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EDITORIAL

Insulin resistance: Is it time for primary prevention?

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Abstract

Insulin resistance is a clinical condition characterized by a decrease in sensitivity and responsiveness to the metabolic actions of insulin, so that a given concentration of insulin produces a less-than-expected biological effect. As a result, higher levels of insulin are needed to maintain normal glucose tolerance. Hyperinsulinemia, indeed, is one of the principal characteristics of insulin resistance states. This feature is common in several pathologic conditions, such as type 2 diabetes, obesity, and dyslipidemia, and it is also a prominent component of hypertension, coronary heart disease, and atherosclerosis. The presence of endothelial dysfunction, related to insulin resistance, plays a key role in the development and progression of atherosclerosis in all of these disorders. Insulin resistance represents the earliest detectable abnormality in type 2 diabetes, and is one of the major underlying mechanisms of hypertension and cardiovascular diseases. Its early detection could be of great importance, in order to set a therapeutic attack and to counteract the higher risk of diabetes and cardiovascular diseases.

Key words: Insulin resistance; Hyperinsulinemia; Type 2 diabetes; Endothelial dysfunction

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INTRODUCTION

Insulin resistance can be defined as a condition in which insulin's target organs are resistant to its action, so that higher concentrations of this hormone are needed to obtain a normal biological effect. Therefore, hyperinsulinemia is an obvious consequence of insulin resistance, which contributes to the development of endothelial dysfunction, playing a key role in the establishment and progression of atherosclerosis. Insulin resistance represents the pivotal mechanism underlying type 2 diabetes, hypertension and cardiovascular diseases. Although a great amount of literature shows the deleterious action of insulin resistance and hyperinsulinemia in increasing the cardiovascular risk, nowadays there are no guidelines for the treatment of insulin resistance, but its early detection should be of great importance, since a prompt and adequate therapeutic attack may counteract the higher risk of diabetes and cardiovascular diseases. In this review of the literature, we explain the principal mechanisms by which insulin contributes to cardiovascular homeostasis, the main correlations among insulin resistance, visceral obesity, diabetes and cardiovascular risk, and, finally, the possible therapeutic approaches actually available.

INSULIN AND CARDIOVASCULAR HOMEOSTASIS

Insulin is a polypeptide hormone implicated in several biological processes, whose action is mediated by a transmembrane tyrosine kinase receptor. The binding of insulin to its receptor in target tissues leads to the activation of complex insulin-signaling pathways, which regulate the transcription of target genes[1-3]. Two major signaling branches have been identified: the phosphoinositide 3-kinase (PI3K)-dependent pathways that mediate the metabolic actions of insulin, including the regulation of glucose metabolism in muscle, adipose and hepatic tissues, and the regulation of nitric oxide (NO) production from endothelium and vascular smooth muscle cells (VSMC)[4-7], and the mitogen-activated protein kinase (MAPK)-dependent pathways that mediate the non-metabolic actions of insulin, including the mitogenic and proliferative effects, the secretion of endothelin-1 (ET-1) by endothelial cells, and the increased expression of adhesion molecules on the vascular endothelium[8,9]. Under normal conditions, both these insulin-signaling pathways contribute to cardiovascular homeostasis, regulating distinct biological functions: the first one (NO-dependent) causes vasodilation, a decrease in vascular resistance, an increase in blood flow, and stimulation of capillary recruitment, whereas the second one (ET-1-dependent) causes vasoconstriction, which contributes to the activation of the sympathetic nervous system induced by insulin, exerting a pro-hypertensive action, and accelerating atherosclerotic damage[10,11]. The effects on vascular homeostasis mainly affect the cardiovascular system and skeletal muscle, which, in turn, is an important target for the metabolic effects of insulin, stimulating glucose uptake and glycogen accumulation. While glucose accumulation is mediated by translocation of glucose channels to the sarcolemma, the stimulation of physiological cardiac growth and contractility are due to the augmented calcium influx and myofilament calcium sensitivity, resulting in an increase in myocardial work and oxygen consumption[12-14]. These observations suggest a tight association between hemodynamic and metabolic actions of the hormone.

In conditions of insulin resistance there is a specific impairment in metabolic PI3K-dependent signaling pathways, whereas other insulin-signaling branches, including non-metabolic MAPK-dependent pathways, are unaffected[15,16]. Compensatory hyperinsulinemia, that typically is associated with insulin resistance in order to maintain euglycemia, overstimulates unaffected MAPK-dependent pathways, leading to an imbalance between PI3K- and MAPK-dependent effects of insulin[17,18]. This results in an overproduction of vasoconstrictor mediators, such as ET-1, and in a reduction of NO synthesis, with a resultant vasoconstrictor effect, a key feature of endothelial dysfunction[8,19,20]. In addition, hyperinsulinemia may lead to the development of systemic hypertension, not only by increasing ET-1 secretion and sympathetic tone, but also by inducing antinatriuretic effects, because it promotes renal sodium retention by enhancing distal tubular sodium reabsorption[21]. Thus, these alterations may contribute to reciprocal relationships between endothelial dysfunction and insulin resistance, typical of both metabolic and cardiovascular diseases[22]. Endothelial dysfunction contributes to impaired insulin action. This establishes a reverberating negative feedback cycle in which progressive endothelial dysfunction and disturbances in glucose and lipid metabolism develop from the insulin resistance (Table 1).

Table 1 Pathologic changes associated with insulin resistance and compensatory hyperinsulinemia

Alterated glucose metabolism:
Impaired fasting glucose
Impaired glucose tolerance
Diabetes
Dyslipidemia:
↑ Triglycerides
↓ HDL-C
↑ Small, dense LDL-particles
Endothelial dysfunction:
↑ Adhesion molecules
↓ Endothelial-dependent vasodilation
↓ NO and ↑ ET-1 production
Hypercoagulability:
↑ Plasminogen activator inhibitor- I
↑ Fibrinogen
Hemodynamic changes:
↑ Sympathetic nervous system activity
↑ Renal sodium retention
↑ Cardiac mass
VSMC hypertrophy
Chronic inflammation:
↑ C-reactive protein, TNF-α, IL-6, resistin, leptin
↓ Adiponectin
↑ Oxidative stress

HDL-C: High density lipoprotein-cholesterol; LDL: Low density lipoprotein; NO: Nitric oxide; ET-1: Endothelin-1; VSMC: Vascular smooth muscle cells; TNF-α: Tumor necrosis factor-α; IL: Interleukin.

VISCERAL OBESITY AND INSULIN RESISTANCE

Visceral obesity is the major risk factor for insulin resistance, since it plays a crucial role in the pathogenesis of this condition. The excess abdominal adipose tissue releases large amounts of circulating free fatty acids (FFA), which substantially impair the insulin-signaling pathways in the main target organs. This alteration leads to widespread changes in glucose and lipid metabolism. Indeed, in the liver, FFA cause an increased production of glucose, triglycerides and very low density lipoprotein-cholesterol (LDL-C). Other associated metabolic abnormalities include a highly atherogenic plasma lipid profile, characterized by an increase in small and dense LDL-C, and a reduction in high density lipoprotein-cholesterol (HDL-C)[23,24]. Concomitant hepatic alterations include a reduction in glucose storage in the form

of glycogen, and an increase in lipid accumulation in the form of triglycerides. FFA also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. The high circulating levels of glucose and FFA cause an increase in oxidative stress, due to the production of reactive oxygen species (ROS) and the increased formation of advanced glycation end-products, an alteration in the local renin-angiotensin system, and an increase in adrenergic activation of VSMC, that may all act in concert to contribute to the development of endothelial dysfunction[25,26].

In addition to the effects on insulin resistance determined by the high levels of FFA, adipose tissue has an essential role in establishing a chronic pro-inflammatory state. Adipose tissue is in fact an active endocrine-paracrine organ, since it produces adipocyte-derived hormones, such as leptin and adiponectin. Leptin is a key regulator of appetite, body weight and energy balance in the central nervous system, beside exerting, under healthy conditions, an NO-dependent endothelium-mediated vasodilatory effect[27]. In pathological conditions, such as in the presence of visceral obesity, there is an alteration in the effects of leptin, which are associated with a promotion of vascular inflammation, oxidative stress and VSMC hypertrophy. This evidence suggests that leptin may potentiate both pro-hypertensive and pro-atherogenic effects of insulin[28]. Adiponectin is an anti-inflammatory peptide whose circulating levels are positively correlated with insulin sensitivity. It enhances NO bioavailability and reduces ROS production in endothelial cells[29]. It seems that adiponectin may be protective against ischemia-reperfusion injury in the heart[30]. In obesity-correlated insulin resistance states the secretion of adiponectin is reduced. Its plasma levels are negatively correlated with insulin resistance, and they may represent a potentially useful clinical marker of insulin resistance. In obese patients with insulin resistance, adipose cells oversecrete several adipo-cytokines, such as tumor necrosis factor-α (TNF-α), resistin[31], plasminogen activator inhibitor-1, and interleukin-6, which promote atherosclerosis, vascular inflammation, and endothelial dysfunction, and impair the effect of insulin and its secretion[32]. TNF-α stimulates the production of C-reactive protein, which is considered an important marker of systemic vascular inflammation, and whose plasma levels are correlated with increased risk of cardiovascular events[33]. All these observations suggest that insulin resistance creates a state of low-grade, chronic, systemic inflammation, which provides a fascinating and physiologically sound reading frame bringing together the metabolic, vascular and hemodynamic hallmarks of atherosclerotic disease and cardiovascular risk. The presence of this constellation of metabolic alterations characterizes the so-called metabolic syndrome[34].

