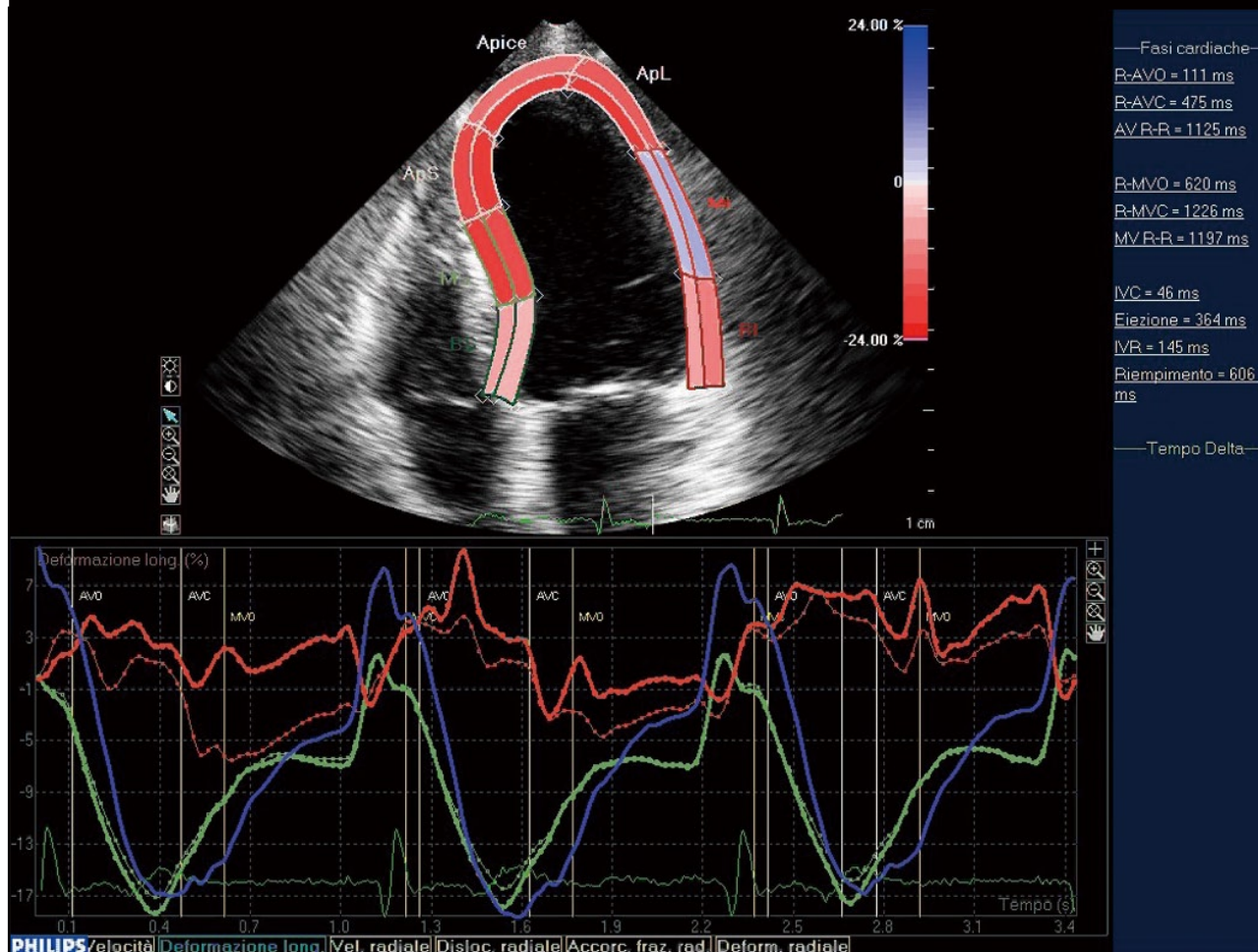




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## Speckle tracking echocardiography: A new approach to myocardial function

Simona Sitia, Livio Tomasoni, Maurizio Turiel

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### Abstract

Echocardiography is the most common diagnostic method for assessing cardiac function but some limitations affect this technique. Until now, visual assessment of wall motion and thickening has allowed only a subjective evaluation of myocardial function and requires long-term training. Recently, new echocardiographic techniques have been introduced to evaluate myocardial mechanics. Tissue Doppler imaging (TDI) technique is limited by angle-dependency such that only deformation along the ultrasound beam can be derived from velocities, while myocardium deforms simultaneously in three dimensions. Speckle tracking echocardiography (STE) is a more recent technique that provides a global approach to left ventricular myocardial mechanics, giving information about the three spatial dimensions of cardiac deformation. In this editorial, we describe the physical and pathophysiological concepts of STE, discussing the differences compared to TDI and underlining the pitfalls of this new technique.

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**Key words:** Myocardial function; Speckle tracking echocardiography; Tissue Doppler imaging

### INTRODUCTION

One of the most important challenges for the cardiologists is the assessment of myocardial function and deformation. Echocardiography represents the most common approach for assessing cardiac function, but is limited by operator-dependency, time-consumption and relatively low sensitivity in detecting subtle abnormalities in myocardial contraction. The early assessment of cardiac involvement is crucial to address therapeutic strategies and to improve the quality of life and the survival of patients in different clinical settings, such as rheumatoid arthritis (RA)<sup>[1]</sup>, renal transplant recipients<sup>[2]</sup>, and systemic inflammatory diseases<sup>[3]</sup>.

Until now, visual assessment of wall motion and thickening according to the recommendations of the American Society of Echocardiography<sup>[4]</sup> has been the most used method to study left ventricular (LV) mechanics, but it allows only a subjective evaluation of myocardial function and requires long-term training.

Furthermore, the visual assessment of LV ejection fraction, which relies mainly on myocardial radial performance with little consideration of longitudinal deformation, is limited by high inter- and intra-observer variability, and provides a subjective evaluation of endocardial thickening and excursion. Thus, we can only

obtain a qualitative assessment of LV function and it is mandatory to highlight that, in different clinical conditions, subtle myocardial function impairment could be present despite normal ejection fraction.

At the same time, LV ejection fraction evaluation using Simpson's biplane method of discs shows some limitations: it is semi-quantitative, operator-dependent and requires an optimal visualization of LV apex and endocardial border.

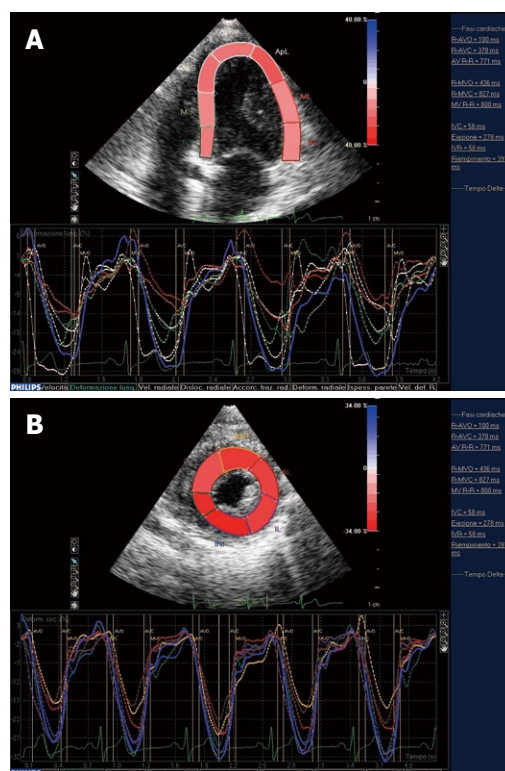
Recently, to overcome standard echocardiographic limitations regarding the study of LV function, tissue Doppler imaging (TDI) has been introduced into clinical practice. It appears more sensitive than ejection fraction for detecting subtle abnormalities in LV myocardial function, but it is limited to longitudinal and radial deformation measurements<sup>[5]</sup>. TDI has been considered a reliable tool to point out subclinical cardiac involvement in systemic sclerosis patients who show normal standard echo parameters<sup>[6]</sup>; moreover, Birdane *et al*<sup>[7]</sup> have demonstrated that RA patients have significant impairment of left and right ventricular TDI parameters compared to healthy controls. However, this method is limited by angle-dependency: whereas myocardium deforms simultaneously in three dimensions, and only deformation along the ultrasound beam can be derived from velocities with TDI<sup>[8]</sup>. In fact, at insonation angle greater than 20 degrees, Doppler-derived deformation is significantly underestimated<sup>[9]</sup>. TDI is also not able to differentiate active and passive myocardial motion<sup>[9]</sup> and high temporal resolution images are required for TDI acquisitions.

