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.

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When new technologies become available, their use tends to be considered in opposition to already available methods. This perception can lead to uncertainty about the role of the new technology and insecurity about the current gold standard in that area when often synergistic benefits are possible. 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 uses an insensitive troponin assay with a high cutoff value (2). MRI is not currently considered more diagnostically sensitive than cardiac biomarkers, nor is it likely to replace them for the evaluation of patients with ACS. In fact, it is likely to be synergistic rather than antagonistic. Imaging can be used for both anatomic diagnosis and physiological and pathophysiological analyses, but the expense and 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 acquisition of several biomarker companies by Siemens and by rumors that more acquisitions may occur. 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 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 the current literature present evidence for the possible interactive use of imaging and biomarkers. They do not address the controversy that exists regarding how much reimbursement will be authorized for imaging or for the combined use of the two technologies.

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).
important clinical question is not who has cardiovascular disease but who has ACS. Patients with low risk and those who are hemodynamically stable are triaged differently, but most patients in this group have at least some risk factors for atherosclerotic vascular disease. This group of patients accounts for much of the litigiousness related to emergency department practice (3).

Multidetector computed tomography (MDCT) is now being investigated for use in these types of patients with possible 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 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 coronary MDCT is high. The positive predictive value is not nearly as robust 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 and calcification 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. When properly configured, MDCT imaging can be used not only to evaluate the coronary tree but also to assess pulmonary circulation for possible pulmonary emboli and the aorta for possible aortic dissection. This “triple rule out” of potentially serious problems is widely con-

![Fig. 1. Coronary artery anatomy as depicted by images from an experimental 256 slice scanner.](image-url)

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 (9) with permission.
considered to be a valuable screening process, but the likelihood of the occurrence in patients at low to intermediate risk is unclear (7, 8). Therefore extrapolation of these data to other groups with different pretest probabilities of disease must be done cautiously. Because 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).

Trying to deal with 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. In addition, given the potential adverse effects of contrast, it is unclear how applicable MDCT will be in patients with renal dysfunction. However, major improvements in these areas are likely as the technique evolves. Another area of concern 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 critical importance in acute management, but possibly benign masses may also be observed at a time when further diagnostic analysis is not possible, complicating care.

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). However, 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. Other studies have shown that troponin measurements are a valuable tool for evaluating patients with possible ACS. The report by Hamm et al. suggested that emergency room triage of patients with acute chest pain could 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 and which ignore the troponin data do not reflect the optimal use of contemporary biomarkers. In addition, often treadmill stress testing is adequate if stress testing is needed at all.

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. Conversely, the exclusion of anatomic coronary disease does not rule out the presence of ACS. Patients can 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 or near 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). Others have changes in a focal electrocardiographic (ECG) distribution and have areas of subendocardial hyper-enhancement indicating myocardial injury. These patients likely have acute ischemic injury (13). The cellular mechanisms for 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, given the lack of specificity of troponin increases for 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 coronary artery 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, many issues require additional clarification. For patients at intermediate risk, the necessity of stress testing is questionable given the availability of sensitive 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 diagnoses are more difficult in patients who present atypically, and the use of imaging may not be as effective in such patients. 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 for acute events has already been ruled out by biomarker evaluation? If so, then perhaps imaging could be per-
formed as an outpatient procedure in the days after initial presentation rather than in the emergency department. With improved positive predictive value of biomarker analysis, perhaps imaging will some day be done to determine the need for anticoagulant therapy and invasive strategies in patients whose biomarker evaluations 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 these patients imaging is unlikely to be necessary acutely.

However, coronary artery evaluation with MDCT might be useful for triage in patients atypical presentation in whom ECG results are inconclusive but must be accomplished rapidly to avoid treatment delays (especially in patients with STEMI). cMR can be used to define the area of risk and to identify individuals with non-STEMI who might benefit from early intervention. Thus far, studies have not shown that patients with non-STEMI ACS require early intervention (14), but perhaps those with large risk regions might.

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 atheroma or clot. Perhaps this knowledge 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 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. 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 contraction of the area of damage in response to scar formation. Biomarkers detect only the acute episode of injury. Thus, there should and will be differences between infarct size determined by biomarkers and imaging. 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 for 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 event 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 how these markers detect risk and define subsets of patients in whom these markers and/or imaging will be particularly useful.

**TREATMENT AFTER PCI**

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 likely associated with cardiac injury in patients with coronary endothelial dysfunction compared to 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 etiology of this damage is likely related to anesthetic, surgical, and preservation techniques rather than primary coronary or graft abnormalities. It is also clear that preoperative biomarker values are key to adequate understanding of biomarker increases after coronary
artery bypass graft, because they result in higher values (36). In general, for procedures using the same techniques, more severe injury is associated with a poorer prognosis (37, 38). Data suggest that a cutoff value for troponin eventually might be defined that is indicative of native artery or graft occlusion as opposed to injury related to the procedure itself. In general, higher troponin values seem to be associated with graft occlusion (39).

Once appropriate cutoff values are determined, this is an area in which the use of noninvasive imaging would be helpful in identifying the subset of individuals who may have injury related to coronary or graft occlusion, findings that may have prognostic significance.

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 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, many patients with myocarditis have chronic disease 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 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 patients with myocarditis, which 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 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 1 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 some have suggested treatment with immune modulation therapy, including immunoabsorption techniques (40), may be helpful. Investigations of myocarditis have 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 and pathogenetic lymphocytes, and to assess 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 troponin 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 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 impor-
tant 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.

Other Situations

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, and to evaluate the possibility that fibrosis is as important as coronary artery disease to the prognosis of these patients. Finally, imaging should help 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 spe-

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**Fig. 6. cMR of the descending aorta before and after treatment for 24 months with a statin.**

Note thinner area of plaque during follow-up. Reprinted from (69) with permission.
cific lipid fractions such as Lp or LpPLa2. However, 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.

REPARATIVE CARDIAC PROCESSES
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.

OTHER AREAS FOR POSSIBLE SYNERGISM
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. 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.

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