INSULIN RESISTANCE, DIABETES AND CARDIOVASCULAR RISK

Insulin resistance, as noted above, is a state in which a given insulin concentration produces a lower-than-expected biological effect on glucose levels. This condition is counterbalanced by a compensatory increase in insulin secretion by pancreatic β cells, in the attempt to maintain normal glucose tolerance. Insulin resistance is the earliest detectable abnormality in the natural history of type 2 diabetes, whose evolution involves defects in both insulin action (insulin resistance) and insulin secretion (β cell dysfunction). Specifically, several studies have conclusively demonstrated that hyperinsulinemia, which develops in response to insulin resistance, precedes, often by many years, the development of type 2 diabetes[35,36]. Therefore, the plasma insulin concentration can be considered as a widely accepted surrogate measure of insulin resistance. The direct "gold standard" technique for the evaluation of insulin resistance is the euglycemic-hyperinsulinemic clamp; however, this is an invasive procedure useful for physiological and proof-of-concept studies, but not a plausible tool for population screening. The homeostasis model assessment of insulin resistance index [HOMA-IR = fasting insulin (μIU/mL) × fasting glycemia (mmol/L)/22.5] can nowadays be considered the best candidate non invasive surrogate marker of insulin resistance, since it correlates well with the "gold standard" clamp-derived values[37-40]. HOMA-IR is easy to measure, repeatable and cheap, therefore representing a useful means to detect insulin resistance both in the context of everyday clinical practice and in wide-scale clinical trials.

Type 2 diabetes can be considered as a cardiovascular disease featuring high plasma glucose levels[41]. Indeed, most diabetic patients already show signs of cardiovascular disease upon diagnosis[42]; it is well recognized that diabetic patients without a history of myocardial infarction have a risk of myocardial infarction comparable to that of non diabetic subjects with previous coronary events[43]. This is the principal reason why, in type 2 diabetic patients, cardiovascular risk factors must be treated as aggressively as in non diabetic patients with prior cardiovascular events (myocardial infarction, stroke), according to secondary prevention guidelines. Based on these observations, the need for an early intervention to screen and treat insulin resistance before type 2 diabetes becomes manifest seems warranted and obvious. Identifying and treating this condition promptly could counteract inflammation, atherogenic dyslipidemia, endothelial dysfunction, and hypercoagulability, all features responsible for the greatly increased cardiovascular risk in patients with insulin resistance. In fact, many studies have shown that insulin resistance, as assessed by HOMA-IR, is an independent predictive factor of cardiovascular disease, and a 1 unit increase in the HOMA-IR value is associated with a 5.4% increase in the cardiovascular risk[44]. The San Antonio Heart Study clearly demonstrated that HOMA-IR was significantly and independently associated with the risk of cardiovascular events in Mexican-American and in white non-Hispanic men and women[44]. Similarly, in another population study, HOMA-IR was predictive of cardiovascular disease, even after correction for age, gender, smoking and LDL-C. The latter study showed a relative risk of the incidence of cardiovascular end-points of

1.49 in insulin-resistant subjects (95% confidence interval, 1.07-2.07)[45]. It has also been shown that about 50% of normotensive subjects with insulin resistance develop some degree of diastolic dysfunction of the left ventricle with a relevant increase of the risk for heart failure[46]. In addition, insulin resistance is highly prevalent among non diabetic patients with chronic heart failure and it is associated with reduced exercise capacity[47]. Other important evidence has been highlighted by the Study of Inherited Risk of Coronary Atherosclerosis, which showed that, among many metabolic and inflammatory biomarkers, leptin and HOMA-IR were strongly and independently associated with coronary artery calcifications[48]. Furthermore, Schelbert demonstrated that insulin resistance was also associated with functional abnormalities in coronary hemodynamics, and that the extent of these abnormalities was proportional to the severity of insulin resistance. In particular, coronary dysfunction initially seems limited to a progressive worsening of endothelium-mediated vasodilatation, progressing to a complete impairment of vasodilatation capacity, in relation to the severity of insulin resistance. This endothelial dysfunction linked to insulin resistance, even in the absence of coronary artery macrovascular lesions, can result in a failure to appropriately increase coronary flow and in a drive towards the development of atherosclerosis, both of which may induce myocardial ischemia[49]. On the same topic, another manuscript reported that insulin resistance was present in young subjects with early myocardial infarction, who had no known factors with a negative action on insulin sensitivity[50]. Both insulin resistance and metabolic syndrome have been proved to be strong and independent predictors of cardiovascular risk in a group of patients with angiographically documented coronary artery disease, during a follow-up of 2 years and 3 mo[51].

In support of the thesis of this review, i.e. that insulin resistance should be considered a strong risk factor for cardiovascular disease, the results of the Bruneck population study are very interesting. This long observational study confirmed that insulin resistance as assessed by HOMA-IR was associated with a greater incidence of cardiovascular events in the general population, independently from other known cardiovascular risk factors. The authors of this study emphasized that treatment of insulin resistance should be considered an important target to reduce the risk of cardiovascular disease[52]. Recently it has been reported that patients with pre-diabetes had defects in myocardial perfusion and transient left ventricular dilatation as measured by technetium (99mTc) sestamibi SPECT scintigraphy on the exercise treadmill, and that these defects correlated with HOMA-IR and waist circumference, independently of glucose levels[53]. Another recent paper reported the results of a study on HOMA-IR and the risk of cardiovascular events in middle-aged non-diabetic Japanese men. In this study, 2548 non-diabetic men aged 35-59 years were followed up for 11 years. The results showed that increased HOMA-IR at baseline predicted subsequent cardiovascular events, and that this association was independent of traditional cardiovascular risk factors and other relevant metabolic disorders[54].

In a recent study published in *Stroke*, insulin resistance, measured by the Gutt index, has been shown to be associated with the risk of incident ischemic stroke in non diabetic older adults[55].

In addition to the data on the pathologic impact of insulin resistance on the cardiovascular system, recent papers have reported that insulin resistance could also be involved in cognitive impairment and neurodegeneration, particularly in Alzheimer's disease (AD). Epidemiological studies had already reported correlations among several metabolic alterations, such as diabetes, dyslipidemia and hypertension, and the risk of AD, but more recent studies have highlighted insulin resistance as potentially contributing to the development of AD. The increased risk of AD was associated with reductions in cerebral glucose metabolic rate, as measured by fluorodeoxyglucose F18-positron emission tomography, and subtle cognitive impairments at the earliest stage of disease[56]. These data have been in part confirmed by the results of the Rotterdam study, which showed that the levels of insulin and the degree of insulin resistance were associated with a higher risk of AD within 3 years of baseline[57].

THERAPEUTIC APPROACHES

The delay in the detection and management of insulin-resistant patients leads inevitably to late diagnosis, often in the presence of overt diabetes and established vascular complications. Therefore, in order to effectively counteract the deleterious effects of early, chronic hyperinsulinemia, screening for insulin resistance should be suggested at least in high risk subjects, such as those with abdominal obesity, and in relatives of diabetics. Once insulin resistance is recognized, current therapeutic approaches mainly involve lifestyle modifications. However, due to poor compliance with weight-loss diets and increased physical activity, pharmacological treatment is often needed to address insulin resistance effectively in the long term. Indeed, the optimal drug therapy should aim at counteracting the underlying negative impact of insulin resistance on metabolism and the cardiovascular system. Biguanides and thiazolidinediones are two classes of oral antihyperglycemic agents currently used in type 2 diabetic patients, that can reduce insulin resistance. Specifically, the effects of biguanides on insulin resistance are most likely correlated with a reduction in plasma FFA concentration[58]; in addition, metformin, the principal biguanide drug used in pharmacotherapy worldwide, induces a reduction in hepatic glucose production, an improvement in glucose uptake by skeletal muscles and adipose tissues, and a reduction in caloric intake and appetite[59,60]. Moreover, metformin has been shown to reduce the incidence of diabetes in persons at high risk, albeit to a lesser extent when compared with lifestyle modification[61]. Studies have shown that metformin lowers fasting glucose and hemoglobin A1c, with beneficial effects on

Table 2 Therapeutic approaches to insulin resistance

	Metformin	Thiazolidinediones	Berberine
Main mechanism of action:	Activation of AMPK	Activation of PPARγ	Activation of AMPK Up-regulation of insulin receptor expression Inhibition of intestinal disaccharidases
Metabolic effects:	Reduction in plasma FFA concentration Reduction in blood glucose, hemoglobin A1c, triglycerides, total and LDL-C, body weight and fat mass	Reduction in the amount of circulating FFA and in the lipolysis Improvement of hepatic production of glucose and insulin sensitivity	Reduction in plasma FFA concentration Reduction of blood glucose, hemoglobin A1c, total and LDL-C, triglycerides, body weight and fat mass
Side effects:	Abdominal discomfort, diarrhea and anorexia, lactic acidosis	Increase in total, LDL-C levels and body weight, hepatotoxicity, cardiotoxicity	Constipation

LDL-C: Low density lipoprotein-cholesterol; FFA: Free fatty acids; AMPK: AMP-activated protein kinase; PPAR: Peroxisome proliferator-activated receptors .

plasma levels of triglycerides, total cholesterol (TC) and LDL-C[60,62]. Most common side effects are abdominal discomfort, diarrhea and anorexia, while lactic acidosis is the most serious, but rare, possible adverse effect[63]. Thiazolidinediones (TZD) exert their action through the activation of the peroxisome proliferator-activated receptor γ[64]. These receptors play an important role in the modulation of glucose metabolism, involving adipocyte differentiation, with a reduction in the amount of circulating FFA and lipolysis. As a result, hepatic production of glucose and insulin sensitivity are improved[65]. In addition, TZD inhibit the activation of nuclear factor-κβ, which controls the expression of many genes involved in immune and inflammatory responses, resulting in an improved endothelium-dependent vasodilation through an increased production of NO from endothelial cells[66]. However, the use of TZD is related to numerous well recognized side effects. TZD increased TC and LDL-C levels as well as body weight[67]. Troglitazone has been withdrawn from the market because of its hepatotoxicity[68], and a recent meta-analysis highlighted that rosiglitazone is associated with a statistically significant increase in myocardial infarction and an increased risk of death from cardiovascular causes[69].