Speckle tracking echocardiography (STE) is an emerging algorithm that is able to analyze echocardiographic imaging, which provides an objective and reproducible quantification of global and regional myocardial function.

## STE AND MYOCARDIAL STRAIN

STE is a new technique of two-dimensional echo image analysis that allows the study of regional myocardial deformation<sup>[10]</sup> expressed by a dimensionless parameter, the strain ( $\epsilon$ ), defined by the Lagrangian formula as the percent change from the original dimension<sup>[11]</sup>. On the other hand, displacement reflects myocardial motion: over a defined period of time, if all parts of a myocardial segment have the same motion, the segment will change position (displacement) but not shape (deformation), whereas when different parts of a segment have different motion, there is overall deformation of the segment. Thus, the study of both  $\epsilon$  and displacement allows one to discriminate between passive movement and active contraction of each myocardial segment<sup>[12]</sup>.

As described for the first time by Heimdal *et al*<sup>[13]</sup>, deformation of a tissue occurs over time during the cardiac cycle and the rate of this deformation, the strain rate (SR), is equivalent to the velocity gradient. Myocardial  $\epsilon$  can be determined both by TDI and STE. Different from TDI, STE is an angle-independent technique that may allow an

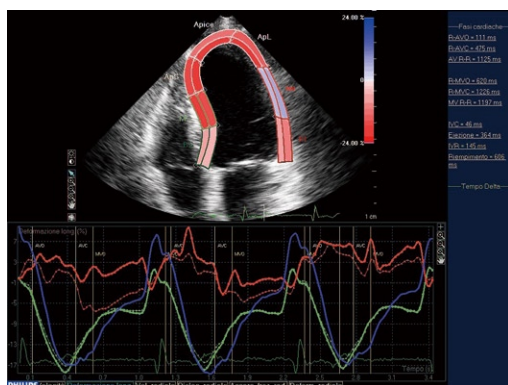


**Figure 1** Systolic myocardial deformation after electro-mechanical activation. A: LV longitudinal strain from the apical four-chamber view: time-strain curves show a negative end-systolic strain representing myocardial shortening during systole; B: LV circumferential strain from the short axis view: time-strain curves show a negative end-systolic strain representing myocardial shortening during systole. End-systole has been identified by the AVC. At this point, we could observe the negative peak of the time-strain curves corresponding to each myocardial segment.

accurate assessment of segmental myocardial deformation by grey-scale based imaging analysis frame by frame. Moreover, the lack of angle-dependency is of great advantage because myocardial  $\epsilon$  could be tracked in two-dimensional echo imaging, along the direction of the wall and not along the ultrasound beam<sup>[8]</sup>. This means that we can analyze myocardial  $\epsilon$  along three spatial axes according to the cardiac muscle physiology. In fact, after electro-mechanical activation, systolic myocardial deformation occurs in three spatial dimensions: a longitudinal and circumferential shortening and a radial thickening. Thus, longitudinal (Figure 1A) and circumferential deformations (Figure 1B) result in a negative  $\epsilon$ , while radial thickening consists of a positive  $\epsilon$ <sup>[14]</sup>. In clinical practice, we can track longitudinal  $\epsilon$  in a four-chamber view with the ultrasound beam along the major LV axis, while circumferential  $\epsilon$  can be detected in the short axis view. Radial  $\epsilon$  can be evaluated in both acoustic windows.

When myocardial deformation is graphically represented as time-strain curves, cardiac cycle phases can be recognized as follows: from the original length, during systole, we observe a negative wave that reaches its peak at the aortic valve closure (AVC), which represents the maximal longitudinal myocardial shortening during con-





**Figure 2 Comparison between epicardial (continuous line) and endocardial border (discontinuous line) in lateral myocardial infarction.** In the mid-septal segment (green line) the endocardial and epicardial curves are indistinguishable and result in an end-systolic shortening, while in the ischemic mid-lateral segment (red line) the epicardial curve separates from the endocardial one. Moreover, in this segment, we can observe the lack of myocardial deformation after the electromechanical activation.

traction. In diastole, strain values progressively increase towards the original length. Recently, the usefulness of STE has been reported to detect early systolic function abnormalities in patients with hypertrophic cardiomyopathy<sup>[15]</sup> and to quantify LV dys-synchrony<sup>[16]</sup>.

Regarding technical issues, STE needs high quality grey-scale images with an optimal frame rate between 50 and 70 frames/s. Amundsen *et al*<sup>[17]</sup> have demonstrated that STE can quantify regional myocardial deformation independently of insonation angle and thus simultaneously assess systolic long-axis and short-axis  $\epsilon$ . Moreover, the same authors have confirmed the accuracy of STE by using sonomicrometry and cardiac magnetic resonance (CMR) imaging as reference methods.

The major clinical applications of STE are represented by the quantitative assessment of regional myocardial function in ischemic disease. Bjork Ingul *et al*<sup>[18]</sup> have described the incremental prognostic value of strain imaging in association with wall motion analysis during dobutamine stress echocardiography. However, this study highlighted the TDI pitfalls that can be overcome by the implementation of STE. As detected by Choi *et al*<sup>[19]</sup>, LV peak systolic longitudinal strain by STE might be a sensitive screening for severe coronary artery disease in the absence of regional wall motion abnormalities at rest.

Leitman *et al*<sup>[10]</sup> have observed that the major difference between normal and ischemic myocardium was the lower peak systolic strain in the hypokinetic segments. Furthermore, STE is able to assess the infarct size adding important diagnostic and prognostic information<sup>[20]</sup>. The study of both epicardial and endocardial border and the comparison between them could provide further information about the transmural of myocardial infarction (Figure 2).

Another interesting challenge for cardiologists is the differentiation between hypertrophic cardiomyopathy and athlete's heart. Even in this field, STE seems to

provide interesting advantages: Richard *et al*<sup>[15]</sup>, comparing global and regional myocardial deformation in professional soccer players, control subjects and patients with hypertrophic cardiomyopathy have suggested that STE analysis can be considered a highly reproducible method to differentiate “physiological” from pathological hypertrophy. A noteworthy application of STE is the evaluation of LV mechanical dys-synchrony. Becker *et al*<sup>[21]</sup> have demonstrated the usefulness of the assessment of circumferential strain in the detailed analysis of the myocardial contraction sequence: the optimal LV lead position results in a greater improvement of LV function and in more reverse LV remodeling.

STE appears to be a reliable tool to detect early subtle cardiac involvement in different clinical settings such as connective tissue diseases<sup>[22,23]</sup>.

Beyond longitudinal and circumferential shortening and radial thickening, LV torsion has been recently evaluated<sup>[24]</sup>. It results from the oblique alignment of the longitudinal fibers arranged in opposite directions between subendocardial and subepicardial layers<sup>[25]</sup>. Until now, CMR with tissue tagging has been used as the gold standard to evaluate LV torsion considering the difference between basal and apical rotation<sup>[26]</sup>. Echocardiography is an alternative noninvasive method and the recent introduction of STE draws new attention to LV torsion. Notomi *et al*<sup>[27]</sup> have demonstrated that STE correlated with CMR assessment of torsion in 13 normal subjects, while Zhang *et al*<sup>[28]</sup> have shown the potential of STE to study the different contribution to LV torsion of the subendocardial and subepicardial myocardium layer. However, further studies are necessary to validate STE in comparison with CMR for the study of LV torsion.

With standard echocardiography, the quantification of regional and global function of the right ventricle is limited by the complex geometry of the chamber. Recently, STE has been used to assess right ventricular free wall longitudinal myocardial deformation in normal subjects<sup>[29]</sup>, and seems to be able to evaluate quantitatively regional and global systolic function of the right ventricle in patients with pulmonary arterial hypertension<sup>[30]</sup>. However, the reliability of STE for the study of the right ventricle function should be validated in larger studies.

## STE LIMITATIONS AND PITFALLS

The major limitation of STE is the need for high quality echocardiographic images because poor endocardial delineation could result in a wrong endocardial border; however, the same situation occurs with manual tracing for measurements of ejection fraction by Simpson's biplane formula. Moreover, reverberations are sometimes tracked or interfere with the frame-by-frame tracking, which results in drift or incorrect calculation of  $\epsilon$  or SR. The optimal frame rate for STE is 50-70 frames/s, lower compared to TDI: this could result in undersampling, especially in patients with tachycardia.

## CONCLUSION

STE is a reliable and feasible tool to evaluate myocardial  $\epsilon$ , which describes the myocardial deformation throughout the cardiac cycle. It seems to overcome the subjective and semi-quantitative study of LV function by visual assessment of wall motion and ejection fraction and appears more trustworthy than TDI. In fact, the lack of angle-dependency allows a global insight in LV myocardial mechanics that investigate circumferential, radial and longitudinal fibers function. Moreover, it is able to provide important information about LV torsion.

