Reviews

Is Early Cardioversion for Atrial Fibrillation Safe in Patients with Spontaneous Echocardiographic Contrast?

Address for correspondence:
S.V. Patel, MD
Mercer University School of Medicine
Department of Internal Medicine
707 Pine Street
Macon, GA 31201, USA
shomeet@yahoo.com

S.V. Patel, MD and Greg Flaker, MD, FACP, FACC, FAHA*
Resident Department of Internal Medicine, Mercer University School of Medicine, Macon, Georgia; *Brent Parker Professor of Medicine, Cardiology Program Director, Director of Cardiology Research and Electrophysiology Laboratory, Division of Cardiology, University of Missouri — Columbia, Columbia, Missouri, USA

ABSTRACT

The 2006 American Heart Association guidelines for management of patients with atrial fibrillation state: "For patients with no identifiable thrombus in the left atrium (LA) or left atrial appendage (LAA), cardioversion (CV) is reasonable immediately after anticoagulation with unfractionated heparin. Thereafter, continuation of oral anticoagulation is reasonable for an anticoagulation period of at least 4 weeks." For patients with thrombus identified by transesophageal echocardiography, guidelines recommend therapeutic oral anticoagulation for 3 weeks prior to and 4 weeks after elective cardioversion.

Patients with spontaneous echo contrast spontaneous echo contrast (SEC) identified by transesophageal echocardiogram (TEE) have a high risk of thromboembolic events,[1–8] however, the guidelines do not address whether patients with SEC without thrombus can be safely cardioverted. This paper reviews the literature describing the pathogenesis of SEC, how it is detected, and whether elective cardioversion is safe.

On the basis of our review, we believe that the risk of cardioembolic stroke after cardioversion of a patient with SEC is low, regardless of anticoagulation. The safe conclusion is that patients with SEC on TEE should receive therapeutic anticoagulation prior to cardioversion if possible and early cardioversion is not contraindicated.

Key words: cardioversion, spontaneous echo contrast, atrial fibrillation, transesophageal echocardiography

Introduction

Spontaneous Echo Contrast

Also known as "smoke," spontaneous echo contrast (SEC) is described as a swirling pattern of increased echogenicity, distinct from white noise artifacts in the left atrium (LA) or left atrial appendage (LAA), caused by ultrasonic backscatter from red blood cell aggregates seen in blood stasis or low-velocity blood flow.[1–8] The clinical importance of SEC is its association with left atrial thrombus, increased thromboembolic complications, and death.[1–8] An SEC is most frequently seen in hypertension and conditions with low blood flow velocity, such as rheumatic mitral stenosis, mitral valve prostheses, atrial fibrillation, dilated left atria, and dyskinetic segments of the left ventricle.[1,7]

Pathogenesis of Spontaneous Echo Contrast

The pathogenesis of SEC is not clearly established. Aging, low blood flow velocities, low shear rate, atrial fibrillation, high erythrocyte sedimentation rate (ESR), increased serum fibrinogen level, elevated hematocrit, and structural abnormalities of the cardiovascular system have all been implicated.[4] Black reported that formation of SEC required red cells and fibrinogen and that intensity of SEC correlated positively with fibrinogen concentration and hematocrit while negatively to shear rate.[2] In low shear rate conditions, such as blood flow stasis, the process of red cell aggregation involves intercellular bridging by fibrinogen. Other studies have shown an increase in whole blood viscosity and fibrinogen, which seems to be caused by an increase in red cell aggregability favored by fibrinogen activation.[2,9] The exact role of platelets in the pathogenesis of SEC is uncertain. Earlier studies show no role for platelets in the pathogenesis of SEC.[2,10] More recent studies have demonstrated activation of platelets in the LA of patients with SEC.[11] Activation of the coagulation system has been documented in patients with atrial fibrillation (AF)[10] and SEC has been related to various markers of coagulation activation such as ESR,[1] thrombin-antithrombin 3 complex, prothrombin fragment 1 and 2.[12]