Another therapeutic option can be represented by the natural alkaloid berberine. Its effects on lipid and glucose metabolism have been demonstrated by several scientific clinical and experimental studies[70-72]. The principal mechanism responsible of its insulin sensitizing action is the upregulation of insulin receptor expression[73,74]. Berberine lowers blood glucose, hemoglobin A1c, TC, LDL-C and triglycerides, and reduces body weight and fat mass[75]. In addition, it seems to have beneficial effects on endothelial function[74]. Its pleiotropic effects on glucose and lipid metabolism make berberine a good candidate for the treatment of dyslipidemic insulin resistant subjects (Table 2).

In conclusion, early detection of insulin resistance through screening of at-risk subjects should be counseled by medical societies in order to deliver prompt treatment to improve insulin resistance and reduce hyperinsulinemia. Therefore, lifestyle interventions of diet and physical exercise initially, and, in the case of poor outcomes, the addition of insulin-sensitizing agents should be applied to the identified subjects, in order to counteract the higher risk of diabetes and cardiovascular diseases. A large multicenter trial should be performed in order to demonstrate the beneficial effects of early screening and intervention in insulin resistance on cardiovascular events, though there would be several issues because of the need for a wide population and a very long term follow-up.

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BRIEF ARTICLE

Clinical and prognostic implications of atrial fibrillation in patients undergoing transcatheter aortic valve implantation

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Abstract

AIM: To study a cohort of consecutive patients undergoing transcatheter aortic valve implantation (TAVI) and compare the outcomes of atrial fibrillation (AF) patients *vs* patients in sinus rhythm (SR).

METHODS: All consecutive patients undergoing TAVI in our hospital were included. The AF group comprised patients in AF at the time of TAVI or with history of AF, and were compared with the SR group. Procedural, echocardiographic and follow-up variables were compared. Likewise, the CHA_2DS_2-VASC stroke risk score and HAS-BLED bleeding risk score and antithrombotic treatment at discharge in AF patients were compared with that in SR patients.

RESULTS: From a total of 34 patients undergoing TAVI, 17 (50%) were allocated to the AF group, of whom 15 (88%) were under chronic oral anticoagulation. Patients in the AF group were similar to those in the SR group except for a trend (P = 0.07) for a higher logistic EuroSCORE (28% *vs* 19%), and a higher prevalence of hypertension (82% *vs* 53%) and chronic renal failure (17% *vs* 0%). Risk of both stroke and bleeding was high in the AF group (mean CHA_2DS_2-VASC 4.3, mean HAS-BLED 2.9). In the AF group, treatment at discharge included chronic oral anticoagulation in all except one case, and in association with an antiplatelet drug in 57% of patients. During a mean follow-up of 11 mo (maximum 32), there were only two strokes, none of them during the peri-procedural period: one in the AF group at 30 mo and one in the SR group at 3 mo. There were no statistical differences in procedural success, and clinical outcome (survival at 1 year 81% *vs* 74% in AF and SR groups, respectively, P = NS).

CONCLUSION: Patients in AF undergoing TAVI show a trend to a higher surgical risk. However, in our cohort, patients in AF did not have a higher stroke rate compared to the SR group, and the prognosis was similar in both groups.

Key words: Aortic stenosis; Transcatheter aortic valve implantation; Stroke; Atrial fibrillation

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INTRODUCTION

Degenerative aortic stenosis (AS) is currently the most prevalent acquired valvular heart disease, occurring in 4.6% of adults ≥ 75 years old[1]. The classic treatment for symptomatic severe AS is surgical aortic valve replacement (SAVR), which modifies the natural history of the disease and has improved survival in historical comparisons[2-4]. Unfortunately, one third of patients who are recognized to need surgery are rejected, generally because of unacceptably high surgical risk[5]. Transcatheter aortic valve implantation (TAVI) has had successful and constant development during the last few years to become a real alternative for these high-risk patients[6].

With more than 10 000 implants in Europe, the TAVI technique has reached maturity with implantation success in ≥ 95% and 30 d mortality < 10% in transfemoral procedures and < 20% in transapical procedures[7-9]. In the randomized Placement of Aortic TraNscatheter Valve Trial (PARTNER), cohort B proved superiority of TAVI compared with medical treatment (including aortic valvuloplasty) in inoperable patients, with an outstanding 20% absolute decrease in mortality at 1 year[10]. In the recently reported results of PARTNER cohort A, the TAVI procedure met non-inferiority criteria compared with SAVR in a high-risk population, thus becoming an alternative to surgery for patients accepted for surgery but with a high surgical risk[11].

One of the limitations, however, of TAVI in the PARTNER cohort A trial was a significantly higher incidence of stroke in comparison with SAVR. In this elderly, high surgical risk population, stroke is one of the biggest concerns a clinician may have because of the associated disability and mortality. Stroke rates after SAVR are reported to be around 5% in a high-risk population[12], and they are associated with aortic cross-clamping and hypoperfusion during cardiopulmonary by-pass. TAVI procedures have reported stroke rates below 5%, albeit with a subclinical incidence of 70%-80% in magnetic resonance studies (40%-50% for similar studies in SAVR)[7,13,14]. It is attributed to manipulation of large catheters in atherosclerotic and calcified aortas and to embolization after valvuloplasty or valve implantation. However, apart from these technical reasons for stroke in patients undergoing TAVI, atrial fibrillation (AF) is a potential confounding factor in the relationship between aortic replacement and stroke, and little has been reported to date on this issue. AF is a well-known risk factor for stroke (approximately 1 in 5 strokes are caused by AF), and is very prevalent in old patients (5%-15% in ≥ 80-year-old patients)[15]. It is also a common comorbid condition in the late stages of aortic valve disease. This study aimed to determine the influence of AF in the TAVI population, on procedure complications and on long-term prognosis, as well as to analyze the antithrombotic treatment at discharge.

MATERIALS AND METHODS

Study population and definitions

At our center, a total of 34 implants have been performed (31 transfemoral and 3 transapical). All TAVI patients were excluded from conventional SAVR because of high surgical risk in a 'heart team' meeting composed of clinical cardiologists, interventional cardiologists, anesthesiologists and cardiac surgeons. In a dedicated prospective database we recorded data from all evaluated patients, implantations and follow-up. Variables included were basal characteristics of the patients, symptoms and intervention indication, EuroSCORE, echocardiographic data, procedural characteristics and complications during the procedure, following the published recommendations[16].

TAVI procedures were performed in a catheterization laboratory under general anesthesia, with most of the patients being extubated before leaving the laboratory. All cases were implanted with the Edwards-SAPIEN transcatheter valve system (Edwards Lifesciences, Irvine, United States)[17]. Vascular access was obtained by surgical cutdown of the femoral artery, and closure was secured by direct suture of the femoral artery. The prosthesis delivery and implantation process has been previously described[18,19]. If significant coronary artery disease was found in the preliminary study, percutaneous coronary revascularization was performed approximately 1 mo prior to the procedure.

For this paper, we divided our implanted population in two groups: those in AF or with a previous history of AF (AF group) and those in sinus rhythm (SR) without a history of AF (SR group). We calculated previously validated CHA_2DS_2VASC and HAS-BLED scores to assess the stroke and bleeding risk, respectively; and the suitability of antithrombotic treatment[15,20,21]. As for the HAS-BLED score, we defined major bleeding as any bleeding requiring hospitalization and/or causing a decrease in hemoglobin of more than 2 g/L and/or requiring blood transfusion, which was not a hemorrhagic stroke[21]. Chronic renal failure was defined as serum creatinine levels ≥ 200 mmol/L (cut-off value of EuroSCORE risk

score). Left ventricular ejection fraction was estimated by the biplanar Simpson method. We also recorded treatment at discharge of all patients. Recommended medical treatment after TAVI is aspirin plus 75 mg clopidogrel for 3-6 mo, and only aspirin afterwards, but final treatment at discharge was open to the clinician's preference. If warfarin was used, target INR values were 2.0-3.0. Patients without AF before TAVI but developing AF during or after the procedure were maintained in the SR group for statistical comparisons, but received special attention and will be described in detail.

Follow-up

Clinical follow-up was obtained in all patients by clinical visits, and/or telephone interview. The following clinical end-points were determined: death, myocardial infarction, stroke, aortic valve surgery, hospitalization because of heart failure, and the combination of all of them (MACE, major adverse cardiac events).