Beyond its potential usefulness in the assessment of myocardial viability and follow-up of the ischemic cardiac disease, evidence has underlined the sensitivity of STE to detect early preclinical cardiac involvement in asymptomatic patients affected by connective tissue diseases and data are available about its role in the study of LV dys-synchrony.

In conclusion, STE analysis seems to provide important information regarding the assessment of myocardial function, already applicable primarily in research, but also in clinical settings. The application of STE has been implemented in several experimental and clinical studies, some of which have been cited representatively in this editorial. However, further studies need to be done to introduce this new technique widely in clinical practice.

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## Congenital solitary coronary artery fistulas characterized by their drainage sites

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### Abstract

Last centuries have witnessed tremendous sophistication and progress in the detection, diagnosis and treatment of coronary artery fistulas (CAFs). In many countries, CAFs were reported to be visualized and treated using several imaging techniques and different management strategies. Reports from nearly all continents of the globe have contributed to the description of CAFs, not only in Asia and Europe but also throughout North and Latin America. However, these reports have to be cautiously analyzed as many of them were published as a case report and careful interpretation is warranted due to possible publication bias. A literature search was performed using PubMed search interface to select papers dealing with congenital CAFs in adult population between 2000-2009. A total of 233 subjects were collected, and analysed according to their drainage site and treatment modality. They were divided into two subgroups: percutaneous transluminal embolization group (PTE group,  $n = 122$ ) and surgical ligation group (SL group,  $n = 111$ ). In the SL group, atherosclerotic coronary artery disease (19%) and associated congenital lesions (23%) were more prevalent compared with the PTE group (9% and 8%), respectively. Infective endocarditis was more frequently seen in the SL group besides syncope, congestive heart failure and hemopericardium. In both groups multimodality diagnostic workup composed of several non-invasive

and invasive imaging techniques for fistula visualization were performed and drainage sites into the different cardiac chambers and intrathoracic great vessels were similarly distributed in the two groups.

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**Key words:** Congenital anomalies; Solitary coronary artery fistulas; Adult population; Diagnostic modalities; Therapeutic options

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### INTRODUCTION

When we consider congenital coronary artery fistulas (CAFs), we have to bear in mind that there are two separate entities: solitary CAFs and coronary artery-ventricular multiple microfistulas (MMFs). The current review focuses exclusively on solitary CAFs.

During the last decennia contributions of different investigators, researchers and scientists across the globe guided us to understand more but not yet all about CAFs.

Although coronary angiography (CAG) is the gold standard for detection and visualization of CAFs, other non-invasive techniques are frequently applied to delineate the anatomical morphological features and assess the function of the fistula. These modalities include transesophageal echocardiography (TEE)<sup>[1]</sup>, 2-dimensional echo<sup>[2]</sup>, 3-dimensional TEE imaging<sup>[3]</sup>, cardiovascular magnetic resonance imaging (CMR)<sup>[4]</sup> and multidetec-



tor computed tomography (MDCT)<sup>[5]</sup>. Furthermore, direct imaging, by different modalities, at the time of surgical correction may be required; intraoperative ECG monitoring can be a very useful tool to guide and detect perioperative ischemic changes and TEE is also helpful to demonstrate wall motion abnormalities<sup>[1]</sup> and confirm the complete ligation of the fistula.

In the last decades, CAFs have been more often discovered and diagnosed as a result of initially raised clinical and echocardiographic suspicion and subsequently due to the frequent application of CAG. The angiographic incidence of CAFs is estimated at 0.2%-0.8% of patients undergoing CAG<sup>[6,7]</sup>. While there is a common opinion that surgical or transcatheter intervention to obliterate the fistula and preserve the normal coronary blood flow should be performed in patients with large shunts, documented ischemic changes, threatening future complications, and concomitant congenital or acquired coronary or valvular heart disorders, the optimal management of asymptomatic or mildly symptomatic patients with a medium-sized left-to-right shunt is not yet established. The hemodynamic indication for intervention as assessed by the pulmonary-to-systemic flow ratio should be more than 1.5<sup>[8]</sup>. The current treatment strategies, depending on the magnitude of left-to-right shunt and the morphological features and functional characteristics of CAFs are: watchful waiting and close follow-up, conservative medical management, percutaneous transcatheter "therapeutic" embolization (PTE) and surgical ligation (SL). The reported success rate of PTE in a mixed (paediatric and adult subjects) series of 15 patients of Alekyan *et al*<sup>[9]</sup> in 2002, was 93% with one early death and no recurrence after a follow-up period up to 13 years. Another series in 2001 by Wang *et al*<sup>[10]</sup> demonstrated that surgical closure of the fistula under cardiopulmonary bypass was successful without residual fistula with no mortality or significant morbidity. Early surgical intervention is safe (100% survival and 100% closure rate) in CAFs with a perioperative mortality of 0%-4% with an increasing incidence with age of postoperative surgical complications and sequelae from less than 1% in patients under 20 years of age to 23% in those above 20 years of age<sup>[11,12]</sup>.

A high successful percutaneous closure rate (75%-87%) has been reported by Reidy *et al*<sup>[13]</sup> in the 1990s and Trehan *et al*<sup>[14]</sup> in 2004, respectively. Armsby *et al*<sup>[15]</sup> reported an angiographic recurrence rate of 9% after PTE and the recurrence after surgical closure varied from 16% to 22% as reported by Kamiya *et al*<sup>[16]</sup>.

A literature search was performed using PubMed search engine to select papers published in English language dealing with congenital CAFs in adult population between 2000-2009. References were then cross-checked for other relevant publications. The keywords used were congenital coronary anomalies, CAFs and adult population. The reports were screened for those that stated the drainage site and adult population group. Papers concerning pure paediatric population were neglected. A total of 63 reports were selected.

From the literature between 2000 and 2009, 233 patients who were treated for congenital CAFs were collected. They were divided into two groups according to the treatment strategy. The first group consisted of 122 subjects treated with percutaneous transluminal "therapeutic" embolization (PTE) techniques<sup>[9,14,15,17-27]</sup> and the second group composed of 111 patients was treated with surgical ligation (SL) of the fistula<sup>[3-5,28-34]</sup>.

## TERMINATION SITES INTO DIFFERENT CHAMBERS OF THE HEART AND TO OTHER THORACIC VESSELS

CAFs are abnormal congenital communications between one or more coronary arteries and any cardiac chamber or intrathoracic vessel bypassing the capillary bed and are classified according to Greenberg *et al*<sup>[35]</sup> as anomalies of termination. CAFs are among the most hemodynamically significant coronary artery anomalies<sup>[36]</sup>.

Two distinct congenital types are recognized: solitary CAFs and MMFs<sup>[37]</sup>. Usually fistulas originate from the right coronary artery in 15%-53% and from the left coronary artery in 42%-67% of cases<sup>[2,6,36,38]</sup>. The overwhelming majority is unilateral (80%-89%) followed by the bilateral fistulas (16%) and finally they may involve all three coronary arteries as multilateral fistulas (4%-5%)<sup>[2,6,36]</sup>. Fernandes *et al*<sup>[2]</sup> reported multiple fistulas in 11% of the subjects without differentiation between bilateral and multilateral contribution. It has been noted that bilateral<sup>[39]</sup> CAFs terminate more often into the pulmonary artery (PA) (56%) while in contrast the unilateral CAFs ended in the PA in 17% of the cases<sup>[36]</sup>.

Several authors have disclosed the termination sites of CAFs as indicated in (Table 1)<sup>[16,36,40,41]</sup>. Termination into the right side of the heart occurs in more than 90% of cases<sup>[2,42]</sup>. Generally, acquired CAFs, coronary artery-ventricular multiple microfistulas and paediatric population are excluded from the current review.

