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Risk stratification of patients with atrial fibrillation: Biomarkers and other future perspectives

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Abstract

Risk stratification of atrial fibrillation (AF) and adequate thromboembolism prophylaxis is the cornerstone of treatment in patients with AF. Current risk stratification schemes such as the CHADS₂ and CHA₂DS₂-VASc scores are based on clinical risk factors and suboptimally weight the risk/benefit of anticoagulation. Recently, the potential of biomarkers (troponin and NT-proBNP) in the RE-LY biomarker sub-analysis has been demonstrated. Echocardiography is also being evaluated as a possible approach to improve risk score performance. The authors present an overview on AF risk stratification and discuss future potential developments that may be introduced into our current risk stratification schemes.

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Key words: Anticoagulation; Atrial fibrillation; Risk stratification; Stroke; Thromboembolism

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RISK STRATIFICATION OF ATRIAL FIBRILLATION: WHERE DO WE STAND?

Stroke and thromboembolism are among the most severe complications of atrial fibrillation (AF)^[1]. Risk stratification is currently based on clinical risk scores: either the CHADS₂^[2] or the CHA₂DS₂-VASc score^[1] are recommended (Table 1).

The CHADS₂ score has an issue with the identification of low risk patients (those with a score of zero), who cannot be truly classified as low risk, since their annual risk of thromboembolic events is around 1.9% a year^[3]. The recently developed CHA₂DS₂-VASc score has succeeded in identifying a truly low risk group of patients: annual stroke risk of 0%^[4,5]. Unfortunately, it tends to be over-inclusive, referring a very high percentage of subjects to oral anticoagulation. This is worrying since some of these subjects would never experience an event even if they remained untreated and using the CHA₂DS₂-VASc score they become exposed to an increased risk of bleeding (BL).

Despite being easy to use and the best currently available option for decision making concerning anti-thrombotic therapy in AF, risk scores have shown limited capability in predicting thromboembolic events, with low values for area under the curve^[4,6,7]. In the CHA₂DS₂-VASc validation cohort (1,084 patients from the Euro

Table 1 Explaining the CHADS₂ and CHA₂DS₂-VASc risk scores

Risk score	Risk factor	Risk score	Risk factor
C	Congestive heart failure	C	Congestive heart failure (or left ventricular systolic dysfunction)
H	Hypertension	H	Hypertension
A	Age ≥ 75 yr	A ₂	Age 65 to 74 yr Age ≥ 75 yr ¹
D	Diabetes mellitus	D	Diabetes mellitus
S ₂	Stroke or transient ischemic attack ¹	S ₂	Stroke or transient ischemic attack ¹
		VASc	Previous myocardial infarction, peripheral arterial disease or aortic plaque Female

All variables are assigned one point, when present, except those marked with (¹), which receive two points. Subjects with a CHADS₂ score of 0 (low risk) should be placed under antiplatelet therapy, those with a score of 1 (intermediate risk) can either undergo oral anticoagulation or antiplatelet therapy and the remaining (high risk) have clear benefit with oral anticoagulation, unless contraindicated. Using the CHA₂DS₂-VASc score, individuals with a score of zero (truly low risk) should be placed under no treatment (preferably) or, as an option, medicated with an antiplatelet agent. Intermediate risk individuals (score of 1) should be placed under oral anticoagulation (preferably) or antiplatelet agents (as an alternative). The remaining patients (score ≥ 2) should be anticoagulated.

Table 2 Clinical risk stratification scores for patients with atrial fibrillation: pros and cons

In favour
Very simple to understand
Easy to use
Solid evidence supporting the use of these classifications
Patients classified as low risk according to the CHA ₂ DS ₂ -VASc score are truly low risk (annual risk of events 0%)
Against
Limited capability to detect patients at risk of thromboembolism
Patients with a high thromboembolic risk are also bound to present a high bleeding risk
Patients classified as high risk present no additional benefit when treated more aggressively
Individuals classified as low risk with the CHADS ₂ score are not truly low risk: 19% risk at ten years
According to the CHA ₂ DS ₂ -VASc score, almost all individuals should be placed under oral anticoagulation (only 8.4% of subjects were classified as having a score of 0 in the validation cohort of this score ^[5]) and, even in the highest risk score, with a CHA ₂ DS ₂ -VASc score of 9, most patients experienced no events after 5 and 10 yr of follow-up

Heart Survey of AF), the calculated C-statistics suggested a modest predictive value of CHA₂DS₂-VASc (C-statistic = 0.606) and CHADS₂ (C-statistic = 0.561) for predicting thromboembolism^[4].

Another issue with these scores is the fact that they share a large number of risk factors with other scores developed to assess BL risk, namely hypertension, stroke history and age ≥ 65 years, which are variables shared both by the CHA₂DS₂-VASc and the HAS-BLED score^[8]. Thus, those individuals classified as high risk for thromboembolism using the CHADS₂ or CHA₂DS₂-VASc scores, who are referred for anticoagulation, may also have a high risk of BL.

This may have been one of the reasons, in the RE-LY trial sub-analysis, for the failure in finding an incremental benefit of higher doses of dabigatran (150 mg *bid*) *vs* dabigatran 110 mg *bid* using warfarin as the common comparator, in patients with higher CHADS₂ score values^[9].

If we had a score that could discriminate both thromboembolic (TE) and BL risk, placing patients in different categories, we would probably be able to treat patients with high TE + low BL risk more aggressively, and those with low TE + high BL risk in a more conservative way (Table 2).

Other risk classifications (like the CRUSADE bleeding score) have been widely used for predicting BL risk in

other situations, such as coronary artery disease^[10]. However, at the present time, besides HAS-BLED, only the HEMORR2HAGES score^[11] has been tested in patients with AF, which makes assessment of such BL risk scores and comparison with the HAS-BLED a worthy field of research in the next few years.

Major issues concerning these clinical risk stratification scores are addressed in Table 2.

FIRST FAVORABLE EVIDENCE FOR BIOMARKERS

The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) was a non-inferiority trial that aimed to evaluate dabigatran (a direct thrombin inhibitor) *vs* warfarin for the prevention of stroke or systemic embolism. The trial comprised 18113 patients with AF and a risk of stroke (average CHADS₂ was 2.1 ± 1.1) and demonstrated that dabigatran 110 mg *bid* was noninferior to warfarin concerning stroke or systemic embolism (1.69% per year with warfarin *vs* 1.53% with dabigatran; $P < 0.001$ for noninferiority) and resulted in less major bleeding (3.36% *vs* 2.71%, $P = 0.003$). As far as the 150 mg *bid* dose was concerned, dabigatran was more effective in preventing stroke or thromboembolism (relative risk 0.66, 95%

CI: 0.53-0.82, $P < 0.001$) and displayed a similar rate of major bleeds (3.11%, $P = 0.31$) when compared to warfarin. Both dabigatran doses were less frequently associated with hemorrhagic stroke (0.12% for 110 mg *bid*, 0.10% for 150 mg *bid* and 0.38% for warfarin; both comparisons, $P < 0.001$)^[12].

In a recently published biomarker sub-study of this trial which included 6189 patients followed for a median of 2.2 years, the prevalence of NT-proBNP and cardiac troponin I (cTnI) elevation and their role in risk stratification were assessed^[13].

Rates of stroke were independently related to the levels of cTnI (2.09%/year in patients with cTnI ≥ 0.040 $\mu\text{g/L}$ *vs* 0.84%/year in those with cTnI < 0.010 $\mu\text{g/L}$; HR = 1.99, 95% CI: 1.17-3.39) and NT-proBNP (2.30%/year in the highest *vs* 0.92%/year in the lowest quartile group; HR = 2.40, 95% CI: 1.41-4.07). The same was also observed concerning vascular mortality both for cTnI (6.56%/year in patients with cTnI ≥ 0.040 $\mu\text{g/L}$ *vs* 1.04%/year in those with cTnI < 0.01 $\mu\text{g/L}$; HR = 4.38, 95% CI: 3.05-6.29) and for NT-proBNP (5.00%/year in the highest *vs* 0.61%/year in the lowest quartile group; HR = 6.73, 95% CI: 3.95-11.49). Only cTnI was significantly associated with major bleeding. The annual rate of major bleeds was 1.72% in patients with undetectable cTnI and rose to 4.38% in those with cTnI ≥ 0.040 $\mu\text{g/L}$ (HR 2.01, 95% CI: 1.39-2.90). No significant association was found between NT-proBNP levels and major bleeding.

Levels of cTnI and NT-proBNP added prognostic information to the CHADS₂ and CHA₂DS₂-VASc scores, with a significant increase in C-statistics both for the prediction of stroke and systemic embolism, and for the prediction of the composite TE outcome (stroke, systemic embolism, pulmonary embolism, myocardial infarction and vascular death, excluding hemorrhagic death). According to this refinement in risk stratification, a group of patients with CHADS₂ score of 0-1 and elevated biomarkers had a higher annual rate of a composite of TE events than those with higher CHADS₂ scores and undetectable biomarkers. Moreover, some patients with higher CHADS₂ scores and undetectable cTnI could also be correctly reclassified as low risk. Lastly, a group of patients with high clinical risk of TE events and positive biomarkers was found to be in the highest category of risk. Therefore, the authors proposed that additional therapy might be necessary for this high TE risk group. Some of the suggested options were: intensified pharmacologic treatment (angiotensin converting enzyme inhibitors, angiotensin receptor blockers or statins), left atrial (LA) appendage closure and LA volume reduction. Furthermore, risk stratification of coronary artery disease also seemed advisable for this very high group^[13].

With respect to troponin, we propose some explanations for its role in risk stratification: First, embolization of small particles that compose dense spontaneous echocardiographic contrast into the peripheral circulation, namely the coronary tree (causing microvascular ischemia, which leads to raised troponin values) and cerebral

circulation. Second, raised troponin may be a result of LA dysfunction due to a more fibrosed left atrium predisposing to thrombosis. Fibrosis may be related to ischemia of the left atrium wall, and since the atria are thin structures, only small rises in troponin are usually detected. Third, troponin elevation may also be a manifestation of endothelial dysfunction or platelet and coagulation activation leading both to microemboli into the coronary tree and to the development of prothrombotic changes in the left atrium. Finally, it is possible that the raised values might be revealing underlying coronary artery disease that is partially responsible for the adverse prognosis.

Hijazi *et al*^[13] proposed that the level of NTproBNP in AF may reflect some degree of atrial dysfunction, which is known to be a marker of atrial thrombus formation and may provide a plausible explanation for the prognostic significance of raised NTproBNP levels.

This was the first published study concerning the putative role of biomarkers in the risk stratification of AF. Preliminary data exist concerning other plausible biomarkers. Some have been evaluated using transesophageal echocardiography in order to measure their association with markers of LA stasis: C reactive protein (CRP)^[14] and cTnI^[15] have been shown to be associated with LA appendage thrombus (LAAT) and dense spontaneous echocardiographic contrast. Thus, they have been shown to increment the predictive power of CHADS₂ and CHA₂DS₂-VASc to predict these transesophageal changes. Other biomarkers have also been shown to be related to the presence of LAAT, such as NTproBNP^[16] and D-dimers^[17].