Also, several echocardiographic studies were performed at follow-up (at discharge, at 6 mo, 1 year, and every year subsequently) to evaluate prosthetic function (maximum and mean trans-aortic pressure gradients, aortic valve area, aortic valve regurgitation, and left ventricular function).

Statistical analysis

Statistical analysis was performed with PASW version 17.0 (SPSS Inc, Chicago, IL). Categorical variables are expressed as proportions (percentages) and continuous variables as mean ± standard deviation unless otherwise specified. Comparisons between groups were performed with the Student *t* test (comparison of 2 means) or Chi-square test (comparison of proportions). Comparative survival analysis was performed with the Kaplan-Meier curves and log-rank test. Associations with a P value < 0.05 were considered statistically significant, although all P values are provided.

RESULTS

Baseline characteristics of patients with vs without AF

Main characteristics of both AF and non-AF groups are shown in Table 1. There were significant differences only in the 'prior warfarin use' item, but there was a trend (P = 0.068) towards a higher prevalence of hypertension and chronic renal failure as well as a higher mean EuroSCORE in the AF group. Echocardiographic features of the valve disease and other coexistent heart diseases were also similar between both groups. All patients had symptomatic AS, with no differences in the accompanying symptoms: similar proportion of heart failure (76.4% in AF patients *vs* 88.2% in SR patients, P = 0.37); a numerically but not statistically higher rate of angina in the AF group (43.8% *vs* 17.7%, P = 0.1); and 4 patients with syncope in each group.

Average CHA_2DS_2-VASC score for the whole AF group was 4.3 (range, 2-7) whereas the average HAS-BLED bleeding score was 2.9 (range, 2-5).

Table 1 Baseline characteristics of the transcatheter aortic valve implantation population in atrial fibrillation and non-atrial fibrillation groups (n = 17) n (%)

	AF group	SR group	P
Male gender	6 (35.3)	7 (41.2)	0.72
Age (yr)	81.3	83.9	0.15
Diabetes	8 (47.1)	6 (35.3)	0.49
Hypertension	14 (82.4)	9 (52.9)	0.07
Peripheral vascular disease	4 (23.5)	1 (5.9)	0.15
Significant coronary disease	6 (35.3)	10 (58.8)	0.17
Prior stroke	3 (17.7)	2 (11.8)	0.63
Chronic respiratory failure	2 (11.8)	4 (23.5)	0.37
Chronic renal failure	3 (17.7)	0	0.07
Hemodialysis	2 (11.8)	0	0.14
Prior warfarin use	15 (88.2)	0	< 0.01
Logistic euroSCORE (mean)	27.9	18.7	0.07
Baseline echocardiogram features			
Aortic valve area (cm^2, mean)	0.66	0.72	0.35
Peak gradient (mmHg, mean)	76.9	71.4	0.42
Mean gradient (mmHg, mean)	44.2	41.8	0.60
LVEF (mean)	55.9%	57.5%	0.66

AF: Atrial fibrillation; SR: Sinus rhythm; LVEF: Left ventricular ejection fraction.

Table 2 Procedural and in-hospital outcomes (n = 17) n (%)

	AF group	Non-AF group	P
Valve size (mm)			0.27
23	13 (76.5)	10 (58.8)	
26	4 (23.5)	7 (41.2)	
Access			0.55
Transfemoral	16 (94.1)	15 (88.2)	
Transapical	1 (5.9)	2 (11.8)	
Procedural success	16 (94.1)	17 (100)	0.31
Any peri-procedural complication	7 (41.2)	7 (41.2)	1.00
Death	2 (11.8)	2 (11.8)	1
Emergent heart surgery	0	1 (5.9)	0.31
Orotracheal intubation > 24 h	0	1 (5.9)	0.31
Proshtesis embolization	0	0	-
Endocarditis	0	0	-
New onset AF	1 (5.9)	1 (5.9)	1.00
Coronary obstruction	1 (5.9)	1 (5.9)	1.00
Myocardial infarction	1 (5.9)	1 (5.9)	1.00
Stroke	0	0	-
Renal failure requiring hemodialysis	0	0	-
New pacemaker implantation	2 (11.8)	1 (5.9)	0.55
Major access site complications	0	2 (11.8)	0.14
Minor access site complications	2 (11.8)	4 (23.5)	0.37
Transfusion	5 (29.4)	2 (11.8)	0.20
Post-procedural stay (mean days)	14.4	10.2	0.22

AF: Atrial fibrillation.

Procedural and in-hospital outcomes

Procedural and in-hospital outcomes of both groups are shown in Table 2. There were no significant differences in any of the peri-procedural outcomes. There were 2 deaths in the AF group: one patient died because of coronary obstruction, myocardial infarction and shock, and the other because of respiratory complications attributed to previous pulmonary fibrosis and severe

Table 3 Antithrombotic treatment at discharge in patients of the atrial fibrillation group who survived to hospital discharge (n = 15)

Patient	Age	Gender	CHA2DS2-VASC	HAS-BLED	Treatment at discharge	Follow up (mo)	Non-fatal events	Follow up (mo)	Survival
1	87	Female	6	5	Warfarin	2	None	2	Alive
2	76	Male	4	4	Aspirin	32	None	32	Alive
3	81	Female	5	3	Warfarin + Aspirin	7	None	7	Alive
4	80	Female	4	3	Warfarin	1	None	1	Alive
5	90	Female	6	2	Warfarin	26	None	26	Alive
6	77	Female	5	3	Warfarin	23	None	23	Alive
7	68	Female	2	2	Aspirin + Clopidogrel	10	None	10	Alive
8	83	Male	7	4	Warfarin + Aspirin	3	None	3	Death, non-cardiac
9	80	Female	3	2	Warfarin	19	None	19	Alive
10	79	Female	5	3	Warfarin + Aspirin	30	Stroke	31	Death, non-cardiac
11	84	Female	5	3	Warfarin + Clopidogrel	1	Heart failure admission	31	Alive
12	87	Female	4	2	Warfarin + Aspirin	6	None	6	Alive
13	83	Female	3	2	Warfarin	5	None	5	Alive
14	82	Male	3	3	Warfarin + Aspirin	2	None	2	None
15	68	Male	3	2	Warfarin + Clopidogrel	1	Heart failure admission	3	Alive

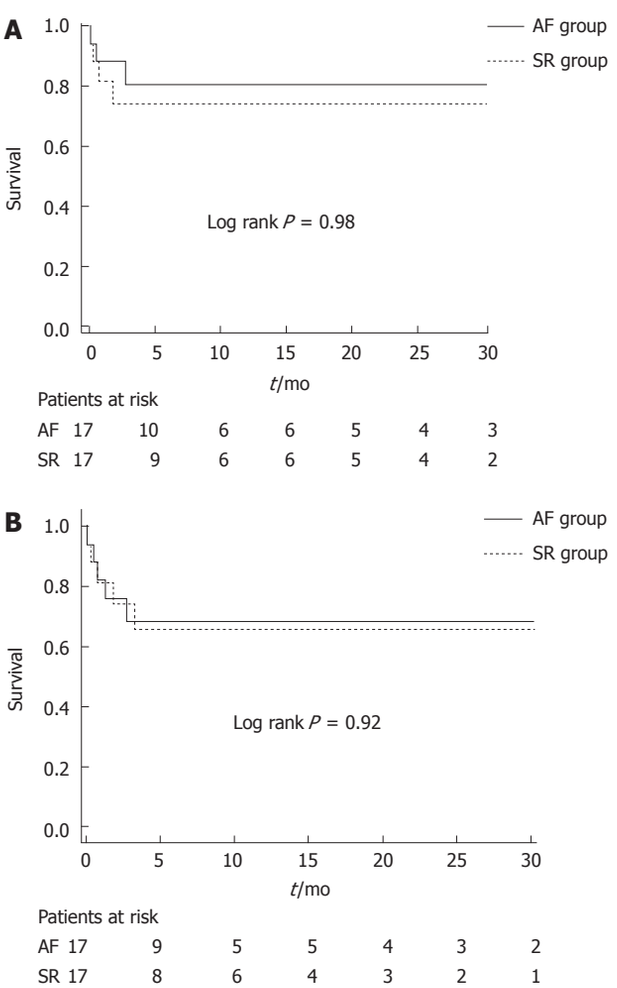

Figure 1 Kaplan-Meier curves. A: Survival; B: Survival free from MACE (death, stroke, myocardial infarction, aortic valve surgery, heart failure admission, and prosthesis failure). AF: Atrial fibrillation; SR: Sinus rhythm.

pulmonary hypertension (no prosthesis dysfunction). There were 2 deaths in the SR group: one transfemoral procedure complicated by perforation with the temporary pacemaker lead, and one transapical procedure with post-procedural severe bleeding at the site of ventricular puncture 48 h after the procedure. Only 2 patients (6%) had new onset AF during TAVI admission. One patient from the SR group had new onset AF 2 d after TAVI and was discharged under warfarin plus clopidogrel (this patient was kept in SR group "per protocol", as described in methods). The other patient from the AF group was in SR at the start of TAVI, but developed AF during the procedure and was discharged with AF under warfarin treatment. None of these patients had events in the follow-up.

Post-discharge management and clinical outcome

During hospitalization (and at 30-d follow-up), 4 patients died: one after transapical and 3 after transfemoral procedures. Therefore, survival at 30 d was 88.2% in the overall study population, 90.3% in patients undergoing transfemoral TAVI, and 66.7% in those undergoing transapical TAVI. Thus, 30 patients were discharged alive: 15 from SR group and 15 from AF group. All patients in the SR group were treated after valve implantation with aspirin 100 mg/d plus clopidogrel 75 mg/d for 3-6 mo. AF patients were treated according to the clinical cardiologist's preference, as shown in Table 3. The most common treatment at discharge was warfarin alone, followed by warfarin plus aspirin.