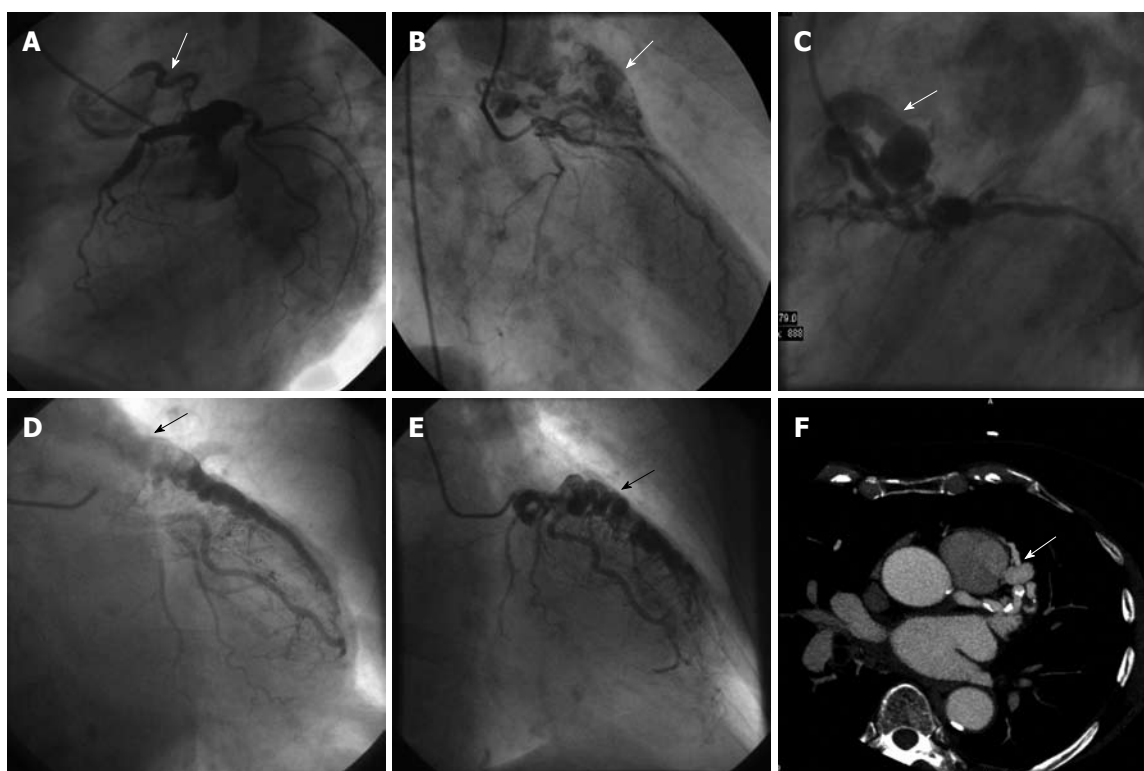
### Right ventricle

Termination into the right ventricle (RV) has been reported from several countries across the globe, Asia and Europe<sup>[9,10,43-45]</sup> represented by several authors. Among the non-invasive diagnostic workup imaging techniques were myocardial perfusion test, echocardiography, CMR and MDCT. The invasive gold standard CAG was performed in all reports. The postoperative course was reported to be uneventful in patients with surgically ligated fistulas<sup>[43]</sup>. Conservative medical management was the therapeutic strategy in the majority of the reports<sup>[9,10,43-45]</sup>. They included symptomatic adult subjects who had continuous cardiac murmur and all were in sinus rhythm.

### Right atrium

Reports about termination to the right atrium (RA) came from North and Latin America<sup>[3,4]</sup>, Asia and Europe<sup>[5,17,18,44-48]</sup>.





**Figure 1** Different morphologic appearances of coronary artery-pulmonary artery fistulas (arrows). A: Left lateral view of coronary angiogram demonstrating a fistula with a single origin, tortuous pathway and single termination (arrow); B: Right anterior oblique (RAO) view showing a fistula with multiple origin and outflow associated with a plexiform pathway (arrow). Shallow filling of the coronary arteries is visible; C: Left lateral projection illustrating a fistula with multiple origin and termination associated with aneurysmal formation (arrow), and total occlusion of the left anterior descending coronary artery (LAD) is appreciated; D and E: Sequential frames in RAO projection depicting a huge tortuous LAD fistulating into the pulmonary artery (arrows); F: Multislice cardiac gated computed tomography scan demonstrating the fistula running from the LAD into the pulmonary artery (arrow), and the fistula is connected to the pulmonary artery at the anterior side.

**Table 1** Termination sites of congenital solitary CAFs (%)

| Termination sites                | McNamara<br>1969 <sup>[40]</sup><br>(n = 172) | Levin<br>1978 <sup>[36]</sup><br>(n = 363) | Hobbs<br>1982 <sup>[41]</sup><br>(n = 122) | Kamiya<br>2002 <sup>[16]</sup><br>(n = 266) |
|----------------------------------|---|--|--|---|
| Right ventricle                  | 40  | 41   | 3  | 34  |
| Right atrium                     | 35  | 26   | 7  | 18  |
| Pulmonary artery                 | 16  | 17   | 66   | 38  |
| Coronary sinus                   | --  | --   | --   | --  |
| Left atrium                      | 6   | 5  | 7  | 2   |
| Left ventricle                   | 3   | 3  | 17   | 5   |
| Superior vena cava               | --  | 1  | --   | --  |
| Right ventricle<br>outflow tract | --  | --   | --   | --  |
| Other sites                      | --  | --   | --   | 3   |

CAF: Coronary artery fistulas; --: Not applicable.

The clinical features were variable including asymptomatic presentations, dyspnoea, congestive heart failure, chest pain, syncope and myocardial infarction<sup>[3-5,17,18,44-48]</sup>. In the reviewed reports, multimodality imaging techniques were instituted including 2D echocardiography<sup>[4,46-48]</sup>, 3D transesophageal echo<sup>[3]</sup>, MDCT, 4-detector row<sup>[47]</sup> or 128-detector row<sup>[5]</sup>, CMR<sup>[4]</sup>, aortogram<sup>[48]</sup>, cardiac catheterization and CAG<sup>[5,17,18,44-47]</sup>.

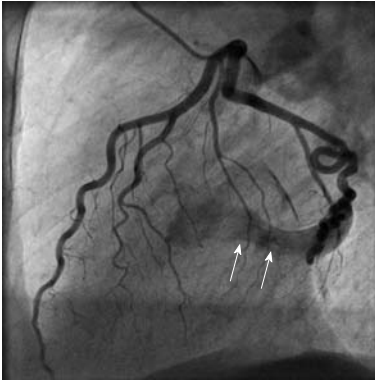
The pulmonary-to-systemic flow ratio was found to be more than 1.5<sup>[17,18,47]</sup>. Normal PA pressure (PAP) was described in some reports<sup>[18]</sup>. Mild to moderate elevation of PAP was also elaborated in some studies<sup>[17]</sup>.

Successful surgical ligation with neither postoperative morbidity nor mortality was performed. The procedures were conducted using cardiopulmonary bypass<sup>[5,48]</sup> or utilizing off-pump technique<sup>[3,4,47]</sup>. In the reports of PTE treated patients, the use of coils<sup>[18]</sup> or Amplatzer duct occluder<sup>[17]</sup> was reported. One report showed complications of myocardial infarction after procedural period<sup>[17]</sup>. The patient required an urgent coronary artery bypass grafting.

## PA

Many papers have reported the drainage of the fistula to the PA (Figure 1). These originated from different continents, Europe<sup>[19,20,28-30,45,49-51]</sup>, Africa<sup>[52]</sup>, Asia<sup>[21,22,53-60]</sup> and North America<sup>[23]</sup>.

Many reports were published describing unilateral<sup>[19,28,30,45,53,58]</sup>, bilateral<sup>[21,29,54,57]</sup> and multilateral<sup>[60]</sup> coronary artery-PA fistulas. All reports included adult symptomatic patients presented with typical or atypical chest pain, acute coronary syndrome, dyspnoea, syncope, fatigue, arrhythmias or congestive heart failure. Non-invasive and invasive diagnostic multimodalities were established and included the following techniques: echocardiography, CMR, myocardial perfusion test, MDCT, cardiac catheterization and CAG<sup>[19-23,28-30,45,49-60]</sup>. The treatment modalities in these reports were conservative medical management, SL with extra corporeal circulation or without cardiopulmonary bypass and endovascular closure of the fistula. The materials used for transcatheter



**Figure 2** A fistula originating from the circumflex coronary artery and terminating into the coronary sinus (arrows).

occlusion of the fistula were coils, detachable balloon and stent-graft (Jostent). Among those reports of surgical or non-surgical exclusion of the fistula, there was no significant morbidity or mortality. One report described the successful application of a harmonic scalpel during SL of quadruple fistula all draining into the PA<sup>[57]</sup>.