Preliminary data from the RE-LY trial in favor of a relationship between some of these markers and clinical events is already available for D-dimers^[18], CRP and interleukin-6 (IL-6)^[19]. Baseline D-dimer levels were significantly associated with the risk of stroke, cardiovascular death and major bleeding. This positive association was independent of CHADS₂ score risk factors.

IL-6 was predictive of stroke and both IL-6 and CRP have been associated with an increased risk of vascular death and cardiovascular events. Only IL-6 was significantly associated with major bleeding^[19] (Table 3).

A small prospective observational study has confirmed the capability of D-dimers for predicting cardiovascular events in patients with AF^[20].

POSSIBLE BENEFIT OF ADDING ECHOCARDIOGRAPHIC PARAMETERS

Transthoracic echocardiography provides a large number of parameters that can be used for improving risk stratification in patients with AF. It is of note that CHA₂DS₂-VASc already includes left ventricle systolic dysfunction as part of the "C"- congestive heart failure^[4].

Most studies concerning the role of LA size as a predictor of TE events have been based on outdated parameters. The mostly widely studied has been LA diameter^[21,22] which is known to represent LA size grossly.

Table 3 Biomarkers associated with thromboembolism in atrial fibrillation

cTnI and NT-proBNP ^[11]	cTnI and NT-proBNP were independently associated with the rate of stroke Both markers were also associated with vascular mortality Only cTnI was associated with bleeding risk
CRP and IL-6 ^[17]	cTnI and NT-proBNP added prognostic information to the CHADS ₂ and CHA ₂ DS ₂ -VASc scores CRP and IL-6 have been associated with an increased risk of vascular death and cardiovascular events
D-dimers ^[16,18]	IL-6 levels were predictive of stroke and major bleeding D-dimers are independently associated with the risk of stroke and cardiovascular death Raised D-dimer levels were associated with major bleeding

cTnI: Cardiac troponin I; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; CRP: C reactive protein; IL-6: Interleukin-6.

Table 4 Echocardiographic parameters associated with thromboembolism in atrial fibrillation

Transthoracic echocardiogram	Left ventricle systolic dysfunction has long been known to be associated with thromboembolism in atrial fibrillation and is currently used in the CHA ₂ DS ₂ -VASc score ^[4] Left atrial diameter was shown to be associated with thromboembolism in old studies. Nowadays, diameter is not considered an appropriate way of assessing left atrial size ^[21] Left atrial area and volume have been shown to be associated with the presence of left atrial appendage thrombus and other markers of left atrial stasis ^[22] . Studies concerning hard clinical endpoints are still lacking ^[23] Left atrial deformation assessment (strain and strain rate) holds promise in this field, since it translates changes in atrial kinetics and function
Transesophageal echocardiogram	Left atrial appendage thrombus, spontaneous echocardiographic contrast and low flow velocities in the left atrial appendage have been associated with a high risk of thromboembolic events and an adverse prognosis ^[22] The invasive nature of this technique makes it inadequate for wide usage in AF patients

Other methods like apical 4-chamber LA area or LA volume (the current gold standard) have been proposed as more accurate^[23]. We have recently demonstrated that by adding echocardiographic parameters (LA area and LV systolic function) to CHADS₂ or CHA₂DS₂-VASc we could achieve a significant improvement in the prediction of transesophageal markers of LA stasis^[24]. An ongoing echocardiographic sub-study from the ENGAGE-TIMI-48 trial will probably clarify this matter using clinical endpoints^[25] (Table 4).

FUTURE PERSPECTIVES

In other fields of cardiology, despite having become more complex and sophisticated, risk scores can now very effectively and accurately predict outcomes. The Grace risk score (GRS), for example, combines the use of clinical, laboratory and ECG data. It requires the use of a calculator for correct assessment, but has become the gold standard for risk stratification in patients with acute coronary syndrome^[26]. Risk models combining clinical and echocardiographic data with biomarkers have not yet been developed for the prediction of thromboembolism in AF. However, we believe that this may be an effective way of fine-tuning the currently available AF clinical risk stratification schemes, further improving their predictive capability.

Due to their complexity, if this type of model ever reaches clinical practice, calculators will be needed to correctly assess the TE risk. This is what currently happens with the GRS, where free calculators are currently available online for global usage^[27]. Despite its higher

complexity, the fact that GRS provides very valuable and accurate information regarding the prognosis of subjects with acute coronary syndrome, and the fact that it can be easily calculated through web applications or calculators, has led to its broad usage worldwide.

Furthermore, TE risk needs a systematic reevaluation and regular adjustment (e.g., annually), unlike what happens in other clinical risk scores where the patient either has the risk factor or not, and once he acquires it, he will preserve it for his entire life.

The immediate cost of the laboratory and echocardiographic assessment for the estimation of risk using combined risk scores can eventually be compensated by the high number of patients that can be spared lifelong anticoagulation due to reclassification into lower risk groups. Moreover, some patients will be reclassified into higher risk classes. If upper reclassified individuals, due to their higher TE risk, are subsequently divided according to their BL risk, we would also likely achieve more net clinical benefit by providing them with more aggressive anticoagulant therapy if they have low BL risk. This may be accomplished either by including risk factors that are only associated with TE events (and have no association with bleeding) or by applying a special adjustment for BL risk (by merging a BL risk score to this tool). Despite the expected increase in complexity, this may lead to a lower incidence of ischemic and bleeding events, and a subsequent decrease in associated costs.

Possibly data from the new anticoagulants mega-trials on AF can be used in the future for this purpose, since a relevant number of the participants have been included in biomarkers (RE-LY and ENGAGE)^[12,25] and echocar-

diographic sub-studies^[25].

CONCLUSION

The CHADS₂ and CHA₂DS₂-VASc scores are extremely useful and simple to use clinical tools for risk stratifying patients with AF. However, they have shown limited power in predicting thromboembolic events.

The incorporation of echocardiographic parameters and biomarkers may be used to further improve these scores. Including variables that could correctly discriminate between TE and BL risk (or adjusting the results according to a BL risk stratification that could be part of the main score) would likely overcome some of the limitations of CHADS₂ and CHA₂DS₂-VASc.

In order to be more accurate, future risk classification schemes may become more sophisticated and complex. A calculator for computing the score will eventually become necessary. Nevertheless, some improvements may arise with complexity, namely the possibility of personalizing treatment and the clear definition of risk groups that can benefit from different therapeutic intensities: a low risk group with less aggressive or nil anticoagulation, an intermediate risk group with standard anticoagulation and a higher risk strata in need of more aggressive therapy (possibly percutaneous closure of the LA appendage alongside standard or higher dosage anticoagulation).

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Effects of ethanol on the properties of platelets and endothelial cells in model experiments

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Abstract

AIM: To investigate effects of ethanol on activity markers of atherosclerosis in an *in vitro* endothelial cell model.

METHODS: After 24 h incubation with ethanol (0.0095%), human umbilical vein endothelial cells were stimulated for 1 h with lipopolysaccharide, and were then incubated in direct contact with activated platelets. Following this incubation, the expression of CD40L and CD62P on platelets, and the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), urokinase plasminogen activator receptor (uPAR), and membrane-type 1 matrix metalloproteinase (MT1-MMP) on endothelial cells were measured by flow cytometry.

RESULTS: The increased expression of VCAM-1 and

uPAR on endothelial cells by proinflammatory stimulation with activated platelets was significantly reduced through pre-incubation with ethanol ($P < 0.05$). Furthermore, platelets in direct contact with ethanol and with endothelial cells pre-incubated in ethanol showed a significant reduction in their CD40L expression ($P < 0.05$). Ethanol had no significant effect on ICAM-1 and MT1-MMP expression on endothelial cells.

CONCLUSION: Ethanol directly attenuates platelet activation and has significant endothelial cell-mediated effects on selected markers of atherosclerosis *in vitro*. These findings underline possible protective effects of ethanol on atherosclerosis.

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Key words: Platelets; Endothelial cells; Ethanol; Inflammation; Atherosclerosis

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INTRODUCTION

Atherosclerosis is a progressive disease characterized by increased expression of proinflammatory markers and

interactions between endothelial cells and platelets^[1,2]. Platelet activation leads to an increased expression of inflammatory factors that stimulate endothelial cells and recruit additional platelets^[3,4]. CD62P and CD40L are expressed on activated platelets and are directly involved in the interaction of platelets with leukocytes and endothelial cells^[5]. Stimulation of endothelial cells and interaction with platelets induces the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which initiate the recruitment of neutrophils, monocytes and lymphocytes^[6,7]. In turn, these result in the expression and release of matrix-degrading proteinases, the matrix metalloproteinases (MMPs)^[8]. In a complex cascade, the urokinase plasminogen activator receptor (uPAR) binds and activates urokinase-type plasminogen activator, and directly degrades various proteins of the extracellular matrix and promotes vascular inflammation.

Augmented and chronic alcohol consumption is accountable for a variety of organ damage including cardiomyopathy^[9], pancreatitis^[10] and chronic alcoholic cirrhosis of the liver^[11]. In contrast, moderate alcohol consumption may reduce the risk of coronary artery disease and total mortality^[12,13]. Therefore, a strict limitation of alcohol consumption (< 30 g/d for men and < 15 g/d for women) is recommended and reasonable. Cardioprotective effects of alcohol may be mediated by antioxidative properties, an increase in high-density lipoprotein (HDL) cholesterol, as well as anti-thrombotic and vasodilatory effects. However, the underlying causative mechanisms remain unclear.

The aim of this study was to investigate the effects of ethanol on the expression of established markers of atherosclerosis on endothelial cells and platelets in an *in vitro* model of atherosclerosis.

MATERIALS AND METHODS

Co-incubation of platelets with ethanol pre-incubated endothelial cells

Human umbilical vein endothelial cells (HUVECs) were prepared as previously described^[14,15] and cultured in endothelial cell basal medium (PromoCell) containing 2% fetal calf serum [1 µg/mL hydrocortisone (HC-500); 0.4% endothelial cell growth supplement (ECGS/H-2); 0.1 ng/mL epidermal growth factor (hEGF-0.05); 1 ng/mL basic fibroblast growth factor (hbFGF-0.5); 5 ng/mL amphotericin and 50 µg/mL gentamicin]. The confluent endothelial cells were added to 12-well plates and incubated for 24 h with ethanol 0.0095% (Merck, Hohenbrunn, Germany). Platelets were prepared from blood of healthy probands as previously described^[16,17]. Washed platelets were stimulated for 30 min with thrombin (0.5 U/mL) and lipopolysaccharide (LPS) (1000 ng/mL). Before coinubation experiments, thrombin activity was antagonized by hirudin (5 U/mL). Pretreated platelets (final concentration 2×10^8 /mL) were added to confluent endothelial monolayers with and without ethanol.

After 60-min co-incubation under cell culture conditions, all platelets were removed by gentle washing, which was confirmed by light microscopy. After an additional 6 h of incubation of the endothelial cells, supernatant was aspirated, centrifuged at 2000 *g* and stored at -80 °C^[18]. Following this incubation, the expression of activity markers on platelets, as well as that on endothelial cells were measured by flow cytometry.

