



CARDIOLOGY *Rounds*

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ST. MICHAEL'S HOSPITAL,
UNIVERSITY OF TORONTO

Primary Cardiac Tumours

By HANI AMAD, MD, FRCPC, and HOWARD LEONG-POI, MD, FRCPC

Primary cardiac tumours are extremely rare. In most autopsy series, they have an incidence of approximately 0.1% and are far less common than secondary tumours that metastasize to the heart that are reported to be 20 times more common. Three-quarters of primary cardiac tumours are benign and the majority of benign tumours are myxomas. They are diagnosed by various cardiac imaging modalities, such as echocardiography, magnetic resonance imaging (MRI), and computed tomography (CT). This issue of *Cardiology Rounds* previews the diagnosis, clinical presentation, and treatment options for some of the more common primary cardiac tumours occurring in clinical practice.

The occurrence of tumours in the heart has been recognized for centuries. In fact, it is reported that Realdus Columbus recognized the existence of cardiac tumours in 1562 AD.¹ However, Albers is credited with providing the first authentic description of a cardiac tumour in 1835. The first successful surgical removal of a cardiac neoplasm occurred in 1936 and the first successful surgical removal of a tumour with cardiopulmonary bypass was performed by Clarence Crafoord in 1954.¹ Primary cardiac tumours usually present either as an incidental finding in asymptomatic patients, or symptomatically with heart failure, embolic phenomenon, arrhythmias, and/or constitutional symptoms.

Clinical presentation

Heart failure: Cardiac tumours may cause signs and symptoms of either backward, congestive heart failure, or forward, low-output failure, or both. Intra-cavitary tumours may cause obstruction of either ventricular filling or outflow, as well as valvular regurgitation that can ultimately lead to congestive heart failure or impaired cardiac output.²

Embolic phenomenon: Embolization of tumour fragments can be a frequent and dramatic clinical occurrence and is often the initial and only clinical presentation of a cardiac tumour. An embolic stroke in a young person without evidence of cerebrovascular disease, especially in the presence of sinus rhythm, should raise the suspicion of a cardiac source of embolus such as an intracardiac tumour or infective endocarditis. Right-sided tumours can result in pulmonary emboli, while left-sided tumours embolize to the systemic circulation and potentially cause stroke, visceral infarction, peripheral limb ischemia, and peripheral vascular aneurysms.²

Arrhythmias: Cardiac tumours, especially those with intramural involvement, may cause disturbances in conduction or rhythm. Atrial tumours such as myxomas and sarcomas can produce a wide variety of supraventricular tachycardias, including atrial fibrillation, atrial flutter, and ectopic atrial tachycardia. Tumours in the area of the AV node – typically angiomas and mesotheliomas – may produce AV conduction disturbances, including complete heart block and asystole. Tumours located in the ventricles, such as fibromas, can cause premature ventricular contractions, ventricular tachycardia, ventricular fibrillation and, last but not least, sudden cardiac death.²

Benign cardiac tumours

Myxomas

Cardiac myxomas comprise approximately 50% of all benign cardiac tumours in most adult clinical series (Table 1).³ The tumour probably originates from subendocardial nests of primitive mesenchymal cells that may differentiate into several cell types, including endothelial and lipidic cells.² In case series, the mean age at the time of presentation is 50 years and two-thirds of

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Benign tumours	% of group		
	Adults	Children	Infants
Myxoma	52	17	0
Papillary fibroelastoma	16	0	0
Lipoma	16	0	0
Rhabdomyoma	1	42	62
Fibroma	3	18	17
Teratoma	1	12	12
Hemangioma	6	5	4
Others	5	4	4

patients are female. Approximately 75% of myxomas occur in the left atrium, where the site of attachment is usually in the region of the limbus of the fossa ovalis.² Myxomas may occasionally be found in the posterior left atrial wall, but these should raise the suspicion of malignant involvement. About 15%-20% of myxomas occur in the right atrium⁴ and about 2% can be found in either ventricle. More than 90% are solitary, although several myxomas within one atrium and myxomas in both atria and ventricles have also been reported. The average size of these tumours is 5-6 cm in diameter, with a range of 1-15 cm.²