### Coronary sinus

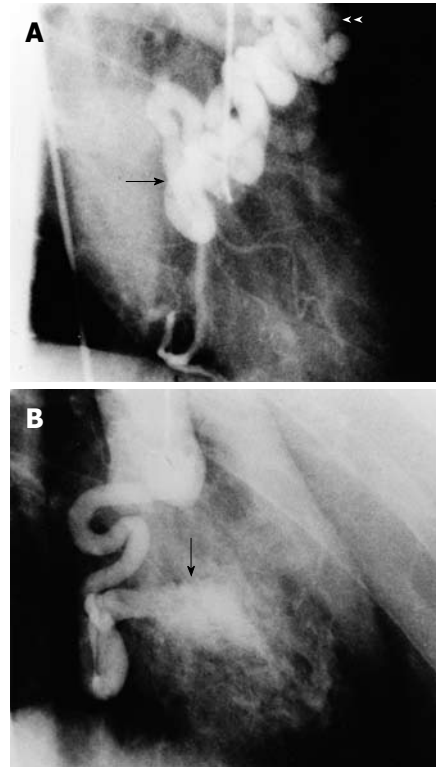
Drainage into the coronary sinus (CS) (Figure 2) has been reported in the world literature from the following continents; Australia<sup>[61]</sup>, Europe<sup>[62-68]</sup>, Asia<sup>[69-76]</sup> and North America<sup>[31,32,77]</sup>.

It was found in these reports that the patients may have lack of symptoms throughout life and others may develop or possess gradual progression of symptoms over the years varying from 5 to 40 years<sup>[67,69,71]</sup>. While some become symptomatic in infancy and childhood requiring early management. The reports<sup>[61-68]</sup> included patients presented with dyspnoea, typical and atypical chest pain, palpitation, atrial fibrillation, continuous cardiac murmur, pericardial effusion and cardiac tamponade<sup>[69-75]</sup>, infective endocarditis, congestive heart failure, abnormal echocardiographic findings, respiratory tract infection and vertigo<sup>[31,32,76,77]</sup>.

Multimodality imaging for the precise diagnosis of CAFs (origin, pathway and termination) is essential. This provides complete anatomical and functional data. Several reports described the diagnostic workups, including non-invasive and invasive techniques such as myocardial perfusion test, transthoracic and TEE, MDCT, CMR, cardiac catheterization and CAG<sup>[31,32,61-77]</sup>. None of the reports mentioned the use of intracoronary Doppler ultrasound.

The reported pulmonary-to-systemic flow ratio was found to be significant<sup>[61,67,69-71,75-77]</sup> in some papers and negligible in others<sup>[62,63]</sup>, calculated by the oxymetric method in all<sup>[61-63,67,69-71,75-77]</sup>. The PAP was normal or proved to be mildly elevated in the majority of the reports<sup>[62,69,72,75,77]</sup>. Only one report described significant elevation of the pulmonary pressure<sup>[67]</sup>.

The reported treatment strategies were SL and conservative medical management. Surgical ligation was



**Figure 3** Different morphologic appearances of a dilated right coronary artery terminating into the pulmonary artery and the left ventricle (arrows).

A: RAO projection of a fistula originating from the proximal segment (arrow) of the right coronary artery and terminating into the pulmonary artery (arrowheads); B: A fistula from the distal segment (arrow) ending to the left ventricle.

performed with cardiopulmonary bypass<sup>[67,68,71,73]</sup>. Conservative medical management consisted of  $\beta$ -blockers and calcium channel antagonists and/or watchful follow-up policy. Non of the reports dealt with PTE. Increased success rate of surgical closure of CAFs draining into the CS could be reached by the instillation of intraoperative fistula image guidance with TEE<sup>[67,68,71,73]</sup> and/or on site CAG<sup>[65]</sup> as a complementary imaging facility to each other. The latter is not widely applied in the operating rooms. These image guidance techniques during surgery could be used in cases with complex anatomy and multiple sites of origin or termination. Generally, cardiopulmonary bypass is especially required in cases with associated valvular or coronary heart diseases, drainage into CS and complex fistula anatomy. This has the advantage of direct intracardiac closure of the fistulous opening and furthermore for identification of the distal end by briefly interrupting the aortic cross-clamp or infusing cardioplegic solution.

### Left ventricle

These coronary-cameral fistulas ending at the left ventricle (LV) (Figure 3) are extremely rare. Arterioarterial shunts cause isolated increased LV pressure and workload. These fistulas are mainly associated with a diastolic heart murmur. Flow through the fistulous shunt occurs exclusively in diastole mimicking aortic regurgitation murmur.

During systole, the fistulous opening draining into the LV is obliterated. In the reports from Europe<sup>[33]</sup> and Asia<sup>[44,78]</sup>, echocardiography suspected the diagnosis of CAFs<sup>[33]</sup> which was confirmed non-invasively by CMR and invasively by CAG. Non-invasive CMR and 64-row MDCT<sup>[78]</sup> delineated the morphologic features of the fistula.

### **Superior vena cava, pulmonary vein, right ventricular outflow tract and left atrium**

Few reports have been collected concerning the termination into superior vena cava, pulmonary vein (PV), right ventricular outflow tract (RVOT) and left atrium mainly from Asia<sup>[10,44,79]</sup> and to a lesser extent from North America<sup>[75]</sup>. Termination into the PV is very rare<sup>[24]</sup>. Drainage to the RVOT is highly infrequent<sup>[79]</sup>. These were all adult symptomatic patients who were treated by surgical closure of the fistula and performed off-pump<sup>[79]</sup> or by percutaneous coil occlusion of the fistula<sup>[24]</sup>. There are very few reports concerning the termination of the fistula into LV<sup>[10,44]</sup>.

## **TREATMENT MODALITY**

In the PTE group, the presenting symptoms were dyspnoea, chest pain and angina pectoris, palpitation and fatigue. On the contrary, besides these symptoms, syncope, congestive heart failure and hemopericardium were found more frequent in the SL group.

Drainage sites were comparable in both groups. The pre-intervention diagnostic workup in the PTE group provided the decision making after echocardiography, myocardial perfusion test, MDCT, cardiac catheterization and CAG. The decision making was reached in the SL group after diagnostic workup using echocardiography, myocardial perfusion test, MDCT, cardiovascular magnetic resonance, chest CT scan, cardiac catheterization and CAG. Clinical presentation with infective endocarditis was found in 10% of the patients in the SL group but in none of the PTE group.

Surgical ligation with cardiopulmonary bypass was used in 67% of the patients in the SL group and off-pump procedures were reported in 9%, while no cardiopulmonary bypass was reported in 24% of the patients.

Occlusion materials used in the PTE group were: all kinds of coils, 84%, stent 3%, ADO and Amplatzer septal occluder 3%, balloon (silicon and latex) 2%, umbrella devices 5% and Grifka and floppy tips of guide wires in 3% of the patients.

Complete closure of the fistula was confirmed with clinical examination, non-invasive and invasive assessment using echocardiography, phonocardiography, myocardial perfusion test and CAG in the PTE group. But in the SL group, echocardiography, myocardial perfusion test, MDCT and cardiac catheterization and CAG were usually used.

## **CONCLUSION**

In the current review, the wide spread spectrum of con-

genital CAFs is not fully represented in this limited series of reports. However, this review does emphasize the two separate manifestations of the fistulas: the congenital solitary CAFs which is the cornerstone of this report and MMFs. MMFs are excluded from the current study because they form a different entity.

CAFs are usually detected on CAG. They may be simply suspected by 2-D echocardiography. Multi-imaging modality (TEE, MDCT, CMR, CAG and cardiac catheterization) is required to adequately demonstrate the precise anatomical features (origin-pathway-termination aneurysmal formation, multilaterality, multiplicity, tortuosity) and accurate functional and shunt flow characteristics. These may be very helpful during the follow-up period for the operated or non-operated patients. Intra-operative image guiding increases the success rate of the surgical results.

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## Renal impairment and heart failure with preserved ejection fraction early post-myocardial infarction

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### Abstract

**AIM:** To study if impaired renal function is associated with increased risk of peri-infarct heart failure (HF) in patients with preserved ejection fraction (EF).

**METHODS:** Patients with occluded infarct-related arteries (IRAs) between 1 to 28 d after myocardial infarction (MI) were grouped into chronic kidney disease (CKD) stages based on estimated glomerular filtration rate (eGFR). Rates of early post-MI HF were compared among eGFR groups. Logistic regression was used to explore independent predictors of HF.

**RESULTS:** Reduced eGFR was present in 71.1% of 2160 patients, with significant renal impairment (eGFR < 60 mL/min every 1.73 m<sup>2</sup>) in 14.8%. The prevalence of HF was higher with worsening renal function: 15.5%, 17.8% and 29.4% in patients with CKD stages 1, 2 and 3 or 4, respectively ( $P < 0.0001$ ), despite a small absolute difference in mean EF across eGFR groups:  $48.2 \pm 10.0$ ,  $47.9 \pm 11.3$  and  $46.2 \pm 12.1$ , respectively ( $P = 0.02$ ). The prevalence of HF was again higher with worsening renal function among patients with preserved EF: 10.1%, 13.6% and 23.6% ( $P < 0.0001$ ), but this relationship was not significant among patients with depressed EF: 27.1%, 26.2% and 37.9% ( $P =$

0.071). Moreover, eGFR was an independent correlate of HF in patients with preserved EF ( $P = 0.003$ ) but not in patients with depressed EF ( $P = 0.181$ ).

