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Fusion of Three-Dimensional Echocardiographic Regional Myocardial Strain with Cardiac Computed Tomography for Noninvasive Evaluation of the Hemodynamic Impact of Coronary Stenosis in Patients with Chest Pain

Victor Mor-Avi, PhD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Mita B. Patel, MD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Francesco Maffessanti, PhD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Universita della Svizzera Italiana, Lugano, Switzerland

Amita Singh, MD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Diego Medvedofsky, MD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

S. Javed Zaidi, MD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Cardiology Department, Advocate Children's Hospital, Chicago, Illinois

Anuj Mediratta, MD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Akhil Narang, MD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Noreen Nazir, MD,

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Nadjia Kachenoura, PhD,

Sorbonne Universités, UPMC University Paris 06, CNRS 7371, INSERM 1146, Paris, France

Roberto M. Lang, MD, and

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Amit R. Patel, MD

Section of Cardiology, University of Chicago Medicine, Chicago, Illinois

Reprint requests: Victor Mor-Avi, PhD, University of Chicago, MC9067, 5758 S Maryland Avenue, Chicago, IL 60637 (vmoravi@bsd.uchicago.edu).

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Abstract

Background—Combined evaluation of coronary stenosis and the extent of ischemia is essential in patients with chest pain. Intermediate-grade stenosis on computed tomographic coronary angiography (CTCA) frequently triggers downstream nuclear stress testing. Alternative approaches without stress and/or radiation may have important implications. Myocardial strain measured from echocardiographic images can be used to detect subclinical dysfunction. The authors recently tested the feasibility of fusion of three-dimensional (3D) echocardiography–derived regional resting longitudinal strain with coronary arteries from CTCA to determine the hemodynamic significance of stenosis. The aim of the present study was to validate this approach against accepted reference techniques.

Methods—Seventy-eight patients with chest pain referred for CTCA who also underwent 3D echocardiography and regadenoson stress computed tomography were prospectively studied. Left ventricular longitudinal strain data (TomTec) were used to generate fused 3D displays and detect resting strain abnormalities (RSAs) in each coronary territory. Computed tomographic coronary angiographic images were interpreted for the presence and severity of stenosis. Fused 3D displays of subendocardial x-ray attenuation were created to detect stress perfusion defects (SPDs). In patients with stenosis >25% in at least one artery, fractional flow reserve was quantified (HeartFlow). RSA as a marker of significant stenosis was validated against two different combined references: stenosis >50% on CTCA and SPDs seen in the same territory (reference standard A) and fractional flow reserve < 0.80 and SPDs in the same territory (reference standard B).

Results—Of the 99 arteries with no stenosis >50% and no SPDs, considered as normal, 19 (19%) had RSAs. Conversely, with stenosis >50% and SPDs, RSAs were considerably more frequent (17 of 24 [71%]). The sensitivity, specificity, and accuracy of RSA were 0.71, 0.81, and 0.79, respectively, against reference standard A and 0.83, 0.81, and 0.82 against reference standard B.

Conclusions—Fusion of CTCA and 3D echocardiography–derived resting myocardial strain provides combined displays, which may be useful in determination of the hemodynamic or functional impact of coronary abnormalities, without additional ionizing radiation or stress testing.

Keywords

Fusion imaging; Cardiovascular CT; 3D echocardiography; Vasodilator stress; Myocardium perfusion; Myocardial strain

In patients with chest pain, combined evaluation of coronary anatomy (i.e., presence and severity of stenosis) and its hemodynamic significance, namely, the presence and extent of ischemia, is essential. This is frequently addressed using downstream radionuclide myocardial perfusion stress testing in patients with abnormal findings on computed tomographic coronary angiography (CTCA), especially those with intermediate-grade stenosis.^{1–5} This is because CTCA is known to overestimate the degree of stenosis and because the presence and extent of myocardial ischemia is more important than the severity of stenosis for identifying patients who would benefit from coronary revascularization.^{6,7} Alternative approaches that do not involve stress and/or radiation may have important implications for greater patient safety and significant cost savings.