Flow cytometric analysis

Flow cytometric analysis of platelets and endothelial cells was performed by gating in forward and side scatter. Platelets were gated back for determination of the expression of CD40L and CD62P. For the analysis of platelets, 100 µL of each sample were stained for 15 min at room temperature with 10 µL aliquots of mouse anti-human CD40L-FITC antibodies (BD Pharmingen, Heidelberg, Germany) and mouse anti-human CD62P-PE antibodies (Beckman-Coulter, Krefeld, Germany). Endothelial cells were gated back for determination of the surface expression of ICAM-1, VCAM-1, uPAR and membrane type 1 matrix MMP (MT1-MMP). For the analysis of endothelial cells, 100 µL of each sample were stained for 15 min at room temperature with 10 µL aliquots of anti-human CD54 PE-Cy5 (ICAM-1 from BD Pharmingen, Heidelberg, Germany), anti-human CD106-FITC (VCAM-1 from R&D Systems, Inc., Wiesbaden, Germany), anti-human CD87-FITC (uPAR from American diagnostica inc., Stamford, United Kingdom), anti-human MT1-MMP (Ab-1) Mouse mAb (114-IF2) (Merck Chemicals Ltd., Nottingham, United Kingdom). Corresponding isotypes (Beckman Coulter, Marseille, France) were used as a control. All flow cytometric analysis was performed on an EPICS XL-MCL analyzer (Beckman Coulter, Krefeld, Germany) equipped with an argon laser tuned at 488 nm. Mean fluorescence intensity was measured and all FACS data is expressed as MFI in this manuscript. System II Version 3.0 software was used for data acquisition and evaluation. Compensation of the four channel fluorescence was precisely adjusted using Cyto-Comp™ reagents and Cyto-TroITM control cells (Coulter Immunotech/Krefeld, Germany).

Statistical analysis

All calculations were performed using SAS release 9.2 (SAS institute Inc. Cary NC, United States). Numerical data were expressed as mean ± SD. A Student *t* test was applied as a parametric test. A two-tailed probability value < 0.05 was considered significant.

RESULTS

Effects of pre-incubation with ethanol on endothelial cell surface markers

HUVEC pre-incubation with ethanol resulted in decreased surface expression of VCAM-1 and uPAR under proinflammatory stimulation with LPS and by direct endothelial contact with activated platelets compared to HUVEC without ethanol. Pre-incubation with ethanol

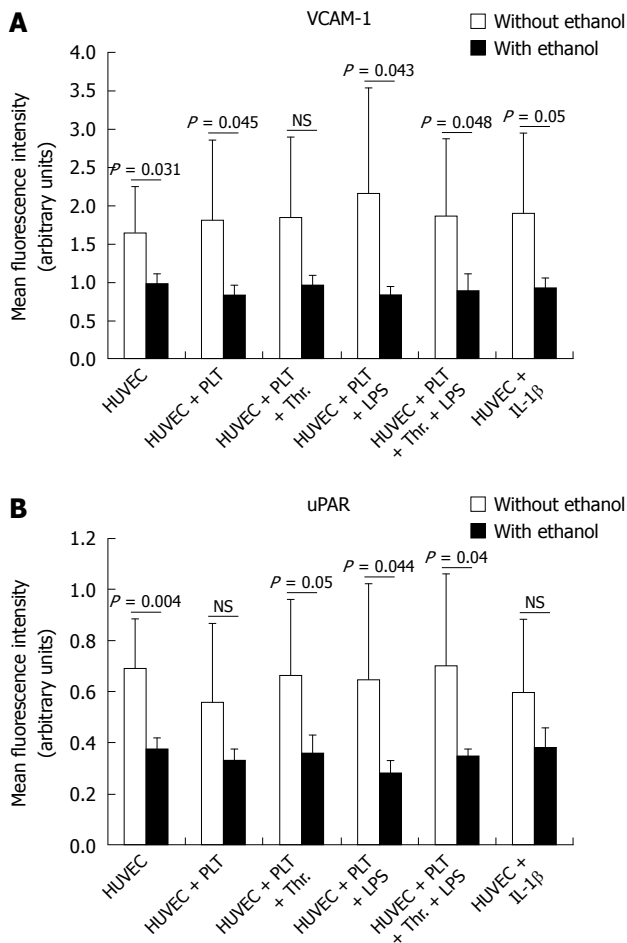


Figure 1 Surface expression of vascular cell adhesion molecule-1 (A) and urokinase plasminogen activator receptor (B) on human umbilical vein endothelial cell with and without 24-h pre-incubation with ethanol. VCAM-1: Vascular cell adhesion molecule-1; uPAR: Urokinase plasminogen activator receptor; HUVEC: Human umbilical vein endothelial cells; PLT: Platelets; Thr.: Thrombin; LPS: Lipopolysaccharide; NS: Not significant.

significantly reduced surface expression of VCAM-1 from 1.809 ± 1.03 to 0.82 ± 0.13 ($P = 0.045$) after contact with resting platelets, from 2.16 ± 1.38 to 0.83 ± 0.11 ($P = 0.043$) after contact with LPS-stimulated platelets, from 1.85 ± 1.02 to 0.89 ± 0.20 ($P = 0.048$) after contact with LPS- and thrombin-stimulated platelets, and from 1.89 ± 1.05 to 0.92 ± 0.11 ($P = 0.05$) after stimulation with interleukin 1- β (Figure 1A). Pre-incubation with ethanol significantly reduced surface expression of uPAR from 0.66 ± 0.30 to 0.35 ± 0.07 ($P = 0.05$) after contact with thrombin-stimulated platelets, from 1.64 ± 0.37 to 0.28 ± 0.02 ($P = 0.044$) after contact with LPS-stimulated platelets and from 0.70 ± 0.35 to 0.34 ± 0.02 ($P = 0.04$) after contact with LPS- and thrombin-stimulated platelets (Figure 1B). Ethanol had no significant effects on ICAM-1 and MT1-MMP expression on endothelial cells.

Endothelial cell-mediated and direct effects of ethanol on platelets

Platelets in direct contact with ethanol-pre-incubated endothelial cells showed a significant reduction in their CD40L expression compared to platelets incubated with

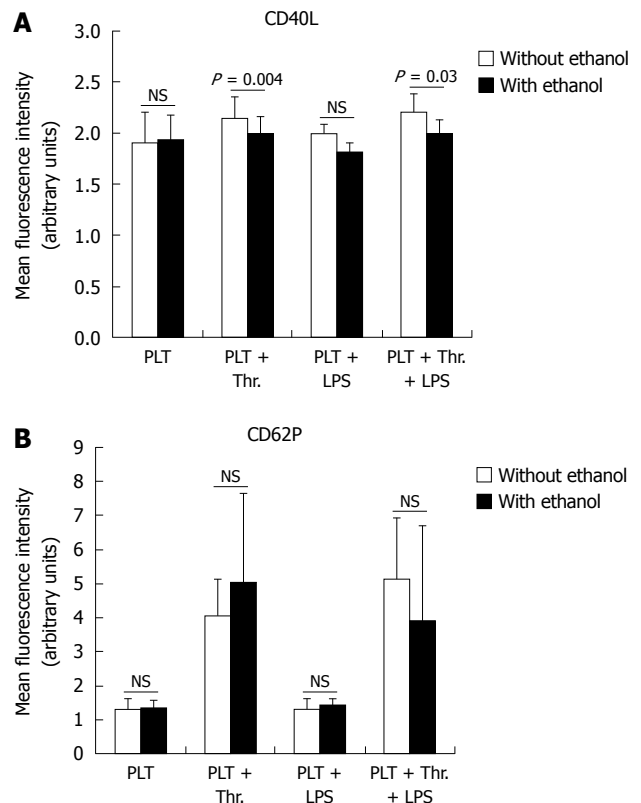


Figure 2 Surface expression of CD40L (A) and CD62P (B) on platelets after 1-h adherence to human umbilical vein endothelial cell with and without ethanol pre-treatment. PLT: Platelets; Thr.: Thrombin; LPS: Lipopolysaccharide; NS: Not significant.

untreated endothelial cells. Surface expression of CD40L on thrombin-stimulated platelets after 1 h in direct contact with HUVECs pre-incubated with ethanol significantly decreased from 2.15 ± 0.19 to 1.98 ± 0.16 ($P = 0.004$) and, when stimulated with thrombin and LPS, significantly decreased from 2.20 ± 0.17 to 1.98 ± 0.14 ($P = 0.03$) (Figure 2A). Ethanol had no significant effects on CD62P on platelets after endothelial cell contact (Figure 2B). To discriminate between effects mediated by pre-treated endothelial cells and possible direct effects of ethanol on platelets, platelets were directly incubated with ethanol alone for 1 h. Here, ethanol incubation significantly decreased CD40L expression on thrombin-stimulated platelets from 2.31 ± 0.17 to 1.92 ± 0.26 ($P = 0.01$) (Figure 3A). Surface expression of CD62P on thrombin-stimulated platelets after 1 h incubation with ethanol was significantly reduced from 3.56 ± 2.17 to 1.83 ± 0.76 ($P = 0.03$) (Figure 3B).

DISCUSSION

Several prospective clinical studies suggest an inverse correlation between moderate alcohol consumption and coronary artery disease. In a prospective study, Rimm *et al.*^[19] studied alcohol intake and prevalence of coronary artery disease in 51 591 males and reported that increasing alcohol intake was inversely correlated with coronary artery disease incidence ($P < 0.001$). Previous experimental

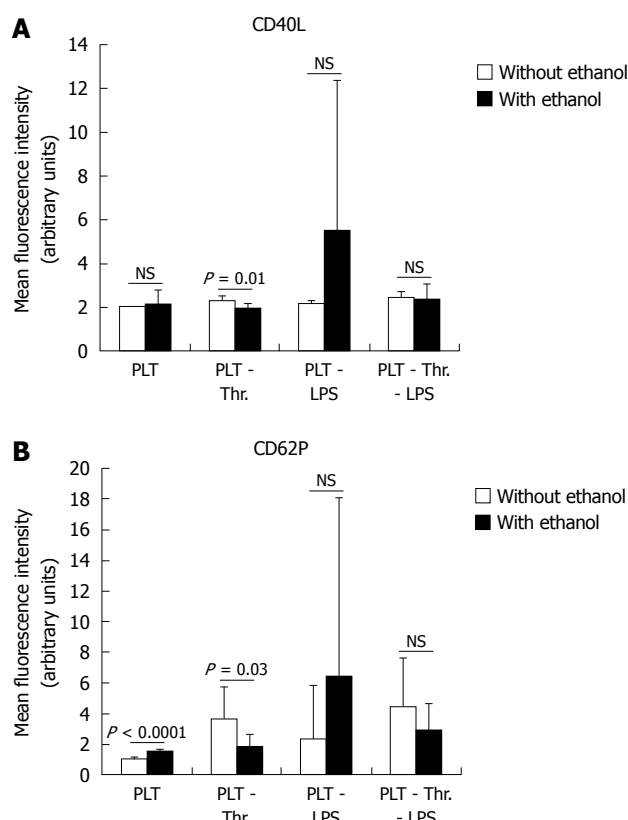


Figure 3 Direct effects of ethanol on surface expression of CD40L (A) and CD62P (B) on platelets. PLT: Platelets; Thr.: Thrombin; LPS: Lipopolysaccharide; NS: Not significant.

studies investigated possible cardioprotective mechanisms of alcohol. Linn *et al*^[20] and Goldberg *et al*^[21] described in a representative sample of the United States adult population, that moderate alcohol consumption (one or two drinks per day) increased circulating levels of HDL by 12% on average. Gil-Bernabe *et al*^[22] compared low- and high-dose treatment with ethanol in a mouse model and showed less dilatation of the aorta and less atherosclerotic plaques in mice treated with low-dose ethanol. Authors discussed the possible mechanism as an increased secretion of stromal cell-derived factor-1 (SDF-1) with subsequent enhanced mobilization of progenitor cells. Although the antiinflammatory signalling mechanisms of ethanol in detail still are unknown, they may be result from an increase in SDF-1 concentration in peripheral blood or an enhancement of the activity of endothelial nitric oxide synthase.