**CONCLUSION:** A significant proportion of post-MI patients with occluded IRAs have impaired renal function. Impaired renal function was associated with an increased rate of early post-MI HF, the association being strongest in patients with preserved EF. These findings have implications for management of peri-infarct HF.

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**Key words:** Heart failure; Myocardial infarction; Kidney disease

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## INTRODUCTION

Impaired renal function is associated with an increased risk of early post-myocardial infarction (MI) heart failure (HF)<sup>[1-4]</sup>, which in turn is a potent predictor of death<sup>[5]</sup>. However, this has not been well documented in patients with preserved left ventricular ejection fraction (EF).

The Occluded Artery Trial (OAT) was a randomized trial in 2201 patients with persistently occluded infarct-related arteries (IRAs) post-MI, a group at high risk of developing peri-infarct HF. Thus, the OAT population provided an opportunity to study the relationship between impaired renal function and peri-infarct HF in patients with a broad range of EFs.

## MATERIALS AND METHODS

### Study population

The design and overall results of OAT have been published<sup>[6,7]</sup>. Briefly, OAT compared optimal medical therapy alone to optimal medical therapy and percutaneous coronary intervention in high-risk but stable patients with oc-

cluded IRAs over 24 h and up to 28 d post-MI. Eligibility criteria included confirmed index MI, occluded IRA and at least one of two high-risk criteria: EF < 50%, or proximal site of occlusion. Important exclusion criteria included significant angina, severe inducible ischemia, left main or triple vessel disease, serum creatinine > 2.5 mg/dL (221 μmol/L), severe valvular disease, New York Heart Association Class III or IV HF, or cardiogenic shock at the time of screening. The study was approved by institutional review committees at participating sites and subjects gave informed consent.

### Data collection

Data recorded included baseline clinical history, qualifying MI characteristics, EF and cardiac catheterization findings. All angiograms were independently reviewed at the angiographic core laboratory. Contrast ventriculograms recorded in the 30° right anterior oblique projection were used to calculate left ventricular volumes, EF, regional wall motion and sphericity index as described previously<sup>[8-10]</sup>.

### Definitions

The Modification of Diet in Renal Disease equation was used to calculate estimated glomerular filtration rate (eGFR):  $\text{eGFR (mL/min every } 1.73 \text{ m}^2) = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$ , where Scr is serum creatinine concentration in mg/dL and age is in years<sup>[11,12]</sup>. Patients were grouped into National Kidney Foundation chronic kidney disease (CKD) stages based on eGFR (mL/min every 1.73 m<sup>2</sup>): CKD stage 1:  $\geq 90$ ; stage 2: 60-89; stage 3: 40-59; and stage 4: 15-39<sup>[13]</sup>.

Early post-MI HF was defined as highest Killip class > I during index MI. Preserved and depressed EF was defined by the EF cut-off of 45%, which was the same as that used in the BNP and I-PRESERVE studies<sup>[14,15]</sup>, and was intermediate between the cut-off points of 40% in the CHARM-PRESERVED study<sup>[16]</sup> and 50% in a community-based observational study<sup>[17]</sup>.

### Statistical analysis

Descriptive data were expressed as percentages and mean  $\pm$  SD. Baseline variables were compared between eGFR groups using one-way analysis of variance for continuous variables and  $\chi^2$  test for categorical variables. A forward stepwise logistic regression model was used to evaluate independent correlates of HF. Continuous variables (including eGFR) were entered as such in the multivariable model. Variables were selected based on  $P < 0.1$  for comparison between eGFR groups. Subsequently, to test data-derived hypotheses, two separate logistic regression models were tested, restricted to patients with preserved and depressed EF, respectively. The pre-specified level of significance for all secondary analyses of OAT was  $P < 0.01$ .  $P \geq 0.01$  and  $< 0.05$  was considered to indicate a strong trend towards statistical significance.

**Table 1** Baseline clinical characteristics by eGFR group (*n* = 2160) (mean  $\pm$  SD)

|  | eGFR $\geq$ 90 ( <i>n</i> = 624) | eGFR 60-89 ( <i>n</i> = 1216) | eGFR 15-59 ( <i>n</i> = 320) | <i>P</i> value        |
|--|----------------------------------|-------------------------------|------------------------------|-----------------------|
| eGFR mL/min every 1.73 m <sup>2</sup>                | 106.0 $\pm$ 16.6                 | 75.5 $\pm$ 8.1                | 50.4 $\pm$ 7.7               | < 0.0001              |
| Age (yr)   | 54.2 $\pm$ 9.7                   | 58.7 $\pm$ 10.5               | 67.2 $\pm$ 9.6               | < 0.0001              |
| Female (%)   | 14.6                             | 20.3                          | 43.4                         | < 0.0001              |
| Diabetes (%)   | 20.4                             | 18.3                          | 30.0                         | 0.009                 |
| Hypertension (%)                                     | 39.3                             | 48.4                          | 69.1                         | < 0.0001              |
| Hyperlipidemia (%)                                   | 50.6                             | 51.7                          | 55.5                         | 0.19                  |
| Family history of CAD (%)                            | 42.6                             | 40.8                          | 32.8                         | 0.01                  |
| Current smoker (%)                                   | 51.9                             | 36.9                          | 22.5                         | < 0.0001              |
| Prior MI (%)   | 9.5                              | 12.2                          | 10.9                         | 0.28                  |
| Thrombolytic use during initial 24 h of index MI (%) | 16.5                             | 20.2                          | 20.3                         | 0.09                  |
| Troponin I divided by ULN (ng/mL) ( <i>n</i> = 1186) | 125.0 $\pm$ 213.9                | 186.3 $\pm$ 443.8             | 231.8 $\pm$ 516.6            | 0.01                  |
| Troponin T divided by ULN (ng/mL) ( <i>n</i> = 281)  | 46.0 $\pm$ 73.4                  | 69.6 $\pm$ 190.4              | 24.1 $\pm$ 28.3              | 0.2                   |
| Days from index MI to randomization                  | 10.1 $\pm$ 7.4                   | 11.2 $\pm$ 7.8                | 11.6 $\pm$ 7.6               | 0.004                 |
| BMI (kg/m <sup>2</sup> )                             | 28.4 $\pm$ 5.1                   | 28.6 $\pm$ 4.9                | 28.5 $\pm$ 5.3               | 0.77                  |
| Heart rate (beats/min)                               | 72.1 $\pm$ 11.5                  | 71.4 $\pm$ 11.9               | 72.7 $\pm$ 12.7              | 0.13                  |
| Systolic BP (mmHg)                                   | 119.4 $\pm$ 17.4                 | 120.7 $\pm$ 17.7              | 123.9 $\pm$ 19.7             | 0.001                 |
| Diastolic BP (mmHg)                                  | 72.6 $\pm$ 11.1                  | 72.3 $\pm$ 11.4               | 71.8 $\pm$ 11.6              | 0.63                  |
| Discharge medications (%)                            |                                  |                               |                              |                       |
| Aspirin  | 97.0                             | 95.9                          | 92.5                         | 0.003                 |
| Ticlopidine or clopidogrel                           | 73.6                             | 73.2                          | 70.2                         | 0.33                  |
| Beta blocker   | 88.9                             | 87.9                          | 85.9                         | 0.19                  |
| ACE Inhibitor  | 76.4                             | 79.0                          | 78.8                         | 0.31                  |
| Lipid lowering agent                                 | 85.4                             | 81.7                          | 73.4                         | < 0.0001              |
| IRA-LAD (%)  | 32.9                             | 36.8                          | 38.4                         | 0.19                  |
| IRA-Circ (%)   | 18.1                             | 13.9                          | 15.0                         |                       |
| IRA-RCA (%)  | 49.0                             | 49.3                          | 46.6                         |                       |
| IRA TIMI Flow Grade 0-1 (%)                          | 99.8                             | 99.5                          | 99.4                         | 0.41                  |
| Two or three vessel disease (%)                      | 15.5                             | 17.3                          | 21.6                         | 0.03                  |
| Collaterals present (Grade 1 and 2) (%)              | 89.2                             | 88.5                          | 86.7                         | 0.29                  |
| Mitral regurgitation (%)                             |                                  |                               |                              |                       |
| Grade 0  | 69.0                             | 66.1                          | 56.9                         | < 0.0001 <sup>b</sup> |
| Grade 1  | 27.3                             | 28.3                          | 30.6                         |                       |
| Grade 2  | 2.7                              | 4.4                           | 7.4                          |                       |
| Grade 3  | 1.0                              | 1.2                           | 5.1                          |                       |
| End-diastolic volume (mL) ( <i>n</i> = 201)          | 137.4 $\pm$ 55.1                 | 124.1 $\pm$ 52.8              | 130.4 $\pm$ 85.6             | 0.36                  |
| End-systolic volume $\pm$ mL) ( <i>n</i> = 201)      | 70.7 $\pm$ 32.7                  | 64.5 $\pm$ 32.2               | 71.7 $\pm$ 54.2              | 0.45                  |
| Ejection fraction ( <i>n</i> = 2145)                 | 48.2 $\pm$ 10.0                  | 47.9 $\pm$ 11.3               | 46.2 $\pm$ 12.1              | 0.02                  |
| Wall motion SD/Chord ( <i>n</i> = 1677)              | -2.9 $\pm$ 0.9                   | -2.9 $\pm$ 0.9                | -3.0 $\pm$ 0.9               | 0.84                  |
| Systolic sphericity index ( <i>n</i> = 1677)         | 23.3 $\pm$ 6.9                   | 22.9 $\pm$ 6.6                | 24.7 $\pm$ 8.5               | 0.003                 |
| Diastolic sphericity index ( <i>n</i> = 1677)        | 30.0 $\pm$ 6.7                   | 30.6 $\pm$ 6.5                | 31.5 $\pm$ 7.4               | 0.02                  |