Another limitation of this diagnostic paradigm is that it is difficult to guarantee that hemodynamic or functional abnormalities are accurately attributed to stenosis in a specific coronary artery, because this requires one to mentally coregister these findings within the complex three-dimensional (3D) anatomy of the heart, given the wide interindividual differences in coronary anatomy. This is particularly problematic in the setting of multivessel disease, when it is unclear which artery is responsible for the symptoms. Fusion imaging may be helpful in this regard, because it provides a unique opportunity to simultaneously view different types of clinically relevant information in a shared space.^{8–17} Specifically, in the context of significance of coronary stenosis, fusion imaging may allow the visualization of each coronary artery and any hemodynamic or functional parameter of interest mapped onto the underlying area of the myocardium, thus lending itself to direct identification of the culprit artery when an abnormality is present.

Several studies have shown that left ventricular (LV) strain derived from echocardiographic images can be used to detect dysfunction secondary to myocardial ischemia in the presence of normal ejection fraction and seemingly normal wall motion.^{18–21} However, the vast majority of published studies that reported the use of myocardial strain to detect subclinical dysfunction were based on global strain measurements, while the usefulness of regional strain is considerably less well established and has been predominantly tested using two-dimensional strain analysis. In fact, the current guidelines state that there is insufficient evidence to support clinical use of regional strain.²² In this study, we hypothesized that fusion of resting 3D echocardiography (3DE)–derived regional LV longitudinal strain with coronary arteries from CTCA might allow determination of the hemodynamic significance of coronary stenosis in patients with chest pain, without the need for additional radiation or stress testing. We recently tested the feasibility of this approach in a small study involving patients referred for computed tomographic (CT) coronary angiographic evaluation of coronary artery disease and found that resting strain abnormalities were more common when stenosis resulted in perfusion abnormalities under stress.²³ These findings suggested that resting regional LV strain abnormalities might be useful for identifying functionally significant coronary stenosis. The aim of the present study was to determine the accuracy of this approach in a larger group of patients with chest pain against a robust reference for hemodynamically significant stenosis.

METHODS

This was a prospective study in which we enrolled patients with chest pain referred for CTCA who agreed to undergo vasodilator stress computed tomography and transthoracic 3DE within 1 hour of CTCA. Figure 1 shows a diagram of the study design. Resting CT images were used for conventional detection of coronary stenosis as well as to extract the coronary tree for fusion. Vasodilator stress CT images were used to obtain perfusion data. Three-dimensional echocardiographic images were used to obtain the 3D endocardial surface and also analyzed to obtain strain data, which were mapped onto the 3D surface and fused with the coronary tree. In addition, stress CT perfusion data were also mapped onto the 3D endocardial surface and separately fused with the coronary tree. These fused displays were used to detect abnormalities in resting strain and stress perfusion defects (SPDs).

Because the choice of a robust reference technique that credibly reflects myocardial ischemia is not trivial, we evaluated several possibilities. One potential reference would be a combination of stenosis on CTCA and a SPD in the territory of the same artery, as a confirmation of its hemodynamic impact.^{24–30} Another possibility is the recently developed and validated fluid dynamics based calculation of fractional flow reserve (FFR) from resting cardiac CT images (CT-FFR),^{31–40} which is rapidly expanding into clinical practice.^{41,42} Accordingly, this study was designed to validate resting strain abnormalities as a marker of hemodynamically significant stenosis against two reference standards: a combination of stenosis >50% on CTCA concomitant with an SPD, reflecting together the anatomic severity and the hemodynamic impact of stenosis (reference standard A),⁴³ and a combination of abnormal CT-FFR with an SPD in the same coronary territory, reflecting the hemodynamic impact in a more robust way than either one of its two components alone (reference standard B).

Population

We prospectively studied 78 patients (mean age, 55 ± 10 years; 46 men; 32 with hypertension; nine with diabetes mellitus; 37 with dyslipidemia; 24 with histories of tobacco use) with chest pain. Patients with relative contraindications to CTCA, including known allergies to iodine, renal dysfunction (creatinine > 1.6 mg/dL), inability to perform a 10-sec breath-hold, and contraindications to β -blockers or vasodilators, such as chronic obstructive pulmonary disease, advanced heart block, or systolic blood pressure < 90 mm Hg, were excluded. This group included the 27 patients reported in our previously published pilot study.²³ The study was approved by the institutional review board, and each patient provided informed consent before participation.