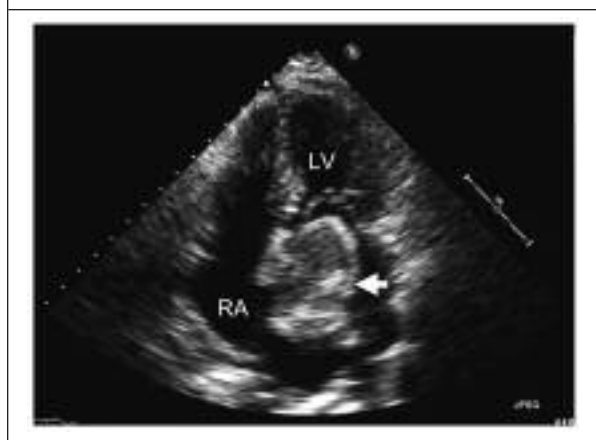
Clinical features: Myxomas can present with one or more of the triad of intracardiac obstruction, systemic embolization, and constitutional symptoms.^{5,6} About 70% of myxomas have associated cardiac symptoms, mainly heart failure and syncope. It is thought that the pedunculated nature of a myxoma, as well as its location within the left atrium, allow it to prolapse into the left ventricle during diastole, potentially obstructing mitral inflow, or to impair valvular closing resulting in mitral regurgitation. Moreover, the recurrent contact between the myxoma and the mitral valve may cause permanent valvular damage. It should also be noted that, in contrast to anatomic mitral valve disease, the mobility of myxomas can potentially lead to paroxysmal symptoms of shortness of breath or syncope that is dependent on body position.^{5,6}

Embolic events are reported to occur in approximately 30% of patients. Of these patients, two-thirds present with cerebral emboli causing transient ischemic attacks, strokes or seizures, and half have peripheral limb emboli. Compared to round and smooth-appearing tumours, tumours that are polypoid, friable, and villous are more than twice as likely to embolize.²

Finally, constitutional symptoms that are unique to myxoma can occur in 40%-90% of patients. Symptoms include myalgias, arthralgias, rash, fever, weight loss, and fatigue. It is postulated that these constitutional symptoms are due to the constitutive synthesis of the tumour and secretion of interleukin (IL)-6, a cytokine that induces an acute-phase response.^{2,5,6}

Physical examination of a left-sided myxoma may reveal signs of pulmonary congestion, as well as mitral

Figure 1: Large myxoma (arrow) in left atrium, attached to the interatrial septum and prolapsing through the mitral annulus during diastole.

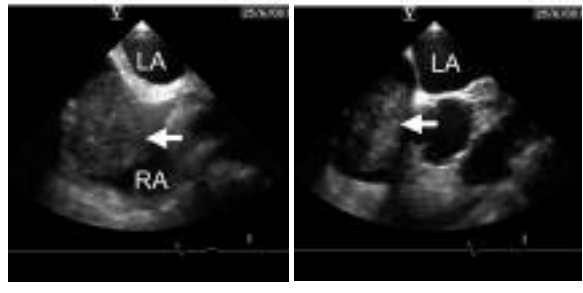


LV = left ventricle, RA = right atrium

systolic and diastolic murmurs. A loud S1 may also occur and may be related to the late onset of mitral valve closure resulting from either increased left atrial pressure or prolapse of the tumour through the mitral valve orifice. In some cases, an early diastolic sound (~100 msec after S2), termed a "tumour plop" can be identified.² It is thought to be produced as the tumour strikes the endocardium or as its excursion is abruptly halted with resultant tension on the tumour stalk. Physical examination of a right-sided myxoma can reveal an elevated jugular venous pressure with a prominent *a* wave and steep *y* descent, peripheral edema, hepatomegaly, and ascites. One can also hear a holosystolic murmur, secondary to tricuspid regurgitation that exhibits respiratory variation. Finally, laboratory investigations in a patient with myxoma may reveal an elevated erythrocyte sedimentation rate (ESR), anemia, leukocytosis, thrombocytopenia or thrombocytosis, and hypergammaglobulinemia.^{2,5,6}

Diagnosis: While myxomas may display several findings on a plain chest x-ray (CXR) that may offer the first clue to their presence (eg, cardiac chamber enlargement or evidence of pulmonary venous hypertension), it has been reported that up to one-third of CXRs are entirely normal. Transthoracic echocardiography (TTE) has become the screening test of choice for cardiac tumours in general, and myxoma in particular.⁷ The advantage of TTE is that it offers real-time, high spatial, and temporal resolution imaging and, thus, can provide information about tumour size, attachment, and mobility. Classic echocardiographic findings include a mobile, distensible mass attached to the interatrial septum in the region of the fossa ovalis (Figure 1). While this attachment is usually via a stalk, more broad-based attachment has been reported, as has atypical sites of attachment such as the posterior atrial wall or the ventricles. Transesophageal echocardiography (TEE) continues to play an important role in further delineating the site of attachment and ruling out the existence of multiple tumours (Figure 2). More recently, CT and MRI have

Figure 2: Large mass seen (arrows) within the RA on transesophageal echocardiogram, confirmed as a right atrial myxoma at surgery.