The present study provides further mechanistic insights and evidence for atheroprotective effects of ethanol by demonstrating significantly reduced expression of VCAM-1 and uPAR on endothelial cells after pre-incubation with ethanol and stimulation with activated platelets. VCAM-1 and uPAR are well established atherosclerotic markers and play an important role in the development of cardiovascular diseases. Furthermore this study investigated direct and endothelial cell-mediated effects of ethanol on platelets, and provides evidence that ethanol has significant attenuating effects on CD40L and CD62P expression on platelets. Since the aim of this study was

to investigate effects of moderate alcohol consumption in an *in vitro* endothelial cell model, the experimental condition of alcohol applied in our study (alcohol concentration of 0.0095%) was equivalent to a human blood alcohol concentration of 0.1%. This dose of ethanol therefore is consistent with moderate alcohol consumption in real life. The present study was not designed to assess different ethanol concentrations *in vitro*. The possibility of different effects of different concentrations of ethanol on endothelial and platelet functions therefore cannot be excluded.

In conclusion, the findings of the present study underline possible protective effects of ethanol on atherosclerosis. Ethanol significantly decreased the expression proatherogenic markers on endothelial cells and has direct inhibitory effects on platelets. Further studies are warranted to confirm our results and to expand scientific knowledge about atheroprotective effects of ethanol on endothelial cells and platelets.

COMMENTS

Background

Moderate alcohol consumption may reduce the risk of coronary artery disease and total mortality. This study investigated the effects of ethanol on the expression of established markers of atherosclerosis on endothelial cells and platelets in an *in vitro* model of atherosclerosis.

Research frontiers

Ethanol, at a moderate concentration equivalent to a human blood alcohol concentration of 0.1%, significantly reduced the expression of vascular cell adhesion molecule-1 and urokinase plasminogen activator receptor, on endothelial cells after pre-incubation with ethanol and stimulation with activated platelets

Innovations and breakthroughs

Ethanol can significantly decrease the expression proatherogenic markers on endothelial cells and has direct inhibitory effects on platelets.

Applications

The study underlined possible protective effects of ethanol on atherosclerosis.

Peer review

This is a brief article regarding the possible mechanisms of ethanol on endothelial cells and platelets. This manuscript provides some insights in understanding the effect of ethanol on vessels.

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Acute myocardial infarction: Clinical features and outcomes in young adults in Singapore

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Abstract

AIM: To investigate the clinical features and in-hospital outcomes of young adults with acute myocardial infarction (AMI) in Singapore.

METHODS: Between January 2005 to September 2010, 333 consecutive patients aged ≤ 45 years old were diagnosed to have AMI at our institution. As Singapore is a multi-ethnic society, we also analysed whether ethnic differences exist between the three dominant ethnic groups, Malay, Chinese and Indian with regards to the clinical features. Clinical data was collected retrospectively on demographic characteristics, presenting signs and symptoms, blood investigation, angiographic findings and in-hospital clinical outcomes.

RESULTS: The mean age at presentation was 40.2 ± 4.0 years with male predominance (94%). The majority of patients were Chinese (51%) followed by Indians (31%) and Malays (18%). The most common risk factor was smoking (74%) followed by hypertension (28.5%) and hyperlipidemia (20.0%). 37% of patients were obese. The majority of patients had single vessel disease (46%) on coronary angiography. The mean

total cholesterol, low-density lipoprotein and high-density lipoprotein levels were 5.6 ± 1.2 mmol/L, 3.8 ± 1.1 mmol/L and 0.93 ± 0.25 mmol/L respectively. The mean left ventricular function was $44\% \pm 10\%$ with the incidence of heart failure 3% and cardiogenic shock 4.5%. Overall in-hospital mortality was low with 4 deaths (1.2%). For ethnic subgroup analysis, Indians have a 3-fold risk of developing premature AMI when compared to other ethnic groups.

CONCLUSION: Young AMI patients in Singapore are characterized by male predominance, high incidence of smoking and obesity. Overall in-hospital clinical outcomes are favourable. Among the 3 ethnic groups, Indians have the highest risk of developing premature AMI.

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Key words: Clinical features; Myocardial infarction; Outcomes; Southeast asia; Young

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INTRODUCTION

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. The burden of AMI can be substantial if the individual is relatively young as they are commonly breadwinners of the family and in the prime of their working life with significant contributions

to the society. Several studies^[1-12] have described the clinical profiles and outcomes of young adults with AMI and its incidence ranged between 2% and 10%. In general, young patients are more likely to be male, have a history of smoking and hyperlipidemia but less likely to have other comorbidities and demonstrate less extensive coronary artery disease (CAD) on coronary angiogram. There is limited data^[11,12] on the clinical features of young adults with AMI in the Southeast Asian region. We therefore sought to investigate the clinical characteristics, angiographic findings and clinical outcomes (in-hospital) of young adults with AMI in Singapore. As Singapore is a multi-ethnic society, we also analysed whether ethnic differences exist between the three dominant ethnic groups i.e., Malay, Chinese and Indian with regards to the clinical features.

MATERIALS AND METHODS

Study population

Between January 2005 to September 2010, 333 consecutive patients aged ≤ 45 years old were diagnosed to have AMI at our institution, a tertiary referral centre in Singapore. Clinical data was collected retrospectively from the medical records on demographic characteristics, presenting signs and symptoms, blood investigation, angiographic findings and in-hospital clinical outcomes.

The diagnosis of AMI was defined as the presence of chest pain and/or electrocardiographic changes suggestive of infarction or ischaemia, associated with increased level of cardiac troponins or cardiac enzymes to at least twice the upper limit of the normal value. All the study patients underwent coronary angiography during the index hospitalisation. Angiographic stenosis was defined as diameter reduction of $\geq 50\%$. The culprit artery for AMI was identified based on morphology including complete occlusion, thrombus and ulcerative stenosis or assumed to be the tightest stenosis if these features were absent. The classification of body weight by body mass index (BMI) was according to the World Health Organization recommendation for an Asian population^[13]. A BMI of more than 27 kg/m^2 was defined as obese. The major clinical outcomes (in-hospital) analysed in our study include all-cause mortality, congestive heart failure (New York Heart Association class III-IV), major arrhythmia events (complete heart block, ventricular tachycardia/fibrillation) and cardiogenic shock.

Subgroup analysis by ethnicity

Singapore is a Southeast Asian city-state which has a multi-ethnic population of 5.1 million. There are 3 dominant ethnic groups namely, Malays, Chinese and Indians with the rest being a mixture of minority ethnic group/foreigners. Based on the government census report, the racial composition of Malays, Chinese and Indians in the general population were 13.4%, 74.2% and 9.2%, respectively.

Statistical analysis

Continuous variables were expressed as mean \pm SE of mean. Dichotomous variables were expressed as counts

and percentages. Statistical comparisons were performed using analysis of variance (ANOVA) and chi square test for trend, as appropriate. A statistically significant effect in ANOVA is followed up by Tukey's range test. Calculations were performed using SPSS software (version 16.0; SPSS, Inc., Chicago, Illinois). All *P* values were 2-sided and *P* values < 0.05 were considered statistically significant. All investigations were carried out in accordance with the Declaration of Helsinki and the study was approved by the local ethics committee.

RESULTS

Table 1 shows the baseline clinical characteristics of our patients. For the overall study group, the mean age at presentation was 40.2 ± 4.0 years (range 25 to 45 years) with male predominance (94%). The most common risk factor was smoking (74%) followed by antecedent hypertension (28.5%), hyperlipidemia (20%) and diabetes mellitus (16.5%). The mean BMI was $26.1 \pm 3.8 \text{ kg/m}^2$ with 37% of young adults considered obese by Asian BMI criteria. The most common risk factor newly identified at presentation was hyperlipidemia (28%) followed by diabetes mellitus (13%) and hypertension (3%). The mean total cholesterol, low-density lipoprotein and high-density lipoprotein levels were $5.6 \pm 1.2 \text{ mmol/L}$, $3.8 \pm 1.1 \text{ mmol/L}$ and $0.93 \pm 0.25 \text{ mmol/L}$ respectively. For those with pre-existing diabetes mellitus, the mean HbA1c level was $7.7 \pm 2.3 \text{ mmol/L}$. The mean left ventricular function was $44\% \pm 10\%$. The mean peak creatine kinase was $2227 \pm 2389 \text{ IU/L}$ and Troponin-I level was $36.0 \pm 33.7 \mu\text{g/L}$.

Table 2 shows the clinical presentation, angiographic findings, procedural variables and clinical outcomes of our patients. The majority of patients presented with ST-elevation MI (66.3%) with a slightly higher rate of inferior-posterior MI than anterior MI. By angiographic analysis, the majority of patients (46%) had single vessel disease followed by double vessel disease (26%) and triple vessel disease (23.4%). Occlusive left main disease was present in 11 patients (3.3%) and 14 patients (4.2%) had normal coronary vessels. Two hundred and forty two patients (73%) were treated with percutaneous coronary intervention (PCI) with the rest receiving medical therapy (thrombolysis/anti-thrombotic therapy). The mean number of stents per patient was 1.32 ± 0.65 , mean stent diameter was $3.05 \pm 0.64 \text{ mm}$ and the average length of stents was $21.7 \pm 6.9 \text{ mm}$. The majority of patients (67%) had bare metal stent implantation during PCI.

Overall in-hospital mortality was low with 4 deaths (1.2%). Three patients died due to complications of AMI whereas the 4th patient died of in-hospital sepsis. The incidence of heart failure was 3% and cardiogenic shock was 4.5%. Only 10 patients (3%) required intraaortic balloon counterpulsation for hemodynamic support. The incidence of major arrhythmia events was 7.2%.

