Key Issues in the Developing Synergism between Cardiovascular Imaging and Biomarkers

Allan S. Jaffe

BACKGROUND: Sophisticated methods of cardiac imaging have the potential to revolutionize the care of patients with cardiovascular disease. The benefits of these state-of-the-art imaging techniques can be enhanced by their use in combination with new cardiac biomarkers. This review addresses potentially useful interactions between imaging and biomarkers.

CONTENT: Areas were defined in which the combined use of novel imaging techniques and biomarkers would be most beneficial. This review addresses multiple cardiovascular conditions for which the useful aspects of imaging and biomarkers are likely to be positively synergistic, including acute and chronic ischemic heart disease, heart failure, myocarditis, hypertension, and atherosclerosis.

CONCLUSIONS: The synergistic use of imaging techniques and biomarkers will enhance the investigation of many key issues and questions and will be an important resource in the future.

When new technologies become available their use tends to be considered in opposition to already available methods, leading to uncertainty about the role of the new technology and insecurity about the current gold standard in that area. If we proceed carefully, however, we may be able to advantageously blend new technologies. Some years ago, an article in Circulation suggested that patients with cardiac damage due to acute coronary syndrome (ACS) could be identified by cardiac MRI even when their troponin values were not increased (1). In retrospect, it became clear that this report described the use of an insensitive troponin assay with a high cutoff value (2). MRI is not currently considered more diagnostically sensitive than cardiac biomarkers or to be likely to replace them for the evaluation of patients with ACS, but its use serves to highlight the need to consider synergistic rather than antagonistic roles of new imaging modalities and biomarkers. Imaging can sometimes be used for both anatomic diagnoses and physiological and pathophysiological analyses, but even so the expense and the logistics associated with this approach make it unlikely that serial imaging evaluations will be used to follow patients. A more likely scenario is the use of simple and inexpensive new biomarkers preceded and at times refined by imaging findings. This review provides perspective concerning potential beneficial interactions between imaging and biomarkers. The potential usefulness of such synergisms is highlighted by the current and rumored future acquisition of several biomarker companies by Siemens and other imaging companies. Such acquisitions indicate the likelihood that this synergism will develop, whether through conjoint business models or the cooperation of independent business entities. This review addresses the potential importance of the interactive relationship between imaging and biomarker technologies. Initial steps that might facilitate such interaction are illustrated by clinical examples, with a focus on coronary artery disease, congestive heart failure, myocarditis, and other cardiovascular comorbidities. These reports from current literature present evidence for the possible interactive use of imaging and biomarkers and also touch on the substantial controversy that exists regarding how much reimbursement will be authorized for the combined use of imaging and biomarkers.

CORONARY ARTERY DISEASE

EVALUATION OF PATIENTS WITH CHEST DISCOMFORT

Evaluation of patients in the emergency department is one of the most critical issues faced by emergency departments and hospital services. Of the more than 5 million individuals who present to emergency departments with symptoms suggesting acute ischemia and possible ACS, only 20% at most may have cardiovascular etiology for such symptoms (3). Furthermore,
many individuals with acute myocardial infarction do not have typical or recognizable symptoms, so the screening for such patients must be broad (4). The important clinical question is not who has cardiovascular disease but who has ACS. The vast majority of patients in this group have at least some risk factors for atherosclerotic vascular disease. In addition, this group of patients accounts for much of the litigiousness related to emergency department practice (3).

Multidetector computed tomography (MDCT) is a new imaging technology being investigated for use in patients with emergent cardiovascular symptoms. This technique is somewhat ahead of cardiac magnetic resonance (cMR) imaging for the evaluation of coronary arteries (5–8), particularly when 64-slice technology is used. Scanners with fewer detectors are clearly not as effective, but the increment of difference is unclear. On the horizon are larger, 256-slice scanners (Fig. 1) that may provide better resolution with faster scan times (9). The negative predictive value of MDCT is high. The positive predictive value is not nearly as robust, however, because the imaging process is compromised by the presence of coronary calcium and resolution is less than ideal, especially at faster heart rates. Because cardiac motion makes quantification of stenoses problematic (8), intermediate-grade lesions often require additional evaluation (5–8). Given these characteristics, MDCT has been selected for use in patients at low to intermediate risk, for whom the negative prognostic value of a study would be important and a large number of negative scans likely. MDCT imaging can be used to evaluate the coronary tree and also to assess pulmonary circulation for possible pulmonary emboli and the aorta for possible aortic dissection. This “triple rule

