probably due to concern about radiation risk and the availability and cost of the radioactive colloid.

Combined surgical and medical approach

In a series of 51 cases of cardiac tamponade caused by lung cancer (90% with positive or suggestive cytology) treated with subxiphoid pericardial window, 31 did not receive any local treatment, 20 had intrapericardial injections of one or more of doses of mitomycin C, tetracycline hydrochloride or doxorubicin[123]. There was no significant difference in either therapeutic response (82% and 90%, respectively) or patient survival rates between the two treatment sub groups; 41 (80%) and 25 (49%) also received systemic CT or RT. Of 28 patients on whom autopsies were done, extensive neoplastic involvement of the heart was found in 6 (21%), diffuse fibrofibrinous adhesion between the epicardium and pericardium in 18 (64%) and partial adhesion with recurrent pericardial effusion in 4 (15%).

DISCUSSION

The epidemiology, possible therapies and prognosis of neoplastic pericardial diseases have changed over time. Currently, symptomatic pericardial effusions are more frequently due to lung cancer, hematologic malignancies and, in some communities, to mesothelioma, while breast cancer is less represented compared to the past. The prognosis of breast cancer pericarditis is better than that of lung cancer. Very few prospective randomized studies have been performed on different therapies, and the comparison of many observational studies is difficult since, in the largest studies, different tumors and/or different treatments were analyzed together. The most important bias in the articles reporting the efficacy of various local treatments is the fact that many or all patients also received systemic CT, making it difficult to discriminate the relative efficacies of the interventions. There is only one study that separately analyzed the patients treated with pericardial sclerosis, local, systemic and combined CT in a group of 137 patients (61 lung cancer). Simple drainage or sclerotherapy had significantly lower success rates compared to any CT. Among solid tumors, both local and combined (systemic and local) CT showed a statistically significant advantage compared to systemic CT alone, while in the lymphoma patients, the outcomes were similar regardless of the method of administration of CT[124]. This finding might be explained in two ways: first, lym-

phomas are usually very chemosensitive, and even lower drug concentrations may be effective; and second, as lung and other intrathoracic tumors metastasize to the heart mostly through the lymphatics, and lymphomas often through the hematogenous route, the effect of a drug administered or reabsorbed through the same way is stronger. In fact, the use of translymphatic CT in lung cancer has been recently proposed[125]. In a study comparing the four main strategies, there was little difference between local CT and local plus systemic CT regarding the rate of effusion control. However, the patients receiving a combined treatment survived longer. The rationale for local CT actually is to obtain local control of the disease, but the addition of systemic CT, acting on other possible metastatic sites, may favorably influence survival. Regarding drugs to be employed locally, it seems reasonable to use the most active drug for each single tumor. Mitoxantrone is effective in breast carcinoma and lymphomas, BLM is currently used in systemic CT of head/neck carcinomas, squamous cell carcinoma, Kaposi sarcoma and both Hodgkin's disease and NHL. Thiotepa is active in breast, bladder, ovarian carcinomas and in Hodgkin's disease. Platinum is indicated in testis, ovarian, bladder, lung (both small cell and non-small cell), gastric carcinomas, in mesothelioma and in NHL. Taxanes are also active in breast and lung carcinoma and have been proven to be effective in animals, but their use for neoplastic pericardial disease in the clinical setting has not yet been reported[126,127].

CONCLUSION

The incidence of neoplastic pericardial disease, in general, and its prevalence among different primary tumors, have shown little change over time and may differ widely among different populations. Overall, it is more frequent in lung cancer patients. The diagnosis may be challenging in some particular patients, but with the use of multiple diagnostic methods (cytology, immunohistochemistry and dosage of neoplastic markers in the pericardial fluid), it may be defined in almost all cases.

Therapy should be limited to the control of symptoms in terminally ill patients only. In all patients that have a chance of surviving at least a few months, the goals should be to obtain a complete and stable control of effusion as long as possible, and to try to improve survival as well. The first goal may be obtained both with sclerosing agents and with local CT. Among the sclerosing agents, BLM and thiotepa (both with cytotoxic effects as well) have been successfully used with fewer side effects compared to tetracyclines and seem to be mostly indicated for breast carcinoma. Among the "pure" chemotherapeutic agents, platinum and mitoxantrone are the most tested and, according to their use in systemic CT, platinum is suggested for lung and ovarian carcinomas and for mesothelioma, and mitoxantrone is suggested for breast and other carcinomas. The second goal (improving survival) may be obtained by systemic chemotherapy, possibly associated with local CT.

In pericardial effusion due to lymphoma, pericardiocentesis may be limited to hemodynamically impaired patients, since systemic chemotherapy may be very effective. Among solid tumors, the most chemosensitive (such as breast and ovarian carcinoma) may also be treated with systemic CT first. Should pericardiocentesis be performed (for worsening effusion or impending cardiac tamponade), local therapy with thiotepa, mitoxantrone, mitomycin C (or other drugs known to be effective for a given cancer in general, or in a particular patient) may be useful. Lung carcinoma is best treated with combined systemic CT and intrapericardial platinum. The most tested was cis-Platinum; different treatment schedules have been used for local instillation (10-20 mg in 20 mL over 3-5 continuous days, 50 mg/50 mL in single bolus) without any evident advantage of one over others. Radiotherapy, balloon pericardiostomy or surgical creation of a pericardial window may be considered in selected cases, such as relapsing tamponade, tumor encasement of the heart or pericardial constriction. With a thoughtful diagnostic and therapeutic approach, many patients with neoplastic pericardial disease may survive without recurrence for several months or even years.

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REVIEW

Aspirin resistance: Fact or fiction? A point of view

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Abstract

Aspirin is a wonder drug that has been used for well over 100 years for its analgesic and antipyretic effects. For the past three decades, it has increasingly been used for the prevention of primary and secondary cardiovascular events. Lately, it has been suggested that a significant number of individuals taking aspirin have become resistant to this drug. The phenomenon of "aspirin resistance" is based on the observation of clinical events in some patients taking aspirin, and/or a diminished platelet aggregation inhibitory response to aspirin therapy. Unfortunately, laboratory assays used to monitor the efficacy of aspirin are far from accurate and the results are not reproducible. Furthermore, results of different platelet function tests are often not congruent. In addition, platelet aggregation studies show marked inter-individual and intra-individual variability. Patients with coronary heart disease take many drugs that interfere with the effect of aspirin on platelet aggregation. Besides inhibiting formation of thromboxane A_2 from arachidonic acid, aspirin has a host of platelet-independent effects that complement its platelet inhibitory effects. Laboratory assays designed to measure platelet function do not take into account these pleiotropic effects of aspirin. In our view, use of the term "aspirin resistance" based on inadequate knowledge of imperfect laboratory tests does a disservice to physicians and patients.

INTRODUCTION

A substance called salicilin was first isolated from the bark of willow tree by Reverend Edmund Stone in 1763[1]. In 1897, acetylsalicylic acid was marketed by the Bayer Company as Aspirin® as an analgesic[2,3]. When other non-steroidal anti-inflammatory drugs (NSAIDs) were introduced in the 1950s, the popularity of aspirin declined. In the 1970s and 1980s, research revealed potent anti-platelet and cyclooxygenase (COX) inhibitory actions of aspirin. Soon thereafter, aspirin started being used as a first-line drug in patients with a variety of cardiovascular disease states.

The Antithrombotic Trialists' Collaboration[4] showed a 12% reduction in major vascular events in primary prevention trials. This was primarily driven by a reduction in myocardial infarction. There was no significant effect of aspirin on the incidence of stroke or vascular mortality. The reduction in major coronary events was similar in both primary and secondary prevention trials [relative risk (RR) 0.82 for primary prevention and RR 0.80 for secondary prevention]. The absolute benefit of aspirin in primary prevention trials was 0.06% per year and in secondary prevention trials was 1% per year. There was a significant 20% reduction in stroke in secondary prevention trials. In

a recent meta-analysis of six studies of aspirin in primary prevention in patients with diabetes mellitus[5], however, no significant reduction in the risk of cardiovascular or all-cause mortality was identified. Although there was a heterogeneity in the rate of myocardial infarction and stroke, aspirin reduced the risk of myocardial infarction in men [odds ratio (OR), 0.57; 95% confidence interval (CI): 0.34-0.94], but not in women (OR, 1.08; 95% CI: 0.71-1.65), and there was no benefit of aspirin against stroke in men or women. Nonetheless, it is now generally accepted that aspirin exerts a powerful effect against cardiovascular events in all secondary, and in some primary, prevention trials. Hence this drug is used in patients with known coronary heart disease and forms the background medication in all patients undergoing coronary, carotid, renal or peripheral artery revascularization.

This issue of "aspirin resistance" is of much interest to patients and physicians, since aspirin is perhaps the most widely used drug worldwide. Almost 30 million people, or 36% of the adult population in the United States, consume 10-20 billion aspirin tablets each year either alone or with other antiplatelet drugs to protect their hearts and brains from platelet-rich clots, the leading cause of heart attacks and strokes.

A recent Medline search by the authors using the words "aspirin-resistance" revealed 364 published articles between 1993 and 2009, 116 published articles using the words "aspirin-resistance coronary disease", and 52 published article using the words "aspirin-resistance stroke".

Antiplatelet therapy, whether it consists of aspirin, clopidogrel, other antiplatelet drugs, or their combination is essentially unmonitored for efficacy. Whether it should remain unmonitored or if the dose or type of drug/s should be tailored for the individual patient is subject to debate. In this context, "aspirin resistance", if there is such a phenomenon, becomes very important.

HOW DOES ASPIRIN WORK?

Aspirin acts on platelets by acetylating the COX enzyme at position serine 529 resulting in the reduced formation of cyclic endoperoxides [prostaglandin G_2 (PGG_2) and PGH_2] from arachidonic acid[6]. The inhibition of the constitutive COX enzyme is irreversible[6,7]. Since platelets are anucleated cells and cannot generate a new COX enzyme, the action of aspirin lasts for the entire lifespan of the platelets which is 7-10 d. The COX enzyme is required for the production of the prostanoid thromboxane A_2 (TXA_2) from cyclic endoperoxides in platelets. TXA_2 is a very potent stimulus for platelet aggregation.

