




Available online at
 ScienceDirect
www.sciencedirect.com

Elsevier Masson France

www.em-consulte.com



CLINICAL RESEARCH

Usefulness of contrast echocardiography for assessment of intracardiac masses

Intérêt de l'échocardiographie de contraste dans l'étude des masses intracardiaques

Nicolas Mansencal*, Laure Revault-d'Allonnes,
Jean-Pierre Pelage, Jean-Christian Farcot,
Pascal Lacombe, Olivier Dubourg

Pôle radiocardiologique, centre de référence pour les maladies cardiaques héréditaires, hôpital Ambroise-Paré, Assistance publique–Hôpitaux de Paris, université de Versailles–Saint-Quentin (UVSQ), Boulogne, France

Received 13 October 2008; received in revised form 11 December 2008; accepted 15 December 2008

Available online 6 March 2009

KEYWORDS

Contrast;
Echocardiography;
Mass;
Thrombus;
Tumour

Summary

Background. — Conventional echocardiography is not a reliable method for characterizing tissue patterns of intracardiac masses.

Aims. — To assess the ability of contrast echocardiography to characterize intracardiac masses.

Methods. — Thirty-one consecutive patients with an intracardiac mass were included in this prospective study. All patients underwent conventional and contrast echocardiographic examinations. Analysis of characteristics by contrast agent allowed classification of intracardiac masses as follows: complete lack of enhancement, suggesting thrombus; partial and/or incomplete enhancement, suggesting myxoma; complete enhancement, suggesting intracardiac tumor. Tissue characteristics of intracardiac masses were also analyzed using at least one of the following techniques: cardiac magnetic resonance, pathology of intracardiac mass and/or mass resolved after anticoagulation during follow-up.

Results. — Using contrast echocardiography, an accurate diagnosis was made in all patients by an experienced investigator and in all patients except one (97%), by a physician trainee ($p=0.31$). Among patients with a history of tumor, echocardiography allowed accurate diagnosis of the nature of the mass in all patients; 50% of these patients presented with a secondary cardiac

* Corresponding author. Service de cardiologie, hôpital universitaire Ambroise-Paré, Assistance publique–Hôpitaux de Paris, 9, avenue Charles-de-Gaulle, 92100 Boulogne, France. Fax: +33 01 49 09 53 44.

E-mail address: nicolas.mansencal@apr.aphp.fr (N. Mansencal).

MOTS CLÉS

Contraste ;
Échocardiographie ;
Masse ;
Thrombus ;
Tumeur

tumor and the others had a thrombus. Of the 14 patients with a thrombus located in the left ventricle, 12 (86%) presented with left ventricular motion abnormalities using conventional echocardiography, whereas wall motion abnormalities were observed in all 14 patients (100%) using contrast agent. In these patients, 91 and 99% of left ventricular segments were well visualized using conventional and contrast echocardiography, respectively ($p < 0.0001$).

Conclusions. – Contrast echocardiography may be useful for the tissue characterization of intracardiac masses.

© 2009 Elsevier Masson SAS. All rights reserved.

Résumé

Contexte. – L'échocardiographie conventionnelle ne permet pas d'analyser les caractéristiques tissulaires des masses intracardiaques.

Objectif. – Évaluer la capacité de l'échocardiographie de contraste à caractériser les différents types de masses intracardiaques.

Méthode. – Trente et un patients avec masse intracardiaque ont été inclus consécutivement dans cette étude prospective. Tous les patients ont bénéficié d'une échocardiographie conventionnelle et d'une échocardiographie de contraste. En échocardiographie de contraste, les masses intracardiaques étaient classées de la façon suivante : une absence complète de prise de contraste était en faveur d'un thrombus, une prise partielle ou incomplète de contraste suggérait un myxome et une prise complète de produit de contraste était en faveur d'une tumeur intracardiaque. Les caractéristiques tissulaires des masses intracardiaques étaient également analysées à partir d'au moins une des méthodes suivantes : imagerie par résonance magnétique, les résultats de l'anatomopathologie et/ou la régression de la masse après anticoagulation.