Three-Dimensional Echocardiographic Imaging and Analysis

Transthoracic 3D echocardiographic data sets were acquired at rest in the harmonic mode from a modified apical four-chamber view using the iE33 ultrasound imaging system (Philips Medical Imaging, Andover, MA) equipped with a matrix-array transducer (X5). Full-volume acquisition was performed using electrocardiographic gating over four consecutive cardiac cycles during a single breath-hold. No medication was given to control heart rate. Imaging depth was minimized to maximize the frame rate, while special care was taken to include the entire LV cavity within the pyramidal scan volume (resulting in frame rates between 18 and 39 frames/sec; mean, 25 ± 6 frames/sec). After gain settings were optimized for endocardial visualization, three or four data sets were acquired and stored digitally for offline analysis. Images were inspected for “stitch artifacts,” and acquisition was repeated as necessary to ensure artifact-free data sets suitable for strain analysis.

Three-dimensional echocardiographic data sets were first analyzed using commercial software (4D LV-Analysis; TomTec Imaging Systems, Unterschleissheim, Germany) designed to track ultrasound speckles in the myocardium in 3D space and measure longitudinal LV strain. Tracking was optimized by visual inspection of dynamic image sequences in different cross-sectional planes with and without the tracked endocardial borders. The software provides dynamic 3D connected meshes of the LV endocardium, which were exported into MATLAB (The MathWorks, Natick, MA), in which custom

software was used to create color-coded maps of longitudinal strain superimposed on the dynamic 3D endocardial surface, depicting gradual phase-by-phase changes in strain throughout the cardiac cycle (Video 1 available at www.onlinejase.com). These strain-coded surfaces were then used for fusion with CTCA-derived coronary arteries.

CT Imaging

Patients received the β -blocker metoprolol orally (50–100 mg, 1 hour before imaging) and/or intravenously (5–15 mg immediately before imaging) as necessary to achieve a target heart rate of <65 beats/min. Sublingual nitroglycerin (0.4–0.8 mg) was also administered, provided that systolic blood pressure was >100 mm Hg. Images were acquired during suspended respiration using a multidetector CT system (256-channel Philips iCT; Philips Medical Imaging). After resting imaging was performed according to a standard clinical CT coronary angiographic protocol, regadenoson (Astellas Pharma US, Northbrook, IL) was administered (0.4 mg, intravenous) 15 min later to ensure contrast clearance. An additional set of images was acquired 1 min after the administration of regadenoson to ensure imaging during peak effect. These images were obtained using retrospective gating at end-systole with dose modulation to minimize radiation exposure,⁴⁴ with gantry rotation time of 270 msec, slice thickness of 0.625 mm, tube current of 600 to 1,000 mA, and tube voltage of 100 to 120 kV (depending on body weight). Patients received a bolus of iodinated contrast agent (~65 mL, 5 mL/sec), which was injected into the right antecubital vein and followed by a 20-mL saline chaser bolus. Image acquisition was triggered by the appearance of contrast in the descending thoracic aorta 5 sec after attenuation increased >50 Hounsfield units.

Stress CT Perfusion Analysis

CT images obtained during vasodilator stress were analyzed using custom software for volumetric analysis and visual display of myocardial perfusion, as described previously.^{44–46} Briefly, following semiautomated identification of the endo- and epicardial 3D surfaces, the 3D region of interest confined between these two surfaces was identified as LV myocardium. Coronary arteries and contrast-filled inter-trabecular spaces were excluded from the myocardium and papillary muscles and trabeculae were excluded from the LV cavity by setting thresholds on the histograms of x-ray attenuation to discard voxels represented by a separate peak or tail outside the normal distribution of the myocardium and the blood pool, respectively.^{44–46} To allow visualization of SPDs, subendocardial attenuation was calculated across the inner 50% of the myocardial thickness and normalized by adjacent LV cavity attenuation for each node in the mesh. After having these calculations completed for the entire myocardium, all values were expressed as percentages of the maximum value, and a median filter was used to smooth the color-encoded display.