Besides arachidonic acid, platelets are activated in response to epinephrine, collagen, thrombin, and adenosine diphosphate (ADP) (Figure 1). When there is injury to the vascular intima, circulating platelets are exposed to subendothelial collagen, proteoglycans, fibronectin and other adhesive proteins. The resulting changes in platelets can be divided into adhesion, secretion and aggregation. For adhesion, von Willebrand factor is necessary and serves as a bridge between collagen and platelets through its receptor glycoprotein (Gp) Ⅰb/Ⅸ[8]. This causes release of cytosolic Ca^{2+} which facilitates the second phase or secretion. In this phase there is release of alpha and dense granules. P-selectin released from alpha granules causes adhesion of monocytes and neutrophils to activated platelets[9]. Dense granules release ADP, a potent mediator of the third phase of platelet activation, namely platelet aggregation. ADP acts through the platelet specific receptor P2Y1 and mediates the action of phospholipase A_2 on membrane phospholipids[6]. This releases arachidonic acid, which is converted to endoperoxides *via* constitutive COX (COX-1); activation of TXA_2 synthase enzyme then converts endoperoxides to TXA_2 in platelets[10]. In addition to ADP and TXA_2, other stimuli, such as 5-hydroxytryptamine and epinephrine can initiate aggregation *via* specific receptors. The cytosolic release of Ca^{2+} also causes a conformational change in platelet GpⅡb/Ⅲa receptors which allows the platelets to bind to fibrinogen[6]. These stimuli lead to a build-up of Ca^{2+}, which causes an autocatalytic reaction of platelet aggregation.

Table 1 Cyclooxygenase-independent effects of aspirin

On platelets
Partially inhibits ADP2Y12 receptor activation responsible for residual arachidonic acid induced platelet activation[11]
Blocks NF-κB activation that facilitates platelet inhibition by neutrophils[12]
Anti-inflammatory effect
Inhibits release of reactive oxygen species[13]
Inhibits release of elastase and soluble ICAM-1[13]
Inhibits formation of malondialdehyde[13]
Inhibits formation of oxidized LDL antibodies[14]
Reduces inflammatory cell activity[13]
Anti-oxidant effect
Inhibits oxidized LDL formation[14]
Blocks transcription of LOX-1[15,16]
Scavenges hydroxyl radicals[17]
Induces synthesis of ferritin[18]
Inhibits nitric oxide synthase[19,20]
Inhibits expression of redox sensitive transcription factor NF-κB[19,20]
Acetylates proteins and prevents their oxidation[21,22]
Endothelial function modification
Prevents adhesion of neutrophils and monocytes[23]
Induction of VCAM-1, ICAM-1 and E-selectin[24,25]
Miscellaneous effects
Inhibits vascular smooth muscle cell function[26]
Inhibits angiogenesis[27-29]
Inhibits γ-carboxylation of coagulation factors[30]

ADP: Adenosine diphosphate; NF-κB: Nuclear factor-κB; ICAM-1: Intracellular adhesion molecule-1; LDL: Low density lipoprotein; LOX-1: Oxidized LDL receptor.

ASPIRIN CAN ACT THROUGH COX-INDEPENDENT PATHWAYS BESIDES A COX-DEPENDENT PATHWAY

Aspirin has a myriad of effects that are not limited to platelet inhibition through COX enzymes (Table 1). In platelets, there is residual arachidonic acid-induced platelet activation in aspirin treated patients even after controlling for

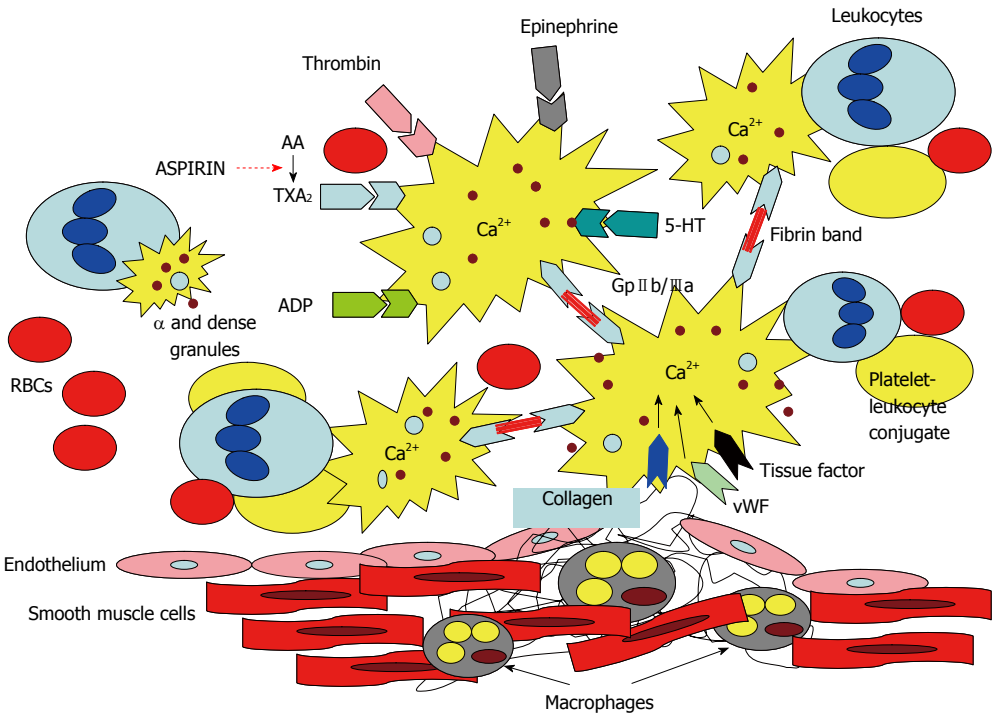

Figure 1 Pathways of platelet aggregation. Platelets can be activated in response to collagen, von Willebrand factor (vWF) and tissue factor when there is injury to the endothelial lining. A host of other stimuli, such as adenosine diphosphate (ADP), 5-hydroxytryptamine (5-HT), epinephrine and thromboxane A_2 (TXA_2), can initiate aggregation *via* specific receptors. The end-point is the rise in cytosolic Ca^{2+} which induces platelet activation/aggregation. Externalization of glycoprotein (Gp) Ⅱb/Ⅲa receptors causes fibrin bands to bind to different platelets. Aspirin interferes with the conversion of arachidonic acid (AA) to TXA_2 and inhibits the rise in cytosolic Ca^{2+} and subsequent platelet aggregation.

non-compliance and under-dosing. This platelet activation is independent of the COX pathway and is dependent on ADP P2Y1 and P2Y2 receptors[11]. Through the nitric oxide/nuclear factor-κB (NF-κB) pathway aspirin facilitates the inhibition of platelet activation by neutrophils[12].

Other agents that inhibit COX expression or activity, such as NSAIDs, or the direct TXA_2 synthase and receptor inhibitors inhibit platelet aggregation, but do not show the same beneficial effect against vascular disease as aspirin, suggesting unique vascular properties of aspirin, independent of the COX-TXA_2 pathway[31].

Activation of inflammatory pathways is intimately related to the pathogenesis of atherosclerosis as well as the precipitation of acute vascular events. Aspirin reduces inflammatory cell activity, release of elastase and soluble intracellular adhesion molecule-1 (ICAM-1), and formation of malondialdehyde and oxidized low density lipoprotein (LDL) antibodies[13].

Aspirin has significant antioxidant properties. Accordingly, it protects LDL-cholesterol from oxidation. Oxidized LDL is now recognized to be a more potent mediator than native LDL in atherogenesis[32]. Aspirin also exerts some of its antiatherogenic effect *via* a reduction in oxidized LDL formation[14]. The salicylate moiety in aspirin blocks the transcription of Oxidized LDL receptor 1, a receptor for oxidized LDL, in endothelial cells[15] and platelets[16]. Aspirin can also scavenge hydroxyl radicals[17]. Aspirin has been demonstrated to induce synthesis of ferritin that sequesters free cytosolic iron which is the main catalyst for oxygen radical formation[18]. Lastly, aspirin induces a small reduction in blood cholesterol[33].

Aspirin inhibits cytokine-inducible nitric oxide synthase gene expression, an effect that involves the activation of redox-sensitive transcription factor NF-κB[19,20]. *Via* its acetyl moiety, aspirin can acetylate ε-amino groups of lysine residues in proteins and prevent their oxidation[21,22]. This effect of aspirin on proteins is important in limiting both lipoprotein and fibrinogen oxidation[21,22], with resultant reduction in inflammation in patients with vascular disease[34].

Aspirin improves the dysfunctional state of the endothelium[23] and prevents the adhesion of neutrophils and monocytes to the activated vascular endothelium. This effect is mediated *via* inhibition of NF-κB activation and induction of various adhesion molecules, such as vascular cell adhesion molecule-1, ICAM-1 and E-selectin[24,25]. In clinical disease states, aspirin has been shown to normalize nicotine-induced endothelial dysfunction[35] and to restore the forearm vasodilatory effect of acetylcholine in hypercholesterolemic patients[36].

Aspirin, in high concentrations, inhibits growth of human vascular smooth cells in culture[26]. This property of aspirin may have a salutary effect after percutaneous intervention in terms of restenosis at the site of angioplasty or stent placement. Aspirin can reverse hypoxia-induced coronary vasoconstriction[37], a mechanism that contributes to aspirin's effect on vascular tone following percutaneous coronary intervention.

Aspirin also has a modest anticoagulant effect. Salicylate, a metabolite of aspirin, can inhibit γ-carboxylation of coagulation factors Ⅱ, Ⅶ, Ⅸ and Ⅹ[27-29]. The fibrinolytic activity of blood increases with aspirin and is mediated by acetylation of the ε-amino groups of lysine residues.

Both COX-1 and COX-2 are important in the regulation of angiogenesis. Aspirin inhibits angiogenesis, which is an essential step in the growth of atherosclerosis. This inhibitory effect of aspirin is mediated *via* inhibition of mitogen-activated protein kinase activity on endothelial cells[30].

WHAT IS "ASPIRIN RESISTANCE"?

There is no consensus definition of "aspirin resistance". This phenomenon has been described based on clinical assessment or on the results of laboratory tests that assess platelet activation. A recent article in the European Heart Journal has aimed at obtaining a consensus definition for aspirin resistance. The clinical definition of "aspirin resistance" relates to the occurrence of thromboembolic events despite aspirin intake. In the laboratory, "aspirin resistance" has been defined as the failure to inhibit platelet reactivity despite taking antiplatelet drugs. However clinical resistance to aspirin has often been termed 'treatment failure'. Not all patients with 'treatment failure' have laboratory evidence of aspirin resistance and *vice versa*[38].