Diagnosis and Grading of Spontaneous Echo Contrast

The two-dimensional transesophageal echocardiography (TEE) is the preferred modality for visualization of both the LA and the LAA, as a result of the close proximity of the transducer to the heart.[4,6] Quantification of SEC in the LAA rather than the LA is more valuable for assessing embolic potential.[13] Weak echocardiograms can be enhanced by increasing the gain, which increases the graininess of the echocardiogram setting enabling the detection of SEC. Subsequently, SEC can be graded subjectively as mild, moderate, or severe, though consistent staging requires

Clin. Cardiol. 31, 4, 148–152 (2008)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20172

Received: March 17, 2007
Accepted: April 19, 2007

consensus of more than 1 independent observer. Other more objective modalities for grading SEC include recording the images and digitizing them into gray scale levels and measuring the videodensity,[14] grading them from absent (0), mild (1+), mild to moderate (2+), moderate (3+), severe/dense (4+)[5] and finally by acoustic densitometry with integrated backscatter using a computerized software program incorporated into the echo equipment.[13] Other investigators classified SEC as dense when it was persistent throughout the LA-LAA at normal gain and faint when localized.[8] A consensus definition is required to further the field.

Prevalence of Spontaneous Echo Contrast

The prevalence of SEC has varied in studies. Kamensky, in a retrospective study of 229 patients undergoing TEE, found the prevalence to be 21.4%[6] while another study reported between 16% and 19%.[4] The prevalence of SEC varies according to the indication of the group, with nonvalvular AF patients having prevalence rates of 55%.[8,13] The prevalence of dense SEC in patients with AF varies from 12% to 67%.[5] As TEE is most often performed in search of cardiac sources of emboli, one must expect an overestimation of prevalence in patients undergoing TEE.

Clinical and Prognostic Factors of Spontaneous Echo Contrast

The TEE identifies predictors of embolic events that may not be evident on clinical exam, such as LA/LAA SEC and/or thrombus. Studies demonstrated appendage thrombi, dense SEC, LAA peak flow velocities <20 cm/s, and complex aortic plaque (CAP) as independently associated with increased thromboembolic risk.[7,8] Goldman[15] identified independent predictors of LAA peak flow velocities <20 cm/s as: age (per decade), constant AF, systolic blood pressure (SBP), ischemic heart disease, and left atrial area. Asinger demonstrated as independent clinical predictors of dense SEC in AF age (per decade), history of hypertension (SBP >160 mm/Hg), constant AF, and tobacco use.[8] The importance of dense SEC was demonstrated by Bernhardt[5] who studied 128 patients with AF and dense SEC. They performed serial, prospective TEE and cranial magnetic resonance imaging (MRI) to detect both clinically apparent neurological deficits and silent embolisms. They concluded that patients with dense SEC have a high likelihood of cerebral embolism (28 of 128 [22%] patients with dense SEC) and/or death, despite oral anticoagulation. Nineteen patients had silent embolisms demonstrated on MRI. Low peak emptying velocities of the LAA and dense SEC were independent predictors of an event.

Treatment of Spontaneous Echo Contrast

Anticoagulation therapy with coumadin is widely used to prevent thromboembolism in patients with LA/LAA SEC.[2,4] Anticoagulation therapy does not affect red cell aggregation in vitro[2] or LA SEC in patients,[2,16,17] but does reduce development of LA thrombus and decreases risk of thromboembolism.[2,3,18] Treatment of the underlying condition causing SEC frequently leads to resolution of SEC. In patients with AF, conversion to sinus rhythm often increases the intensity of SEC.[2] This is thought to occur secondary to atrial stunning; with the resolution of stunning, SEC usually disappears.[19,20]