Image Fusion

Resting CT coronary angiographic images were exported in the Digital Imaging and Communications in Medicine format into MATLAB to extract the coronary tree using custom software as previously described in detail.²³ The registration between the coronary tree and the 3D echocardiographic data set, from which the LV endocardial surface was derived, was performed using three pairs of landmarks specified by the user, including the aortic root, the midpoint of the mitral valve, and the LV apex. This resulted in a dynamic

combined 3D display of the coronary anatomy and ventricular function. The entire processing time was between 15 and 20 min, once the data files were loaded. This display, with longitudinal strain color-encoded onto the endocardial surface, was viewed from different angles at end-systole when strain reaches its peak value (Video 2 available at www.onlinejase.com). This was done to determine the presence of a strain abnormality, defined as an area of reduced strain magnitude visualized by nonuniform color coding, in the territory of each artery.

In addition, the aforementioned subendocardial stress perfusion data were also mapped onto 3DE-derived endocardial surface and fused with the coronary arteries, resulting in a combined 3D display of the coronary anatomy and myocardial perfusion. This display was also viewed from different angles to determine the presence of a perfusion defect in the territory of each artery (Video 3 available at www.onlinejase.com).

Combined Reference Standards for Significant Stenosis

CT coronary angiographic interpretation of coronary anatomy, performed on the resting images by an experienced reader, included determination of the presence, location, and extent of stenosis in percent of luminal narrowing. Coronary arteries were then divided into three categories, according to findings on CTCA: (1) <50% luminal narrowing and no clear perfusion defect, (2) >50% luminal narrowing and a visible perfusion defect, and (3) either a perfusion defect without stenosis >50% or stenosis >50% without a perfusion defect. This classification was the basis for reference standard A.

In patients with stenosis >25% in at least one artery, CT-FFR analysis was performed from the resting CT data sets (HeartFlow, Redwood City, CA). This analysis included fluid dynamics–based calculation of FFR for each of the three coronary arteries and their major branches. Similar to findings on CTCA, CT-FFR values were used to categorize each coronary artery as follows, using a cutoff of 0.80: (1) CT-FFR ≥ 0.80 and no clear perfusion defect, (2) CT-FFR < 0.80 and a visible perfusion defect, and (3) either a perfusion defect with CT-FFR ≥ 0.80 or CT-FFR < 0.80 without a perfusion defect. This classification was the basis for reference standard B.

For both reference standards A and B, arteries in category 1 were considered normal, and those in category 2 were considered to have hemodynamically significant stenosis, while those in category 3 were considered inconclusive and were not used for comparisons with 3DE-derived strain.

Detection of Significant Stenosis Using Longitudinal Strain

Strain abnormalities when present in the territory of a coronary artery were first compared with three simple reference techniques reflecting different aspects of disease in that artery: stenosis resulting in >50% luminal narrowing on CTCA, the presence of an SPD, and CT-FFR < 0.80. Thereafter, to determine the diagnostic accuracy of this approach against more robust, combined reference standards that more reliably reflect the hemodynamic significance of stenosis than each of these criteria alone, the strain abnormalities were compared against the aforementioned combined reference standards A and B, which define

hemodynamically significant stenosis either by luminal narrowing $> 50\%$ with an associated SPD (reference standard A) or by CT-FFR < 0.80 with an SPD (reference standard B).

Reproducibility Analysis

To assess the reproducibility of strain abnormalities, 3D strain analyses were repeated in a random sample of 20 study patients, using a different cardiac cycle. A contingency table was created in which positive and negative findings were counted for both first and second measurements on a coronary artery basis (a total of 60 arteries). Kappa statistics were used to quantify the level of agreement between repeated analyses. The calculated κ coefficients were judged as follows: 0 to 0.2, low; 0.21 to 0.4, moderate; 0.41 to 0.6, substantial; 0.61 to 0.8 good, and >0.8 , excellent.

Statistical Analysis

To determine the diagnostic accuracy of strain abnormalities for the detection of hemodynamically significant coronary stenosis, for every comparison, sensitivity, specificity, positive and negative predictive values, and overall accuracy were calculated from the numbers of true or false positive or negative classifications, using standard definitions. Significance of the differences in the prevalence of resting longitudinal strain abnormalities in territories of coronary arteries with and without hemodynamically significant stenosis (categories 1 and 2) was tested using χ^2 statistics. Statistical analysis was performed using Excel (Microsoft, Redmond, WA).