LV = left ventricle, RA = right atrium

achieved greater applicability in the diagnosis of cardiac tumours. They allow more soft tissue characterization, as well as assessment of surrounding structures and, hence, extent of tumour spread and invasion, specifically to extra-cardiac structures.^{8,9}

Pathology: Grossly, myxomas can be gelatinous, smooth and round, or irregular and friable. They exhibit areas of calcification, hemorrhage, and necrosis. Diagnosis is made by the observation of cords, rings, or florets of cells (termed lipidic cells) embedded in a myxoid stroma.²

Treatment: Surgical removal is the only treatment modality. The classical approach to a typical left atrium (LA) myxoma is through the right atrium and across the interatrial septum at the fossa ovalis. When technically feasible, an attempt is made to excise a full-thickness section of the atrial tissue surrounding the tumour to prevent any residual tissue from causing recurrence.² Operative mortality is reported to be around 1%, depending on the presence of comorbidities. It is reported that 1%-5% of myxomas recur.⁵

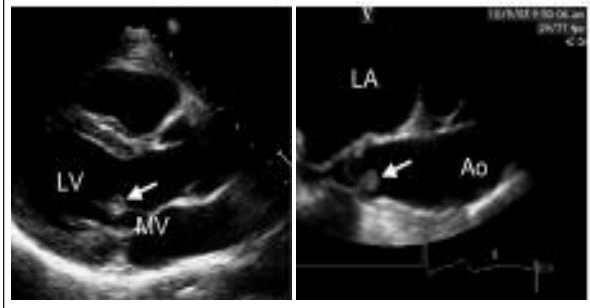
Papillary fibroelastoma

Papillary fibroelastomas, the most common tumours of the cardiac valves, are essentially benign papillomas of the endocardium. They have an estimated frequency of 0.0017%-0.33% in autopsy series.¹⁰ The average age at detection is 60 years, with no predilection for either sex. Their median diameter is about 8 mm, with the largest reported being 40 mm.² Papillary fibroelastomas are found predominantly on the surface of cardiac valves, but can also occur on papillary muscles, chordae tendinae, and in the atria. They are usually found on the upstream side of valves and generally do not cause valvular dysfunction.

Clinical features: Although many are clinically insignificant, papillary fibroelastomas have the potential to embolize to vital structures. In fact, they can mimic infective endocarditis with the combination of embolic events and a valvular mass. Tumours on the aortic valve have been reported to partially obstruct the coronary arterial orifice and lead to myocardial ischemia or infarction.¹¹

Diagnosis: Echocardiography is the diagnostic modality of choice,¹² since these tumours can be very small and

Figure 3: Mobile masses attached by stalks (arrows) on the MV (left) on TTE, and aortic valve (right) on TEE, consistent with papillary fibroelastomas.



LA = left atrium, LV = left ventricle,
MV = mitral valve, Ao = ascending aorta

attached to highly mobile valve leaflets that limit imaging by CT or MRI. TTE is reported to have a sensitivity of 62%; this rate increases to about 90% when tumours <2mm are excluded. The higher resolution of TEE allows for an improved sensitivity for detection (Figure 3).

Pathology: On gross inspection, papillary fibroelastomas have a characteristic frond-like appearance resembling a sea anemone.² These tumours are usually solitary. All the cardiac valves can be affected, however to varying degrees; the aortic valve is affected most frequently (29%), followed by the mitral (25%), tricuspid (17%), and finally the pulmonic valves (13%).

Treatment: Since the risk of embolic events has been reported to be as high as 25% over 3 years, complete resection of this tumour is generally recommended, especially for larger, left-sided tumours. More than 90% can be resected using a conservative, valve-sparing approach. No recurrences have been reported in the literature.