<sup>b</sup>*P* < 0.0001 for linear association between eGFR group and mitral regurgitation grade; *P* < 0.002 for linear association between eGFR group and presence of mitral regurgitation (grade  $\geq$  1). ULN: Upper limit of the local laboratory normal; LAD: Left anterior descending coronary artery; RCA: Right coronary artery; Circ: Left circumflex coronary artery; TIMI: Thrombolysis in myocardial infarction; BMI: Body mass index.

## RESULTS

### Baseline characteristics by eGFR group

Data on eGFR at the time of randomization, a median of 8 d post-MI, was available in 2160 of 2201 patients enrolled in OAT (98.1%). Of these, 71.1% had reduced eGFR, with 56.3% in stage 2, 14.5% in stage 3, and 0.3% in stage 4 (Table 1).

Baseline clinical features associated with lower eGFR were older age, female sex, diabetes, hypertension, lower frequency of smokers, longer duration from MI to randomization, higher systolic blood pressure at randomization, and less frequent use of aspirin and lipid-lowering agents. In addition, patients with reduced eGFR showed a strong trend toward lower frequency of family history of coronary artery disease (CAD) and higher troponin I (Table 1).

Angiographic features associated with lower eGFR were higher systolic sphericity index and higher frequency and grade of mitral regurgitation. There was a strong trend toward significant association between lower eGFR and presence of multivessel CAD, lower EF and higher diastolic sphericity index (Table 1).

### Prevalence of HF by eGFR group

Of 2151 patients with data on eGFR and HF available, 406 (18.9%) had HF during the index MI. The prevalence of HF was higher with worsening renal function: 15.5% in patients with stage 1 CKD, 17.8% with stage 2 and 29.4% with stage 3 or 4 (*P* < 0.0001). The odds ratio (OR) for HF was 2.3 [95% confidence interval (CI): 1.6-3.1] in patients with stage 3 or 4 compared with stage 1, despite a small absolute difference in mean EF between eGFR groups (*P* = 0.02, Table 1). This prompted

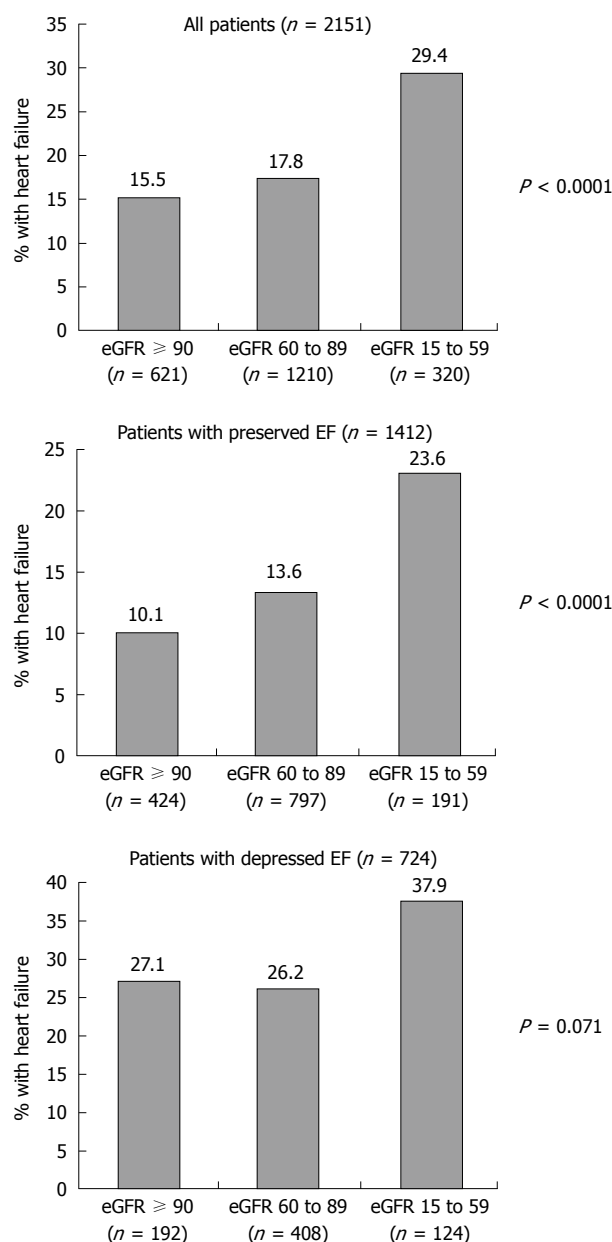


Figure 1 Prevalence of HF by eGFR group and EF.

us to evaluate whether there was an association between eGFR group and HF in patients with preserved EF (Figure 1).

Of the study population of 2151 patients, 1412 had preserved EF and 724 had depressed EF. Of the 406 patients with HF, 196 (48.3%) had preserved EF, 206 (50.7%) had depressed EF, and EF was missing in four patients. Among patients with preserved EF, the prevalence of HF was again higher with worsening renal function: 10.1%, 13.6% and 23.6% ( $P < 0.0001$ ). The OR for HF was 2.7 (95% CI: 1.7-4.3) in patients with stage 3 or 4 compared with stage 1. However, this relationship was not significant among patients with depressed EF: 27.1%, 26.2% and 37.9% ( $P = 0.071$ ). The OR for HF was 1.6 (95% CI: 1.0-2.7) in patients with stage 3 or 4 compared with stage 1.

Table 2 Multivariable correlates of heart failure

| Covariates                            | P value  | OR    | 95% CI      |
|---------------------------------------|----------|-------|-------------|
| All patients (n = 2096)               |          |       |             |
| Decreasing EF <sup>1</sup>            | < 0.0001 | 1.554 | 1.398-1.727 |
| Increasing BMI                        | 0.001    | 1.037 | 1.015-1.059 |
| Decreasing eGFR <sup>1</sup>          | 0.006    | 1.088 | 1.025-1.156 |
| Increasing age <sup>1</sup>           | 0.007    | 1.171 | 1.044-1.315 |
| Increasing heart rate <sup>1</sup>    | 0.001    | 1.183 | 1.075-1.302 |
| Collaterals not present (Grade 0)     | 0.045    | 1.397 | 1.007-1.939 |
| Patients with preserved EF (n = 1402) |          |       |             |
| Increasing BMI                        | 0.0001   | 1.060 | 1.029-1.093 |
| Decreasing eGFR <sup>1</sup>          | 0.003    | 1.140 | 1.044-1.245 |
| Prior MI                              | 0.021    | 1.701 | 1.082-2.673 |
| Increasing age <sup>1</sup>           | 0.031    | 1.185 | 1.015-1.383 |
| Increasing heart rate <sup>1</sup>    | 0.030    | 1.161 | 1.014-1.328 |
| Patients with depressed EF (n = 715)  |          |       |             |
| Decreasing EF <sup>1</sup>            | < 0.0001 | 2.096 | 1.633-2.689 |
| Decreasing eGFR <sup>1</sup>          | 0.181    | 1.056 | 0.975-1.143 |
| Increasing heart rate <sup>1</sup>    | 0.006    | 1.210 | 1.055-1.388 |
| Collaterals not present (Grade 0)     | 0.036    | 1.632 | 1.032-2.581 |

<sup>1</sup>Odds ratios (ORs) and confidence intervals (CIs) reported for a 10 unit change. The addition of an EF\*eGFR interaction term did not contribute significantly to the model for all patients, when EF within the interaction term was entered as a continuous variable ( $P = 0.575$ ) or as a dichotomous variable, i.e. preserved *vs* depressed ( $P = 0.151$ ).