Clinical follow-up was completed in 100% of the patients. Mean follow-up for the whole cohort was 10.4 mo, with a maximum of 32 mo. Kaplan-Meier curves for survival are shown in Figure 1A. Mean survival was similar in both groups: 23.8 mo in the SR group *vs* 25.6 mo in the AF group (log-rank, Mantel-Cox: P = 0.98; hazard ratio (HR), 0.99; 95% confidence interval (CI), 0.26-3.75). Survival at 30 d was 81.4% in the SR group *vs* 88.2% in the AF group. Survival at 1 year was 74% in the SR group *vs* 80.9% in the AF group. Figure 1B depicts

survival free from a composite MACE endpoint (death, stroke, myocardial infarction, aortic valve surgery, heart failure admission, and prosthesis failure). Survival free from MACE was similar: 21.4 mo in SR *vs* 21.7 mo in AF (log-rank, Mantel-Cox: $P = 0.92$; HR, 0.94; 95% CI, 0.29-3.11). Survival at 30 d was 81.4% in the SR group *vs* 82.4% in the AF group; whereas survival at 1 year was 65.8% in the SR group *vs* 68.4% in the AF group.

Importantly, there were 2 strokes in the follow up. One took place in the AF group at 30.3 mo (a patient treated with aspirin and warfarin), and contributed to the patient's death due to respiratory complications. The other happened at 3.3 mo in the SR group (aspirin), and was classified as atherosclerotic with the patient remaining in SR, and the patient was discharged with mild sequelae. There were no documented major bleedings either in AF or non-AF patients in the entire follow-up.

Echocardiographic follow-up

Follow-up echocardiography was performed at 6 mo, 1 year, and every year subsequently. For this study we selected the longest available echocardiographic follow-up, with a mean of 14.7 mo. There were no differences between AF and non-AF patients in any of the echocardiographic items during the follow-up (Table 4). There were no cases of prosthesis thrombosis, or prosthesis failure.

Table 4 Follow-up echocardiographic evaluation of the prosthetic valve (mean follow-up 14.7 mo)

	AF group	SR group	*P*
Aortic valve area (cm^2, mean)	1.66	2.05	0.18
Peak gradient (mmHg, mean)	18.6	19.3	0.86
Mean gradient (mmHg, mean)	9.5	11.0	0.51
LVEF (mean)	59%	62.9%	0.14
Valvular aortic regurgitation			
No	70%	66.7%	-
Mild	30%	33.3%	-
Moderate	0%	0%	-
Severe	0%	0%	-
Paravalvular aortic regurgitation			
No	10%	55.6%	-
Mild	70%	44.4%	-
Moderate	20%	0%	-
Severe	0%	0%	-

DISCUSSION

The PARTNER trial cohort A results have lifted the TAVI procedure from "alternative procedure" to "non-inferior" compared to surgery in patients acceptable for surgery but with a relatively high risk. However, a new concern appeared, as stroke rates were significantly higher in the TAVI arm compared to the SAVR group (8.3% *vs* 4.3% at 1 year, $P = 0.04$)[11]. This was not totally unexpected, because 3-5% of patients undergoing cardiac surgery suffer a periprocedural stroke[22], and prior studies with TAVI had described similar or even higher subclinical brain ischemic events[13,14].

We analyzed the potential influence that AF, a first-line risk factor for stroke, could have in the stroke rate of the TAVI population. Our cohort had a slightly higher prevalence of AF compared to PARTNER population (50% *vs* 41% in the PARTNER TAVI arm), and interestingly AF patients had higher risk compared to non-AF patients (logistic EuroSCORE 27.9 *vs* 18.7), with otherwise no relevant differences in baseline characteristics. However, this higher risk did not translate into differences in TAVI procedure complications, with only a trend toward a longer hospital stay (14 d *vs* 10 d, $P = 0.22$) and a more frequent need of transfusion in the AF group (29% *vs* 12%, $P = 0.2$). In our cohort, we had no strokes during admission and the stroke rate in the follow-up was as low as 6%, with no differences among groups. The fact that the 2 strokes occurred during follow-up after discharge and not in the peri-operative period does not support the use of embolic protection devices during TAVI, that has been proposed by some groups[23].

Survival and other long-term events were also similar between patients with and without AF before TAVI, as well as prosthesis hemodynamics. The follow-up estimated valve area was higher (non-significantly) in the non-AF group, but that was probably due to the lower number of patients with 26 mm valves in the AF group. This is supported also by the similar gradients found in both groups (Table 4).

In spite of the long experience with bioprosthesis, treatment at discharge of patients with aortic bioprostheses is still controversial, and the recommendations after TAVI are based only on expert consensus. Guidelines for the management of patients with valvular heart disease published by the American Heart Association and the European Society of Cardiology all recommend the prescribing of aspirin to all recipients of bioprosthetic heart valves (Class I , Level of evidence C) as well as the consideration of warfarin use during the first 3 mo, notwithstanding the lack of evidence[4,24]. Some studies have found no advantage of 3-mo warfarin treatment in patients with no other indication for anticoagulation[25,26].

Our AF cohort received antithrombotic treatment according to stroke and bleeding scores, as recommended in the AF guidelines and irrespective of the presence of the aortic bioprosthesis[27,28]. This led to similar rates of stroke, major hemorrhage and MACE events, supporting this management.

The main limitation of this paper was the small study population that could make some differences among groups non-significant. Nevertheless this is somewhat balanced with a long-term follow up of the patients, that showed similar survival and event-free survival curves. We performed no routine brain imaging, assuming the under-detection of clinically silent cerebral events, but focused on clinically evident strokes that were of major relevance to the clinician. All treatment data was observational, so it should only be used for hypothesis-generating purposes, with limited value due to the heterogeneity of therapeutic strategies.

In the absence of specific guidelines or previous literature to choose a specific antithrombotic treatment

after TAVI in AF patients, the treatment at discharge was tailored to each patient, according to both bleeding and stroke scores. This treatment obtained similar rates of stroke, bleeding or MACE events during follow-up. In our cohort, AF patients undergoing TAVI had similar prognosis despite the trend toward a higher risk compared with the non-AF patients.

COMMENTS

Background

Transcatheter aortic valve implantation (TAVI) has become a safe and effective alternative for high surgical risk aortic stenosis patients. Stroke rates in a recent randomized trial were found to be superior in the TAVI group than in the surgical group. Atrial fibrillation (AF) is a potential confounding factor as it is related to age and stroke, and has not been studied in this setting. Furthermore, there are no specific recommendations for antithrombotic treatment in the TAVI population, and its influence in the follow-up

Research frontiers

Stroke rates in patients undergoing TAVI procedures are a major concern for the clinician, and the influence of AF in this setting has not been addressed. Antithrombotic treatment of AF patients after TAVI implantation is not well established.

Innovations and breakthroughs

Clinically relevant strokes after TAVI were globally low, and there are no differences among AF and sinus rhythm (SR) patients. Antithrombotic treatment after TAVI tailored according to stroke and bleeding risks, and irrespective of the presence of the transcatheter valve obtained similar stroke rates to SR patients in the follow-up.

Applications

The study suggest tailoring the long-term antithrombotic treatment of AF patients undergoing TAVI to the stroke and bleeding risks, irrespective of the presence of the transcatheter valve. Future studies with larger population should verify this hypothesis and confirm the finding of similar stroke rates in this setting.

Peer review

The paper investigated the potential influence of AF on the stroke rate in a consecutive TAVI collection. Herein, they found no strokes during admission and no differences between the AF- and non-AF-group in the follow up.

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BRIEF ARTICLE

Prognostic significance of heart rate in hospitalized patients presenting with myocardial infarction

Lorenzo Fácila, Pedro Morillas, Juan Quiles, Federico Soria, Alberto Cordero, Pilar Mazón, Manuel Anguita, Cándido Martín-Luengo, Jose Ramón Gonzalez-Juanatey, Vicente Bertomeu, on behalf of the "The Prevalence of Peripheral Arterial Disease in Patients with Acute Coronary Syndrome" (PAMISCA) Investigators

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Abstract

AIM: To investigate the prognostic significance of resting heart rate in patients with acute coronary syndrome (ACS), independent of other known factors.

METHODS: Patients 40 years of age or older who had been admitted with acute coronary syndrome (ACS) to one of the 94 hospitals participating in the Prevalence of Peripheral Arterial Disease in Patients with Acute Coronary Syndrome (PAMISCA) study were included. Patients were divided into two groups based on their resting heart rate (HR $\geqslant$ or < 70 bpm). Complications were recording during a follow-up period of 1 year.

RESULTS: There were 1054 ACS patients analyzed (43.5% with ST segment elevation and 56.5% without elevation). Mean age was 66.6 ± 11.7 years, 70.6% were male and 29.4% of subjects were female. During follow-up, more patients in the HR $\geqslant$ 70 bpm group were hospitalized for heart failure and they also had a higher mortality rate. In the multivariate analysis, a heart rate of $\geqslant$ 70 bpm was independently related to overall mortality during the follow-up period (hazard ratio 2.5; 95% confidence interval, 1.26-4.97, P = 0.009).