The reported prevalence of "aspirin resistance" is variable[39-74] with a rate of approximately 8.3% in healthy adults (Table 2). In subjects with one or more risk factors its prevalence ranges from 0.7% to 23.4%. In patients with stable coronary artery disease, again a wide range has been noted, with the prevalence as high as 29%. In patients with acute myocardial infarction, congestive heart failure and peripheral vascular disease, and in others undergoing coronary artery bypass grafting or percutaneous coronary intervention, the reported prevalence of "aspirin resistance" has been as high as 50%-70%. However, based on the results from a combination of three of the most commonly used laboratory tests (VerifyNow®, optical aggregometry, PFA-100®), the prevalence rate is approximatively 2% in patients with transient ischemic attacks and stroke[74].

Laboratory evaluation of platelet activation

Most of the variability in the prevalence of "aspirin resistance" is due to different platelet function tests that are used to assess platelet activation. The tests used include light transmission aggregometry, whole blood aggregation, flow cytometry and point-of-care tests. Indirect measurement of TXA_2 formation include serum TXB_2 and urinary 11-dehydro-TXB_2. However, measurement of TXA_2 metabolites does not take into account formation of TXA_2 by non-platelet sources, such as endothelial cells, leukocytes and renal tissue[11].

Light transmission and impedance aggregometry have been the gold standard for measuring platelet aggregation function. Many point-of-care assays have been developed to study platelet activation. Some of these assays assess COX-dependent pathways and others include COX-independent pathways. The most common of these point-of-care assays are VerifyNow® and PFA-100®. A comparison between PFA-100®, platelet aggregometry and GpⅡb/Ⅲa flow cytometry found little correlation between the results obtained from these three methods[75]. Some investigators have also used measurement of aspirin metabolites and bleeding time to assess the efficacy of aspirin.

Table 2 Reported prevalence of "aspirin resistance"

	Prevalence (%)	Ref.
Healthy adults	8.3	[38]
Risk factors	0.7-23.4	[39,40]
Stable CAD	0.4-29.2	[41-48]
CVD	12.5-56	[49-55]
CABG	7.1-54	[56-60]
PCI	12.7-26.2	[61-64]
MI	0.5-70.1	[65-70]
CHF	55.0	[71]
PVD	9.6-60	[72,73]

CAD: Coronary artery disease; CVD: Cardiovascular disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; CHF: Congestive heart failure; PVD: Peripheral vascular disease.

PFA-100® assay

This test uses cartridges coated with platelet agonists (either collagen/ADP or collagen/epinephrine). The time for platelet plug to close the central opening (closing time) is used as a measure of platelet reactivity[10,76]. This test is thought to simulate platelet function *in vivo* and can be considered an *in vitro* equivalent of bleeding time[76]. "Aspirin resistance" is defined as: closing time < 193 s using collagen/epinephrine, and < 121 s using collagen/ADP as agonists[44]. This test is unfortunately not aspirin-specific. It correlates well with light transmission aggregometry.

VerifyNow® assay

This is a point-of-care platelet aggregation test that correlates with the results obtained with light transmission aggregometry. Response to aspirin is reported in aspirin resistance units. The extent of COX inhibition is believed to be measured by this assay[77,78]. "Aspirin resistance" is usually taken as ⩾ 550 units[46].

Light transmission and impedance aggregometry assays

Light transmission aggregometry measures optical density of plasma after platelet aggregation with an agonist. The problem with this test is lack of standardization as to the choice of agonist/s and their concentration. For example, platelet aggregation in a given person may be abnormal in response to ADP 1-5 μmol/L, but completely normal using higher concentrations. Furthermore, there is a marked variability in aggregation response to different agonists. Impedance aggregometry has the same principle, but utilizes whole blood instead of plasma and measures

electrical impedance instead of light transmission[10]. This test assesses the role of blood components including leukocytes and clotting factors besides platelets in thrombus formation as a mild electrical current is passed through the whole blood. Again, the ideal agonist for thrombus formation has not been defined.

TXA_2 metabolites

Serum TXB_2 and urinary 11-dehydro-TXB_2 are metabolites of TXA_2. They have been used to assess "aspirin resistance". These are COX-1 dependent tests and are not platelet specific and do not necessarily reflect platelet reactivity. Serum TXB_2 reflects TXA_2 formation by endothelial cells and leukocytes in addition to platelets. Urinary 11-dehydro-TXB_2 usually requires 24 h urine collection and reflects TXA_2 formation by renal tissues besides platelets and leukocytes[79]. These tests were initially quite popular, but have lost their popularity because of the time delay between aspirin intake and measurement in the laboratory.

Thromboelastogram and impact cone and platelet analyzer

The thromboelastogram platelet mapping system is a point-of-care system that measures clot formation and lysis. This uses whole blood and requires pipetting. The impact cone and platelet analyzer is a point-of-care test that assesses shear-induced platelet adhesion[80].

Flow cytometric analysis

Monoclonal antibodies against platelet surface antigens, such as GpⅡb/Ⅲa, P-selectin, platelet monocyte aggregates, thrombospondin and CD-40 ligand can be used to measure expression of certain antigens. Expression of these antigens has been found to be lower in patients treated with aspirin than controls[81].

Rapid platelet function assay

In this test, blood is run through a transparent fibrinogen-coated cartridge with platelet agonists. When a thrombus forms on the surface, light transmission changes and reflects platelet aggregation[79]. This test is not aspirin-specific.

Platelet reactivity

Venous blood is mixed with either EDTA-buffer or EDTA-formaldehyde buffer; activated platelets are dispersed in the former and fixed in the latter. The mixture is then centrifuged and only non-activated platelets remain in the supernatant. Platelet count in the supernatant (*vs* the platelet count in blood) is a reflection of adherent platelets[79].

Bleeding time

This is the only *in vivo* test that measures platelet activation. It is independent of coagulation factors and is a reasonably good index of platelet function[79].

A recent consensus statement by the Working Group for antiplatelet drug resistance[38] states that the term laboratory resistance should be reserved for pharmacodynamic resistance resulting from changes in enzyme or receptor. Aspirin hyporesponsiveness is defined as more than 10%-20% with light transmittance aggregometry and more than 0 ohms with impedance aggregometry. For determining aspirin-specific effects, the recommended test is arachidonic acid-induced aggregation or serum TXB_2 levels. However, it should be noted that there is no evidence that any of these laboratory values are associated with an adverse cardiovascular outcome.

DOES "ASPIRIN RESISTANCE" REALLY EXIST?

The phenomenon of "aspirin resistance" is characterized by attenuated inhibition of platelet aggregation in some patients taking aspirin. The term "aspirin resistance" came into use because some patients manifesting this phenomenon had cardiovascular events, presumably on the basis of platelet activation[82]. However, a direct correlation between evolution of cardiovascular events and *ex vivo* platelet activation has never been demonstrated. Also, the reduced platelet response (aggregation inhibition) in studies showing "aspirin resistance" was identified by different methods in different studies; some used platelet-rich plasma, others used whole blood to assess platelet aggregation, and yet others used serum TXB_2 measurement. The concentration of agonists used for inducing platelet aggregation varied widely in different studies, and the agonists were different in different studies. Pitfalls in studying platelet activation with different stimuli have been described earlier. Some investigators have shown that "aspirin resistance" may be present in some individuals using one particular stimulus, but not another. In addition, a person with "aspirin resistance" may not have "aspirin resistance" a week or two later.

As mentioned earlier, there is residual platelet activation (primary wave of aggregation) which is unaffected by aspirin treatment and is independent of non-compliance and under-dosing of aspirin. The residual platelet aggregation may be quite marked in some individuals. As stated earlier, there are multiple pathways of platelet aggregation (Figure 1) and most laboratory tests assess only one or two of these pathways. Most of these pathways are not entirely TXA_2-dependent and, therefore, not aspirin-specific. Further, most studies on "aspirin resistance" did not measure baseline platelet function (i.e. before aspirin treatment). In our opinion, the wide variation in the prevalence of "aspirin resistance" reflects the underlying heterogeneity in platelet response from patient to patient.

There are multiple reasons for the phenomenon of diminished inhibition of platelet aggregation in patients taking aspirin (Table 3). Non-compliance is perhaps the most likely cause of "aspirin resistance"[49,83]. Use of concomitant medications, such as NSAIDs and proton pump inhibitors (PPIs), which affect COX enzyme kinetics, can contribute to "aspirin resistance". Age, gender

Table 3 Underlying causes of "aspirin resistance"

Abnormal pharmacokinetics
Non-compliance
Inadequate dosing
Tachyphylaxis
Interaction with other drugs, such as NSAIDs and PPIs
Clinical conditions
Advanced coronary artery disease, acute coronary syndromes, CABG
Diabetes mellitus
Heart failure
Infection/inflammation
Obesity
Genetic
COX-1 gene mutation
COX-2 overexpression
GpⅡb-Ⅲa polymorphisms
Molecular
Increased turnover of platelets
PGH_2 substrate is provided to platelets by monocytes or endothelial cells
Incomplete inhibition of TXA_2 formation
Increased platelet sensitivity to ADP and collagen
Increased COX-2 expression on platelets

COX: Cyclooxygenase; NSAIDs: Non-steroidal anti-inflammatory drugs; PPIs: Proton pump inhibitors; Gp: Glycoprotein; TXA_2: Thromboxane A_2; PGH_2: Prostaglandin H_2; ADP: Adenosine diphosphate.

and smoking also reduce the platelet inhibitory effect of aspirin[47]. Hormonal changes in women have been shown to enhance platelet activation, and thus women may be more prone to show "aspirin resistance"[84]; others have disputed the presence of this phenomenon[41]. There is also a diurnal as well as a seasonal increase in platelet activation related to catecholamine surge in the morning hours and during the winter months which may manifest as a diminished response to aspirin. Variation in pharmacokinetics is another cause of "aspirin resistance". Clinical conditions, such as diabetes mellitus, advanced coronary disease, chronic kidney disease, acute coronary syndromes, inflammation, obesity and bypass surgery, are characterized by an increased platelet aggregatory response to different stimuli, which may be characterized as "aspirin resistance". We have observed serum TXB_2 levels to rise with continued use of aspirin (unpublished data), perhaps a response to the increase in platelet turnover and/or activation of alternate sources of TXA_2 generation.

Genetic polymorphisms have been noted to contribute to the diminished effect of aspirin on platelet biology. Genetic polymorphisms involving GpⅢa (P1A1/A2 polymorphism)[41,85,86] and COX-1 and COX-2[85-87] can lead to a variable effect of aspirin on platelet function.