### Multivariable correlates of HF

On multivariable analysis, HF was significantly associated with older age, higher heart rate at enrollment, lower EF, higher body mass index (BMI) and lower eGFR, while there was a strong trend towards significant association with absence of collaterals (Table 2).

In the logistic regression model restricted to patients with preserved EF, lower eGFR and higher BMI were independently correlated with HF, and there was a trend toward significant association with prior MI, older age and higher heart rate at enrollment (Table 2). Conversely, in the model restricted to patients with depressed EF, lower eGFR was no longer correlated with HF, while lower EF and higher heart rate were strongly correlated, and there was a trend toward significant association with absence of collaterals (Table 2).

## DISCUSSION

Decreased eGFR was associated with an increased risk of early post-MI HF, the association being strongest in patients with preserved EF, in whom it was an important independent predictor of HF.

### Frequency of impaired renal function in acute MI

Overall, we noted decreased eGFR ( $< 90$  mL/min every  $1.73 \text{ m}^2$ ) in 71.1% and significant renal impairment (eGFR  $< 60$  mL/min every  $1.73 \text{ m}^2$ ) in 14.8% of this large series of patients with persistently occluded IRAs post-MI. Prior studies in patients with MI reported significant renal impairment in 18.9%-33.5%<sup>[1,2,4,18]</sup>. Impaired renal function is associated with CAD risk factors such as older age, hypertension and diabetes<sup>[1-4]</sup>, and has been found to



be associated with a higher rate of MI in epidemiological studies<sup>[19,20]</sup>.

### **Impaired renal function and early post-MI HF**

Previous studies have demonstrated higher Killip class during acute MI in patients with impaired renal function<sup>[1-4]</sup>. We found that patients with lower eGFR had a higher prevalence of early post-MI HF, despite a small difference in EF between eGFR groups. Our multivariable models showed a significant continuous gradation of risk of post-MI HF with decreasing eGFR, even after adjusting for variables that differed between eGFR groups. The lower limits of the confidence intervals for the ORs probably reflect the wide spectrum of eGFR, with 624 of 2160 patients in the study having a normal eGFR (and consequently low risk of post-MI HF). Verma *et al.*<sup>[21]</sup> found no significant difference in early post-MI EF between eGFR groups, but demonstrated higher left ventricular mass index in patients with lower eGFR. In addition to the association with diastolic dysfunction, higher left ventricular mass in patients with impaired renal function may be a marker for increased renin-angiotensin-aldosterone activity<sup>[22]</sup>, which in turn, may contribute to HF through diverse mechanisms, including impaired sodium and water excretion and decreased venous capacitance<sup>[23,24]</sup>.

### **Influence of EF on the relationship between impaired renal function and HF**

The relationship between renal function and early post-MI HF was complex and was influenced by the degree of systolic dysfunction. Although, in general, patients with impaired renal function had a significantly higher prevalence of HF, this relationship was strongest in patients with preserved EF and weakest when EF was low.

Other studies have explored the potential influence of EF on the relationship between impaired renal function and clinical outcome. In a single-center study of non-ST elevation acute coronary syndrome, there was a step-wise increase in 1-year all-cause mortality with worsening renal function in patients with preserved as well as depressed EF<sup>[25]</sup>. However, rates of HF were not reported in this study and patients with ST elevation MI were excluded. In a pooled analysis of the three arms of the CHARM study, there was no interaction between eGFR and EF for a composite endpoint of cardiovascular death or HF hospitalization<sup>[26]</sup>. However, the entry criterion for CHARM was symptomatic HF of at least 4 wk duration and patients with recent MI (within 4 wk) were excluded.

### **Clinical implications**

Traditionally, assessment of a patient's risk of post-MI HF has been based on knowledge of post-MI EF. However, there is a complex relationship between EF, renal function and post-MI HF. This study suggests that the use of EF for post-MI risk stratification in patients with impaired renal function has limitations. Furthermore, risk stratification can be improved by factoring in eGFR, particularly in patients with preserved EF. Of note, HF

with preserved EF accounts for nearly half the cases of post-MI HF, and is associated with increased mortality following MI<sup>[27]</sup>. Renin-angiotensin-aldosterone blockade is well documented to reduce rates of late post-MI HF, particularly in patients with depressed EF. It is not known if intensive renin-angiotensin-aldosterone blockade during the acute phase of MI affects rates of early post-MI HF in patients with preserved EF and impaired renal function.

### **Strengths and limitations**

This study specifically analyzed the association of impaired renal function with HF and the influence of EF on this association in a large series of patients with occluded IRAs post-MI. A major strength of this study is that data were collected prospectively using pre-defined criteria, and important angiographic analyses were performed by a core laboratory blinded to clinical information. A potential limitation is that patients with creatinine > 2.5 mg/dL at randomization were excluded. Point measurements of serum creatinine were used to estimate GFR. The present study was not designed to address the possible mechanisms underlying our observations. Further studies are needed to address the precise mechanisms of post-MI HF in patients with impaired renal function, particularly in the presence of preserved EF.

In conclusion, a significant proportion of post-MI patients with persistently occluded IRAs have impaired renal function. Impaired renal function was associated with an increased rate of early post-MI HF, and the association was stronger in patients with preserved EF. The association between impaired renal function and HF in patients with preserved EF has important implications for management of peri-infarct HF and for post-MI risk stratification.

## **COMMENTS**

### **Background**

Patients with impaired renal function are at increased risk of heart failure (HF) early after a myocardial infarction (MI). HF after MI in turn is a potent predictor of death.

### **Research frontiers**

The relationship between impaired renal function and post-MI HF has been demonstrated mainly in patients with depressed ejection fraction (EF). However, this relationship has not been well studied in patients with preserved EF. In this study, the authors demonstrate that impaired renal function increases the risk of post-MI HF in patients with a wide range of EF.

### **Innovations and breakthroughs**

This study furthermore shows that the relationship between impaired renal function and risk of post-MI HF is stronger in patients with preserved EF compared to patients with depressed EF.

### **Applications**

Traditionally, estimation of EF has been used to identify patients who are at increased risk of adverse clinical outcome following a MI. By understanding the influence of impaired renal function on the risk of HF, we may include measures of renal function in the risk stratification of patients with MI, particularly in patients with preserved EF.

### **Terminology**

EF is the proportion of the blood volume in the left ventricle at the end of diastole that is ejected in systole. EF is expressed as a percentage and is a measure of



left ventricular systolic function. Renal function in this study was assessed by an estimation of the glomerular filtration rate.

# Peer review

This is an interesting substudy from a well respected trial (Occluded Artery Trial). It can be published, however, the paper would gain a lot including echo and further scoring data (i.e. GRACE score) and revision.

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S- Editor Cheng JX L- Editor Kerr C E- Editor Zheng XM

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## Meetings

### Events Calendar 2010

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

October 16-19  
Copenhagen, Denmark  
Acute Cardiac Care 2010

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

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

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

## Instructions to authors

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### Acknowledgments

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### Format

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

- 1 Jung EM, Clevert DA, Schreyer AG, Schmitt S, Rennert J,

## Instructions to authors

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

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

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

*In press*

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

*Organization as author*

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

*Both personal authors and an organization as author*

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

*No author given*

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

*Volume with supplement*

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

*Issue with no volume*

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

*No volume or issue*

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

## Books

*Personal author(s)*

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

*Chapter in a book (list all authors)*

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

*Author(s) and editor(s)*

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

*Conference proceedings*

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

*Conference paper*

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

*Electronic journal (list all authors)*

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

*Patent (list all authors)*

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

## Statistical data

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

## Statistical expression

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

## Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose)  $6.4 \pm 2.1$  mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5  $\mu$ g/L; CO<sub>2</sub> volume fraction, 50 mL/L CO<sub>2</sub>, not 5% CO<sub>2</sub>; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, etc. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: <http://www.wjgnet.com/wjg/help/15.doc>.

## Abbreviations

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

## Italics

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

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

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

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

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