Résultats. – Un diagnostic exact en échocardiographie de contraste était fait chez tous les patients par un observateur expérimenté et chez tous les patients, sauf un (97%) par un débutant. Parmi les patients ayant des antécédents de cancer, l'échocardiographie permettait de poser le bon diagnostic chez tous les patients : 50% de ces patients avaient une tumeur secondaire et l'autre moitié un thrombus. Parmi les patients ayant un thrombus localisé dans le ventricule gauche, 12/14 patients (86%) présentaient un trouble de la cinétique segmentaire détecté en échocardiographie conventionnelle alors qu'en utilisant du produit de contraste, un trouble de la cinétique segmentaire était détecté chez tous les patients (100%). Chez ces patients, 91 et 99% des segments ventriculaires gauches étaient analysables respectivement en échocardiographie conventionnelle et en échocardiographie de contraste.

Conclusion. – L'échocardiographie de contraste pourrait être intéressante dans la caractérisation tissulaire des masses intracardiaques.

© 2009 Elsevier Masson SAS. Tous droits réservés.

Abréviations

CMR	cardiac magnetic resonance
F/U	follow-up
LA	left atrium
LV	left ventricle
RA	right atrium
RV	right ventricle

Background

Intracardiac masses are found rarely [1]. Most are thrombi after myocardial infarction [2–5], although primary cardiac tumors or metastatic involvement of the heart may occur [6]. Echocardiography is the technique of choice for the detection of intracardiac masses in routine practice [7]. However, conventional echocardiography is not a reliable method for characterizing the tissue patterns of these masses. Cardiac magnetic resonance (CMR) can also be used

to detect intracardiac masses and may offer clues that can help to determine tumor type [8–11], but CMR is not available in most centres and its availability is restricted.

Contrast echocardiography using new contrast agents has been proposed recently for the detection of thrombi and to distinguish thrombi from tumors [12–14]. However, few studies have evaluated the accuracy of echocardiography using contrast agents. The aim of this study was to assess the ability of contrast echocardiography to characterize intracardiac masses.

Methods

From January 2004 until March 2008, we studied prospectively 31 consecutive patients presenting with an intracardiac mass detected by transthoracic echocardiography. All patients underwent a conventional echocardiographic examination followed by an echocardiographic examination using contrast agent.

The tissue characteristics of the intracardiac masses were also analyzed systematically using at least one of the following methods: CMR, pathology of intracardiac mass (sample of mass taken through femoral puncture or cardiac surgery), left ventricular angiography and/or mass resolved after anticoagulation and detected by serial echocardiographic studies during follow-up. These methods were considered to be our gold standards for determining the tissue characteristics of an intracardiac mass. CMR (1.5 T General electric medical systems, Milwaukee, WI, USA) was performed using T1- and T2-weighted spin-echo images with a multislice–multiphase technique. Gadolinium enhancement T1-weighted spin-echo imaging was performed with an intravenous injection of 0.2 ml/kg Dotarem (Guerbet, Aulnay, France). The image interpretation was performed by two experienced radiologists, allowing determination of the tissue characteristics of the intracardiac masses. Masses resolved after anticoagulation were considered to be thrombi.

Transthoracic echocardiography was performed using a Siemens/Sequoia acuson system (Acuson, Mountain view, CA, USA), equipped with multifrequency transducers and capable of low energy (0.2 to 0.3 mechanical index). Conventional echocardiography was performed by two investigators (N.M. and O.D.) according to guidelines [7,15,16]. All examinations were performed using second harmonic imaging with a 1.9 mechanical index. We analyzed intracardiac masses systematically using apical 4-, 3- and 2-chamber views. We classified masses according to their location (left ventricle [LV], right atrium [RA] or left atrium [LA]). At the end of conventional transthoracic echocardiography, contrast echocardiography was performed systematically by peripheral venous injection. Right and left heart opacification was obtained with Sonovue (Bracco Altana Inc., Milan, Italy). We used a low mechanical index (0.2 to 0.3), avoiding the destruction of microbubbles. After a 1.0 ml intravenous bolus of Sonovue (and, if necessary, a second 0.5 ml intravenous bolus), and using CPS software (Siemens/Acuson, Mountain view, CA, USA), we analyzed the characteristics of the intracardiac mass. Once cardiac chambers were opacified by contrast, an ultrasound impulse of high mechanical index (1.9) was transmitted for at least four frames to destroy microbubbles within the mass. In case of enhancement of mass by contrast, this method allowed visualization of the gradual contrast replenishment of the mass after this impulse. Analysis of contrast characteristics allowed classification of intracardiac masses as follows:

- complete lack of enhancement, suggesting thrombus;
- partial and/or incomplete enhancement, suggesting myxoma;
- complete enhancement, suggesting intracardiac tumor (Fig. 1).

No continuous infusion of contrast agent was performed in accordance with limitations placed on its use in France. All contrast echocardiographic studies were recorded anonymously and were interpreted by two independent observers who were unaware of the clinical data and diagnoses of the masses: an experienced investigator (observer 1) and a physician trainee (< 15 contrast analyses; observer 2). Among patients with left ventricular masses, the quality of endocardial delineation in 17 left ventricular segments

was assessed systematically by observer 1 and was used to determine the number of well-visualized left ventricular segments by second harmonic imaging and by contrast agent.

Statistical analysis

Statistical analysis was performed using StatView version 4.5 (Abacus Concepts, Inc, NC, USA). Continuous variables are presented as means \pm SD and ranges. Continuous variables were compared using Fisher's exact test or a paired *t* test. Interobserver agreement in the interpretation of contrast echocardiography was assessed. A *p*-value less than 0.05 was considered to be significant.

Results

Population characteristics

The characteristics of the population are presented in Table 1. The mean age was 65 ± 16 years (range 29 to 93). Thirteen (42%) and ten (32%) patients had a history of myocardial infarction and tumor, respectively. Thirty-one patients with intracardiac mass were screened using conventional transthoracic echocardiography: 13 masses were present in the RA, four in the LA and 14 in the LV. According to the results of CMR, pathology and/or follow-up (resolution of thrombus by anticoagulation demonstrated on serial echocardiographic studies), the final diagnoses of the masses were as follows: 21 thrombi, seven tumors and three myxomas. The characteristics of the intracardiac masses are presented in Table 1. Using conventional echocardiography, a misdiagnosis was made in seven patients (23%).

Contrast echocardiography

The intracardiac mass was visualized correctly by contrast agent in all patients (100%). No side-effects were detected after Sonovue injection. The correct location of the mass was detected by both observers using contrast echocardiography. The mean area of intracardiac mass was $5.3 \pm 4 \text{ mm}^2$ (range 0.7 to 15.3) with conventional echocardiography and $5.3 \pm 3.9 \text{ mm}^2$ (range 0.7 to 14.6) with contrast agent (*p* = 0.53). Using contrast echocardiography, observer 1 (experienced investigator) classified the intracardiac masses as follows: complete lack of enhancement (suggesting thrombus) in 21 patients; partial enhancement (suggesting myxoma) in three patients; and complete enhancement (suggesting intracardiac tumor) in seven patients. All patients (100%) were classified correctly by observer 1 using contrast echocardiography compared with the final diagnosis of the mass determined by the gold standard method. Among patients with masses located in the RA (*n* = 13), seven had no enhancement, whereas complete enhancement was observed in six patients. Among patients with masses located in the LA (*n* = 4), three had partial enhancement whereas complete enhancement was observed in one patient. Among patients with masses located in the LV (*n* = 14), all had no enhancement.