It is also important to recognize that in conditions that are associated with infection and inflammation, non-platelet sources such as monocytes, macrophages and endothelial cells, activate the COX-2 enzyme, resulting in increased formation of TXA_2 and increased levels of F2-isoprostanes. Such COX-1-independent mechanisms are especially relevant to patients with diabetes mellitus, hyperlipidemia, smoking and heart failure, all of which are associated with augmented lipid peroxidation of arachidonic acid and consequent overproduction of isoprostanes. Failure of usual doses of aspirin to completely inhibit TXA_2 may be misinterpreted as aspirin resistance.

MANAGEMENT OF DIMINISHED RESPONSE TO ASPIRIN

The 2005 position paper of the working group on aspirin resistance concluded that there was not enough evidence of clinical improvement in changing treatment in aspirin resistance[83]. Some experts have recommended increasing the dose of aspirin to overcome "aspirin resistance"[88,89]; others have refuted the usefulness of this approach[6]. We believe that while most patients have adequate inhibition of platelet aggregation with low doses of aspirin, others need higher doses. Which patients are in the latter group is not known. Accordingly, we tend to prescribe a 325 mg daily dose to patients with multiple risk factors with evidence of ongoing vascular injury and inflammation, and to those who show evidence of repeated coronary artery occlusion. Addition of other antiplatelet agents such as clopidogrel and prasugrel to aspirin therapy might also help. A recent study shows that addition of an omega-3 fatty acid can overcome "aspirin resistance"[90].

In general, the use of NSAIDs and PPIs in patients needing aspirin should be curtailed or kept at a minimum as these agents tend to reduce the availability of aspirin. There may well be other agents that influence the pharmacokinetics of aspirin. Point-of-care tests, in our view, are not helpful in defining who is "aspirin resistant" and who is not.

CONCLUSION

Aspirin is a remarkable drug that reduces cardiovascular events and limits atherogenesis and perhaps development. This drug works through a host of mechanisms which are complementary to its platelet inhibitory effect. As such, use of the term "aspirin resistance" based on imperfect test-tube measurements is a disservice to the legacy of this very useful compound.

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REVIEW

Hypertrophic cardiomyopathy and sudden cardiac death

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Abstract

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiovascular disease that affects the left ventricle. HCM can appear at any age, with the majority of the patients remaining clinically stable. When patients complain of symptoms, these include: dyspnea, dizziness, syncope and angina. HCM can lead to sudden cardiac death (SCD), mainly due to ventricular tachyarrhythmia or ventricular tachycardia. High-risk patients benefit from implantable cardioverter-defibrillators. Left ventricular outflow tract obstruction is not a rare feature in HCM, especially in symptomatic patients, and procedures that abolish that obstruction provide positive and consistent results that can improve long-term survival. HCM is the most common cause of sudden death in young competitive athletes and preparticipation screening programs have to be implemented to avoid these tragic fatalities. The structure of these programs is a matter of large debate. Worldwide registries are necessary to identify the full extent of HCM-related SCD.

GENETICS

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease[1] and is associated with sudden death, especially in young adults[1-3]. For that reason, HCM constitutes a vast domain of clinical and experimental research and thousands of reports have been published in the international literature. HCM is defined as the presence of a hypertrophied, non-dilated left ventricle that occurs in the absence of another cardiac or systemic disease that could produce a similar degree of hypertrophy[2,4-6]. HCM is a relatively common, primary heart disease that affects one individual in every 500 in the general population[3,7]. It is inherited predominantly as a an autosomal dominant trait[1,8]. At least 24 genes have been associated with HCM and over 400 mutations have been discovered to date[9-14]. Although the majority of these genes encode sarcomeric proteins[1,6,15], recent research has indicated that some disease patterns might involve different pathways[9,16].

Genome studies that have identified new loci or pathways have indicated that there is long way ahead to un-

derstand completely the etiology of HCM[16-18]. These studies have basically followed two research approaches: (1) beginning from a mutation phenotype and advancing towards the identification of the mutated gene (forward genetics); and (2) beginning from a cloned DNA segment or a peptide sequence, they have introduced programmed mutations that aim to assess gene and protein function (reverse genetics)[19-23]. The mutations of any particular gene might lead to different phenotypic expressions as well as different disease time courses[1,6]. Furthermore, specific genes have been associated with favorable or unfavorable prognosis[6,8,9]. Some studies have managed to correlate septal morphology in HCM with a specific genotype[24,25], thus providing echocardiographic guidance to genetic screening. However, the phenotypic expression of HCM is further complicated by the existence of possible modifier genes or environmental factors[3,26]. Therefore, although promising, this discovery has a long way to go before its full implementation in screening protocols[27,28]. In addition, there is a possibility that genes implicated in ion channel abnormalities play a significant role in cardiomyopathy *via* a common pathway, or the possibility that genes that encode the same family of proteins might be implicated in different pathologies (such as HCM and arrhythmogenic right ventricular cardiomyopathy)[8]. For the moment, genetic screening can identify a mutation in 50%-60% of patients [29]. Additional factors or genetic loci remain to be discovered.

PATHOPHYSIOLOGY

Cellular changes

In the healthy myocardium, myocytes have a typical parallel alignment, however, in HCM they become hypertrophied, enlarged and distorted, which leads to disorientation of adjacent cells and arrangement in a random pattern (myocyte disarray). This disarray might be localized and surrounded by normal myocardium or it can occupy the majority of the ventricular surface. Pathological myocyte morphology leads to premature cellular death and continuous myocardial tissue remodeling, with the participation of cardiac fibroblasts. Furthermore, increased depositions of collagen are observed between the smooth muscle cells of the intramural coronary arteries[2,3,30].

Structural changes

Changes in myocyte architecture lead to ventricular hypertrophy, and the development of fibroblasts between myocytes results in fibrosis and extensive myocardial scarring. Collagen accumulation leads to thickened and narrowed intramural coronary artery walls[3,6,31].

Clinical pathophysiology

The aforementioned cellular and structural changes have major functional consequences, such as ventricular stiffness and reduced ventricular compliance, which in turn can lead to prolonged relaxation times that result in diastolic filling impairment and reduced cardiac output with increased filling pressure. Myocardial ischemia also develops, and combined with the increased muscle mass, has a potent ischemic effect[6,31].

Hypertrophy, fibrosis, myocardial ischemia and abnormal intramural coronary arteries can exist separately or simultaneously in HCM. Therefore, the resultant scarred myocardial tissue is an unfavorable substrate for both conduction and propagation of electrical impulses. Myocardium in HCM comprises zones of normal myocytes adjacent to or embedded in scar tissue, which decelerates or interrupts conduction. In addition, dispersion of repolarization occurs because of abnormalities in gap junction function and distribution. Furthermore, both left ventricular (LV) relaxation and contraction might not be uniform, because of the varied distribution of LV hypertrophy (LVH)[32]. These malfunctions lead to multiple asynchronized electrical impulses traversing the myocardium, and through reentry mechanisms, to ventricular tachyarrhythmia[10,32-35]. Of course, supraventricular arrhythmias are also frequent in this setting (10%-40% in HCM)[31,36,37]. In fact, atrial fibrillation (AF) is the most common sustained arrhythmia in HCM[1].

The increased ventricular wall stress, as in cases of LV outflow tract obstruction (LVOTO), can lead to increased oxygen demand, cell death and replacement fibrosis[3]. The elevated filling pressure might also result in subendocardial ischemia, and systolic compression of arteries can also occur. In addition, the disturbed reflex control of the vasculature is an important cause of myocardial ischemia, especially during exercise, where inappropriate hypotension occurs and results in myocardial hypoperfusion[6,31].

It is estimated that approximately 25% of the patients with HCM have LVOTO under resting conditions[38,39]. This mechanical impedance[39,40] creates outflow gradients of > 30 mmHg[41]. In HCM, outflow gradients are characteristically dynamic. This means that any given patient might present a large outflow gradient in some circumstances, but a reduced gradient in others (e.g. exercise, valsalva maneuver, or sudden standing from a squatting position)[1,6].

Until recently, clinical assessment and identification of LVOTO were undertaken in resting conditions to determine the obstructive form of HCM and commence further treatment. In 2003, the American College of Cardiology and the European Society of Cardiology, in their consensus document on HCM, proposed a division of the overall HCM disease spectrum into hemodynamic subgroups, (based on the representative peak instantaneous gradient as assessed with continuous wave Doppler) to facilitate decision making in treatment and to detect latent forms of LVOTO[3]. There are now indications that LVOTO is a more common feature in most patients with HCM (up to 70%) under exercise conditions. These observations could have clinical implications for both the evaluation and management of patients with HCM, especially whether subaortic gradients should be assessed in all patients[31,42].

NATURAL HISTORY

HCM is a disease that can appear at any age, from infancy to very old age, with a varied clinical course. Most patients remain clinically stable or asymptomatic, and in some cases, their symptoms might even improve over the course of time[1]. HCM has an annual mortality rate of 1%. Clinical deterioration is usually slow and elderly patients (> 75 years) can constitute up to 25% of the total patients[1,3]. The disease course might follow a specific subgroup pattern or interchange between patterns. It is estimated that about 5% of the patients among the vast HCM spectrum evolve towards the end-stage phase of the disease, which is LV wall thinning (extensive fibrosis), cavity dilatation and systolic impairment[1,29,43]. However, the most common mode of demise in HCM and its most serious complication is sudden death[1,6].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms

Many patients with HCM can be completely asymptomatic. Symptomatic patients present commonly with symptoms associated with LVOTO. Dyspnea can be encountered in 90% of symptomatic patients[1,6]. Fatigue, dyspnea, exercise intolerance, dizziness, presyncope and syncope are also common. An important etiological factor for syncope or palpitations is cardiac arrhythmia. Patients with HCM might present with AF, premature ventricular depolarization, ventricular couplets, non-sustained ventricular tachycardia (VT), or sustained VT, which can deteriorate to ventricular fibrillation (VF). However, it should be noted that there is no particular course of progress (or deterioration) of arrhythmic events in HCM, and that patients with minor previous arrhythmic events might suffer VF cardiac arrest[10]. Congestive heart failure can be manifested with palpitations and/or paroxysmal nocturnal dyspnea. Chest pain (angina pectoris) can be experienced in 75% of symptomatic patients. It is attributed to the imbalance between oxygen supply and demand, pathological intramural coronary arteries, and increased LV wall pressure. Another contributing factor for myocardial ischemia could be pre-existent atheromatous disease in older patients. The severity of these symptoms, which are affected by many factors such as exertion or even dietary factors such as alcohol consumption, or a heavy meal, can change throughout the day[1,26]. Unfortunately, sudden death might be the first and only manifestation of HCM.