Subgroup analysis by ethnicity

Figure 1 shows the relative risk of each ethnic group for developing AMI in relation to racial composition in the

Table 1 Baseline clinical characteristics of patients

	Overall (<i>n</i> = 333)	Malay (<i>n</i> = 59)	Chinese (<i>n</i> = 171)	Indian (<i>n</i> = 103)	<i>P</i> value
Mean age at presentation (yr)	40.2 ± 4.0 (25-45)	40.3 ± 4.8 (25-45)	40.4 ± 3.6 (30-45)	39.9 ± 4.2 (26-45)	0.62
Male:female	329:23 (93.5:6.5)	53:6 (89.8:10.2)	160:11 (93.6:6.4)	100:3 (97.1:2.9)	0.06
Ever smoker	246 (73.8)	48 (81.4)	127 (74.3)	71 (68.9)	0.08
Hypertension	95 (28.5)	15 (25.4)	54 (31.6)	26 (25.2)	0.78
Hyperlipidemia	66 (19.8)	10 (16.9)	32 (18.7)	24 (23.3)	0.28
Diabetes	55 (16.5)	10 (16.9)	23 (13.5)	22 (21.4)	0.31
Mean BMI (kg/m ²)	26.1 ± 3.8	26.2 ± 4.7	25.8 ± 3.6	26.7 ± 3.7	0.15
Newly diagnosed hyperlipidemia	93 (27.9)	19 (32.3)	49 (28.7)	25 (24.3)	0.26
Newly diagnosed diabetes	43 (12.9)	3 (5.1)	23 (13.5)	17 (16.5)	0.047 ^a
Newly diagnosed hypertension	9 (2.7)	5 (8.5)	2 (1.2)	2 (1.9)	0.04 ^a
Mean total cholesterol (mmol/L)	5.6 ± 1.2	5.9 ± 1.1	5.6 ± 1.2	5.5 ± 1.3	0.16
Mean LDL (mmol/L)	3.8 ± 1.1	4.1 ± 1.1	3.7 ± 1.0	3.8 ± 1.1	0.08
Mean HDL (mmol/L)	0.93 ± 0.25	0.92 ± 0.22	0.95 ± 0.27	0.89 ± 0.22	0.14
Mean HbA1c (mmol/L)	7.7 ± 2.3	7.7 ± 2.3	7.4 ± 2.3	8.15 ± 2.4	0.04 ^a
LVEF (%)	44 ± 10	41 ± 10	45 ± 9	43 ± 11	0.008 ^a
Creatine kinase (IU/L)	2227 ± 2389	1870 ± 2064	2350 ± 2656	2220 ± 2055	0.41
Troponin (ng/mL)	36 ± 34	32 ± 34	36 ± 34	38 ± 33	0.55

^a*P* < 0.05. BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; HbA1c: Glycosylated hemoglobin; LVEF: Left ventricular ejection fraction.

Table 2 Clinical presentation, angiographic findings, procedural variables and clinical outcomes (in-hospital) of patients

	Overall (<i>n</i> = 333)	Malay (<i>n</i> = 59)	Chinese (<i>n</i> = 171)	Indian (<i>n</i> = 103)	<i>P</i> value
Presentation					
Anterior STEMI	109 (32.7)	19 (32.2)	59 (34.5)	31 (30.1)	0.68
Inferior/posterior STEMI	112 (33.6)	14 (23.7)	59 (34.5)	39 (37.9)	0.08
NSTEMI	112 (33.6)	26 (44.1)	53 (31.0)	33 (32.0)	0.18
Number of diseased vessels on angiography					
0	14 (4.2)	1 (1.7)	10 (5.8)	3 (2.9)	0.95
1	153 (45.9)	23 (39)	78 (45.6)	52 (50.5)	0.15
2	88 (26)	18 (30.5)	45 (26.3)	25 (24.3)	0.40
3	78 (23.4)	17 (28.8)	38 (22.2)	23 (22.3)	0.40
Left main	11 (3.3)	2 (3.4)	8 (4.7)	1 (1.0)	0.27
Procedural variables					
DES:BMS	80:162 (33:67)	11:26 (29.7:70.3)	45:79 (36.3:63.7)	24:57 (29.6:70.4)	0.75
Mean number of stents	1.32 ± 0.65	1.41 ± 0.72	1.37 ± 0.69	1.21 ± 0.52	0.14
Mean stent diameter,mm	3.05 ± 0.64	3.03 ± 0.72	3.13 ± 0.57	2.94 ± 0.69	0.11
Stent length,mm	21.7 ± 6.9	21.4 ± 7.3	22.4 ± 7.1	20.8 ± 6.4	0.25
Clinical outcomes					
All-cause mortality	4 (1.2)	0 (0)	2 (1.2)	2 (1.9)	0.27
Congestive heart failure	10 (3.0)	2 (3.4)	3 (1.8)	5 (4.9)	0.43
Major arrhythmic event	24 (7.2)	1 (1.7)	17 (9.9)	6 (5.8)	0.32
Cardiogenic shock	15 (4.5)	0 (0)	9 (5.3)	6 (5.8)	0.12

STEMI: ST-elevation myocardial infarction; NSTEMI: Non ST-elevation myocardial infarction; DES: Drug eluting stent; BMS: Bare metal stent.

general population. Indians have a 3-fold risk of developing AMI before age of 46 compared to Malays (1.25-fold risk) and Chinese (0.7-fold risk) respectively. As shown in Table 1, there was no significant difference between the 3 ethnic groups with regards to antecedent cardiovascular risk factors. Indians were however more likely to be diagnosed with new-onset diabetes mellitus at presentation and also, have the highest HbA1c values in pre-existing diabetics when compared with the other ethnic groups. On the other hand, Malays were more likely to be diagnosed with new-onset hypertension at presentation when compared to the rest. As shown in Table 2, there was no significant difference among the 3 ethnic groups in terms of clinical presentation and severity of CAD by coronary

angiography. The incidence of in-hospital major complications and in-hospital mortality also did not differ between the 3 ethnic groups. Although there were ethnic differences in the mean left ventricular function (Table 1), this did not translate to any significant difference in the clinical outcomes.

DISCUSSION

To our knowledge, this is the largest cross-sectional study looking at the clinical profile of young adults with AMI in the Southeast Asian region. Young adults represented 8%-12% of all AMIs during the 5-year study period. Our study demonstrated that young adults with AMI in

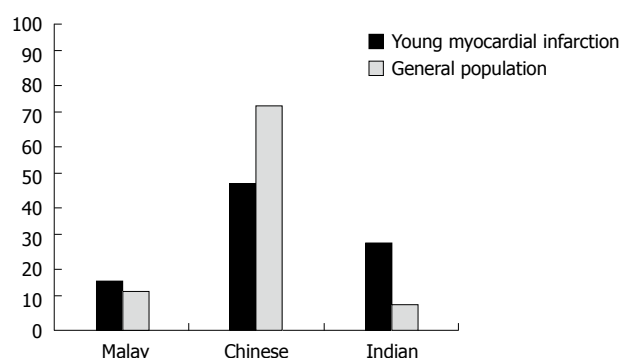


Figure 1 Relative risk of premature acute myocardial infarction of different ethnic groups in relation to racial composition in the general population.

Singapore are characterized by male predominance, high incidence of smoking and obesity. This is consistent with findings of prior studies^[1-12] in which young patients are more likely to be male, have a history of smoking and hyperlipidemia but less likely to have other co-morbidities. Smoking remains the single most important modifiable risk factor in causing premature MI in all the reported studies^[1-12,14]. This is also confirmed in our study as 74% of our patients had history of tobacco use. The other common risk factors are antecedent hyperlipidemia and hypertension with varying rates of prevalence reported in different studies. In our study, 28.5% of patients had antecedent hypertension and 20% had antecedent hyperlipidemia. On the other hand, 16.5% of patients had antecedent diabetes mellitus and this rate is relatively high (> 10%) when compared to other studies. Obesity is also a common risk factor in our patients as 37% were found to be obese at presentation. Both these risk factors are likely a reflection of the rising rate of metabolic syndrome^[15,16] in Asia which is increasingly recognised as a growing public health problem.

Previous studies^[1-11] have shown that young patients demonstrated less extensive CAD on coronary angiogram ie the majority of patients had single vessel disease. This was also true for our cohort of patients, however, the percentage of single vessel disease was < 50% in our study. On the other hand, the percentages of two vessel disease and triple vessel disease were relatively higher, 26% and 23.4% respectively. These angiographic features suggest that our overall cohort of patients have relatively “extensive” CAD at presentation when compared to patients described in prior studies. This finding have potential implications as it suggests our patients might be at higher risk for future major adverse cardiac events if risks factors are not optimally controlled. They also would have a higher likelihood of needing multi-vessel PCI or coronary artery bypass surgery if the CAD progressed.

As for in-hospital clinical outcomes, only 4 patients (1.2%) died during the index hospitalisation. The incidence of heart failure and cardiogenic shock were 3% and 4.5% respectively. Our findings are consistent with results of prior studies^[1-11] which had shown favourable clinical outcomes for young adults with AMI. This is possibly due to better cardiac reserve for young patients (who

have less co-morbidities) with a better capacity to recover from acute cardiac injury than older patients.

Our study is also one of the few studies^[11,12,17] to examine whether there were ethnic differences in clinical features and outcomes in a multi-ethnic population for premature AMI. A local study (inclusive of residents aged 20 to 64 years old) by Mak *et al*^[18] had shown that the MI event rates rate for Indians and Malays were much higher than Chinese with overall rate ratios of 3.1 and 2.1 respectively. We extended this previous observation in a much younger patient population and demonstrated that Indians have a 3-fold risk of developing premature AMI in comparison to the other ethnic groups. Prior studies^[18-22] have shown that Indians have at least double the risk of CAD than than of white patients after adjustment of risk factors. The causes of this ethnic predisposition to CAD are likely to be multi-factorial ie interaction between genetic and environmental factors. The role of inherited predisposition to coronary thrombosis is limited to certain genetic factors as shown by a recent study^[23] in young north Indian survivors of AMI. More importantly, several studies^[19-22] have shown that Indians are prone to developing metabolic abnormalities at a lower BMI and lower waist circumference. They were also found to have high serum levels of apolipoprotein B (which forms low density lipoprotein) and triglycerides and demonstrated low levels of apolipoprotein A1 and high density lipoprotein. All these factors lead to incremental risk of having metabolic syndrome which acts as a “fertile ground” for the development of diabetes mellitus and premature CAD in Indians.

In our study, Indians were more likely to be diagnosed with new-onset diabetes mellitus whereas Malays were more likely to be diagnosed with new-onset hypertension at presentation when compared to other ethnic groups. The former also had poorly controlled diabetes mellitus in those with pre-existing diabetes mellitus. This suggests subtle differences in the risk factor profile for each ethnic group and can help tailor the focus of primary preventive measures.

There were several limitations to our study. Although our sample size was relatively large, our study was a retrospective non-randomised study from a tertiary referral center, hence, selection bias was inevitable and would impact on our findings. Family history do play an important role in contributing to premature CAD but we were not able to evaluate this association adequately in our study due to lack of query/documentation in medical records.

We found that young adults with AMI in Singapore are characterized by male predominance, high incidence of smoking and obesity. Overall in-hospital clinical outcomes are favourable. Among the 3 ethnic groups, Indians have the highest risk of developing premature AMI. Primary preventive measures with special focus on smoking cessation and early screening for modifiable risk factors of CAD remain the best strategy to prevent AMI in young adults in Singapore. Obesity is a growing problem which needs to be tackled aggressively with early intervention programs. Further studies are needed to assess

the long term clinical outcomes of this group of patients with possible genetic studies to look into each ethnic predisposition for premature CAD.

COMMENTS

Background

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. The burden of AMI can be substantial if the individual is relatively young as they are commonly breadwinners of the family and in the prime of their working life with significant contributions to the society. Several studies have described the clinical profiles and outcomes of young adults with AMI but there is limited data on the clinical features of young adults with AMI in the Southeast Asian region.