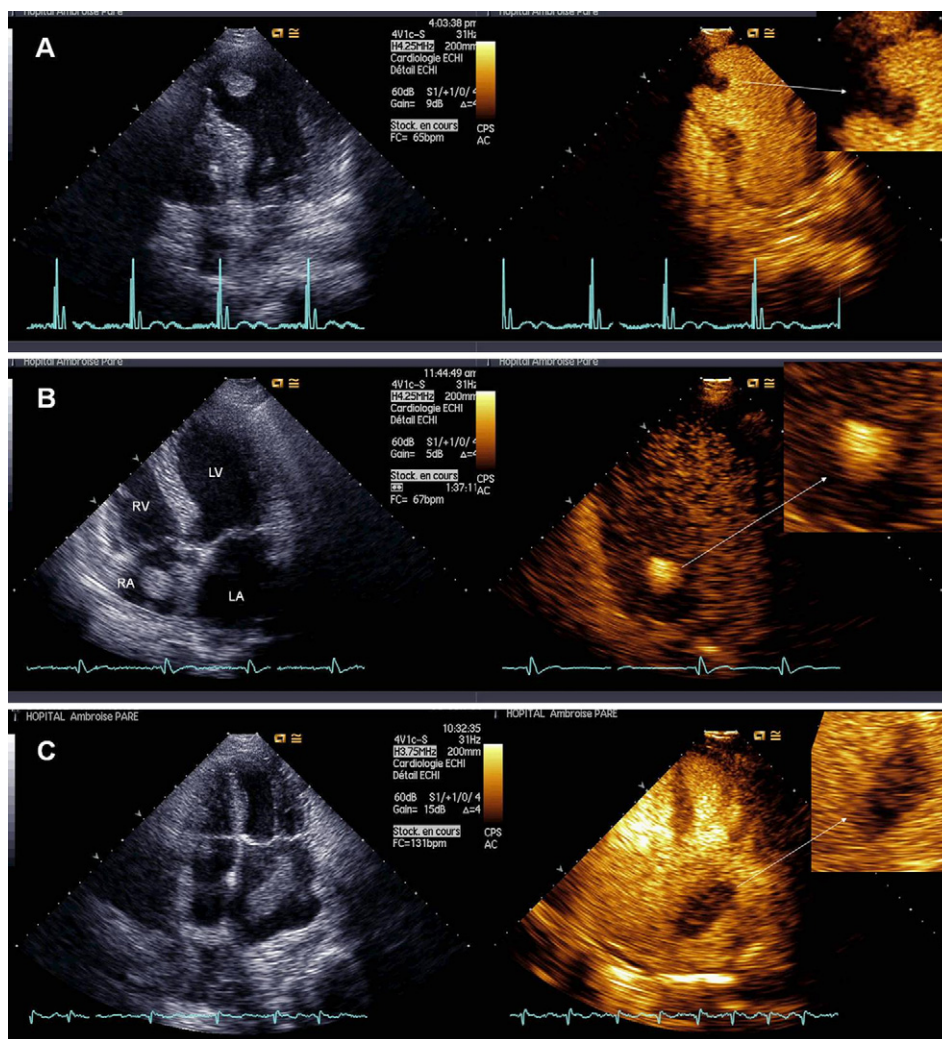


Figure 1. Three examples of intracardiac mass in apical 4-chamber view according to the results of contrast echocardiography. A. Left ventricular apical thrombus in a patient with a history of myocardial infarction. Contrast echocardiography revealed no enhancement of the mass. B. Secondary cardiac tumour (renal sarcoma) located in the RA, with a complete enhancement of mass by contrast agent. C Left atrial myxoma, with a partial enhancement of mass by contrast agent.

Observer2 (physician trainee) classified the intracardiac masses as follows: complete lack of enhancement in 21 patients, partial enhancement in two patients and complete enhancement in eight patients. An accurate diagnosis was made by observer2 in all patients except one (97%); in this single case of misdiagnosis, the intracardiac mass was classified as a complete enhancement (intracardiac tumor), whereas the enhancement was actually partial (myxoma), as noted correctly by observer 1. Interobserver agreement in performing an accurate diagnosis using contrast echocardiography was 97%. Furthermore, the diagnosis of the intracardiac masses improved significantly in both observers using contrast echocardiography compared with the first suspected diagnosis performed by conventional echocardiography according to previous history, clinical status and echocardiographic characteristics of mass ($p=0.005$ for observer 1 and $p=0.02$ for observer 2).