Physical examination

Physical examination can be normal in asymptomatic patients. In the presence of LVOTO, precordial examination might reveal a hyperdynamic apical precordial impulse, or a double apical impulse as a result of LV forceful contraction. A less common feature is a triple apical beat that occurs secondary to the addition of a palpable atrial gallop[37]. Carotid artery palpation can reveal a brisk rise in the pulse, with subsequent decline in mid-systole, followed by a secondary rise in late systole in cases of LVOTO[6,37]. In auscultation, S_1 is normal, but an S_4 can be heard during atrial systole. In patients with severe LVOTO, paradoxical S_2 splitting might be noted[37]. Auscultation can also reveal a harsh crescendo-decrescendo characteristic systolic murmur in patients with outflow obstruction. It usually starts after S_1 and can be heard from the apex until the sternal notch. Although characteristic of HCM, this murmur is not found in the majority of patients[37].

Physical examination should not be oriented only towards the cardiovascular system. For example, a hypertrophied left ventricle might also be encountered in genetic syndromes such as Fabry disease, or LEOPARD Syndrome. Sensorineuronal deafness, and eye and skin disorders should be carefully assessed with explicit attention, to make the diagnosis of HCM from other pathological entities[44,45].

Electrocardiographic manifestations

The majority of patients with HCM have abnormal electrocardiographic (ECG) patterns[37], which can be present even in cases in which hypertrophy is not yet echocardiographically detectable[26,46] as in adults with cardiac myosin-binding protein C mutations[30,47], which means that it is a helpful diagnostic tool in these cases. The most common abnormalities are ST segment and T-wave changes and large QRS complexes, which are evidence of LVH[3,48]. Deep, narrow Q-waves are present in 20-50% of cases, and involve inferior (Ⅱ, Ⅲ, aVF) and lateral leads (Ⅰ, aVL, V_5, V_6)[26]. High-voltage R-waves might also be present in the precordial leads[26,49]. Although QRS, ST and T-wave changes are the most common in HCM, Q-wave changes are more characteristic and should be given proper attention when encountered[37]. However, all these different ECG patterns can neither be accurately related to the degree of LVH nor predict HCM-related death[1,50].

Diagnosis

Marked ECG abnormalities, exertion fatigue, presyncopal events, dyspnea or palpitations of recent onset or discovery of a murmur in a routine evaluation should raise suspicion of HCM. Diagnosis is customarily made with 2D echocardiography or magnetic resonance imaging (MRI) when ultrasound studies are technically inadequate or segmental LV wall thickening is difficult to visualize with ultrasound[1,51-54]. Furthermore, MRI might play a significant role in the future in the evaluation of patients with HCM, because it can reliably estimate the degree of LVH[52] and the existence of intramural coronary arteriole dysplasia[53]. Furthermore, MRI with late gadolinium enhancement can detect early structural changes at the microvascular level, thus providing not only a helpful tool of significant diagnostic and prognostic importance, but also a means that could promote early intervention in the disease course[55,56].

HCM diagnosis is established by the identification of a hypertrophied and non-dilated left ventricle in the absence of other cardiovascular diseases that are capable of producing a similar magnitude of hypertrophy[1,3,4,54]. With normal wall thickness estimated at no more than 12 mm, echocardiography might reveal cases that range from mild hypertrophy (13-15 mm) to massive (> 30 mm) or even more extensive hypertrophy[48,57,58]. Usually echocardiography will also reveal some of the following features: small LV cavity, reduced septal motion, mitral valve prolapse or a hypokinetic septum.

SUDDEN CARDIAC DEATH IN HCM

Mechanisms of sudden cardiac death

LVOTO, myocardial ischemia and changes in vascular architecture play a significant role in sudden cardiac death (SCD), with a varied impact. A bimodal pattern in the circadian variability of SCD has been observed, with a distinctive peak in the early morning hours and a second, less prominent peak in the early evening. Recent studies, however, after the implementation of implantable cardioverter-defibrillators (ICDs), have reported a modest but significant increase in appropriate ICD interventions between noon to midnight, which indicates that there is a disparity in circadian variability of SCD in HCM patients[59,60]. These studies also suggest that ventricular tachyarrhythmia and/or VT is the most probable mechanism of SCD in HCM. SCD in HCM is rarely due to bradyarrhythmia (when the conduction system is infiltrated)[1,29,61].

Sudden death is the major and frequently the only complication of HCM. In fact, HCM is the most common cause of SCD in young people including competitive athletes[3,62]. Although adolescents and adults younger than 35 years of age show a high incidence of SCD, this does not mean that the other age groups are risk-free. SCD can occur during any kind of activity, from sleep to very severe exercise[2]. SCD has been reported to affect as much as 6% of the patients in selected cohorts from tertiary centers[3,40,63].

Risk stratification

Identification of HCM patients at high-risk for SCD is an important as well as difficult task, given the fact that SCD is a devastating complication, and many of these patients might have no symptoms at all before the fatal outcome. The heterogeneity of clinical expression of the disease has made the identification of a single prognostic index difficult. However, several observational studies[3,40,48,57,64-66] have managed to distinguish features of the disease that are indicative of a higher SCD risk. These risk factors have been categorized as "major" and "possible in individual patients" by successive consensus documents from the American College of Cardiologists, the American Heart Association and the European Society of Cardiology (Table 1)[3,67].

Table 1 Risk factors for sudden cardiac death in hypertrophic cardiomyopathy

Major risk factors	Possible in individual patients
Cardiac arrest (VF)	AF
Spontaneous sustained VT	Myocardial ischemia
Family history of premature sudden death	LVOTO
Unexplained syncope	High-risk mutation
LV thickness ⩾ 30 mm	Intense (competitive)
Abnormal exercise BP	physical exertion
Non-sustained spontaneous VT	

VF: Ventricular fibrillation; VT: Ventricular tachycardia; BP: Blood pressure; LV: Left ventricular; AF: Atrial fibrillation; LVOTO: Left ventricular outflow tract obstruction.

Genetic testing might play a role in HCM risk stratification in the future, but for the time being, it is bound by many limitations, such as the vast phenotypic variations of specific gene mutations, and the fact that it is a method restricted to research laboratories and not available to every day evaluation. In addition, the prevalence of identifiable mutations in HCM has reached only 60% of studied cohorts, which leaves more than a third of the patients with genetically unexplained disease[4,8,68,69]. Nevertheless, there are indications that genotype-phenotype associations can be established in HCM (mutations in cardiac myosin-binding protein C have a rather benign course, and prognosis in patients with β-myosin chain mutations is allele dependent and varies considerably)[8,9,11,15]. Finally, genetic analysis could be helpful in families with HCM, by providing a presymptomatic diagnosis and genetic counseling.

Many of the aforementioned risk factors are interdependent and the positive predictive value of each one individually is limited. Thus, multiple risk-factor estimation could lead to a better prediction of risk of SCD. In contrast, their high negative predictive values can be safely used as an estimate for favorable prognosis[31,48,67,70].

Role of electrophysiological studies

Induction of ventricular tachyarrhythmia by programmed ventricular stimulation is of limited value and does not offer any advantage over noninvasive risk stratification in HCM[10,67,71]. Even if invasive testing has not been abandoned, other methods are being studied, such as paced electrogram fractionation analysis (which might be able to detect patients at risk of VF)[72], but are still far from having an established value in risk stratification for SCD.

MANAGEMENT OF HCM AND PREVENTION OF SCD

Patient assessment

In a patient with HCM, routine examination should comprise personal and family history, physical examination, 12-lead ECG, 24-h Holter ECG, 2D echocardiography,

and exercise testing. Risk analysis should not be forgotten and should be performed based on the clinical situation. These patients should not participate in competitive sports. Intense exertion and other strenuous physical activities should be avoided[1,10,29]. However, these patients should not refrain from all physical activities. Asymptomatic patients with no LVOTO, no risks for SCD, and mild LVH can participate in recreational sports of mild to moderate intensity [73,74]. When a patient is diagnosed with HCM, first-degree relatives should be examined by ECG and echocardiography and clinical screening should be undertaken every 2 years in young relatives and about every 5 years in adults[10,29].

The wide range of phenotypic expressions of HCM and its possible devastating complications, especially in young asymptomatic populations, have created great concern and debate about how to prevent SCD. In 2006, the American College of Cardiologists, the American Heart Association and the European Society of Cardiology released new guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[67]. In this document, the role of ICDs in the prevention of SCD is primary, in contrast to the role of pharmacological treatment and electrophysiological testing. ICD therapy is strongly warranted (class I indication, level of evidence: B), as secondary prevention for SCD, for patients with HCM who have sustained VT and/or VF (prior cardiac arrest). ICD implantation is recommended as a reasonable procedure (class Ⅱa) for primary prophylaxis in patients with HCM who have one or more major risk factors. Nevertheless, since the positive predictive value of each individual risk factor for SCD is limited, caution has to be taken in not implanting ICDs in patients who do not need them, and putting them in danger from complications from the procedure. Thus, multiple risk factors are considered to offer a greater possibility of SCD[3,29,54,67]. However, data from a large multicenter registry study from ICDs implanted over a 17-year period have indicated that there was no significant difference in the probability of appropriate ICD discharges between patients with 1, 2, 3 or more noninvasive risk factors[75]. The matter of ICD implantation for primary prophylaxis needs further clarification. A possible logical approach would be that management approaches should be based on assessment of each patient's overall clinical profile[31,75]. There is a debate whether all ventricular arrhythmias occurring in non-ischemic cardiomyopathies are truly potentially fatal, or the majority of them are self-limited, thus making ICD implantation potentially harmful[75,76]. Nevertheless, data are strongly in favor of ICD implantation in selected patients. ICDs provide highly effective discharges, even in primary prevention of SCD in HCM[10,75,77,78], significantly reduce mortality[78], improve long-term survival, and increase quality-adjusted life expectancy[79,80].

Pharmacological therapy has little place in prevention of SCD in HCM. Amiodarone is the agent indicated because of its antiarrhythmic properties. Amiodarone can be used in patients with a history of sustained VT and/or VF (class Ⅱa), and can be considered (class Ⅱb recommendation) for primary prophylaxis for SCD in patients with one or more major risk factors for SCD, if ICD implantation is not feasible[67]. Furthermore, there is strong evidence of ineffectiveness of Amiodarone in preventing SCD in HCM, as indicated by several studies and the high incidence of appropriate ICD discharges in patients receiving amiodarone[75,81,82].