**Fig. 1.** Coronary artery anatomy as depicted by images from an experimental 256 slice scanner. There is a stenosis in the right coronary artery (RCA) seen with computed tomographic angiography (A) confirmed by angiography (B). The stenosis is also seen in the volume-rendered reconstruction (C) and in the cross-sectional reconstruction (D). Reprinted from (10) with permission.
The negative predictive value of MDCT in most studies using 64-slice technology is 98%–100% (5–8), this method may be an easy way to screen patients with chest discomfort who are at intermediate risk (Fig. 1).

Correcting MDCT imaging problems may involve heart-rate control, which often requires administration of β blockers, or adjustment of the doses of contrast media or radiation. Given the potential adverse effects of contrast, it is unclear how applicable MDCT will be in patients with renal dysfunction. Major improvements in these areas are likely as the technique evolves. Another area of concern that is likely to be addressed more efficiently with time is how to deal with findings termed incidentalomas. For example, unexpected detection of a lung cancer in the process of assessing cardiac symptoms might be of key importance in acute management, but benign masses may also be observed at a time when further diagnostic analysis is not possible.

Most studies comparing the use of MDCT with conventional methods for patient evaluation have suggested that this new technology may enable patients seen in emergency departments to be treated more rapidly and at lower cost (5–8). In addition, most studies have found that serious conditions that mimic coronary artery disease, such as aortic dissection and pulmonary embolism, occur only rarely (5–8). Comparison of these studies may be skewed by differences in the use of troponin as a market for cardiac risk. Unfortunately, many reported studies do not include optimum use of troponin measurement or do not indicate how troponin data were used, whereas other studies have shown that troponin measurement is a valuable tool for evaluating patients with possible ACS, such as the report by Hamm et al. that suggests that emergency room triage of patients with acute chest pain can be performed without stress testing, by determination of troponin concentrations (10). The most recent generation of more analytically sensitive troponin assays, which became available after the study by Hamm et al., could further impact this issue. Cost comparisons that include studies in which expensive imaging stress tests were routinely used for patients without increased troponin, and thus not at high risk, may not reflect the optimal use of contemporary biomarkers or of simple treadmill stress testing.

Although exclusion of coronary artery disease is an important process in patients with chest pain, a finding of coronary disease does not always indicate that chest pain is due to unstable coronary disease; symptoms may be due to reflux, musculoskeletal pain, or other noncardiac causes. On the other hand, successful exclusion of coronary disease does not rule out the presence of ACS. Some patients may have typical symptoms of ischemic heart disease without anatomic coronary abnormalities. In patients who present with ACS, approximately 10% have coronary arteries that appear normal at angiography. Most studies have shown that these patients have an adverse prognosis (11). In some of these individuals, chest discomfort and increased biomarkers are attributable to other serious conditions such as myocarditis (12), and some have changes in electrocardiogram (ECG) distribution showing areas of subendocardial hyperenhancement indicating myocardial injury, suggesting the presence of acute ischemic injury (13). The etiology of the damage in these situations is unclear but may be attributable to lysed clots that were present before the angiogram was obtained or to coronary endothelial dysfunction. In these patients, unlike those with anatomic coronary disease who have increased biomarkers, treatment with aggressive anticoagulant therapies or an early invasive strategy may not be beneficial (14).

Furthermore, the lack of specificity of troponin increases for diagnosing ischemic heart disease, troponin increases in such patients may indicate conditions requiring different therapeutic approaches, such as myocarditis, infiltrative disease, apical ballooning, or small-vessel disease (13). Some of these individuals may have microvascular dysfunction, as has been documented with MRI and dobutamine stress echocardiography (15).

In this critical area, key issues require additional clarification. For patients at intermediate risk, the necessity of stress testing is questionable given the availability of troponin assays and the low recommended cutoff values. If stress tests are not needed, then evaluations of the cost-effectiveness of MDCT coronary imaging should not assume that they are. Whether the emergency department is the right place to screen for coronary artery disease in intermediate-risk patients is another question that must be addressed. Chest discomfort is statistically likely to be associated with coronary disease in affected patients, but diagnosis is more difficult in patients who present atypically, and the use of imaging may not be as effective in such patients. Thus another question to be answered is whether decisions about hospital admission should be based on the presence of CAD, the presence of increased biomarkers, or both.