Malignant cardiac tumours

Sarcoma

About one-fourth of all cardiac tumours exhibit malignant histological characteristics and invasive or metastatic behaviour. Nearly all (95%) of these are sarcomas (Table 2), thus making these tumours second only to myxomas in overall frequency.^{2,13} However, primary sarcoma of the heart remains exceptionally rare. They may occur at any age, but most commonly occur between the 3rd and 5th decades of life. Sarcomas derive from mesenchyme and, therefore, may display a wide variety of morphological types, including angiosarcoma (37%), rhabdomyosarcoma (10%), osteosarcoma (3%-9%), and undifferentiated (24%) types.¹³

Clinical features: The cardiac findings are determined primarily by the location of the tumour and by the extent of intracavitary obstruction. Many patients present with progressive, unexplained dyspnea and evidence of heart failure, particularly on the right side. Tumours can obstruct blood flow and interfere with valve function. Local invasion can cause arrhythmias and pericardial effusion with

Malignant tumours	% of group		
	Adults	Children	Infants
Angiosarcoma	28	6	0
Rhabdomyosarcoma	11	41	50
Fibrosarcoma	8	18	17
Malignant fibrous histiocytoma	6	6	0
Osteosarcoma	7	0	0
Leiomyosarcoma	5	0	17
Myxosarcoma	3	6	0
Other sarcomas	14	12	0
Undiff. sarcoma	12	12	17
Lymphoma	6	0	0

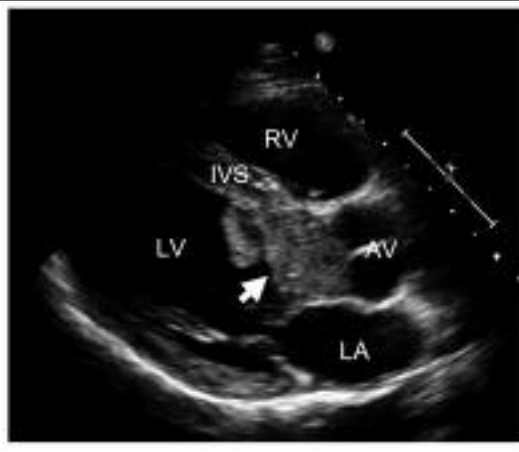
tamponade. In fact, 29% of patients have an effusion at presentation. Tumour fragments can also embolize. Patients may complain of chest pain, fever, malaise, and weight loss.¹³

Angiosarcomas – the most common sarcoma – arise preferentially in the right atrium. In distinction to most other cardiac sarcomas, in which the sex distribution is equal, there appears to be a 3:1 male-to-female ratio among patients with angiosarcomas. These tumours are either intracavitary and polypoid, or diffuse and infiltrative, with sheet-like involvement of the pericardium occurring in the latter forms. Metastases develop in 47%-89% of patients, most commonly to the lungs, but also to the brain, bone, and colon. Because these tumours arise mostly in the right atrium, they tend to be discovered late and may not be amenable to complete resection and, hence, portend a poor prognosis.

Diagnosis: TTE is a reasonable initial screening tool (Figure 4). However, TEE may offer important additional clues as to the malignant nature of the lesion by showing intramyocardial and, for right atrial masses, vena caval invasion. CT and MRI offer superior soft tissue characterization and allow determination of the extent of the tumour infiltration, in particular to extravascular structures. However, it should be noted that there are no pathognomonic imaging signs since most sarcomas show heterogeneous signal intensity due to focal areas of hemorrhage and necrosis. Often, diagnosis is not confirmed till pathologic specimens are obtained surgically.

Treatment: Sarcomas proliferate rapidly and display a rapid downhill course. Death is due to widespread infiltration of the myocardium, obstruction of flow within the heart, or distant metastases. Mean survival for most sarcomas is 9-11 months. Complete surgical excision should be considered to achieve local control

Figure 4: Large mass (arrow) filling the LV outflow tract, attached to and infiltrating the interventricular septum (IVS). Pathology at time of surgical resection confirmed the diagnosis of poorly differentiated sarcoma.



