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EDITORIAL COMMENT

Determinants of Myocardial Recovery in Myocarditis

Has the Time Come for Molecular Fingerprinting?*

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The clinical presentation of viral myocarditis is quite variable, ranging from asymptomatic left ventricular (LV) dysfunction to fulminant heart failure culminating in death. Although longitudinal follow-up studies of patients with suspected viral myocarditis suggest that spontaneous recovery of myocardial function occurs in approximately 40% to 60% of patients (1,2), the clinical prognosis is far less sanguine for those patients in whom myocardial recovery is limited or absent (2,3). Indeed, for patients who developed persistent LV dysfunction in the Myocarditis Treatment Trial the mortality was 60% during the follow-up period (mean duration 18 months) (2). Thus, the ability to prospectively identify subsets of patients in whom myocardial recovery is limited, and (by extension) patients whose clinical prognosis is less favorable, would appear to be of significant clinical importance, insofar as the ability to identify these patients would allow clinicians to design appropriate treatment strategies earlier in the course of the disease, before the transition to symptomatic heart failure occurs.

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In this issue of the *Journal*, Sheppard et al. (4) report on a series of patients enrolled in a gene expression substudy of the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) trial (5). These investigators examined myocardial expression levels of messenger ribonucleic acid (mRNA) for a portfolio of genes that have been linked to cardiac myocyte apoptosis, including tumor necrosis factor (TNF), tumor necrosis factor receptor-1 (TNFR1), Fas, Fas ligand (FasL), and FLICE (Fas-associated death domain-like interleukin-1 beta-converting enzyme) in relation to recovery of LV function at six months (n = 20 patients). The authors found that subjects with the highest tertile of Fas expression had minimal improvement in LV function at six months. In contrast, patients who had intermediate or lower tertiles of Fas mRNA expression had spontaneous improvement in their LV function. A similar inverse relationship was observed for the expression levels of TNFR1 and LV function. In contrast, analysis of mRNA levels for TNF, FasL, and FLICE by tertiles did not predict myocardial recovery. Given that the cytoplasmic tails of both TNFR1 and Fas contain so-called "death-domains" that serve as docking stations for activation of pro-apoptotic caspases, the authors suggest that ongoing apoptosis may limit myocardial recovery in viral myocarditis. Before discussing the significance of these findings, it is useful to digress for a moment and discuss what is known about our ability to predict myocardial recovery in viral myocarditis.

MYOCARDIAL RECOVERY IN VIRAL MYOCARDITIS

Although a number of studies have reported prognostic factors that predict clinical recovery for patients with myocarditis, far less is know with respect to predicting myocardial recovery. As shown in Table 1, clinical studies have demonstrated relatively few clinical or biological markers that predict myocardial recovery. Bossone et al. (6) have shown that neither New York Heart Association (NYHA) functional class nor ejection fraction (EF) at presentation predicted LV recovery, whereas a small left atrial and LV size were both predictive of myocardial recovery (n = 15 patients). Scintigraphic evidence of increased uptake of anti-myosin antibodies (presumably reflecting increased myocyte necrosis) was also shown to weakly predict short-term recovery of LV function in patients with suspected myocarditis (n = 50 patients) (7). However, in a different study neither creatinine kinase, cardiac troponin I, nor myoglobin levels predicted LV recovery (n = 22 patients), suggesting that factors other than myocyte necrosis contribute to the acute LV dysfunction observed in myocarditis (8). In the Myocarditis Treatment Trial (n = 111 patients) the use of immunological biomarkers (cardiac and general immunoglobulin G titers, helper T-cell count, natural killer cells) and total white blood cell count was not predictive of LV myocardial recovery (2,9). Moreover, histological analyses of myocardial biopsy samples have yielded mixed results in terms of predicting LV recovery. That is, neither the presence of white cell infiltrates (2) nor the presence of myofibrillar degeneration predicted LV recovery (3), whereas the absence of Azan-Mallory staining of cardiac myocytes (a marker of cellular edema and/or myocytolysis) predicted LV recovery in biopsy-proven myocarditis (n = 20 patients) (10). Finally, the presence of enteroviral minus strand ribonucleic acid (indicative of actively replicating virus) on a myocardial biopsy has been shown to predict progression to a dilated cardiomyopathic phenotype (n = 45 patients) (3,11). Thus, save for a few single-center studies conducted on relatively small numbers of patients, there are virtually no reliable clinical tools for predicting LV recovery in the setting of viral myocarditis.

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Table 1. Determinants of Myocardial Recovery in Myocarditis

NYHA functional class at presentation	Independent of LV recovery (6)
2-D echocardiography	
EF at presentation	Independent of LV recovery (6)
Small LA size	Predicts LV recovery (6)
Small LV dimensions	Predicts LV recovery (6)
Serological biomarkers	
Troponin I	Independent of LV recovery (8)
Creatinine kinase	Independent of LV recovery (8)
Myoglobin	Independent of LV recovery (8)
WBCs	Independent of LV recovery (2)
Immunological markers	Independent of LV recovery (2)
Histologic markers	
Inflammation	Independent of LV recovery (9)
Myofibrillar degeneration	Independent of LV recovery (3)
Poor Azan-Mallory staining	Predicts LV recovery (10)
Molecular markers	
Enteroviral minus-strand RNA	Progression to DCM (3,11)

DCM = dilated cardiomyopathy; EF = ejection fraction; LA = left atrial; LV = left ventricular; NYHA = New York Heart Association; RNA = ribonucleic acid; WBCs = white blood cells; 2-D = two-dimensional.