Transesophageal Guided Cardioversion

The conventional treatment for patients in atrial fibrillation >48 h who are to undergo cardioversion is pretreatment for 3 weeks with coumadin. This duration of anticoagulant therapy is associated with increased risk of bleeding, continued morbidity from AF, continued (though decreased) risk of embolism, additional cost for medicines and monitoring for level of anticoagulation, scheduling difficulties, delay of cardioversion, and increased refusal of patients to undergo cardioversion.[21–24] The conventional treatment strategy has never been properly evaluated in a clinical trial.[21] Manning[25] reported from studies done in the 1960s (prior to the widespread use of anticoagulants in AF) that up to 7% of patients in AF undergoing cardioversion without anticoagulation experienced clinical thromboembolism; this may have contributed to the adoption of the conventional treatment strategy. The incorporation of anticoagulants into routine use for patients in AF undergoing cardioversion (CV) has significantly reduced the thromboembolic risk, making it impossible to reassess the incidence of thromboembolism in unanticoagulated AF patients undergoing CV.

With advances in TEE multiplane technology, LA or LAA thrombi can be detected with >95% accuracy when compared with intraoperative identification in patients undergoing mitral valve surgery.[23,26,27] Using precardioversion TEE, Manning[24] assessed early cardioversion in patients with AF for longer than 48 h without atrial thrombi. Patients without thrombus received anticoagulation with heparin prior to and for 24 h after either pharmacological or electrical cardioversion. Approximately, two-thirds of these patients received coumadin post cardioversion. Ninety-four patients underwent TEE, and 82 received early cardioversion. Seventy-eight patients were successfully converted to sinus rhythm and none suffered an embolic event 24 h post-cardioversion or during 1 month follow-up (Table I). The authors concluded that early cardioversion in patients in whom LA and/or LAA thrombi have been excluded with TEE, is a safe and effective therapy.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20172

TABLE 1: Review of literature and summary of studies

Study	Total TEE patients	Patients with SEC alone	Patients with SEC cardioverted n (%)**	Pre-CV anticoagulation	Type of anticoagulation (anticoagulation goal)	Complications/ events (%)	Follow-up duration
Manning[24]	94	42	42 (44)	Yes	Heparin (PTT 1.4–1.7)	0	30 days
Manning[25]	230	85	85 (36)	Yes	Heparin (PTT 1.4–1.7)	0	30 days
Stoddard[28]	266	71	54[#] (20)	Yes: 46 No: 107	Unknown	0	28 days
Orsinelli[29]	39	NA	NA	Yes: 19 No: 9	Unknown	0	N/A
Corrado[30]	183	68	68 (37)	Yes	Warfarin (INR $\geqslant$ 2.0) LMWH (PTT 1.5–2.5)	0	30 days
ACUTE pilot[31]	56	37	37 (66)	Yes	Warfarin (INR 2.0–3.0) LMWH (PTT 1.5–2.5)	0	28–56 days
ACUTE trial[21]	549	NA	NA	Yes	Warfarin (INR 2.0–3.0) LMWH (PTT 1.5–2.5)	5 (0.8)	56 days
Malatagliati[32]	757	525	472[$] (62)	Yes: 78 No:51[@]	Warfarin (INR 2.0–3.0) LMWH (PTT 1.5–2.5)	1 (0.15)	N/A
Strandberg[33]	346	70	70 (20)	Yes	Warfarin, LMWH Unknown	1 (0.36)	365 days

N/A = Not mentioned in study; ** = percentage of total TEE patients; [#] = 17 patients were treated by conventional strategy and did not receive early CV; [$] = 53 patients had sludge–extreme echo contrast–CV postponed; [@] = Few patients receiving anticoagulation, but subtherapeutic. *Abbreviations*: ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography; CV = cardioversion; INR = internal normalized ratio; LMWH = low molecular weight Heparin; PTT = partial thromboplastin time; SEC = spontaneous echo contrast; TEE = transesophogeal echocardiogram.

In the above study, LAA thrombus was found in 10 patients during TEE. Of these 10 patients, 9 (90%) had associated SEC. In the remaining 84 patients, 42 (50%) demonstrated SEC during TEE. These patients underwent cardioversion without any embolic complications.