Should coronary imaging be restricted to use in intermediate-risk patients in whom high-risk status has already been ruled out by biomarker evaluation? If so, then perhaps imaging could be performed as an...
outpatient procedure in the days after initial presentation rather than in the emergency department. Given the improved positive predictive value of biomarker analysis, another question is whether imaging should be done to determine the need for anticoagulant therapy and invasive strategies in patients whose biomarker evaluation results indicate high risk.

PATIENTS AT HIGH RISK
With rare exceptions, patients who clearly have ACS, such as those with ST-segment elevation myocardial infarction (STEMI) or those with ECG changes and typical presentation, should be treated rapidly without further evaluation. Patients with increased biomarker concentrations are at high risk, and will benefit from specific therapies (14); in patients imaging is unlikely to be necessary. In some cases, however, evaluation with MDCT, cMR, or other invasive or noninvasive imaging modalities may be used along with biomarker measurement.

Coronary artery evaluation with MDCT might be useful for triage in patients atypical presentation in whom ECG results are inconclusive. Broad definitions of this patient group are not useful because they may lead to dangerous treatment delays (especially in patients with STEMI). In high-risk patients, cMR can be used to define the area of risk and to identify individuals with non-STEMI who might benefit from early intervention, although studies have not shown that patients with non-STEMI ACS require early intervention (14).

Mechanical complications from intracoronary interventions may lead to acute or delayed total occlusion and/or restenosis. Improved interventions may be facilitated by the use of imaging techniques that enable definition of the length of the coronary plaque, the site of rupture, or the degree of coronary occlusion due to atheromas or clots. It is not known, however, whether prior knowledge of the etiology of the ACS, be it plaque rupture, erosion, or dissection, would lead to improved treatment. Noninvasive coronary imaging may eventually enable such evaluations, but so might approaches such as intravascular ultrasound (16), thermography (17), and/or ultraviolet imaging (18). Eventually new imaging techniques may be used for this purpose, such as MDCT (8, 9) or cMR (19). Perhaps total coverage of the plaque area would improve interventions or enable refinement of the nature, intensity, or duration of anticoagulant therapy.

Coronary imaging with MDCT and/or cMR with gadolinium might permit pre hoc identification of those individuals who might benefit from coronary artery bypass grafting rather than percutaneous coronary intervention (PCI), but the problems related to contrast issues, radiation burden, heart rate, and gadolinium use, which is of particular concern in patients with impaired renal function, must be overcome (20). These imaging modalities may also allow for the testing and validation of novel biomarkers (21).

FOLLOW-UP CARE OF ACS PATIENTS
The conjoint use of imaging and biomarkers may be applied to the mechanistic and clinical issues involved in follow-up care of ACS patients. Recent reports suggest an approach in which imaging is used to define the extent of infarction and biomarkers enable facile clinical implementation of these techniques.

cMR with delayed hyperenhancement has become the gold standard for the estimation of myocardial infarction size, and troponin values correlate well with cMR-determined infarct size (Fig. 2 and Fig. 3) (22-24). The use of cMR combined with troponin may facilitate clinical research trials with infarct size as an endpoint. Biomarkers and imaging detect different things, however. Imaging detects the aggregate amount of cardiac injury, integrating old and new insults. In addition, infarct size changes over time on cMR images (25), an effect attributable to damage contraction due to scar formation. Biomarkers detect only the acute episode of injury and do not change with time. Thus, there should and will be differences between infarct size determined by biomarkers and imaging. Thus the synergistic use of these approaches should be valuable.

Angiography is commonly used to evaluate coronary abnormalities in patients with ACS to determine prognosis and the need for revascularization. Imaging with MDCT, positron emission tomography, or cMR can combine anatomic with physiological imaging and may enable conjoint myocardial and coronary imaging that could be useful for defining hypoperfused areas that may be at risk for injury after an acute event, viable areas (26), or areas that could lead to malignant arrhythmias (27). β-Blockers are an effective therapy with the use of such secondary prevention, and imaging may help to identify additional opportunities for secondary prevention. Recent data suggest that lipoprotein-associated phospholipase A2 (LpPLA2) (28) may have a role in this area, and data from the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial (29) suggest that c-reactive protein measured 4–6 weeks after a cardiac events can also be used to identify patients at risk. An imaging interface might allow for evaluation of novel approaches such as measuring the total cholesterol content of erythrocyte members (30). Imaging will likely help to define the mechanisms for these markers and define subsets of patients in whom these markers will be particularly useful.
Controversy exists regarding increases in biomarkers after PCI. Confirmation of the veracity of post-PCI biomarker measurements was provided by cMR imaging indicating that areas of necrosis were present with only minor increases of biomarkers (31). A multiplicity of mechanisms can result in post-PCI myocardial injury, including the loss of a major coronary branch vessel, downstream embolization of plaque-related or thrombotic material, and abnormalities in endothelial function, which may be caused or exacerbated by PCI (32).