HCM pharmacological management is symptom-based. Patients with obstructive symptoms or heart failure are treated with β-blockers or calcium channel antagonists (principally verapamil). Reduced heart rate and decreased contractility resulting from their action, might alleviate symptoms related to LVOTO, such as presyncope, dyspnea, and angina. Both agents improve diastolic filling (by reducing the heart rate and improving relaxation, respectively) and can decrease the outflow gradient[1,3,54]. Disopyramide has also been used, probably for its depressing action on ventricular systolic performance[83].

The group of patients (5%) that progress to the end-stage phase of HCM should be treated for heart failure with the progressive addition of diuretics, ACE inhibitors and possibly digitalis. The final therapy point might be heart transplantation[1,3,54,84]. In cases that are unresponsive to drugs, septal surgical myectomy or percutaneous alcohol septal ablation (ASA) should be performed. Through a transaortic approach, myectomy is performed by excising a portion of the hypertrophied muscle. ASA creates a transmural scar in the proximal hypertrophied ventricular septum, by delivering alcohol through an angioplasty catheter, which reduces the outflow gradient[85]. Both interventions have been proven to be equally effective at reducing outflow obstruction[86], which results in substantial and consistent symptomatic benefit, and restoration of quality of life throughout long-term follow-up[87-89]. Furthermore, both techniques appear to have a comparable risk for procedural death and complications[90]. ASA creates a sizeable transmural myocardial infarction that comprises about 10% of the left ventricle, which could serve as a substrate for potentially life-threatening ventricular tachyarrhythmias and sudden death[90]. Hence in 2003, an expert consensus panel from the American College of Cardiology and the European Society of Cardiology suggested surgical myectomy as the primary treatment for patients with obstructive HCM and unrelenting symptoms, with ASA reserved as an alternative option for those patients who are judged not to be appropriate surgical candidates[3]. However, there is emerging evidence that ASA might not affect the occurrence of arrhythmic episodes[91,92]. It should be noted in this context that large cohort studies[93-96] have demonstrated an association between LVOTO abolition and improvement of overall survival. Furthermore, there are indications that myectomy is beneficial before ICD implantation[97]. These observations along with more careful diagnostic processes will probably change our view of HCM as a progressive heart muscle disorder with continued LV remodeling, despite the best available treatment interventions[3].

AF, a common feature in HCM, is associated with embolism, heart failure and is independently associated with heart-failure-related death and stroke[36,98]. Anticoagulant therapy with warfarin is warranted in patients with AF[79]. Amiodarone can be effectively used in paroxysmal AF[1,3,54].

Future therapeutic strategies

Recent research has unraveled the role of protein kinases in the regulation of myocyte repair, growth, contractility and myogenic differentiation. Furthermore, histone deacetylases (HDACs) seem to play a regulatory role in hypertrophic cardiac growth, in association with protein kinases[99-103]. Even if there is no clinical impact for the present, HDAC inhibitors, specific kinase-inhibitors in association with targeted gene therapy are expected to play a central role in the future.

Prevention of SCD in athletes

Sports participation increases the risk of SCD in HCM patients[1,62]. HCM is the single most common cause of young athlete mortality in the United States[104]. Therefore, attention has focused on development of preparticipation screening strategies on both sides of the Atlantic[104,105]. However, a major determinant in all prevention strategies is cost-effectiveness and that is a major issue of debate in the current literature of sports-related SCD prevention in patients with HCM. Thus, based on the Italian experience[106,107] of preparticipation screening of young competitive athletes, the European Society of Cardiology recommends a preparticipation screening strategy that comprises family and personal history, physical examination, and 12-lead ECG[105]. In contrast, the American Heart Association focuses on medical history (family and personal) and physical examination[104]. Recent data from the United States suggest that, in demographically similar regions of the United States and Italy, athlete sudden death rates have not differed significantly in recent years, despite different preparticipation screening strategies[108]. Nevertheless, it is a fact that preparticipation screening followed in Italy has given surprising and most importantly, life-saving results[105-107,109]. Both programs seem to be effective. However, it is probably more important to establish a worldwide registry that is aimed at determining the precise incidence of sudden death in young athletes than to further pursue a debate founded at different starting points.

CONCLUSION

The diagnosis of HCM has to be founded on a concrete basis and should not be confused with other syndromes with LVH. In this context,genetic testing will probably play a more significant role in the future. HCM course and gravity seems to be closely related to LVOTO. Procedures that abolish this obstruction are beneficial and improve survival, and their role could become more central provided that a solid diagnostic procedure is followed. Although unpredictable, HCM is a disease with symptoms that are amenable to treatment, and newer diagnostic strategies and interventions will hopefully prove helpful in preventing more sudden deaths. As for the sports-related deaths, certainly the implementation of preparticipation screening programs is indispensable. The proper strategy has yet to be elucidated. Additional attention should probably be paid to equipping public places and stadia with automated external defibrillators and implementing wide lay training programs.

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BRIEF ARTICLE

Comparative analysis of the predictive power of different endothelial progenitor cell phenotypes on cardiovascular outcome

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Abstract

AIM: To compare the predictive power of different endothelial progenitor cell (EPC) phenotypic markers for future cardiovascular events.

METHODS: Peripheral blood was collected from 76 consecutive patients with acute coronary syndromes (ACS) who underwent percutaneous coronary intervention in our institute. The various EPC phenotypes of peripheral blood mononuclear cells were CD34+CD133+, CD34+KDR+, and CD 133+KDR+. The outcome endpoint included cardiovascular mortality, recurrent ACS, and hospitalization for decompensated heart failure during a 24-mo follow-up period.

RESULTS: CD34+CD133+ cells (P = 0.034), but not CD34+KDR+ (P = 0.35) or CD 133+KDR+ cells (P = 0.19), were found to predict recurrent ACS. We found no correlation between EPCs measured by any of the three phenotypic combinations of accepted CD markers and the total combination of these separate outcomes.

CONCLUSION: The EPC CD34+CD133+ phenotype, but not the CD34+KDR+ or the CD 133+KDR+ phenotypes, is predictive of future adverse cardiovascular outcomes.

Key words: Stem cells; Endothelial progenitor cells; Acute coronary syndrome; Biomarkers

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INTRODUCTION

Endothelial progenitor cells (EPCs) are a scarce population of bone-derived cells that can play an important role in neoangiogenesis after tissue ischemia has occurred[1,2]. EPCs are positive for CD34 or the more immature mark-

er protein CD133. Recent studies have shown that expression of the CD34 surface antigen is shared by EPCs, hematopoietic progenitor cells, as well as mature endothelial cells[3].

As they mature, EPCs lose the CD133 marker and acquire vascular endothelial growth factor (VEGF) receptor-2, also known as KDR[4-6]. Circulating numbers of EPCs correlate negatively with risk factors for atherosclerosis and with disorders associated with vascular dysfunction[7-9]. In acute coronary syndrome (ACS) patients, there appears to be a trend toward an elevated number of EPCs, suggesting that these cells are possibly mobilized in an attempt to participate in vessel repair after severe ischemia[10-12].

While there is strong evidence to link a reduced number of EPCs to cardiovascular risk factors or disorders, the relationship between levels of EPCs and cardiovascular outcomes is not clear. A recently published large prospective observational study in patients with stable coronary artery disease (CAD) confirmed by angiography showed that a low number of circulating CD34+KDR+ EPCs is associated with a significantly higher risk of death from cardiovascular disease, a first major cardiovascular event, revascularization and hospitalization in comparison to patients with high EPC numbers. However, no significant association was detected between EPC levels and acute myocardial infarction (MI) and death from any cause[13].

Similarly, Schmidt-Lucke *et al*[14] found, in a mixed population of patients with CAD and healthy individuals, that reduced numbers of EPCs, also characterized by fluorescence-activated cell sorting (FACS) analysis as CD34+KDR+ EPCs, were a significant independent predictor of adverse cardiovascular events over a median follow-up period of 10 mo.

Although attractive, a major obstacle in incorporating FACS analysis of EPCs as a practical biomarker in cardiovascular risk assessment is the lack of fully corroborated and mutually comparative methods for characterizing the putative EPCs[6,15]. Thus, different investigators employ different FACS marker combinations for assessment of EPCs: CD34+KDR+[16,17], CD34+133+[18] or CD34+CD133+KDR+[5]. Both KDR- and CD133-positive cells were shown to differentiate into endothelial cells and were thus suggested as identifying membrane antigens[6].

The purpose of this study was to compare the predictive power of different EPC populations with regard to future adverse cardiovascular events in patients with ACS undergoing coronary angiography.

MATERIALS AND METHODS

Study subjects

We studied a total of 76 consecutive patients with ACS (33 patients had ST-elevation MI, 43 had non-ST-elevation MI), who underwent coronary angiography in our institution. There were 53 males and 23 females, aged 42-86 years (median, 68 years). Table 1 summarizes the demographic and clinical characteristics of the patient population. The institutional ethics committee approved the study and informed consent was obtained from all patients.

Table 1 Baseline characteristics of the patient population and drug treatment *n* (%)

Characteristics	*n* = 76
Demographic data	
Male/female	53 (70)/23 (30)
Median age (range, yr)	69 (42-86)
Current smoker	35 (46)
Comorbidities	
Hypertension	48 (63)
Diabetes mellitus	20 (26)
Hyperlipidemia	39 (51)
Peripheral vascular disease	4 (5.3)
CVA/TIA	5 (6.3)
Drug treatment	
Statin	71 (93.4)
Beta blocker	71 (93.4)
ACEI/ARB	75 (99)
Spironolactone	40 (69)
Diuretics	9 (12)
CCBs	5 (6.6)
Nitrates	12 (16)

CVA: Cardiovascular accident; TIA: Transient ischemic attack; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker.

Preparation of blood samples

Blood samples were drawn immediately after insertion of a femoral sheath. Peripheral blood mononuclear cells (PBMNCs) were isolated from 30 mL of freshly drawn heparinized blood using Isopaque-Ficoll (Amersham Biosciences, Buckinghamshire, United Kingdom) gradient centrifugation.

Flow cytometry evaluation

The number of circulating EPC was assessed by FACS analysis by staining 5 million cells for three-color FACS analysis employing the following monoclonal antibodies: fluorescein isothiocyanate-anti-CD34 (IQ products), allophycocyanin-anti VEGF-receptor 2 (KDR, R&D systems) and phycoerythrin-anti-CD133 (R&D systems). The various EPC phenotypes assessed were CD34+CD133+, CD34+KDR+, and CD 133+KDR+.