To validate their findings, Manning included the previous patient population in a prospective 4.5 year study[25] based on identical objectives, background, and methods. This prospective study had 233 eligible patients; 230 underwent TEE to assess for thrombus. Thirty-four patients had LA thrombi. Of these patients, 27 (79%) had SEC; of the 196 patients without thrombi, 85 (43%) had SEC. All 196 patients underwent cardioversion and 186 were successfully converted to sinus rhythm. None of the 196 patients undergoing cardioversion experienced a clinical thromboembolic event immediately post-CV or during the 1 month follow-up period. In this study, 85 patients with SEC underwent cardioversion and suffered no complications. The authors concluded that early cardioversion post-TEE had a safety profile similar to conventional therapy and minimized both the duration of anticoagulation and AF.

Since then numerous trials have been published demonstrating the benefit of TEE guided early cardioversion.[21,28–33] Though these trials did not directly look at the relationship between the presence of SEC on TEE and postcardioversion thromboembolic risk, they did incorporate a large number of patients with SEC into the cardioversion group (Table I). These studies showed a low thromboembolic risk despite varying methods of anticoagulation, including studies with no or subtherapeutic anticoagulation[28,29,32] prior to cardioversion.

Not all authors consider early cardioversion safe in patients in whom SEC is demonstrated on TEE. Roijer[34] and Fonseca[35] attempted to identify a low-risk group of patients for immediate cardioversion. To be eligible, patients had to be free of LA or LAA thrombus and SEC and have an LAA outflow velocity >0.25 m.s^{-1}. Patients with one or more of these risk factors were treated by the conventional treatment strategy. No thromboembolic complications occurred in either group following cardioversion.

Though these studies have demonstrated that an argument can be made for either early or delayed cardioversion in patients with AF and associated SEC, early cardioversion of patients with AF has benefits. Stoddard[28] demonstrated that patients receiving anticoagulation following conventional treatment had a higher prevalence of both thorombus and SEC in LA compared with patients who underwent cardioversion early. Corrado[30] demonstrated that patients

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20172

with and <4 weeks duration of AF had a significantly better immediate success rate of CV than those with longer duration of AF (96.9% versus 85%); improved outcome was maintained at 1 month. This study helped show that not only did patients tolerate abbreviated anticoagulation, but also earlier termination of AF had a positive effect on immediate success and maintenance of sinus rhythm.

The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial[21] is the only randomized trial performed to compare TEE-guided early cardioversion with conventional therapy. No significant difference in the rate of embolism was found between the 2 groups. The few patients (5 of 619 patients) in the early cardioversion group who did suffer from complication had numerous comorbid risk factors for thromboembolic complications. The investigators concluded that TEE-guided early cardioversion could be considered an effective alternative to conventional therapy. The study demonstrated that the rate of hemorrhagic events was significantly lower in the TEE group. They also had a shorter time to cardioversion and a greater rate of restoration of sinus rhythm.

The majority of these studies mention the presence or absence of SEC on TEE, but they do not quantify/grade SEC. Maltagliatti[32] graded SEC from grades 0 to 4, and defined severe spontaneous echo contrast with distinct intermediate stage of thrombosis as "sludge" (extreme echo contrast with clot formation). Sludge was demonstrated in 53 of 757 patients (7%) and was considered a contraindication to early CV. Grade 4 SEC was found in 77 of the 757 patients undergoing TEE (10%) and was not considered a contraindication to CV. As long as thrombus or sludge was not demonstrated on TEE, all patients underwent early CV. Only 1 of the 648 patients who underwent CV suffered a clinical embolic event. That event was an episode of hemianopsia, which resolved completely in 12 h.

Conclusion

As our review shows, numerous studies have evaluated the efficacy and safety of TEE guided cardioversion.[21,23–25,28–33] Though these studies acknowledge SEC as a condition associated with thrombus formation and a risk factor for thromboembolism, most have not considered its presence a contraindication to early cardioversion. Additionally, while these studies were not designed to evaluate the outcomes of early cardioversion in patients with SEC, they were able to demonstrate clinical benefits associated with early cardioversion.