Research frontiers

The authors therefore sought to investigate the clinical characteristics, angiographic findings and clinical outcomes (in-hospital) of young adults with AMI in Singapore. As Singapore is a multi-ethnic society, the authors also analysed whether ethnic differences exist between the three dominant ethnic groups, Malay, Chinese and Indian with regards to the clinical features.

Applications

The study results showed that young adults with AMI in Singapore are characterized by male predominance, high incidence of smoking and obesity. Overall in-hospital clinical outcomes are favourable. Among the 3 ethnic groups, Indians have the highest risk of developing premature AMI. Primary preventive measures with special focus on smoking cessation and early screening for modifiable risk factors of coronary artery disease remain the best strategy to prevent AMI in young adults in Singapore. Obesity is a growing problem which needs to be tackled aggressively with early intervention programs. Further studies are needed to assess the long term clinical outcomes of this group of patients with possible genetic studies to look into each ethnic predisposition for premature AMI.

Terminology

AMI: Commonly known as a heart attack, results from interruption of blood supply to a part of the heart, causing heart cells to die. This is most commonly due to blockage of a coronary artery which can cause damage or death (infarction) of heart muscle tissue if left untreated for a sufficient period of time; Coronary angiography: A special X-ray evaluation (invasive procedure) of the coronary arteries in which dye is injected down the coronary arteries. The arteries then show up clearly on an X-ray and the exact site and severity of any narrowing of the coronary arteries can be identified; Low density lipoprotein: Commonly known as "bad cholesterol" particles which drive progression of atherosclerosis leading to adverse cardiovascular events and death; High density lipoprotein: Commonly known as "good cholesterol" particles. Higher levels are associated with fewer adverse cardiovascular events and death; Heart failure: The inability of the heart to provide sufficient pump action to distribute blood flow to meet the needs of the body; Cardiogenic shock: Caused by the failure of the heart to pump effectively and is defined by sustained hypotension with tissue hypoperfusion despite adequate left ventricular filling pressure.

Peer review

The authors have performed an interesting descriptive study investigating baseline clinical characteristics and in-hospital outcomes in a total of 333 young AMI patients in Singapore. The authors should be complimented for providing thorough baseline clinical data, angiographic findings and clinical outcomes. The study findings adds important data to the existing literature on premature AMI as data from Southeast Asian region is scarce.

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Repeat recurrence of takotsubo cardiomyopathy related to inhaled beta-2-adrenoceptor agonists

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Abstract

Takotsubo cardiomyopathy (also referred to as transient apical ballooning syndrome, broken heart syndrome or stress cardiomyopathy) is an increasingly recognized entity in the western world typically characterized by reversible left ventricular dysfunction that develops in the setting of acute severe emotional or physical stress. Increased catecholamine levels have been proposed to play a central role in the pathogenesis of the disease, although the specific pathophysiology of this condition remains elusive at the present moment. In recent times, there have been reports of takotsubo cardiomyopathy (TC) following medical interventions such as invasive or surgical procedures or specific medical regimens. In the current report, we present a patient with multiple recurrences of TC triggered by the same medical therapeutic intervention; in our particular case, repetitive exposure to inhaled beta-2-adrenoceptor agonist.

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Key words: Takotsubo; Beta-2-adrenoreceptor agonist; Recurrence; Ventricular dysfunction; Heart failure

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INTRODUCTION

Takotsubo cardiomyopathy (apical ballooning syndrome or stress cardiomyopathy) is an increasingly recognized entity in the western world characterized by reversible left ventricular dysfunction that develops in the setting of acute severe emotional or physical stress. Increased catecholamine levels have been proposed to play a central role in the pathogenesis of this condition^[1]. Recently, there have been reports of takotsubo cardiomyopathy (TC) following medical interventions^[2]. We present a patient with multiple recurrences of TC triggered by the same medical therapeutic intervention; in our case, repetitive exposure to inhaled beta-2-adrenoceptor agonist.

CASE REPORT

A 76-year-old woman with a history of chronic obstructive lung disease, depression and hypertension presented to the emergency department after experiencing worsening dyspnea and wheezing. Upon arrival, she received continuous nebulization of terbutaline and intravenous dexamethasone. Despite continuous therapy and close follow-up, she failed to clinically improve. Six hours after her initial presentation, she reported an oppressive chest pain associated with worsening of her dyspnea. Electrocardiogram showed diffuse prominent T wave inversions that were not present upon admission. Initial set of cardiac enzymes were normal but rose after 6 h with a cardiac troponin I 0.91 ng/mL. An acute coronary syndrome was suspected, and intravenous heparin, aspirin, and beta-blocker were started. An echocardiogram performed at

the bedside showed depressed left ventricular function with an ejection fraction of 40% with apical dyskinesis. Urgent cardiac catheterization was performed demonstrating normal epicardial coronary arteries; left ventriculography showed depressed left ventricular function and an apical ballooning pattern. She was diagnosed with TC and was treated with furosemide, metoprolol and lisinopril that was continued as an outpatient. She soon thereafter recovered, and was discharged on her 4th hospital day. Subsequent echocardiogram 4 wk after discharge showed recovery of ventricular function with ejection fraction of 65% and normal wall motion.

Seven months after her initial presentation, she developed another episode of dyspnea and wheezing, which she described as her usual pulmonary exacerbation. She denied any acute stressors or active illnesses. Her beta-2-agonist rescue inhaler was used more than 20 times per day for 2 d achieving only partial relief. Once again, she presented to the emergency department and received serial treatments with inhaled short acting beta-2-agonists and intravenous steroids with subsequent improvement. Shortly after therapy, she experienced oppressive chest pain and new clinical and radiological signs of pulmonary congestion, leading to progressive hypoxia requiring intubation. A new electrocardiogram demonstrated new diffuse T wave inversions and repeat troponin I levels were now elevated (1.39 ng/dL, normal < 0.9 ng/dL). Cardiac catheterization found absence of obstructive coronary disease and ventriculography showed moderate systolic dysfunction with apical akinesis. She was started on loop diuretics, beta-blockers and an angiotensin-converting-enzyme-inhibitor, after which she markedly improved over the subsequent several days. She was discharged after 5 d in-hospital.

One year after her second episode, she experienced another acute exacerbation of her pulmonary disease, where she was admitted to an outside hospital. During her second hospital day, she developed recurrent chest pain and signs of volume overload with new electrocardiographic changes similar to her prior episodes along with abnormal cardiac enzyme elevations. She was taken urgently to the cardiac catheterization laboratory where no obstructive coronary disease was noted and similar ventriculographic findings were reported (moderate regional systolic dysfunction with apical akinesis).

After the third episode, her medical regimen was changed. Frequent use of beta-2-agonists was discontinued; she has been stable with a regimen of inhaled steroids, ipratropium bromide, lisinopril and metoprolol. As of her last follow-up 6 mo after the third presentation, she has developed mild pulmonary exacerbations but no further episodes of TC.

DISCUSSION

TC usually presents after an identifiable trigger such as an emotional or physical stressor. Prior studies report an identifiable trigger in 66% of the retrospective series

and up to 98% in the prospective series^[3,4]. Common stressors include acute fear or panic after a natural catastrophe, death of a relative or a sense of self danger^[5,6]. Recent reports have proposed acute exacerbations of multiple medical conditions such as asthma, pneumothorax, gastrointestinal bleeding or hypoglycemia as potential triggers^[4]. Common medical interventions have also been found to elicit this phenomenon^[2]. In our case, we hypothesized the use of excessive short acting beta-2-agonists such as albuterol or terbutaline as a possible trigger of this entity. Our patient only developed clinical and electrocardiographic evidence of TC after continuous exposure to beta-2-adrenergic agonists despite the partial improvement of her pulmonary status.

Increase beta-2-adrenoceptor activity in the setting of a high catecholaminergic state has been proposed as possible reproducible model for this entity, inducing cardiac dysfunction and myocyte injury through calcium leakage due to hyperphosphorylation of the ryanodine receptor 2^[7]. Increased beta-2 concentration gradient from apex to base could play an important role in the apical myocardial dysfunction and ballooning commonly found in TC cases^[8]. Furthermore, the characteristic apical contractile dysfunction has been attenuated with the administration of beta-2-adrenergic blockers^[9] and other beta blockers^[10]. Unfortunately, most of this evidence has been gathered from animal experimental studies and most of the presumed pathophysiologic mechanisms are a result of assumption and extrapolation from the animal to the human model.

Recurrence of a TC is a rare phenomenon but has been described previously^[11-13]. Postulated recurrence rates range from 7.7% to 11.4%. To the best of our knowledge, we report for the first time multiple recurrences of TC triggered by the same therapeutic intervention. Our patient was diagnosed 3 times with TC based on the widely accepted Mayo guidelines for TC, notably in the absence of head trauma, intracranial bleeding, pheochromocytoma, hypertrophic cardiomyopathy or myocarditis. Prevention with medical surveillance, changes in her medical regimen and avoidance of proposed triggers, in this case short acting beta-2-agonist use, have been the key to prevent further exacerbations.

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Ventricular fibrillation as primary presentation of takotsubo cardiomyopathy after complicated cesarean delivery

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Abstract

Takotsubo cardiomyopathy typically affects post-menopausal women under severe psychological or physical stress; it also has been reported to develop after medical procedures or surgery. We herein report the rare case of a 30-year-old woman who presented with an episode of ventricular fibrillation after a very complicated cesarean delivery and was successfully resuscitated. Subsequent electrocardiography and echocardiography showed a typical Takotsubo pattern. Within 3 wk, left ventricular systolic function returned to normal.

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Key words: Anesthesia; Ventricular fibrillation; Takotsubo cardiomyopathy; Cardiac arrest; Cesarean delivery; Oxytocin

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INTRODUCTION

Takotsubo cardiomyopathy (TCM), also known as “transient left ventricular apical ballooning syndrome” or “stress-induced cardiomyopathy”, is characterized by reversible left ventricular dysfunction, chest pain or dyspnea, new electrocardiographic abnormalities (ST-segment elevation and/or T-wave inversion) and minor elevations in cardiac enzymes in the absence of significant coronary artery disease^[1].

The pathophysiological mechanism of this syndrome is not completely understood, and several possibilities have been suggested such activation of α - and β -adrenoceptors as triggers of stress-induced physiologic and molecular changes, and catecholamine-mediated myocardial stunning as the result of epinephrine-mediated effects on cardiomyocytes^[2-4]. Patients affected by the disease are predominantly postmenopausal women who experience intense emotional or physical stress and subsequently develop chest pain and dyspnea^[5]. Although cases of TCM in young women during pregnancy and even during delivery have already been described^[6-8], this entity in young premenopausal women appears to be rather unusual.

We herein report a rare case of Takotsubo-like cardiomyopathy which occurred in a young woman after hysterectomy performed for uterine apoplexy after cesarean delivery who presented with cardiac arrest due to ventricular fibrillation.

CASE REPORT

A 30-year-old healthy Asian woman with no risk factors

for coronary artery disease was admitted to our hospital at 40 wk' gestation for elective cesarean delivery because of a macrosomic fetus. Her past medical history was unremarkable. Routine electrocardiography (ECG) recorded prior to delivery was normal.