CONCLUSION: A resting heart rate $\geqslant$ 70 bpm in patients who survive an ACS is an indicator of a high risk of suffering cardiovascular events during follow-up.

Key words: Heart rate; Myocardial infarction; Prognosis

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INTRODUCTION

Heart rate (HR) is increasingly being postulated as a modifiable risk factor for cardiovascular disease. Previous studies have shown a relationship between elevated resting HR and the risk of cardiovascular disease in the general population[1] and in patients with stable coronary artery disease with or without hypertension[2-6]. However, the threshold at which risk increases in coronary patients and the quantitative relationship between HR increase and outcome are less well defined. Data from the Coronary Artery Surgery Study suggested that risk increases at around 83 beats per minute (bpm) and above[2], whereas analysis by the International Verapamil SR/Trandolapril Study suggested increased risk above 75 bpm, well below the conventional definition of tachycardia (> 90 bpm)[7]. The results of the BEAUTIFUL study (Evaluation of the if inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) have recently demonstrated that, in a large population with coronary artery disease and left-ventricular systolic dysfunction who were well treated in terms of cardiovascular prevention, a resting HR at baseline of ⩾ 70 bpm is a marker for subsequent cardiovascular death and morbidity[8]. Results were recently published in patients with heart failure and ventricular dysfunction in whom treatment with ivabradine to decrease HR was effective and reduced cardiovascular risk[9].

There are few observational studies[10] which have analyzed the prognostic impact of resting HR in patients with acute coronary syndrome (ACS), independent of the presence of factors associated with advanced arteriosclerotic heart disease (peripheral artery disease and kidney disease). The objective of this study is to analyze the prognostic impact of resting HR in patients who have survived the acute phase of a coronary syndrome, establishing the cut-off point at 70 bpm as in the BEAUTIFUL study.

MATERIALS AND METHODS

The PAMISCA registry (Prevalence of Peripheral Arterial Disease in Patients with Acute Coronary Syndrome), is an observational, prospective, multicenter study, designed to investigate the prevalence of peripheral arterial disease in patients admitted to Spanish hospitals with a diagnosis of ACS. A detailed description of the method used in the PAMISCA registry has been published previously[11]. Informed consent was obtained from all patients and the study was carried out following the principles of the Declaration of Helsinki (Edinburgh Amendment, 2000). The study was approved by an ethics committee. Data on risk factors, cardiovascular history and medical treatment of ACS patients were collected at discharge using a standard questionnaire. Cardiovascular risk factors included hypertension, diabetes mellitus, hypercholesterolemia, smoking habit, previous ischemic events (ACS, stable angina, stroke) and previous heart failure (hospital admission). Left ventricular ejection fraction was obtained by trans-thoracic echocardiography or ventriculography during catheterization. Glomerular filtration rate, assessed by the Modification of Diet in Renal Disease Study equation, was also recorded. HR was determined between day 3 and 7 of the event, once the patient was stable. The study population was divided into subgroups, depending on whether a patient's HR was ⩾ or < 70 bpm, with the differential characteristics of each subgroup being studied. This cut-off point was selected in accordance with the most recent bibliography[8].

Follow-up of the study population

Patients were followed up to 12 mo after hospital discharge to ascertain the occurrence of clinical events. Clinical complications were defined by the registry investigators' committee and included in the data questionnaire. The primary endpoint was mortality (cardiovascular and non cardiovascular death). Secondary endpoints were hospital admission for myocardial infarction (elevation of serum markers of myocardial damage), heart failure, angina, coronary revascularization and stroke. Angina was defined as the presence of chest pain or discomfort with dynamic changes in the electrocardiogram. Heart failure was defined as the new onset of signs and symptoms of abnormal cardiac function and one imaging diagnosis (X-ray verification of pulmonary congestion or echocardiography diagnosis of left ventricular systolic or diastolic dysfunction). All cardiovascular endpoints were confirmed by hospital reports. Every case of death reported by the medical staff was certified by the investigator of each hospital (death certificates or hospital records at the time of death, or direct contact with the family of patients). Follow-up was performed by medical visits or telephone calls.

Statistical analysis

All data collected in the study was described in terms of central trend, dispersion measurements and relative frequencies. The Student *t* test was used for comparison of quantitative variables, the Chi-squared test for comparison of the categorical variables and one-way analysis of variance for comparison of the continuous variables between multiple groups. We used a Cox multivariate regression analysis with adjustment based on the likelihood ratio. The variables entered into the model were those with a *P* value < 0.1 in the univariate analysis: age, sex, hypertension, diabetes, previous myocardial infarction, previous stroke, ejection fraction < 40%, end-stage renal disease, revascularization at admission (thrombolysis or percutaneous coronary intervention), treatment at discharge with aspirin, clopidogrel, statins, β-blockers or angiotensin receptor blockers, existence of peripheral vascular disease, and HR ⩾ 70 bpm. Calibration of the multivariate model was tested by Hosmer-Lemeshow statistic and the discriminative power by the area under the ROC (receiver-operating characteristics) curve obtained by the analysis of the probability of the prognostic value of the multivariate model. The Kaplan-Meier survival method was used for the comparison of survival according to the HR (⩾ or < 70 bpm) using the log-rank test. A value of $P \leqslant 0.05$ was considered statistically significant. Data were analyzed using SPSS 15.0 software (SPSS Inc., Chicago, IL).

Table 1 Baseline characteristics (mean ± SD) *n* (%)

	HR < 70 (*n* = 480)	HR ⩾ 70 (*n* = 561)	*P*
Mean age	65.8 ± 11.9	67.3 ± 11.4	0.035
Women	128.0 (41.7)	179.0 (58.3)	0.037
Abdominal circumference (cm)	99.5 (11.9)	100.3 (13.0)	NS
Body mass index	28.1 (3.9)	28.1 (4.0)	NS
Hypertension	372.0 (77.5)	470.0 (83.8)	0.011
Diabetes mellitus	136.0 (28.3)	236.0 (42.1)	< 0.001
Dislipidemia	416.0 (86.7)	471.0 (84.0)	NS
Smokers	144.0 (30.3)	154.0 (27.5)	NS
History of heart disease	208.0 (43.3)	234.0 (41.7)	NS
History of CVA	37.0 (7.7)	57.0 (10.2)	NS
Peripheral Artery Disease	62.0 (12.9)	108.0 (19.3)	0.004
Previous heart failure	22.0 (4.6)	61.0 (10.9)	< 0.001
EF < 40%	32.0 (7.5)	83.0 (17.0)	< 0.001
Mean SBP (mmHg)	124.3 (18.5)	129.6 (22.4)	< 0.001
Mean DBP (mmHg)	71.8 (11.2)	74.2 (13.4)	NS
Mean HR (bpm)	60.3 (5.9)	80.6 (12.6)	< 0.001
Glucose (mg/dL)	116.7 (46.5)	131.4 (55.0)	< 0.001
Hemoglobin (g/L)	13.6 (1.6)	13.2 (1.9)	0.002
Total cholesterol (mg/dL)	180.6 (40.3)	180.9 (42.8)	0.015
LDL cholesterol (mg/dL)	109.9 (34.1)	109.5 (34.6)	NS
Creatinine (mg/dL)	1.03 ± 0.31	1.13 ± 0.82	NS
GFR (mL/min every 1.73 m^2)	77.70 ± 23.80	75.30 ± 26.10	NS
ASA	409.0 (87.6)	446.0 (86.1)	NS
Diuretics	81.0 (16.9)	137.0 (62.8)	0.003
β-blockers	387.0 (80.6)	379.0 (67.6)	< 0.001
Calcium antagonists	72.0 (15.0)	119.0 (21.2)	0.010
ACE inhibitors	255.0 (53.1)	304.0 (54.2)	NS
Angiotensin Ⅱ receptor blockers	51.0 (10.6)	80.0 (14.3)	NS
Statins	413.0 (86.0)	453.0 (80.7)	0.025
Coronary revascularization (PCI/thrombolysis)	294.0 (61.2)	287.0 (53.9)	0.001

HR: Heart rate; EF: Ejection fraction of the left ventricle; SBP: Systolic blood pressure; CVA: Cerebrovascular accident; DBP: Diastolic blood pressure; ASA: Acetylsalicylic acid; ACE: Angiotensin converting enzyme; GFR: Glomerular filtration rate; LDL: Low density lipoprotein cholesterol; SD: Standard deviation; PCI: Percutaneous coronary intervention.

Table 2 Outcomes *n* (%)

	HR < 70 (*n* = 480)	HR ⩾ 70 (*n* = 561)	*P*
Total deaths	13 (2.7)	45 (8.0)	< 0.001
Cardiovascular death	11 (2.3)	35 (6.2)	0.001
Non-cardiovascular death	2 (0.5)	10 (1.8)	0.035
Hospitalized for heart failure	22 (4.6)	63 (11.2)	< 0.001
Revascularization (PCI or surgical)	48 (10.0)	53 (9.4)	NS
Hospitalized for AMI	22 (4.6)	31 (5.5)	NS

HR: Heart rate; PCI: Percutaneous coronary intervention; AMI: Acute myocardial infarction.