Considering these points, should finding SEC delay early cardioversion? The pathology of SEC makes thrombus formation more likely, but the presence of SEC is not equivalent to thrombus and therefore may not be a contraindication for cardioversion. Through the use of appropriate therapeutic anticoagulation during the precardioversion period, the risk of thrombus formation and thromboembolism may be decreased.

A limitation of these studies is that they have not evaluated silent microembolism in patients with SEC undergoing early cardioversion. Until studies specifically address early cardioversion in patients with SEC one cannot unequivocally say that early cardioversion is safe. The relationship between the grade of SEC and thromboembolic risk needs to be undertaken, with special emphasis on the effect of dense SEC.

In conclusion, on the basis of pathology and the numerous studies that have shown high success rates, we believe that the risk of cardioembolic stroke acutely after cardioversion in a patient with SEC on TEE is low, regardless of anticoagulation. However, the risk of long-term stroke in a patient with SEC on TEE is high. The safe conclusion is that patients with SEC on TEE should receive therapeutic anticoagulation prior to cardioversion if possible and early cardioversion is not contraindicated.

References

1. Fatkin D, Herbert E, Feneley MP: Hematologic correlates of spontaneous echo contrast in patients with atrial fibrillation and implications for thromboembolic risk. *Am J Cardiol* 1994;73(9):672–676
2. Black IW: Spontaneous echo contrast: where there's smoke there's fire. *Echocardiography* 2000;17(4):373–382
3. Fatkin D, Kelly RP, Feneley MP: Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *JACC* 1994; 23(4):961–969
4. Ansari A, Maron BJ: Spontaneous echo contrast and thromboembolism. *Hosp Pract* 1997;32(1):109–111
5. Bernhardt P, Schmidt H, Hammerstingl C, Luderitz B, Omran H: Patients with atrial fibrillation and dense spontaneous echo contrast at high risk a prospective and serial follow-up over 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. *JACC* 2005;45(11):1807–1812
6. Kamensky G, Drahos P, Plevova N: Left atrial spontaneous echo contrast: its prevalence and importance in patients undergoing transesophageal echocardiography and particularly those with a cerebrovascular embolic event. *J Am Soc Echocardiogr* 1996;9(1):62–70
7. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, et al.: Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. *J Am Coll Cardiol* 1998;31(7):1622–1626
8. Asinger RW, Koehler J, Pearce LA, Zabalgoitia M, Blackshear JL, et al.: Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: II. *J Am Soc Echocardiogr* 1999;12(12):1088–1096
9. Turchetti V, Bellini MA, Ricci D, Lapi A, Donati G, et al.: Spontaneous echo-contrast as an in vivo indicator of rheological imbalance in dilatative cardiomyopathy. *Clin Hemorheol Microcirc* 2001;25(3–4):119–125