Imaging might enable definition of the mechanisms leading to myocardial injury and thus lead to improved post-PCI treatment.

The use of cMR to define these subsets of post-PCI myocardial injury may allow validation of markers to be used as surrogates. In patients with endothelial dysfunction, LpPLa2 is increased, and often a Doppler gradient can be detected across the coronary vasculature (33). Such abnormalities can also be documented by cMR (32) and by positron tomography. It is unknown if this marker provides similar information in ACS or after elective angioplasty. Different prognoses are associated with cardiac injury in patients with coronary endothelial dysfunction and in those who have lost a small branch vessel. The identification of such patient subsets may be important, because recent data suggest that the majority of post-PCI troponin increases are related to pre-PCI increases (34). In some patients, however, these data might provide prognostic information because of their relationship to the underlying pathophysiology of the injury.

CORONARY ARTERY BYPASS GRAFT

The conjoint use of imaging such as cMR and biomarkers could be used to evaluate approaches aimed at reducing the amount of myocardial injury in cardiac procedures such as coronary artery bypass graft. Recent data suggest that the majority of observed injury and increases in troponin are related to subendocardial injury (Fig. 4) often found at the cardiac apex (35). The

**Fig. 2. Infarct size estimated by MRI in all patients (top) and those with STEMI (left lower) and non-STEMI (NSTEMI) (right lower).**
TnT indicates troponin T; MI, myocardial infarction. Reprinted from (28) with permission.

**Fig. 3. Relationship of cardiac troponin I (cTnI) on various days and cMR-determined infarct size in patients with STEMI.**
Reprinted from (29) with permission.

---

Clinical Chemistry 54:9 (2008)
MYOCARDITIS

Myocarditis is an area of tremendous interest (40). It may be a very common disease, but diagnosis is difficult. Myocarditis can mimic acute ischemic heart disease, and patients can present with symptoms of myocardial infarction (12, 41, 42). At present, biomarkers cannot be used to distinguish myocarditis from ischemic heart disease, but myocarditis can be identified with cMR (42, 43) (Fig. 5). In addition to those patients who present acutely, in many myocarditis patients the disease has chronic manifestations requiring diagnosis and treatment (44). cMR may play an additional and very important role in the identification of these patients and perhaps in the development of facile tests that would allow for screening of individuals who might benefit from a more definitive evaluation with imaging. In general, the cMR pattern in myocardial disease is diffuse with predominantly epicardial involvement, often initially involving the lateral wall (12, 42, 43). Myocarditis rarely involves the subendocardial wall, which is where abnormalities are observed in patients with ACS. Many patterns have been observed in myocarditis, however, and they may in part reflect different etiologies for the disease (44). Given the heterogeneity of involvement, it can be difficult to obtain adequate tissue samples for diagnosis. In one small series a markedly increased yield of biopsy procedures was obtained with cMR-directed biopsy (44). The diversity of possible presentations of myocarditis has also been demonstrated. Some cases appear to be related to infiltrative disease with eosinophils and some manifest giant cells, but the stimuli for these processes remain unclear (44). Analysis of biopsy specimens can be used to isolate and amplify viral DNA to make a diagnosis (45), and immunohistochemical analysis can be used to identify pathogenic pools of lymphocytes (46). Some data suggest that biomarkers such as Fas ligand and interleukin 10 can be used for prognostic prediction (40). Data also indicate that antibodies to myocardial proteins such as cardiac troponin I may be associated with myocarditis (47). Some investigators have suggested that patients who present acutely may have an aggressive immune response that causes symptoms but may shorten the disease and prevent long-term involvement. Long-term disease may cause cardiomyopathy and may be treated with immune modulation therapy, including immunoabsorption techniques (40). Investigation of myocarditis has been challenging because of the difficulty in making a definitive diagnosis, but now cMR that can provide a rapid and accurate diagnosis.