Cesarean delivery was performed following the administration of standard spinal anesthesia, and oxytocin was administered for easy release of the placenta. Two hours later, the patient underwent emergency hysterectomy and right ovariectomy for hemorrhagic shock due to uterine apoplexy. One hour later, she experienced a cardiac arrest due to ventricular fibrillation; advanced cardiac life support maneuvers and step-by-step adrenaline was immediately performed; sinus rhythm was then restored after 6 DC shocks.

Initial laboratory values showed anemia (hemoglobin 7.6 g/dL), hematocrit 23.2%, low platelet count ($95 \times 10^3/\mu\text{L}$), normal renal and liver function and normal serum electrolytes. Cardiac injury markers were increased (troponin I 2.47 ng/mL, creatine kinase isoenzyme MB 8.97 ng/mL).

In the intensive care unit (ICU) she was intubated, treated with red blood cell and platelet transfusion and received norepinephrine; this treatment rapidly allowed an improvement in the patient's hemodynamic and respiratory status. Twelve-lead ECG obtained soon after ICU admission showed sinus rhythm (90 beats/min) with diffuse T wave inversion and a markedly prolonged QT interval (QTc interval 523 ms) (Figure 1). Shortly after, an echocardiography was performed and showed reduced global left ventricular function with an ejection fraction of 32%, an impairment of contractility of all distal-apical segments, but sparing the base and midventricular regions, and mild mitral regurgitation (Figure 2A and B). Repeated measurements of cardiac injury markers 12 h later, showed a further increase in troponin I (13.49 ng/mL); thereafter, a rapid decrease in troponin I was observed and it normalized within 6 d.

Based on the patient's history and age, and the absence of cardiovascular risk factors, we decided against performing urgent coronary angiography because of the occurrence of a sudden new rapid anemia due to hemoperitoneum requiring an urgent left ovariectomy.

She was successfully weaned off inotropic support 4 d later, and on day 6 she was successfully extubated.

Serial ECG showed stable T wave inversion with a progressive normalization of QT interval and continuous ECG monitoring did not record further ventricular arrhythmias. After 7 d in the ICU, she was transferred to the postnatal ward in good overall condition. A repeat echocardiogram performed 3 wk later, revealed complete normalization of left ventricular function (Figure 3A and B). The patient was discharged on lisinopril 2.5 mg once a day and carvedilol 6.25 mg twice a day on the 24th post delivery day. One month later, the patient was completely asymptomatic and stress myocardial perfusion scintigraphy was normal.

DISCUSSION

Since the first description by Dote *et al*^[9], an increasing

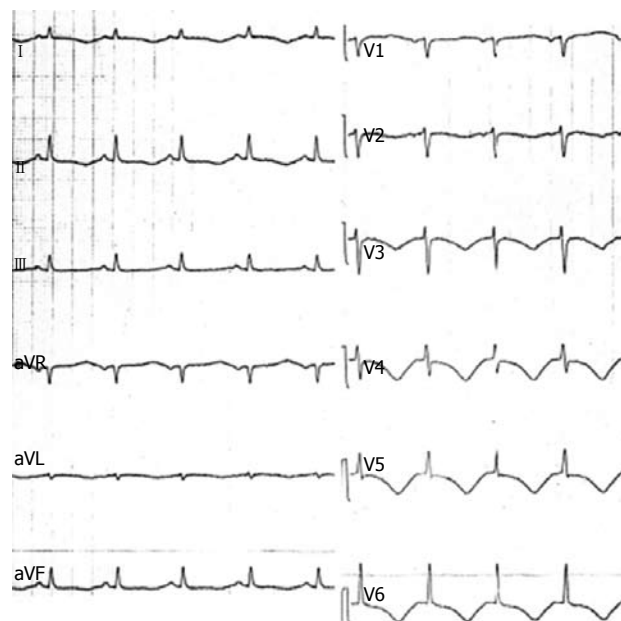


Figure 1 Electrocardiography performed in the acute setting showing diffuse T waves inversion and QT-prolongation.

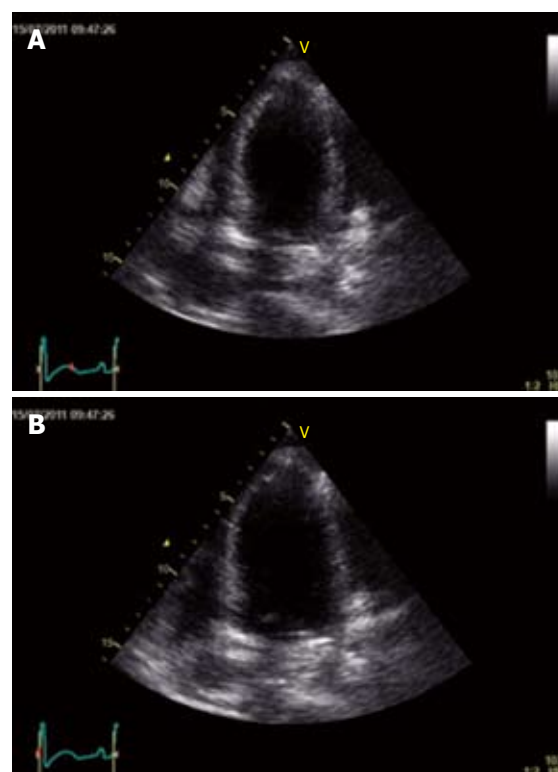


Figure 2 Baseline echocardiography recorded at the end of systole (A) and diastole (B) showing impairment of contractility of all distal-apical segments, but sparing the base and midventricular regions.

number of reports of TCM have been published. The name TCM was given to this entity in the early 1990s of the last century because of the resemblance of the appearance of the left ventriculogram to the traditional Japanese octopus trap or takotsubo. It is a form of reversible cardiomyopathy mimicking acute myocardial infarction

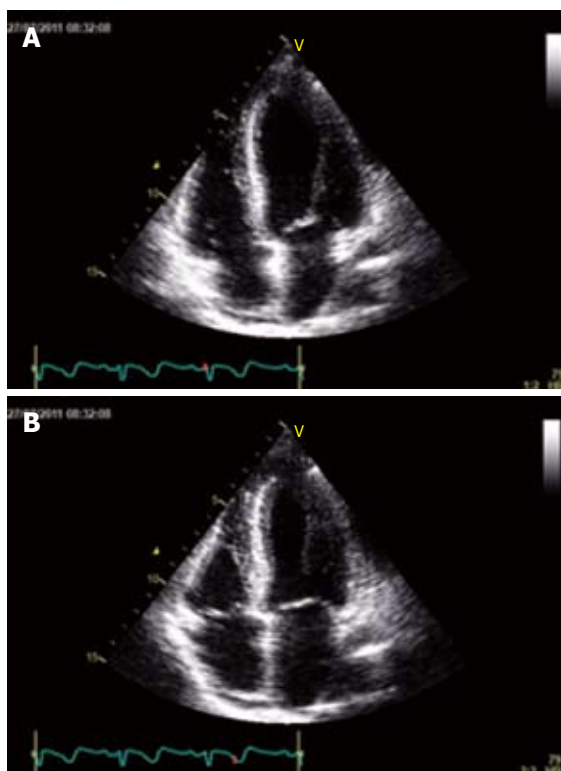


Figure 3 Echocardiography performed 3 wk later showed complete normalization of left ventricular function and resolution of contractility abnormalities, at the end of diastole (A) and at the end of systole (B).

in both symptomatology and ECG findings, but without significant coronary artery disease on angiography^[10].

The condition is typically seen in postmenopausal women, suggesting a protective effect of estrogens, but TCM in pregnant women has also been described in the peripartum period irrespective of mode of delivery^[11,12]. Very recently, Zdanowicz *et al*^[13] reported a case of a young woman undergoing elective cesarean section with apparent symptoms of acute coronary syndrome who was later diagnosed with TCM. The authors also performed a literature search on the occurrence of TCM in pregnancy; they identified 5 other published cases that occurred during elective cesarean delivery at term^[6,7,14-16]. Patients' age ranged from 30 to 42 years and only 2 had cardiovascular risk factors; in 4, the symptoms appeared intraoperatively, and in the remaining 2, symptoms did not appear until after surgery (1 h and a few hours postoperatively). All patients received either spinal or epidural anesthesia combined; this kind of anesthesia is generally perceived as a frightening procedure, especially as patients are awake during the entire process. The authors underlined the role of catecholamines/vasoconstrictive substances and possibly also of oxytocin and prostaglandins.

In our case a combination of extraordinary stress situations was present: a cesarean section performed in an awake patient after spinal anesthesia and oxytocin administration, and a very complicated immediate outcome with severe anemia and hemorrhagic shock which required hysterectomy.

Our patient presented another peculiarity: the initial manifestation was a cardiac arrest due to ventricular fibrillation. Although the electrocardiographic ST-T-wave changes that accompany the presentation of TCM are often associated with prolongation of the QT interval (as in our case), paradoxically ventricular arrhythmias are reported to be uncommon^[17]. In a recent paper, Syed *et al*^[18] reviewed all available series of TCM that reported on arrhythmia and reviewed a total 816 published cases; there were only 15 reported cases of ventricular fibrillation with a prevalence of 1.8%. It is currently unclear whether TCM is the cause or effect of arrhythmia; insight from magnetic resonance imaging has given an understanding of the evolution of TCM at a tissue level, characteristically with an absence of scar formation^[19]. This suggested re-entry was an unlikely mechanism for arrhythmia and supported catecholaminergic, automatic, or fascicular tachycardias as more likely entities, with related cytosolic calcium overload^[18]. In this setting, β -blockers may have a pivotal role, consistent with the finding of Dib *et al*^[20] that suggested that pre-existing β -blocker administration may protect from ventricular arrhythmias.

The optimal duration of ECG monitoring in this condition is unclear, as is the risk of recurrent events after initial recovery. Currently there is insufficient data on which to recommend internal defibrillator use, which, at present, can only be considered on a case-by-case basis^[18].

TCM is characterized by minor elevations in serum levels of cardiac enzymes which is usually not proportional to the initial left ventricular dysfunction. In our patient, a relevant increase in troponin I was recorded but this finding can be explained by the number of delivered shocks required to convert ventricular fibrillation to sinus rhythm. Based on the patient's history and age, with the absence of cardiovascular risk factors, and based on the dramatic clinical course which required 2 surgical interventions because of life-threatening hemorrhagic shock, we could not conduct urgent coronary angiography; nevertheless, the psychological and physical stressful circumstances under which the symptoms appeared, the initial echocardiographic pattern which completely normalized after 3 wk and the absence of inducible myocardial ischemia on a treadmill test seemed to confirm the diagnosis of TCM.

In conclusion, this case demonstrates that TCM may occur in young women with no pre-existing cardiomyopathy and a complicated delivery, especially in combination with spinal anesthesia and oxytocin administration. Women with these characteristics may represent another vulnerable group for TCM; recognition of this disease is clinically important to avoid potentially lethal complications.

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Giant left ventricular pseudoaneurysm presenting with hemoptysis

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INTRODUCTION

Left ventricular (LV) pseudoaneurysm is a contained cardiac rupture, which is sealed by layers of organized thrombus and hematoma. It is encircled by a thin layer of adherent pericardium without any myocardial layer, which makes it susceptible to rupture. The clinical presentation of pseudoaneurysm is variable. We hereby report an unusual case of giant LV pseudoaneurysm, presenting with recurrent hemoptysis and congestive cardiac failure. The role of various imaging modalities and surgical treatment of pseudoaneurysm is discussed.