LA = left atrium, LV = left ventricle, AV = aortic valve, RV = right ventricle

and relieve symptoms. Unfortunately, that may not be possible in most cases due to the delayed diagnosis. In these cases, incomplete resection, adjuvant chemotherapy using an anthracycline-based regimen, and/or radiation therapy may be attempted.^{2,13}

Therapeutic outcomes for primary cardiac tumours

Surgical resection

Centofanti et al¹⁶ did a retrospective analysis of 91 patients who underwent evaluation and surgical treatment of primary cardiac tumours between 1980 and 1997. In their cohort, 91% had myxomas, 3.2% had benign nonmyxoma tumours, and about 5% had sarcomas. For the myxoma patients, there were 3 hospital deaths (3.6%). Early morbidity included atrial arrhythmias in 31 (37%), AV block in 3 (3.6%), and pericardial effusion in 1 patient. Late mortality was 6.5% (5/80). There was recurrence of myxoma over a follow-up of 7±5 years. Five sarcoma patients were operated on, all of whom survived the operation. In 3 of the patients, a redo-operation was necessary because of tumour recurrence. Unfortunately, all patients died within 3 years of the first operation (mean 13±14 months).

Centofanti's study demonstrates that survival chances are excellent for patients with myxoma with no recurrences after a long follow-up. On the other hand, chances for survival are extremely poor for patients with malignant tumours. From the findings of their retrospective analysis, they concluded that surgical resection remains the treatment of choice. It is curative in benign tumours and it may prolong life in

malignant tumours. There remain no randomized trials of surgical intervention for primary cardiac tumours and, thus, treatment is predominantly based on consensus and expert opinion. Given the poor prognosis for malignant primary cardiac tumours, even with surgical resection, improvement in adjuvant or alternate therapy is clearly needed.

Adjuvant chemotherapy

Llombart-Cussac et al¹⁷ examined the role of adjuvant chemotherapy for primary cardiac sarcoma. They reported their experience with 15 patients who were diagnosed and treated in the period between 1979 and 1995. Their patients received a doxorubicin-containing regimen within 6 weeks of optimal resection of their sarcoma. By the time they published their findings, 13 patients had relapsed. Overall, 12 of the patients died, with an overall median survival of 12 months. The 2-year survival rate was 26%. They did find that survival was significantly longer for patients with completely resected tumours (22 vs 7 months $p=0.02$) and those who did not have angiosarcoma (18 vs 7 months $p=0.04$). Thus, their study failed to show any benefit to chemotherapy.

Autotransplantation

Reardon et al¹⁸ examined the role of autotransplantation in a retrospective analysis of 11 consecutive patients who underwent the procedure between 1998-2006. This technique involves cardiac explantation, *ex-vivo* tumour resection with cardiac reconstruction, and cardiac reimplantation. Of the 11 patients, 8 had malignant primary tumours and 3 were benign. Patients with sarcoma received adjuvant chemotherapy. In their study, there was no in-hospital mortality and 4 patients were reported to be still alive by the time of the publication. Overall, median survival was 18.5 months. They concluded that autotransplantation is a feasible technique for resection of complex left-sided cardiac tumours. More importantly, they concluded that operative mortality and overall survival compare favourably with survival reported after standard resection and orthotopic heart transplant.

Conclusion

Primary cardiac tumours are exceedingly rare and most are benign. Myxomas comprise over 50% of benign tumours and have an excellent prognosis post-surgical resection. Sarcomas comprise 90% of malignant tumours; unfortunately, they portend an extremely poor prognosis despite complete resection, adjuvant chemotherapy, as well as autotransplantation. Novel therapies are, therefore, needed to improve survival in patients who are diagnosed with this aggressive tumour.

Dr. Hani Amad is a cardiology trainee at St. Michael's Hospital.

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Abstracts of Interest

Therapy Insight:

Malignant Primary Cardiac Tumors

REARDON MJ, WALKES JC, BENJAMIN R.

Benign cardiac tumors are resected with a high degree of success with modern cardiac surgical techniques. Malignant cardiac tumors, however, continue to pose a therapeutic challenge to cardiac surgeons and oncologists because of the technical difficulty involved in extensive cardiac resections and the aggressive biological nature of the tumors. The majority of malignant cardiac tumors are sarcomas and can be categorized as right heart sarcoma, left heart sarcoma or pulmonary artery sarcoma. Right heart sarcomas are generally angiosarcomas, which infiltrate widely and metastasize early. A combination of chemotherapy and surgical resection is the preferred therapy. Left heart sarcomas, although large, are often less infiltrative and metastasize later than right heart sarcomas, but a similar approach to treatment is usually employed. Surgical resection is more-frequently necessary for left heart sarcomas because of intracardiac blood

flow obstruction and congestive heart failure, although the anatomic position and relation of these tumors to cardiac structures can complicate surgery. We have developed and employed the technique of cardiac autotransplantation, which involves cardiac excision, ex vivo tumor resection with cardiac reconstruction, and cardiac reimplantation, to lessen these technical difficulties. Pulmonary artery sarcomas can be treated by radiotherapy, as well as by the other therapies, because the myocardium can be avoided by the radiation fields. Surgical resection of this sarcoma type often requires pneumonectomy and can require pulmonary root replacement.