Follow-up

Information on vital status, reinfarction, recurrent percutaneous coronary intervention, and cardiovascular events was collected using hospital records and telephone interviews. Telephone follow-up each 6 mo was performed for a maximum period of 40 mo. The outcomes censored were either a recurrent ACS event (MI or unstable angina) or mortality, and hospitalization due to acute decompensated heart failure.

Table 2 Different endothelial progenitor cell combinations stratified by outcomes *n* (%)

	Total mortality	Recurrent UA/MI	ADHF	Any MACE
CD34+CD133+ = 0 (*n* = 7)	1 (14.3)	7 (100)	1 (14.3)	7 (100)
CD34+CD133+ > 0 (*n* = 69)	6 (8.7)	43 (62.3)	12 (17.4)	47 (68.1)
CD34+KDR+ = 0 (*n* = 57)	6 (10.5)	40 (70.2)	11 (19.3)	43 (75.4)
CD34+KDR+ > 0 (*n* = 17)	1 (5.3)	10 (52.6)	2 (10.5)	11 (57.9)
CD133+KDR+ = 0 (*n* = 57)	6 (10.5)	41 (71.9)	12 (21.1)	44 (77.2)
CD133+KDR+ > 0 (*n* = 19)	1 (5.3)	9 (47.4)	1 (5.3)	10 (52.6)

UA: Unstable angina; MI: Myocardial infarction; ADHF: Acute decompensated heart failure; MACE: Major adverse cardiac event.

Statistical analysis

All data were summarized and displayed as mean and standard deviation for the continuous variables and as the number of patients and percentage in each group for categorical variables.

Because of the relatively small number of patients and outcome events, and the relatively long follow-up period, the comparison of the rate of events for each outcome between the groups according to EPC phenotype combination categories was performed by log-rank statistics with the Kaplan-Meier estimate.

For a sample of 80 patients, in order to detect a survival difference from 70% to 90% with $\alpha = 0.05$ at the end of the study, we calculated a power $(1 - \beta)$ of 60%.

In order to evaluate the performance of classification schemes of the different variables and to compare the classification of the different outcome measures, we used a receiver operated characteristic curve analysis. We calculated the area under the curve to compare the classifiers and the asymptotic statistical significance to reject the hypothesis that the curve is similar to the reference line, which is a random classifier.

All above analyses were considered significant at $P < 0.05$ (two-tailed). The SPSS statistical package was used to perform all statistical evaluations (SSPS Inc., Chicago, IL, USA).

RESULTS

Table 2 shows various EPC combinations stratified by the events censored [total major adverse cardiac event (MACE) or secondary outcomes]. Since the relative EPC numbers were small (0%-0.1% of PBMNCs) and in most cases equal to zero, we chose a binary method of value report, whereby EPCs were categorized as either 0 if non-measurable or 1 if greater than zero. The correlations between the various EPC phenotypes and MACE-free or ACS-free survival are shown in Figures 1-3. We found that recurrent ACS was predicted significantly by the CD34+CD133+ combination ($P = 0.034$; Figures 2 and 3), but not by the CD34+KDR+ ($P = 0.35$) or by the CD133+KDR+ ($P = 0.19$) combinations (Figure 1). However, this positive correlation was found to be relatively weak (area under curve = 0.65).

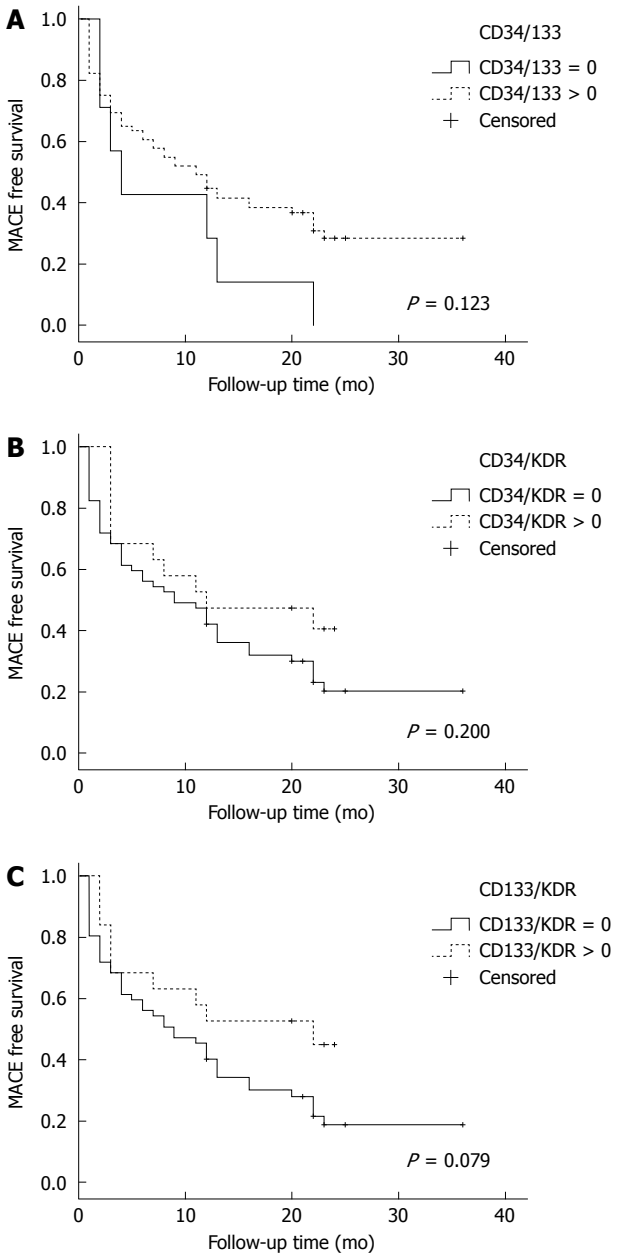

Figure 1 Kaplan-Meier survival chart for the outcome of total major adverse cardiac event stratified by positive (dashed line) and negative (solid line) fluorescence-activated cell sorting analysis. A: CD34+CD133+ cells; B: CD34+KDR+; C: CD133+KDR+. MACE: Major adverse cardiac event.

We did not find any significant correlation between the various EPC combinations and total MACE (Figure 3).

DISCUSSION

The factors regulating EPC numbers in acute MI include VEGF[19], interleukin-8[20] and stromal cell-derived factor-1[21]. However, one of the major limitations in studying EPCs is the lack of unifying phenotypic markers that are employed by different investigators. Indeed, the surface marker profile changes during the process of mobilization and maturation. For example, CD34-133+ progenitors differentiate into CD34+133+ EPCs that

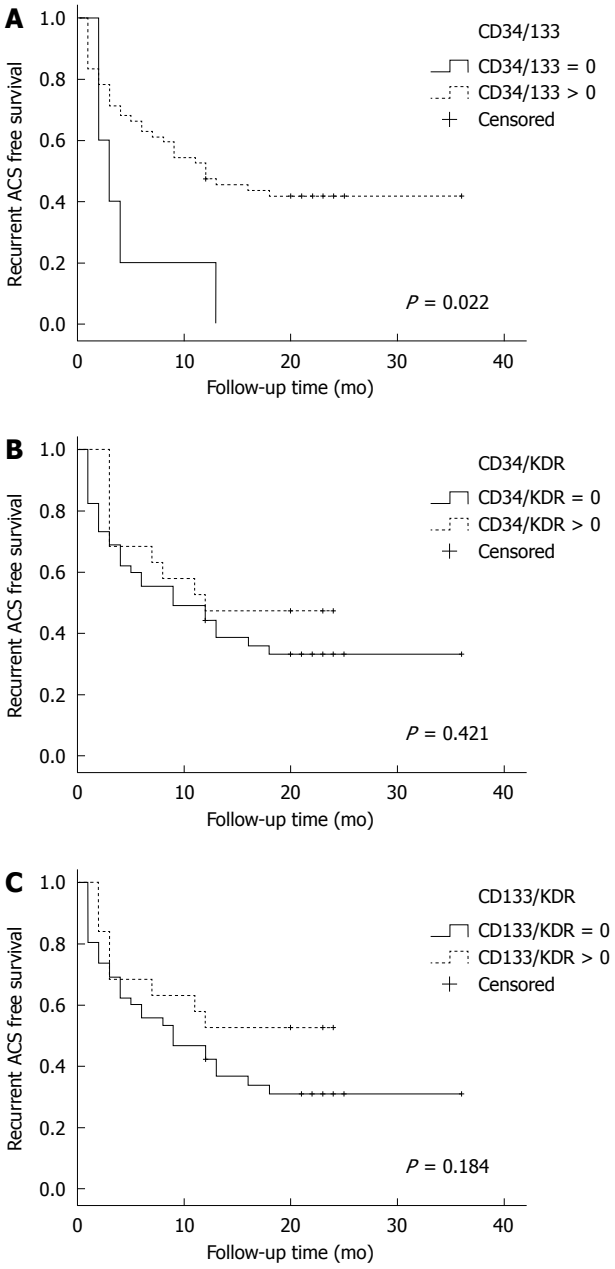

Figure 2 Kaplan-Meier event free survival for the secondary endpoint of acute coronary syndrome (recurrent myocardial infarction or unstable angina) stratified by patients with positive fluorescence-activated cell sorting analysis (dashed line) *vs* patients with negative fluorescence-activated cell sorting analysis (solid line). A: CD34+CD133+ cells; B: CD34+KDR+; C: CD133+KDR+. ACS: Acute coronary syndrome.

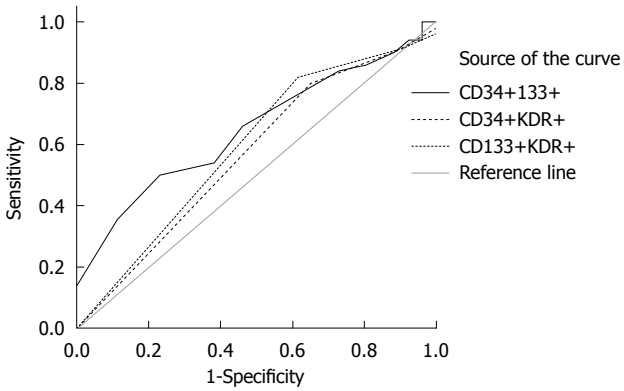

Figure 3 Receiver operating characteristics curve analysis for the endpoint of acute coronary syndrome (recurrent myocardial infarction or unstable angina) as a function of the various endothelial progenitor cell populations. Only CD34+133+ correlated significantly with this outcome ($P = 0.034$); the *P*-value for CD34+KDR+ was 0.35 and for CD133+KDR+ was 0.19).

possess more pronounced angiogenic properties[22]. This leads to confounding results and an inability to perform cross-sectional comparative analyses between different studies.