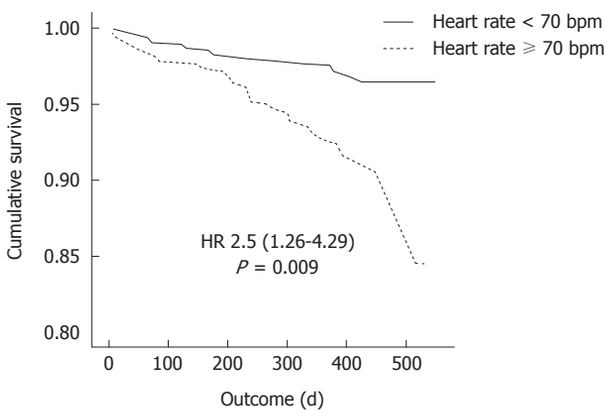

Figure 1 Kaplan-Meier curve for cumulative survival. Threshold heart rate (HR) ⩾ or < 70 bpm.

RESULTS

Baseline characteristics

A total of 1410 patients were included in the baseline study and 13 died before hospital discharge. Investigators were then invited to provide follow-up for the 1397 remaining patients for 1 year. A total of 23 investigators participated in the study, while 241 patients declined the invitation. Therefore, the prospective phase of the study included 1156 patients; 1054 (91.2%) of these completed follow-up. The analysis was carried out in 1054 patients with ACS, of which 43.5% had ST segment elevation and 56.5% had no ST segment elevation. The mean age of included patients was 66.6 ± 11.7 years, 744 (70.6%) were male and 310 (29.4%) were female. Table 1 presents the characteristics of the study population.

Fifty-three percent (53%) of patients had a resting HR ⩾ 70 bpm. These patients were elderly with a higher percentage of women, hypertension, diabetes, history of heart failure and diagnosed with peripheral artery disease (Table 1). During admission, these patients had higher blood sugar and cholesterol levels, while their hemoglobin levels were lower. Mean systolic blood pressure was higher in patients with HR ⩾ 70 bpm, as was the percentage of patients with left ventricular ejection fraction < 40% at admission. Patients with HR ⩾ 70 bpm received more diuretics and calcium antagonists, while the use of β-blockers, statins and coronary revascularization was lower (Table 1).

During the follow-up period of approximately 1 year (median 382 d, interquartile range 66), patients with HR ⩾ 70 bpm had a poorer outcome (Figure 1), with more hospitalizations for heart failure and higher cardiovascular and non-cardiovascular mortality rates. No differences were observed with respect to ischemic complications (re-infarction or need for revascularization) (Table 2).

In the multivariate analysis, HR ⩾ 70 bpm was independently correlated with mortality during follow-up (hazard ratio 2.5; 95% confidence interval (CI), 1.26-4.97, $P = 0.009$), along with peripheral artery disease during hospitalization, ejection fraction < 40%, age and type 2 diabetes mellitus. In-hospital revascularization (in the form of thrombolysis or angioplasty) acted as a protective factor (Table 3). The multivariate analysis was accurately calibrated (P = NS; $\chi^2 = 18.5$) and had discriminative power (area under the curve 0.81; 95% CI, 0.74-0.90, $P < 0.01$).

DISCUSSION

Our study revealed the prognostic significance of resting

Table 3 Multivariate analysis using Cox regression of overall mortality

Variable	Hazard ratio	95% CI	*P*
Heart rate ⩾ 70 bpm	2.50	1.26-4.97	0.009
Peripheral artery disease	1.51	1.14-2.01	0.004
Revascularization at admission	0.53	0.29-0.97	0.040
EF < 40%	1.87	0.98-3.58	0.057
Age (per year)	1.08	1.03-1.12	< 0.001
Type 2 diabetes mellitus	1.80	1.01-3.22	0.047

EF: Ejection fraction of the left ventricle. The analysis includes: treatment with β-blockers, acetylsalicylic acid, angiotensin converting enzyme inhibitors, sex, history of ischemic heart disease and previous heart failure and all the variables in the table. C-Statistic: 0.61.

HR in patients who survived ACS. We found that HR ⩾ 70 bpm identified a population that is at high risk of suffering cardiovascular events (death or heart failure) during follow-up.

These results confirm those from studies which demonstrated that baseline HR is directly and independently related to ischemic events, sudden death, cardiovascular death and mortality from any cause, both in patients with known ischemic events and in the normal population or in patients with increased cardiovascular risk[2,7,8]. It is probable that HR is not only a prognostic marker, but also has a detrimental cardiovascular effect due to several mechanisms: (1) an atherogenic effect (an increase in shear stress in the artery which causes increased parietal stress and decreased distensibility); (2) increased sympathetic tone (which would induce a procoagulant state); (3) increased blood pressure (regardless of other factors); and (4) an increase in the metabolic needs of the heart. The above abnormalities could explain the cardiovascular complications in these patients[12-15].

The relationship between HR (its increase) and cardiovascular mortality has long been known, but its importance as a risk factor was only established in an article published in 1980 by Dyer *et al*[10]. Subsequently, several studies have observed how, in individuals with no previous evidence of cardiovascular disease, there is a very significant relationship between baseline HR, an increase in blood pressure and the adjusted rate of all fatal and non-fatal coronary events. Risk increased starting at a value of 60 bpm; risk was five times greater if baseline HR was > 90 bpm, regardless of age, sex and weight.

In a sample of 24913 patients with suspected or proven coronary artery disease monitored for an average of 14.7 years, Diaz *et al*[2] recently highlighted that total mortality, cardiovascular mortality and re-hospitalization due to cardiovascular causes were associated with an increase in HR ($P < 0.0001$). Patients with HR ⩾ 83 bpm in the baseline study had total mortality 32% higher than the reference group after adjusting for multiple variables. In our study conducted in patients with acute myocardial infarction who survived after admission, HR ⩾ 70 bpm during hospitalization (once stabilized) was associated with a higher overall mortality, irrespective of important variables such as age, treatment upon discharge or ejection fraction in long-term follow-up. These findings concur with recent data from the BEAUTIFUL study which demonstrated that patients with a history of ischemic heart disease and depressed systolic function who had a resting HR ⩾ 70 bpm were at higher risk of cardiovascular complications and death[8]. However, they did not concur with regard to adverse events, which were not significant in our study. The absence of long-term follow-up in our study could explain these differences.

These epidemiological data are supported by the findings of various clinical trials which have demonstrated that a decrease in HR using drugs, such as β-blockers or ivabradin improves prognosis in patients with acute myocardial infarction[16], heart failure[9,17-20], and angina[21-25], and is an essential part of the beneficial effect of these drugs in prognosis. In this respect, an important finding in our study is the decreased use of β-blockers, statins and coronary revascularization in patients with a higher HR, even though they were at higher risk. The reason behind this therapeutic nihilism could be due to a lack of awareness that increased HR can be related to poorer prognosis and therefore greater risk, in which case therapeutic strategies should be more aggressive.

The limitations of our study are those inherent to any observational registry, from which only an association between variables can be established (and not a cause-effect relationship), the limitations of obtaining medical history data, and of the comorbidities that could explain the changes in HR.

In conclusion, our study reflects that a resting HR ⩾ 70 bpm after an ACS identifies a population that is at high risk of suffering cardiovascular events, with a higher mortality during follow-up. It is possible that more aggressive treatment of these patients, especially with the use of HR-lowering drugs, could translate into an improvement in their prognosis.

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COMMENTS

Background

Heart rate (HR) is increasingly being postulated as a modifiable risk factor for cardiovascular disease. Previous studies have shown a relationship between elevated resting HR and the risk of cardiovascular disease in the general population. There are few observational studies which have analyzed the prognostic impact of resting HR in patients with acute coronary syndrome, independent of factors which suggest advanced arteriosclerotic heart disease (peripheral artery disease and kidney disease).

Research frontiers

HR is of great interest if confirmed as a cardiovascular risk factor, as measures can be taken to reduce it. Thus we are developing a series of drugs for its reduction (such as ivabradine), and for the possible prevention of cardiovascular events.

Innovations and breakthroughs

It is possible that more aggressive treatment of these patients, especially with the use of HR-lowering drugs, could translate into an improvement in their prognosis.

Applications

The study results suggest that the HR is a predictor of cardiovascular events, and treatment to reduce HR is beneficial for patients with ischemic heart disease.

Terminology

HR is the number of heartbeats per unit of time, typically expressed as beats per minute (bpm). HR can vary as the body's need to absorb oxygen and excrete carbon dioxide changes, such as during exercise or sleep. Ivabradine is a novel medication used for the symptomatic management of stable angina pectoris. Ivabradine acts on the If (f is for "funny", so called because it had unusual properties compared with other current systems known at the time of its discovery) ion current, which is highly expressed in the sinoatrial node. If is a mixed Na+-K+ inward current activated by hyperpolarization and modulated by the autonomic nervous system. It is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial (SA) node. Ivabradine selectively inhibits the pacemaker If current in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, slowing the HR and allowing more time for blood to flow to the myocardium.

Peer review

This is a good descriptive study in which authors analyze the the prognostic impact of HR in patients with non-ST elevation acute coronary syndrome (ACS). The authors reflects that a resting HR $\geqslant$ 70 bpm after an non-ST ACS identifies a population that is at high risk of suffering cardiovascular events, with a higher mortality during follow-up. It is possible that more aggressive treatment of these patients, especially with the use of HR-lowering drugs, could translate into an improvement in their prognosis.