The conjoint use of imaging and biomarkers may be used to determine how frequently myocarditis is the etiology of increased troponin values in patients who present acutely with possible ACS (12). Imaging and biomarkers may also be used synergistically to guide biopsy studies to evaluate tissue for viral genomes, pathogenetic lymphocytes, and the antigenic response (40). Such data may also be used to evaluate new biomarkers, be they for specific lymphocytic subsets, antigens, cytokines, or genomic products that might help to elucidate the etiology and pathogenesis of myocarditis and the distinguishing characteristics of what are likely many varied types. The development of biomarkers to track treatment response and disease processes...
may also be facilitated by imaging and biomarkers. It is likely that different markers may be needed for different etiologies of disease.

CONGESTIVE HEART FAILURE

Only recently have biomarkers been identified and studied to aid in the diagnosis and treatment of congestive heart failure. Both troponin and the natriuretic peptides have a major role (48, 49). Detection of increases in natriuretic peptides can be helpful in distinguishing heart failure from other causes of dyspnea (48). Increases of natriuretic peptides and of biomarkers of cardiac injury also define higher and lower risk subsets of patients with heart failure (49). The complexity of the natriuretic peptides is just now being recognized, including issues related to what fragments are being measured and which ones have biological effects, as well as the need to consider effects of patient sex, age, and body weight and shape (50). The presence of myocyte injury is undoubtedly an adverse prognostic signal, but because troponin measurements detect cardiac injury in so many situations, it is often difficult to determine the etiology of the cardiac injury (51). Most of the research in this area has focused on systolic heart failure, and it is now clear that roughly half of the heart failure seen clinically is due predominantly to abnormalities that affect diastole (52). This patient group is less studied and more difficult to evaluate. Thus, additional markers and/or diagnostic approaches would be helpful.

Several biomarkers have been proposed for the study of fibrosis. Matrix metalloproteinase and their counterregulatory inhibitors (53) have been studied by some investigators, whereas others have focused on markers of collagen deposition such as precollagen peptides 1 and 3 and tenascin C. These markers appear to be useful, but a gold standard test is needed and may be developed by use of cMR. Experimental and clinical studies suggest that delayed enhancement protocols can provide an accurate estimate of the extent of fibrosis (54). Furthermore, there appear to be patterns such as the midwall fibrotic strip that may predict the presence of malignant arrhythmias (55). Elucidation of such patterns may enhance understanding of a large number of biochemical processes that may be involved.

Fig. 5. cMR images from patients with acute myocarditis and at follow-up (FU), during which some resolution of the abnormalities is noted. Reprinted from (53) with permission.
in the development of fibrosis and may lead to the new therapeutic approaches.

Studies using positron tomography have clearly demonstrated that coronary endothelial dysfunction, which is hard to diagnose clinically, may be an important contributor to the mortality observed in patients with end-stage heart failure (56). How to translate these findings into some sort of practical clinical approach is unclear. Recent data suggest that LpPLa2 (33) may be helpful in this regard, but this marker has not been evaluated in patients with congestive heart failure. Having the ability to use imaging as a gold standard is likely to facilitate such evaluations.

Some preliminary areas that may be amenable to study include comparing markers related to the development of fibrosis with a gold standard measurement method such as cMR and comparing changes in fibrosis with changes in biomarkers. Other areas include developing and evaluating new markers for coronary endothelial dysfunction predicated on direct evaluation of coronary vasoreactivity and correlating changes in coronary vasoreactivity in response to therapy with changes in biomarkers.

**RENAL DYSFUNCTION AND CARDIOVASCULAR DISEASE**

The high mortality of patients with renal dysfunction and cardiovascular disease should provide impetus for the use of imaging and biomarkers to develop better treatment approaches. The most common cause of death in patients with severe renal disease is cardiovascular disease. Patients with severe renal disease often have increased cardiac troponin, especially cardiac troponin T, which is invariably associated with cardiac pathology (57) and an adverse prognosis (58, 59). Inflammatory markers such as c-reactive protein may also play a role (59). Treatment options for these patients are unclear. Because of the relationship between troponin increases and coronary artery disease, coronary artery disease is often suspected, but coronary artery disease may not be the only prognostic mediator (57). Troponin is also related to left ventricular hypertrophy and thus presumably hypertension (60, 61). Renal patients with left ventricular hypertrophy are at particularly high risk. Poor quality dialysis and a variety of other factors involved in the dialysis process have also been reported to be of critical importance. Recent cMR data (62) show little evidence of myocardial infarction, suggesting the involvement of other processes. Natriuretic peptides also have important prognostic significance in this patient group (63).