According to the interpretation of both observers, the diagnoses of intracardiac masses using contrast echocardiography were accurate for all masses located in the RA and

LV. Among the ten patients with a history of tumor, echocardiography allowed accurate diagnosis of the nature of the mass in all patients; 50% of these patients presented with a secondary cardiac tumor and the others had a thrombus. Among patients with thrombus located in the LV ($n=14$), 12 (86%) presented with left ventricular motion abnormalities using second harmonic imaging, whereas wall motion abnormalities were observed in all 14 patients (100%) using contrast agent. In these patients, 252 left ventricular segments were analyzed: 230 (91%) and 249 (99%) segments were well visualized using second harmonic imaging and contrast echocardiography, respectively ($p<0.0001$).

Discussion

The main finding of our study is that transthoracic echocardiography using contrast agent is an accurate method for the tissue characterization of intracardiac mass in routine practice.

Table 1 Characteristics of 31 patients with intracardiac mass.

No.	Age (yrs)/Sex	Location of mass	Previous history	Diagnosis of mass	Modality of diagnosis ^a	Contrast enhancement pattern	
						Observer 1 ^b	Observer 2 ^b
1	29/F	RA	Melanoma	Thrombus	CMR & F/U	None	None
2	37/F	RA	–	Angiosarcoma	CMR & pathology	Complete	Complete
3	41/F	LV	Myocardial infarction	Thrombus	LV angiography & F/U	None	None
4	44/M	LV	Myocardial infarction	Thrombus	LV angiography & F/U	None	None
5	47/F	RA	–	Thrombus	CMR & F/U	None	None
6	47/M	LV	Myocardial infarction	Thrombus	CMR & F/U	None	None
7	49/F	RA	Sarcoma	Thrombus	CMR, pathology & F/U	None	None
8	55/M	LV	Myocardial infarction	Thrombus	Pathology	None	None
9	55/M	LV	Myocardial infarction	Thrombus	LV angiography & F/U	None	None
10	62/F	RA	Melanoma	Secondary cardiac tumour	CMR & pathology	Complete	Complete
11	62/F	RA	Renal carcinoma	Secondary cardiac tumour	CMR	Complete	Complete
12	62/M	LV	Myocardial infarction	Thrombus	LV angiography & F/U	None	None
13	64/F	RA	Lymphoma	Secondary cardiac tumour	CMR	Complete	Complete
14	64/M	RA	Leiomyosarcoma	Thrombus	CMR & F/U	None	None
15	64/F	LA	–	Myxoma	Pathology	Partial	Partial
16	67/M	LV	Myocardial infarction	Thrombus	LV angiography & F/U	None	None
17	68/F	LA	Indifferentiated adenocarcinoma	Secondary cardiac tumour	Pathology	Complete	Complete
18	69/F	RA	Melanoma	Thrombus	CMR & F/U	None	None
19	72/F	LV	Recurrent stroke	Thrombus	CMR & pathology	None	None
20	73/M	LV	Myocardial infarction	Thrombus	LV angiography & F/U	None	None
21	74/F	RA	–	Thrombus	CMR & F/U	None	None
22	74/M	LV	Myocardial infarction	Thrombus	Pathology	None	None
23	75/F	LV	Myocardial infarction	Thrombus	F/U	None	None
24	77/M	LV	Myocardial infarction	Thrombus	LV angiography & F/U	None	None
25	79/F	RA	Renal carcinoma	Thrombus	CMR & F/U	None	None
26	82/F	RA	–	Sarcoma	CMR & pathology	Complete	Complete
27	82/M	LV	Myocardial infarction	Thrombus	F/U	None	None
28	83/F	LA	–	Myxoma	Pathology	Partial	Complete
29	84/M	LV	Myocardial infarction	Thrombus	F/U	None	None
30	85/M	RA	Lung adenocarcinoma	Secondary cardiac tumour	CMR	Complete	Complete
31	93/M	LA	–	Myxoma	CMR	Partial	Partial

^a F/U defined as mass resolved after anticoagulation and detected by serial echocardiographic studies during F/U.

^b Observers 1 and 2 were blinded to clinical and imaging data.