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20172

10. Lip GY: Hypercoagulability and haemodynamic abnormalities in atrial fibrillation. *Heart* 1997;77(5):407–411
11. Zotz RJ, Muller M, Genth-Zotz S, Darius H: Spontaneous echo contrast caused by platelet and leukocyte aggregates? *Stroke* 2001;32:1127–1133
12. Soncini M, Casazza F, Mattioli R, Bonfardeci C, Motta A, et al.: Hypercoagulability and chronic atrial fibrillation: the role of markers of thrombin generation. *Minerva Med* 1997; 88(12):501–505
13. Ito T, Suwa M, Nakamura T, Miyazaki S, Kpbashi A, et al.: Quantification of left atrial appendage spontaneous echo contrast in patients with chronic nonalvular atrial fibrillation. *J Cardiol* 2001;37(6):325–333
14. Kwaan HC, Sakurai S, Wang J: Rheological abnormalities and thromboembolic complications in heart disease: spontaneous echo contrast and red cell aggregation. *Semin Thromb Hemost* 2003;29(5):529–534
15. Goldman ME, Pearce LA, Hart RG, Zabalgoitia M, Asinger RW, et al.: Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: I. *J Am Soc Echocardiogr* 1999; 12(12):1080–1087
16. Tsai LM, Chao TH, Chen JH: Association of follow-up change of left atrial appendage blood flow velocity with spontaneous echo contrast in nonrheumatic atrial fibrillation. *Chest* 2000; 117(2):309–313
17. Ito T, Suwa M, Nakamura T, Miyazaki S, Hirota Y, et al.: Influence of warfarin therapy on left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *Am J Cardiol* 1999;84(7):857–859
18. Zabalgoita M, Leonard A, Blackshear JL, Safford R, Baker VS, et al.: The stroke prevention in atrial fibrillation investigators committee on echocardiography: transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. *Ann Intern Med* 1998;128:639–647
19. Khan IA: Atrial stunning: basics and clinical considerations. *Int J Cardiol* 2003;92:113–128
20. Dagres N, Karatasakis G, Panou F, Athanassopoulos G, Maounis T, et al.: Pre-treatment with Irbesartan attenuates left atrial stunning after electrical cardioversion of atrial fibrillation. *Eur Heart J* 2006;27(17):2062–2068
21. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Stat M, et al.: Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. ACUTE Trial. *N Engl J Med* 2001;344(19):1411–1420
22. Black IW, Fatkin D, Sagar KB, Khandheri BK, Leung DY, et al.: Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation. *Circulation* 1994;89:2509–2513
23. Asher CR, Klein AL: Transesophageal echocardiography in patients with atrial fibrillation. *Pacing Clin Electrophysiol* 2003; 26:1597–1603
24. Manning WJ, Silverman DI, Gordon S, Harlan M, Douglas PS: Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. *N Engl J Med* 1993; 328:750–755
25. Manning WJ, Silverman DI, Keighley CS, Oettgen P, Douglas PS: Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5-year study. *JACC* 1995;25:1354–1361
26. Manning WJ, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, et al.: Accuracy of transesophageal echocardiography for identifying left atrial thrombi. *Ann Intern Med* 1995;123: 817–822
27. Fatkin D, Scalia G, Jacobs N, Burstow D, Leung D, et al.: Accuracy of biplane transesophageal echocardiography in detecting left atrial thrombus. *Am J Cardiol* 1996;77:321–323
28. Stoddard MF, Dawkins PR, Prince CR, Longaker RA: Transesophageal echocardiographic guidance of cardioversion in patients with atrial fibrillation. *Am Heart J* 1995;129(6):1204–1215
29. Orsinelli DA, Pearson AC: Usefulness of transesophageal echocardiography to screen for left atrial thrombus before elective cardioversion for atrial fibrillation. *Am J Cardiol* 1993;72(17):1337–1339
30. Corrado G, Santarone M, Beretta S, Tadeo G, Tagliagambe LM, et al.: Early cardioversion of atrial fibrillation and atrial flutter guided by transoesophageal echocardiography. *Europace* 2000;2(2):119–126
31. Klein AL, Grimm RA, Black IW, Leung DY, Chung MK, et al.: Cardioversion guided by transesophageal echocardiography: The ACUTE Pilot Study. *Ann Intern Med* 1997;126(3):200–209
32. Maltagliati A, Galli CA, Tamborini G, Calligaris A, Doria E, et al.: Usefulness of transoesophageal echocardiography before cardioversion in patients with atrial fibrillation and different anticoagulant regimens. *Heart* 2006;92(7):933–938
33. Strandberg M, Raatikainen MJ, Niemela M, Luotolahti M, Hartiala J, et al.: Clinical practicality and predictive value of transoesophageal echocardiography in early cardioversion of atrial fibrillation. *Europace.* 2006;8(6):408–412
34. Roijer A, Eskilsson J, Olsson B: Transoesophageal echocardiography-guided cardioversion of atrial fibrillation or flutter. *Eur Heart J* 2000;21(10):837–847
35. Fonseca N, Caetano F, Santos J, Seixo F, Bernardino L, et al.: Transesophageal echocardiography-guided cardioversion of atrial fibrillation. *Rev Port Cardiol* 2004;23(3):365–375

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20172