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CASE REPORT

Asymptomatic melanoma of the superior cavo-atrial junction: The challenge of imaging

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Abstract

Metastatic lesions in the superior vena cava and the right atrium are difficult to diagnose: in computed tomography (CT), they are easily misinterpreted as artifacts, and the same region may be difficult to access using echocardiography. We present a case of asymptomatic metastasis of a malignant melanoma which was overlooked initially due to deficiencies in imaging. Using 18F-fluorodeoxyglucose positron emission tomography-CT, the metastasis was clearly identified and finally treated successfully. We discuss the diagnostic value of the various imaging modalities for intracardiac masses.

Key words: Cardiac metastasis; Staging; Computed tomography; Positron emission tomography

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INTRODUCTION

The incidence of primary melanomas has increased significantly[1,2]. In autopsy studies, cardiac metastases are shown to be frequent in malignant melanoma (MM) patients[3]. However, *in vivo*, the diagnosis is rarely established. Early stages are usually asymptomatic whereas the occurrence of hemodynamic symptoms often indicates inoperability. Follow-up in melanoma patients usually includes whole body computed tomography (CT) examination. In CT scans, however it may be difficult to identify small cardiac masses due to artifacts secondary to movement and contrast media inflow. In this report we compared different imaging modalities and describe the successful diagnosis and treatment of an asymptomatic metastasis of the right heart.

CASE REPORT

We report the case of a 41-year-old Caucasian with a metastasis in the superior vena cava (SVC). Five years prior to admission, the patient was diagnosed with MM of the left foot. He experienced a 2-year history of recurrent isolated metastases in the ipsilateral groin lymph nodes. Each time the tumors were excised successfully. During his follow-up the patient was asymptomatic and in excellent physical condition. In a whole body contrast-enhanced CT scan, a metastatic lymph node localized near the left common iliac artery was the only pathological finding. An additional 18F-fluorodeoxyglucose positron emission

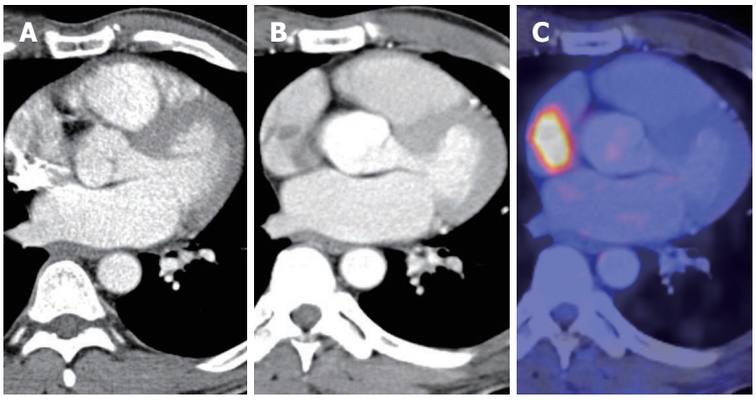

Figure 1 Computed tomography scan. A: Initial computed tomography (CT) scan, with artifacts in the right atrium; B: CT of better quality; C: 18F-fluorodeoxyglucose positron emission tomography-CT with specific tracer accumulation.

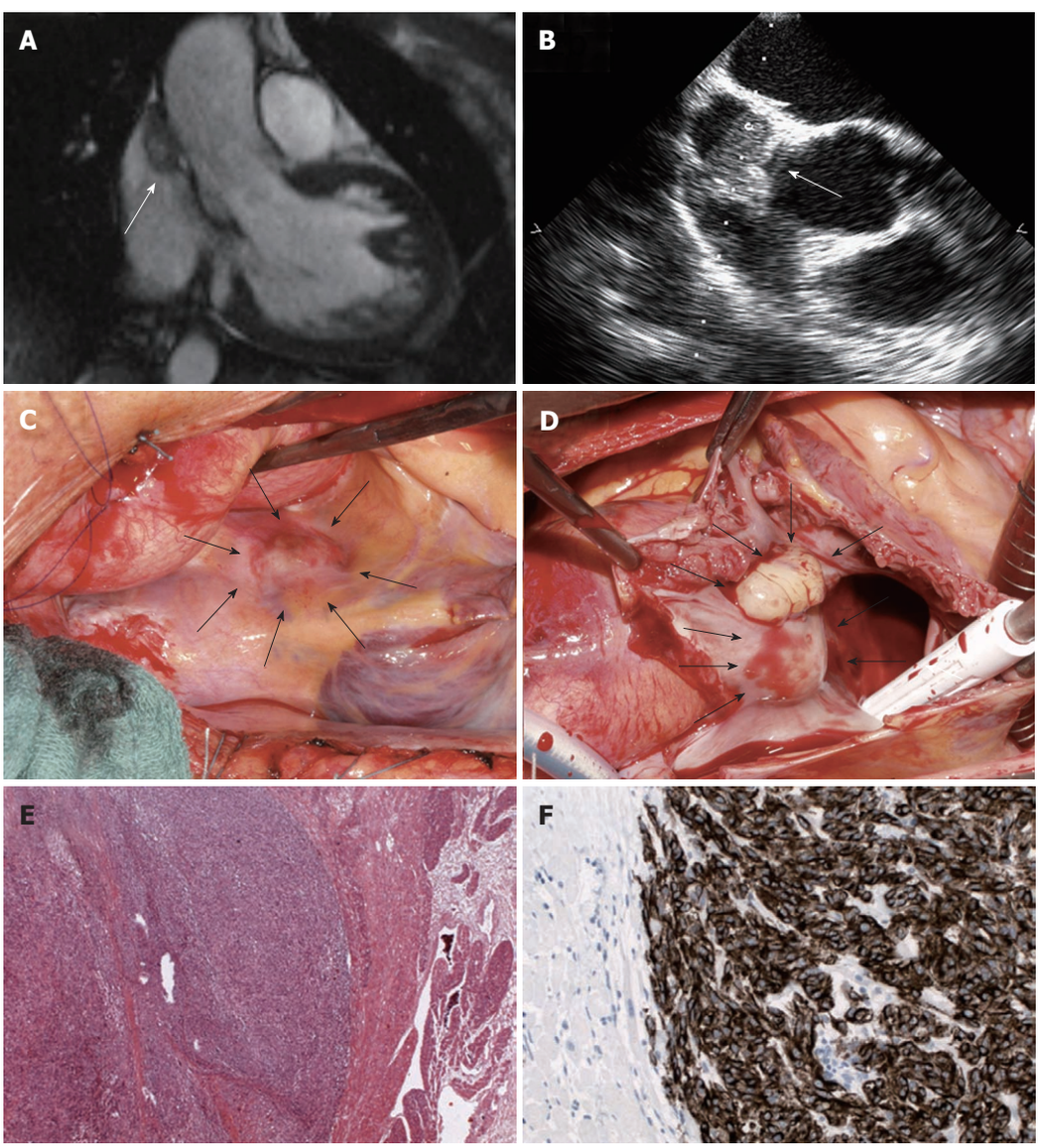

Figure 2 Tumor imaging and histology. Magnetic resonance imaging (A) and transesophageal echocardiography (B) showing the tumor in the inflow of the right atrium. Intraoperative views of the superior vena cava from the outside (C) and the inside (D); Histologic examination reveals intracardiac metastasis of a malignant melanoma (E, F). Arrows indicate tumor localization.

tomography-CT (FDG PET-CT) examination however, showed a high tracer uptake in the SVC close to the right atrium (RA) (Figure 1C). This lesion was not seen in the initial CT scanning due to artifacts caused by contrast media inflow (Figure 1A), but suspected in a CT-scan of better quality (Figure 1 B). Magnetic resonance imaging (MRI, Figure 2A) and transesophageal echocardiography (TEE, Figure 2B) demonstrated a soft tissue nodule in the superior cavo-atrial junction corresponding to the area of PET-CT tracer uptake whereas the tumor was not visible during transthoracic echocardiography (TTE). A combined surgical approach was chosen including resection of the iliac lymph node and the cardiac lesion. Following median sternotomy, the tumor was identified at the superior cavo-atrial confluence. It was completely excised within healthy tissue margins using cardiopulmonary bypass of the beating heart with venous cannulae in the deep jugular and inferior caval veins. The tissue defect was patched with autologous pericardium (Figure 2C and D). The recovery was uneventful and the patient was discharged 7 d after surgery. Histology confirmed a cardiac metastasis of MM (Figure 2E and F).

DISCUSSION

The present case demonstrates potential deficiencies in the diagnosis of cardiac masses. In particular, lesions in the SVC and the RA are easily overlooked or misinterpreted as artifacts in CT. Moreover, the same region may be difficult to access using TTE. On the other hand, PET-CT, MRI and TEE are expensive and of limited availability. However, one should consider the diagnostic values of the various imaging modalities for specific lesions. In the present case, FDG PET-CT scanning revealed the presence of an asymptomatic cardiac metastasis with significant impact on the therapeutic strategy and possibly on patient survival. FDG PET-CT may be a helpful imaging technique for diagnosis and follow-up, especially in patients with melanoma and other malignancies[4,5], in order to detect or exclude additional metastases, particularly in otherwise asymptomatic patients.

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Events Calendar 2012

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

March 30-April 1, 2012
Frontiers In CardioVascular Biology 2012
London, United Kingdom

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

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

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

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

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

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

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

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

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

May 3–5, 2012
EuroPRevent 2012
Dublin, Ireland

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

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

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

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

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

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

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

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

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

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

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

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

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

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

October 20-23, 2012
Acute Cardiac Care 2012
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INSTRUCTIONS TO AUTHORS

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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]

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Personal author(s)

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

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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

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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

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± 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).

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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.

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