Kirkpatrick et al. [12] demonstrated that pixel intensities in the intracardiac masses and in the adjacent section of myocardium after injection of contrast agent allow the different types of intracardiac mass to be distinguished. Contrast enhancement resulted in greater pixel intensity detected by dedicated software and was suggestive of tumor, whereas decreased pixel intensity compared with the myocardium was indicative of myxoma or thrombus. However, dedicated software for the analysis of pixel intensity is not widely available. Thus, in our study, we scored intracardiac masses visually as three groups: those with a complete lack of enhancement by contrast agent, suggesting thrombus; those with partial enhancement, suggesting myxoma; and those with complete enhancement, suggesting intracardiac tumor. This visual assessment may be performed whatever the type of echocardiogram.

The different echocardiographic patterns can be explained by the characteristics of each mass. Most malignant tumors have abnormal neovascularization, with high blood supplies, which explains why these tumors present an enhancement of mass by contrast agent. Myxomas have poor blood supplies, with partial enhancement by contrast agent. Finally, thrombi are avascular, with no enhancement. In our study, a correct diagnosis was made by an experienced investigator and a physician trainee in 100 and 97% of cases, respectively, using contrast echocardiography. Thus, regardless of the experience of the physician, contrast echocardiography is highly reproducible and gives an accurate diagnosis with a simple and fast injection of contrast agent, which permits heart opacification.

The introduction of second harmonic imaging has led to the widespread use of transthoracic echocardiography for the detection of intracardiac masses, except when exploring the left atrial appendage [3,7]. Conventional echocardiography is useful for detecting left ventricular thrombi in most patients presenting with acute myocardial infarction [3]. However, we have demonstrated recently that contrast echocardiography is more reliable than conventional echocardiography for the detection of these thrombi [13]. Left ventricular thrombi are usually associated with wall motion abnormalities. In this study, the use of contrast agent allowed us to detect all these wall motion abnormalities, whereas conventional echocardiography was not efficient in their detection in 14% of patients. This lack of accuracy with conventional echocardiography is explained by the acquisition of a better endocardial border definition using contrast agent. Most patients included in our study had thrombi, as would be expected in routine practice. The previous medical history may sometimes be helpful in the interpretation of echocardiography, particularly in patients with previous myocardial infarction. Interestingly, in patients with a history of tumor, as was the case for ten patients in our study, the accurate diagnosis of intracardiac mass is more difficult. Indeed, only 50% of these patients presented with an intracardiac tumor, whereas the others had a confirmed thrombus. Although conventional echocardiography is unable to distinguish tissue characteristics, with the use of contrast agent, it gave an accurate diagnosis of the masses in all these patients.

In our study, all contrast echocardiographic studies were performed using specific imaging settings. Indeed, the use of contrast agent needs a low mechanical index (0.2 to

0.3), whereas conventional transthoracic echocardiography needs a high mechanical index. We performed contrast echocardiography with CPS software that we use in routine practice in our echocardiographic laboratory. Most recent echocardiograms have specific on-board software, allowing automatic use of low mechanical index, with adequate imaging. However, in echocardiograms without dedicated contrast software, it is always possible to use contrast agent with a manual setting of mechanical index, and we believe that assessment of intracardiac mass by contrast agent may be performed regardless of the software used, giving a reliable diagnosis with this noninvasive technique.

The assessment of intracardiac masses by contrast echocardiography requires specific contrast agent with right and left heart opacification. A few months ago, the United States food and drug administration issued “black-box” warnings on use of perflutren-based ultrasound contrast agents. However, a recent analysis of patients undergoing clinically-indicated echocardiography showed no increased mortality risk associated with the use of contrast agent [17,18].

The main limitation of this study is the small number of patients with cardiac tumors. Intracardiac tumors are a very rare finding and can be complex to assess. Furthermore, perfusion imaging may be different according to the type of mass and this must be taken into account for their interpretation.

Conclusion

This study demonstrates that two-dimensional echocardiography using contrast agent with right and left heart opacification is an accurate method for the identification of intracardiac thrombi. Despite the small number and variety of cardiac tumors, contrast echocardiography may also be useful for the tissue characterization of intracardiac masses. Moreover, despite different clinical settings, contrast echocardiography is a reliable means of differentiating between tumor, myxoma and thrombus.