Can expression levels of mRNA levels for one or more genes be used as a method for predicting LV recovery in viral myocarditis? As noted at the outset, the study by Sheppard et al. (4) in this issue of the *Journal* suggests that subjects with the highest tertile of Fas and TNFR1 expression had minimal improvement in LV function at six months. Given that both TNFR1 and Fas belong to the TNF receptor superfamily of receptors that play a critical role in the induction of apoptosis, as well as T-cell and natural killer cell-mediated toxicity (12), and that circulating levels of soluble Fas (the circulating "shed" form of the Fas receptor) and soluble Fas ligand predict adverse patient outcomes in myocarditis (13), the results of the study by Sheppard et al. (4) make sense from a biological point of view. That is, ongoing Fas and/or TNFR1-induced apoptosis and progressive myocyte loss would be expected to attenuate or prevent the spontaneous LV recovery that occurs in myocarditis. Unfortunately, there was insufficient tissue to examine the presence or absence of cardiac myocyte apoptosis in relation to mRNA levels for that Fas and TNFR1 in the study by Sheppard et al. (4). Thus, it is unclear whether the elevated levels of mRNA levels of Fas and TNFR1 represent a mechanism or a marker for persistent LV dysfunction. Nonetheless, this provocative study raises the broader question of whether it might be possible to identify genetic profiles or "molecular fingerprints" in myocardial biopsy samples that predict worsening LV function and untoward clinical outcomes in patients with myocarditis. Apart from the invaluable mechanistic information these types of investigations would provide, studies of this nature would also be vitally important in terms of designing clinical trials for novel antiviral therapies, knowing when to remove LV assist devices used as a "bridge" to recover hemodynamically unstable patients, as well as implementing appropriate supportive therapy for patients recovering from myocarditis. Although this represents an ambitious challenge to the field, and would likely require data collection from multiple centers, the recent striking advances in gene expression profiling and bioinformatics now make it possible to ask and answer this question. And indeed, our colleagues in oncology have already begun to use molecular fingerprinting for developing new therapies for treating patients with breast and lung cancers (14), as well as lymphomas (15). Although the results of the study by Sheppard et al. (4) should be viewed as provisional because of the small numbers of selected patients, their findings do suggest that the advent of molecular fingerprinting could lead to new targets and treatments for patients with viral myocarditis.

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REFERENCES

1. Quigley PJ, Richardson PJ, Meany BT. Long term follow up of acute myocarditis. Correlation of ventricular function and outcome Eur Heart J 1987;8 Suppl J:39–42.
2. Mason JW, O'Connel JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 1995;333: 269–75.
3. Dec GW Jr., Fallon JT, Southern JF, Palacios IF. Relation between histological findings on early repeat right ventricular biopsy and ventricular function in patients with myocarditis. Br Heart J 1988;60:332–7.
4. Sheppard R, Bedi M, Kubota T, et al. Myocardial expression of Fas and recovery of left ventricular function in patients with recent-onset cardiomyopathy. J Am Coll Cardiol 2005;46:1036–42.
5. McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 2001;103:2254–9.
6. Bossone E, Shea MJ, Nicklas JM, Abrams GD, Das SK. Early spontaneous recovery of left ventricular function in patients with myocarditis. Ital Heart J 2000;1:758–61.
7. Narula J, Southern JF, Dec GW, et al. Antimyosin uptake and myofibrillarlysis in dilated cardiomyopathy. J Nucl Cardiol 1995;2:470–7.
8. Ammann P, Naegeli B, Schuiki E, et al. Long-term outcome of acute myocarditis is independent of cardiac enzyme release. Int J Cardiol 2003;89:217–22.
9. Dec GW, Palacios IF, Fallon JT, et al. Active myocarditis in the spectrum of acute dilated cardiomyopathies. Clinical features, histologic correlates, and clinical outcome. N Engl J Med 1985;312:885–90.
10. Sakai A, Fukunami M, Nagareda T, et al. Presence of poorly stained myocytes in acute myocarditis predicts improvement in cardiac function. J Cardiol 1996;28:213–20.
11. Pauschinger M, Chandrasekharan K, Noutsias M, Kuhl U, Schwimmbeck LP, Schultheiss HP. Viral heart disease: molecular diagnosis, clinical prognosis, and treatment strategies. Med Microbiol Immunol (Berl) 2004;193:65–9.
12. Seko Y, Kayagaki N, Seino K, Yagita H, Okumura K, Nagai R. Role of Fas/FasL pathway in the activation of infiltrating cells in murine acute myocarditis caused by Coxsackievirus B3. J Am Coll Cardiol 2002;39:1399–403.
13. Fuse K, Kodama M, Okura Y, et al. Predictors of disease course in patients with acute myocarditis. Circulation 2000;102:2829–35.
14. Pharoah PD, Caldas C. Molecular genetics and the assessment of human cancers. Expert Rev Mol Med 1999;1999:1–19.
15. Wiestner A, Staudt LM. Towards molecular diagnosis and targeted therapy of lymphoid malignancies. Semin Hematol 2003;40:296–307.