Nat Clin Pract Cardiovasc Med 2006;3(10):548-53.

Cardiac Autotransplantation for Primary Cardiac Tumour

REARDON MJ, MALAISRIE SC, WALKES JC, VAPORCIYAN AA, RICE DC, SMYTHE WR, DEFELICE CA, WOJCIECHOWSKI ZJ.

BACKGROUND: Complete tumor resection is the optimal treatment of cardiac tumors. Anatomic accessibility and proximity to vital structures complicates resection of tumors involving the left heart. The results of standard resection and resection with orthotopic heart transplantation are dismal. We, therefore, reviewed our series of patients with complex left-sided primary cardiac tumors who underwent tumor resection with cardiac autotransplantation.

METHODS: Since April 1998, 11 consecutive patients with complex left atrial or left ventricular intracavitary cardiac tumors underwent 12 resections using cardiac autotransplantation-cardiac explantation, ex vivo tumor resection with cardiac reconstruction, and cardiac reimplantation. Demographics, tumor histology, operative data, and mortality were analyzed. Follow-up was complete in all patients.

RESULTS: Complete resection by cardiac autotransplantation was used in 7 patients with left atrial sarcoma, 1 patient with left ventricular sarcoma, 2 patients with left atrial paraganglioma, and 1 patient with a complex giant left atrial myxoma. Eight patients had previous resection of their cardiac tumor, and 1 patient had a repeat autotransplantation for recurrent disease. There were no operative deaths. Median overall survival was 18.5 months in patients with sarcomas. All patients with benign tumors are alive without evidence of recurrence.

CONCLUSIONS: Cardiac autotransplantation is a feasible technique for resection of complex left-sided cardiac tumors. Recurrent disease after previous resections can be safely treated with this technique. Operative mortality and overall survival seems favorable in this series of patients. Benefits of this technique include improved accessibility and ability to perform a complete tumor resection with reliable cardiac reconstruction. *Ann Thorac Surg* 2006;82(2):645-650.

Differential Diagnosis of Cardiac Masses using Contrast Echocardiographic Perfusion Imaging

KIRKPATRICK JN, WONG T, BEDNARZ JE, ET AL

OBJECTIVES: We investigated the usefulness of echocardiographic contrast perfusion imaging in differentiating cardiac masses.

BACKGROUND: Two-dimensional echocardiography is the primary diagnostic modality for cardiac masses. However, differ-

entiation between the different types of cardiac masses may be difficult at times. We hypothesized that echocardiographic contrast perfusion imaging would differentiate the neo-vascularization of malignancies from the avascularity of thrombi and the sparse vascularity of stromal tumors.

METHODS: Sixteen patients with cardiac masses underwent power-modulation imaging after echocardiographic intravenous contrast administration. Pixel intensities in the mass and an adjacent section of myocardium were analyzed visually and by dedicated software. All masses had a pathologic diagnosis or resolved after anticoagulation. In a subset of patients, video-intensity curves of contrast replenishment in the mass and myocardium over time were generated. The post-impulse steady-state pixel intensity (A) and initial rate of contrast replenishment after impulse (beta) were compared with an index of blood vessel area on pathology.

RESULTS: In seven of 16 patients, contrast enhancement resulted in greater pixel intensity in the mass than in the adjacent myocardium. All of these masses were classified pathologically as malignant (n = 6) or benign and vascular (n = 1). Nine masses demonstrated decreased pixel intensity, compared with the myocardium, and were diagnosed pathologically as myxomas (n = 2) or thrombi (n = 5), or they resolved with anticoagulation (n = 2). For the subset of patients, beta correlated with the vessel area index (r = 0.60).

CONCLUSIONS: Echocardiographic contrast perfusion imaging aids in the differentiation of cardiac masses. Compared with the adjacent myocardium, malignant and vascular tumors hyper-enhanced, whereas stromal tumors and thrombi hypo-enhanced. *J Am Coll Cardiol* 2004;43(8):1412-9.

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