CASE REPORT

A 60-year-old chronic smoking male presented in August 2009 with symptoms of chronic stable angina class 2 of 1 year duration, which worsened to class 3 in the preceding month. He had suffered an inferior wall myocardial infarction (MI) 3.5 years previously. His general physical examination was unremarkable. His cardiac examination revealed a LV 3rd heart sound, and chest examination revealed basal crepitations in both lung fields. An electrocardiogram showed T inversion in the inferior limb leads. An echocardiogram revealed global LV hypokinesia and an ejection fraction of 0.30. There was no mitral regurgitation. Coronary angiography revealed diffuse 70% mid right coronary artery (RCA) stenosis (Figure 1A). The left coronary artery and its branches were normal. He had

Abstract

Left ventricular (LV) pseudoaneurysm is a late mechanical complication of myocardial infarction (MI). A giant LV pseudoaneurysm is a rare presentation. We report a case of a giant LV pseudoaneurysm in a post MI patient, who presented with hemoptysis. Hemoptysis is a rare clinical presentation of LV pseudoaneurysm. The patient had successful surgical repair of the aneurysm and had a favorable outcome in 9 mo' follow-up. The imaging modalities and surgical treatment of a pseudoaneurysm is discussed.

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Key words: Left ventricle pseudoaneurysm; Hemoptysis; Myocardial infarction; Surgical repair

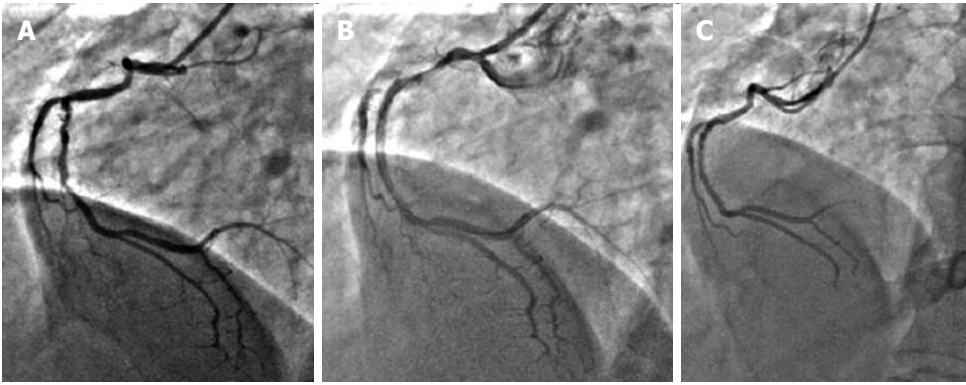


Figure 1 Right coronary angiogram in left anterior oblique 30° view. A: Mid right coronary angiogram (RCA) shows 70% diffuse stenosis; B: Mid RCA shows no luminal narrowing after stenting; C: Patent mid RCA stent at 2 years of follow up.

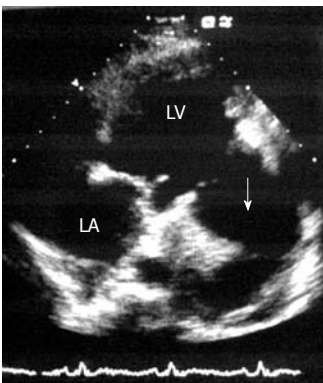


Figure 2 Echocardiography in apical 4-chamber view shows a large sub-mitral pseudoaneurysm (white arrow) containing a thrombus. LV: Left ventricular; LA: Left atrial.

successful percutaneous coronary intervention (PCI) of the mid RCA with a 2.75 mm × 33 mm bare metal stent (Presillion stent, Cordis Corp., Miami, Florida) (Figure 1B). Subsequently, he remained well on medical treatment.

At 2 years' follow-up in July 2011, he presented with recurrent hemoptysis of 1 wk duration. There was about 5-10 mL of blood in each bout of hemoptysis. A chest X-ray showed a cardio-thoracic ratio of 0.75; there was no radiological abnormality in either lung field. An echocardiogram showed a LV ejection fraction of 0.30 and no mitral regurgitation. There was a large LV pseudoaneurysm at the sub-mitral position, measuring 110 mm × 100 mm with a 44 mm neck. The pseudoaneurysm cavity was partially filled with a thrombus (Figure 2). A computed tomography (CT) scan of the chest showed a large contrast filled LV pseudoaneurysm arising from postero-lateral wall (Figure 3A), measuring 110 mm × 100 mm × 78 mm with a 42 mm neck. It was compressing the adjacent bronchus and lung parenchyma. The rest of the lung fields were normal. A small non-delineated communication of pseudoaneurysm with the lung parenchyma or bronchus was considered to be consistent with recurrent hemoptysis. A repeat cardiac catheterization revealed a patent RCA stent (Figure 1C) and normal left coronary artery system. A LV angiogram showed a large pseudoaneurysm arising from the lateral wall of the left ventricle.

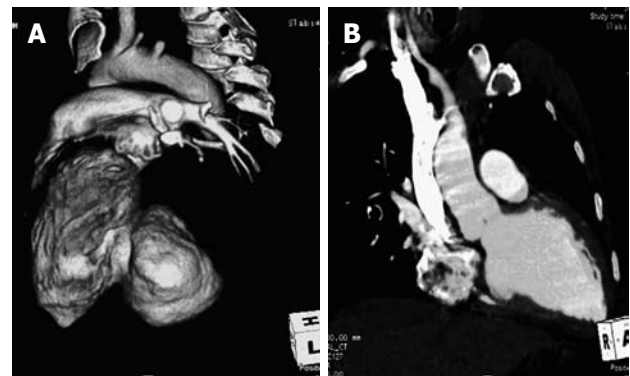


Figure 3 Computed tomography image of the heart. A: Volume-rendered image shows a large pseudoaneurysm arising from the postero-lateral wall of the left ventricle; B: Postoperative reconstructed oblique coronal image shows opacified left ventricular cavity without a pseudoaneurysm.

The patient underwent surgical repair of the pseudoaneurysm. The left lateral wall of the heart was mobilized under cardio-pulmonary bypass. It was densely adherent to the pericardium and adjacent lingular segment of the left lung. Under cardioplegic arrest, the pseudoaneurysm was opened leaving a small rim of sac wall towards the lung. The pseudoaneurysm sac was filled with a blood clot (Figure 4A) and had a circular gap of about 40 mm diameter through which it was connected to the LV cavity (Figure 4B). The defect was closed using a polytetrafluoroethylene (PTFE) patch with interrupted 4-0 Prolene suture (Figure 4C). The false sac was tailored to make two flaps which firmly covered the PTFE patch. Biological glue was spread between the two layers before tying the last suture of the sac. The patient was weaned from cardiopulmonary bypass and had an uneventful postoperative recovery. A postoperative CT scan of the chest revealed normal LV outline without any leakage (Figure 3B). He was discharged on the 7th postoperative day. He remained asymptomatic at 9 mo' follow-up with no recurrence of hemoptysis.

DISCUSSION

LV pseudoaneurysm is seen in patients having MI, cardiac infection, and following cardiac interventions or trau-

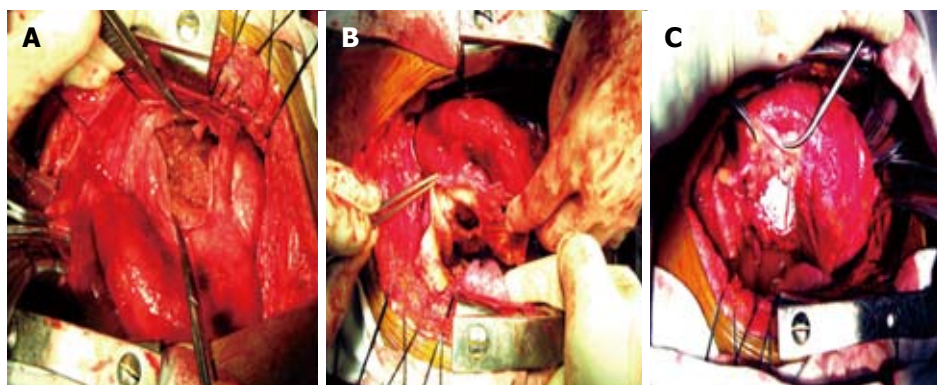


Figure 4 Operative photograph of the pseudoaneurysm. A: Incised pseudoaneurysm sac showing a thrombus in the cavity; B: A circular connection 40 mm in size between the true left ventricular cavity and pseudoaneurysm sac; C: Polytetrafluoroethylene patch repair of the pseudoaneurysm.

ma^[1]. MI is the most frequently observed etiology in LV pseudoaneurysm cases. It is a late mechanical complication of MI presenting within a few months of infarction. A very late presentation after years of MI as observed in the index case is very rare^[2]. There was no evident pseudoaneurysm on echocardiographic evaluation at the time of PCI of the RCA, which was performed 3.5 years after MI. During subsequent follow-up following PCI, his heart failure symptoms were attributed to low ejection fraction of 0.30, though the LV pseudoaneurysm would have also contributed to it. In general, patients do not have specific symptoms pertaining to pseudoaneurysm^[1], hence the timely diagnosis may be difficult. In the index case also, the pseudoaneurysm could have been diagnosed earlier if periodic echocardiography screening was performed following PCI. A giant LV pseudoaneurysm has been reported to cause mitral regurgitation and compression of the adjacent vascular structures^[3-5]; however there were no such complications in the present case. Hemoptysis is a rare presentation of LV pseudoaneurysm^[6]. It occurs following ventriculo-pulmonary communication and, if not diagnosed in time, carries a poor prognosis^[6]. Due to our earlier experience of managing a case of intractable hemoptysis with LV pseudoaneurysm^[6], we suspected pseudoaneurysm in this case also, and confirmed it by echocardiography and a subsequent CT scan. A high clinical suspicion and periodic echocardiographic screening can diagnose this entity in time for it to be properly managed. Both echocardiography and CT angiography are good noninvasive imaging modalities for pseudoaneurysm diagnosis^[1,2,5,6]. A CT scan delineates the extent of a pseudoaneurysm, the involvement of adjacent cardiac and non-cardiac structures, and rules out other primary pulmonary causes of hemoptysis^[6]. Surgery was indicated

in the index case because of the symptomatic status, and the large size and impending rupture of the pseudoaneurysm, as manifested by recurrent hemoptysis. Surgery itself carries a high mortality^[1]. Nevertheless we performed a successful PTFE patch repair of the pseudoaneurysm and the patient had an uneventful 9 mo of follow-up.

In conclusion, LV pseudoaneurysm can be a very late complication of MI. Hemoptysis is a rare presentation of LV pseudoaneurysm and indicates an impending rupture. A high clinical suspicion and periodic echocardiographic screening should be performed for early diagnosis and appropriate management of such cases.

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MEETINGS

Events Calendar 2012

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

March 30-April 1, 2012
Frontiers In CardioVascular Biology

2012
London, United Kingdom

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

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

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

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

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

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

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

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

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

May 3-5, 2012
EuroPREvent 2012
Dublin, Ireland

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

GENERAL INFORMATION

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

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

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

ticles, 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

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Columns

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

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No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

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

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

Conference proceedings

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

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- 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

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

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