Conflicts of interest

None.

Acknowledgement

We are indebted to Anne-Sophie Lot, MD for assistance in the statistical analysis of the article.

References

- [1] Reynen K. Frequency of primary tumors of the heart. *Am J Cardiol* 1996;77:107.
- [2] Buda AJ. The role of echocardiography in the evaluation of mechanical complications of acute myocardial infarction. *Circulation* 1991;84:1109–21.
- [3] Domenicucci S, Chiarella F, Bellotti P, Bellone P, Lupi G, Vecchio C. Long-term prospective assessment of left ventricular thrombus in anterior wall acute myocardial infarction and

- implications for a rational approach to embolic risk. *Am J Cardiol* 1999;83:519–24.
- [4] Nayak D, Aronow WS, Sukhija R, McClung JA, Monsen CE, Belkin RN. Comparison of frequency of left ventricular thrombi in patients with anterior wall versus non-anterior wall acute myocardial infarction treated with antithrombotic and antiplatelet therapy with or without coronary revascularization. *Am J Cardiol* 2004;93:1529–30.
- [5] Rehan A, Kanwar M, Rosman H, et al. Incidence of post myocardial infarction left ventricular thrombus formation in the era of primary percutaneous intervention and glycoprotein IIb/IIIa inhibitors. A prospective observational study. *Cardiovasc Ultrasound* 2006;4:20.
- [6] Lam KY, Dickens P, Chan AC. Tumors of the heart. A 20-year experience with a review of 12,485 consecutive autopsies. *Arch Pathol Lab Med* 1993;117:1027–31.
- [7] Peters PJ, Reinhardt S. The echocardiographic evaluation of intracardiac masses: a review. *J Am Soc Echocardiogr* 2006;19:230–40.
- [8] Constantine G, Shan K, Flamm SD, Sivananthan MU. Role of MRI in clinical cardiology. *Lancet* 2004;363:2162–71.
- [9] Gulati G, Sharma S, Kothari SS, Juneja R, Saxena A, Talwar KK. Comparison of echo and MRI in the imaging evaluation of intracardiac masses. *Cardiovasc Intervent Radiol* 2004;27:459–69.
- [10] Kaminaga T, Takeshita T, Kimura I. Role of magnetic resonance imaging for evaluation of tumors in the cardiac region. *Eur Radiol* 2003;13:L1–10.
- [11] Srichai MB, Junor C, Rodriguez LL, et al. Clinical, imaging, and pathological characteristics of left ventricular thrombus: a comparison of contrast-enhanced magnetic resonance imaging, transthoracic echocardiography, and transesophageal echocardiography with surgical or pathological validation. *Am Heart J* 2006;152:75–84.
- [12] Kirkpatrick JN, Wong T, Bednarz JE, et al. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. *J Am Coll Cardiol* 2004;43:1412–9.
- [13] Mansencal N, Nasr IA, Pilliere R, et al. Usefulness of contrast echocardiography for assessment of left ventricular thrombus after acute myocardial infarction. *Am J Cardiol* 2007;99:1667–70.
- [14] Thanigaraj S, Schechtman KB, Perez JE. Improved echocardiographic delineation of left ventricular thrombus with the use of intravenous second-generation contrast image enhancement. *J Am Soc Echocardiogr* 1999;12:1022–6.
- [15] Abergel E, Bernard Y, Brochet E, et al. Update of the French society of cardiology recommendations on indications for doppler echocardiography published in 1999. *Arch Cardiovasc Dis* 2008;101:249–89.
- [16] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79–108.
- [17] Aggeli C, Giannopoulos G, Roussakis G, et al. Safety of myocardial flash-contrast echocardiography in combination with dobutamine stress testing for the detection of ischaemia in 5250 studies. *Heart* 2008;94:1571–7.
- [18] Kusnetzky LL, Khalid A, Khumri TM, Moe TG, Jones PG, Main ML. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. *J Am Coll Cardiol* 2008;51:1704–6.