There are two reports in which circulating EPC were shown to predict outcome in patients with ACS[13,14]. However, both studies were performed in different populations of patients and both used a single phenotype in FACS analysis (CD34+KDR+ cells). We have previously shown that different methods used to assess EPC in humans are not correlated[15]. Thus, it is of interest to assess the relative outcome predictive power of different phenotypic combinations in patients with ACS.

Herein, we failed to detect a significant association between EPCs measured by any of three phenotypic combinations of accepted CD markers and total MACE according to the log-rank statistics with the Kaplan-Meier method. In line with previous studies[13,14], however, we found that a lower number of EPCs (defined as CD34+CD133+) was predictive of recurrent ACS in the population we studied. However, CD34+KDR+ EPCs tested in the aforementioned studies were not found to associate with recurrent ACS or MACE in our study. The apparent discrepancy between our study, showing that CD34+CD133+ but not CD34+KDR+, exhibited a predictive value on outcome in ACS patients could be partially attributed to the negligible number of CD34+KDR+ EPCs in blood samples and the relatively small number of patients. Furthermore, EPC numbers assessed by FACS analysis are extremely low and therefore interobserver variability in assessing their quantity is considerable. We thus chose to differentiate ACS subjects as those having detectable and non-detectable numbers of EPCs. We believe that this approach partially overcomes the inherent need for subjective gating in the FACS analysis that may influence the results and limits potential error stemming from the fact that the numbers of CD34+CD133+ EPCs were considerably higher than those of CD34+KDR+ and CD 133+KDR+.

Why would CD34+CD133+ EPCs be more reflective of a recurrent ACS event than other markers? A low number of EPCs may be associated with a compromised ability to form new blood vessels and restore endothelial integrity by vasculogenesis. An intact vasculogenic process may be required to preserve endothelial function and thus prevent plaque rupture with subsequent progression towards ACS. In recent years, it has become apparent that the most important mechanism by which EPCs promote angiogenesis and vasculogenesis is by paracrine secretion of proangiogenic cytokines. As EPCs become committed

to the endothelial lineage, they lose CD133 and acquire KDR and this transition is associated with phenotypic properties more closely related to a mature endothelium but a reduced paracrine capacity. The early EPCs (CD34+CD133+) therefore are probably more potent in elaborating a panel of proangiogenic and vasculogenic cytokines as compared to the more mature EPCs. According to this hypothesis, early EPCs are more powerful in their ability to preserve endothelial integrity and thus prevent stent thrombosis and plaque rupture both of which result in recurrent ACS. Indeed, our findings support the notion that a reduced number of early rather than mature EPCs is predictive of recurrent ACS.

In summary, we have found that in the setting of ACS, circulating CD34+CD133+ EPCs are potentially prognostic of cardiovascular outcome. Further studies in larger numbers of patients are needed in order to establish the feasibility of using certain EPC populations as potential biomarkers of cardiovascular events. Confirmation of the CD34+CD133+ phenotype combination as a significant adverse biomarker in ACS would then engender further research into the putative mechanism, and is likely to enhance our understanding of the role of this ambiguous population of hematopoietic progenitor cells in post-ischemic vasculogenesis.

COMMENTS

Background

Precise phenotypic definition of endothelial progenitor cells (EPCs) is currently controversial and relates to different maturation stages of these cells. Scattered reports in the literature found an association between low levels of EPCs as defined by CD34 and KDR membrane antigen markers and adverse cardiovascular events, but the applicability of these findings to other phenotypic definitions of these cells is unknown.

Research frontiers

To compare the predictive power of different EPC populations with regard to future adverse cardiovascular events in patients with acute coronary syndrome (ACS) undergoing coronary angiography.

Innovations and breakthroughs

Given the controversy pertaining to the precise EPC phenotype definition, we sought to evaluate the cardiovascular outcome predictive value of several accepted antigen marker combinations of EPCs in light of the only CD34+KDR+ phenotypic combination that had been examined previously.

Applications

By demonstrating differences among the various EPC phenotypic combinations in cardiovascular outcome predictive ability, the study could improve current understanding of the biology of these cells.

Terminology

EPCs are a scarce population of progenitor cells derived from the bone marrow that play an important role in vascular regeneration after ischemia. They have been characterized by the presence of different combinations of certain membrane antigen markers, including CD34, CD133 and KDR.

Peer review

The topic is new, and could be of interest to readers. The study is well described, methods are accurately reported, and results clearly showed. However, clinical implications of these findings and the opportunities for developing new possible diagnostic and therapeutic options might be better deepened in the discussion section.

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Meetings

Events Calendar 2010

January 12-13
Riyadh, Saudi Arabia
1st International Cardiovascular Pharmacotherapy Conference

January 17-21
Hollywood, United States
22nd Annual International Symposium on Endovascular Therapy

January 20-23
Sao Paulo, Brazil
World Cardiology, Metabolism and Thrombosis Congress

January 21-24
Phoenix, United States
13th Society for Cardiovascular Magnetic Resonance Annual Scientific Sessions

January 28-30
Brussels, Belgium
29th Belgian Society of Cardiology Annual Scientific Meeting

January 28-31
Nashville, United States
31st Annual Meeting of The American Academy of Cardiovascular Perfusion

February 3-6
Snowbird, United States
35th Annual Cardiovascular Conference at Snowbird

February 4-5
Leuven, Belgium
Leuven Symposium on Myocardial Velocity and Deformation Imaging

February 6-9
St. Petersburg, United States
10th Annual International Symposium on Congenital Heart Disease

February 8-10
Tel Aviv, Israel
10th International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy

February 11-12
London, United Kingdom
2nd National Chronic Heart Failure and Hypertension

February 18-21
Istanbul, Turkey
The 2nd World Congress on Controversies in Cardiovascular Disease (C-Care)

February 22-25
Maui, United States
Arrhythmias & the Heart Symposium

February 22-26
Cancun, Mexico
15th Annual Cardiology at Cancun-Advances in Clinical Cardiology and Multi-Modality Imaging

February 25-28
Valencia, Spain
First International Meeting on Cardiac Problems in Pregnancy

February 26-28
Hong Kong, China
International Congress of Cardiology

February 28-March 4
Scottsdale, United States
International Congress XXIII on Endovascular Interventions

February 28-March 5
Keystone, United States
Keystone Symposia: Cardiovascular Development and Repair (X2)

March 3-5
Kish Island, Iran
Islamic Republic of 4th Middle East Cardiovascular Congress

March 4-7
Newport Beach, United States
30th Annual CREF: Cardiothoracic Surgery Symposium

March 7-12
Snowmass Village, United States
Interventional Cardiology 2010: 25th Annual International Symposium

March 14-16
Atlanta, United States
American College of Cardiology 59th Annual Scientific Session

March 18-20
Rome, Italy
VIII Congress of the Italian Society of Cardiovascular Prevention

March 18-20
Prague, Czech Republic
XI International Forum for the Evaluation of Cardiovascular Care

March 24-25
Jeddah, Saudi Arabia
12th KFAFH Cardiovascular Conference: A balanced approach to treatment of cardiovascular diseases

April 8-11
Guangzhou, China
The 12th South China International Congress of Cardiology

April 14-15
Tel Aviv, Israel
The 57th Annual Congress of the Israel Heart Society in Association with The Israel Society of Cardiothoracic Surgery

April 15-18
Izmir, Turkey
59th European Society for Cardiovascular Surgery International Congress

May 5-7
Prague, Czech Republic
EuroPRevent 2010-Cardiovascular Prevention: a Lifelong Challenge

May 8-9
St. Paul, United States
Controversies in Cardiovascular Disease: Practical Approaches to Complex Problems: Medical and Surgical

May 12-16
Marrakesh, Morocco
7th Metabolic Syndrome, type II Diabetes and Atherosclerosis Congress

May 17-20
Whistler, Canada
6th IAS-Sponsored HDL Workshop on High Density Lipoproteins

May 21-22
Sydney, Australia
3rd Cardiovascular CT, Concord Conference 2010

May 29-June 1
Berlin, Germany
Heart Failure Congress 2010

June 1-4
Seoul, Korea, Republic of
9th Asian-Pacific Congress of Cardiovascular & Interventional Radiology (APCCVIR 2010)

June 16-19
Beijing, China
World Congress of Cardiology Scientific Sessions

June 17-19
Port El Kantaoui, Tunisia
The 7th Tunisian and Europeans Days of Cardiology Practice

July 1-3
Singapore, Singapore
6th Asian Interventional Cardiovascular Therapeutics Congress

July 16-19
Berlin, Germany
Frontiers in CardioVascular Biology 2010-1st Meeting of the CBCS of the ESC

July 24-27
Vancouver, Canada
15th World Congress on Heart Disease, Annual Scientific Sessions 2010

August 13-15
Krabi, Thailand
East Meets West Cardiology 2010

September 16-18
Athens, Greece
5th International Meeting of the Onassis Cardiac Surgery Center

September 25-29
Belo Horizonte, Brazil
65th Brazilian Congress of Cardiology

September 30-October 2
Berlin, Germany
5th International Symposium on Integrated Biomarkers in Cardiovascular Diseases

October 10-13
Rochester, United States
26th Annual Echocardiography in Pediatric and Adult Congenital Heart Disease Symposium

October 16-19
Copenhagen, Denmark
Acute Cardiac Care 2010

October 20-23
Boston, United States
2010 Cardiometabolic Health Congress

November 25-26
London, United Kingdom
13th British Society for Heart Failure Annual Meeting

December 9-11
Lisbon, Portugal
Heart, Vessels & Diabetes-The European Conference

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Instructions to authors

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 350 experts in cardiology from 41 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.

Maximization of personal benefits

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 articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

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 consensuses and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

Name of journal

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SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or

stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJC* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

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Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

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Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more 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 more than 140 words); RESULTS (no more 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.

Text

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.

Illustrations

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.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

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..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

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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-diarrhoea. *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**, Spierings 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 billiary 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**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek 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

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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 ± SD or mean ± 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 υ (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 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; 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 quantums 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: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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