Attempts to develop better treatment for these patients can benefit from novel imaging approaches. Imaging modalities can be used to define in greater detail the frequency of coronary artery disease in patients on dialysis. Care must be used in regard to the adverse effects of gadolinium in renal patients, but perhaps less so with regular contrast dyes. Imaging can be combined with biomarkers to confirm prior data suggesting that increased troponin is often not associated with ischemic myocardial injury, to establish the relationship of left ventricular hypertrophy to biomarker changes and prognosis, to evaluate the possibility that fibrosis is as important as coronary artery disease to the
prognosis of these patients, and to define the etiology of increases in natriuretic peptide.

DEVELOPMENT OF ATHEROSCLEROSIS

Most individuals in the US have risk factors for atherosclerosis (64). Although conventional risk factors are generally present in those with disease, their specificity for disease is in question. Thus, there have been continual attempts to introduce new markers such as inflammatory markers (65). Apolipoprotein measurements are again being advocated as better predictors of atherosclerotic disease (66). New markers have been developed that count lipid particles (67) and/or specific lipid fractions such as Lp(a) or LpPLa2. Some investigators argue that these markers do not facilitate improved disease assessment (68). A major impediment to progress in this area has been the lack of a gold standard. Most studies use surrogate endpoints or rely on long-term follow-up, but surrogate endpoints are fraught with confounders and long-term follow-up results may be difficult to interpret because of changing secular trends. Recent data from Mount Sinai raise the prospect that the progression of atherosclerosis may be monitored in large blood vessels such as the aorta (Fig. 6) (69). Eventually such imaging could extend to the coronary arteries. If so, testing can reveal which markers or panels of markers to use to assess risk and which ones presage progression.

Some aspects clearly amenable to examination include evaluation of population cohorts who have atherosclerotic disease and of the biomarkers associated with its presence, evaluation of those markers associated with atherosclerotic disease progression, and confirmation of findings in the coronary arteries.

REPARATIVE CARDIAC PROCESS

Some of the most exciting work in cardiology today involves the potential for myocyte regeneration (70). It is unclear whether this regeneration is attributable to stem cells and their specific characteristics, pluripotent cells that reside in the heart, paracrine effects, or all of these. Nonetheless, in experimental models such cells can be labeled and their fate followed sequentially. Strategies are being developed to protect such cells from destruction once they are introduced. The use of imaging and biomarkers in this research should allow the measurement of biomarkers that may provide similar information, thus permitting the more rapid introduction of these advances into clinical use.

Minor abnormalities of cardiac function or structure have been observed in other conditions. For example, minor increases in troponin are seen in patients with burns and in patients with myocardial contusion (51). Although myocardial contusions are identifiable with markers such as cardiac troponin, the mechanisms for such injuries, how well they heal, and whether there is a need to intervene when they are observed is unclear and might be elucidated by imaging approaches. It may be that patients at risk for myocardial contusion have a particular geometry of their chest wall that predisposes them to injury. If this were to be the case, individuals who might be prone to trauma, such as race car drivers, might be screened for such abnormalities and protected if their chest-wall configuration seems one that may be at risk. This is an area that could be investigated with imaging. Hypertension is another area of concern that affects many individuals. Patients with left ventricular hypertrophy are known to have fibrosis and reduced subendocardial blood flow, which make them prone to increases in myocardial stiffness and myocyte injury. Some of these processes may be reflected in markers related to the extra cellular matrix (53). Elucidation of the pathophysiology by which hypertension affects cardiac function by observing these processes over time may enable the development of facile biomarkers for long-term monitoring. Similar circumstances exist in a variety of other conditions such as diabetes, in which an independent cardiomyopathy (71) can exist before and/or concurrently with coronary disease. Were this to be identifiable, the ability to segregate various components of the clinical syndrome would be highly valuable.

With the necessary innovation and resources, new imaging techniques may provide an anatomic/pathologic and physiologic basis for the development of new biomarkers and may revolutionize the processes of diagnosis, monitoring, and treatment.

References