RESULTS

Of the 234 coronary arteries in 78 study patients, CTCA depicted stenosis $>70\%$ in 13 arteries, stenosis between 50% and 70% in 25 arteries, stenosis $<50\%$ in 60 arteries, and 136 arteries free of any luminal narrowing. Fifty-seven patients (73%) had resting strain abnormalities in territories of 82 arteries (35%), while 40 patients (52%) had perfusion defects at stress in territories of 57 arteries (24%). Of the 78 study patients, 22 patients had $>25\%$ stenosis in at least one coronary artery and underwent CT-FFR analysis. In this subgroup, 63 arteries were evaluated, while the remaining three had stents and were excluded from analysis. CT-FFR < 0.80 was found in 20 of the 63 arteries (32%).

The combined 3D displays allowed visual appreciation of resting myocardial strain and subendocardial perfusion at peak vasodilator stress in the territory of each artery. Figure 2 shows an example of combined 3D displays obtained in a patient with no significant stenosis. These displays depicted fairly uniform resting strain (*top*) and stress subendocardial perfusion (*bottom*). Figure 3 shows an example of a patient who had intermediate grade stenosis in the distal left anterior descending coronary artery (LAD) and underwent CT-FFR analysis, which showed reduced FFR only in the distal LAD segment (*left*). The resting strain map showed no obvious abnormalities (*right*). In contrast, Figure 4 shows an example of another patient who had hemodynamically significant mid-LAD stenosis, confirmed by CT-FFR analysis for a large portion of the artery (*left*). The color map depicted reduced resting strain in the LAD territory, reflecting a strain abnormality, with uniformly preserved normal strain in the rest of the myocardium (*right*). Figure 5 is

another example of a patient with severe coronary stenosis in the left circumflex artery, confirmed by reduced CT-FFR (*left*), which resulted in a resting strain abnormality (*middle*) and a SPD in the same area of the myocardium (*right*).

Overall, compared with reference A, of the arteries in category 1 (i.e., no stenosis >50% and no SPDs [$n = 99$]), considered as normal, 19 (19%) had resting strain abnormalities. In contrast, of the arteries in category 2 (i.e., stenosis >50% and SPDs, hemodynamically significant [$n = 24$]), a considerably higher percentage showed resting strain abnormalities (17 [71%]). This difference was statistically significant ($\chi^2 = 11.2$, $P < .0001$).

Table 1 summarizes the results of the diagnostic accuracy of the resting strain abnormalities against reference standards A and B, as well as against their individual components. Compared with either stenosis >50% or perfusion defects, sensitivity was similarly modest at 0.67 and 0.68, and the overall accuracy was similar (0.71 and 0.75), while comparison with perfusion resulted in higher specificity. Combining the two criteria together (reference standard A) resulted in small changes in sensitivity and specificity, but accuracy increased to 0.79. Compared with CT-FFR alone, resting strain abnormalities showed considerably higher sensitivity of 0.79, with specificity and accuracy similar to that in the comparison against stenosis alone. Finally, combining CT-FFR with perfusion (reference standard B) resulted in the highest sensitivity (0.83), specificity (0.81), and accuracy (0.82).

Table 2 shows the agreement between repeated analyses in the detection of strain abnormalities, with concordant interpretation in 51 of 60 arteries (85% agreement). The corresponding κ value was 0.638 (95% CI, 0.424–0.852), reflecting good intermeasurement agreement.

DISCUSSION

Although the use of CTCA to rule out coronary artery disease in patients with chest pain has been steadily increasing,⁴⁷ intermediate-grade stenosis or inconclusive CT coronary angiographic examinations due to suboptimal image quality can lead to stress testing aimed at elucidating the hemodynamic significance of coronary artery disease.^{1–5} We recently explored the feasibility of 3D fusion of CTCA-derived coronary arteries and echocardiography-derived myocardial strain maps for the evaluation of the hemodynamic or functional significance of coronary stenosis in this patient population.²³ This approach was based on the premise that myocardial strain may be a sensitive alternative to conventional echocardiographic measures, which are not always sensitive enough to detect subtle changes in myocardial function. There is growing evidence in the literature that regional myocardial strain may aid in the early detection of subtle changes in myocardial function caused by ischemia, when wall motion abnormality cannot be visually detected.^{18,20,48–50} This ability stems from the fact that longitudinal strain mostly reflects contractile function of the subendocardial fibers, which are predominantly affected by ischemia.⁵¹

Our recent pilot study indicated that spatial coregistration of coronary arteries with strain maps may indeed depict the culprit artery and the impact of stenosis in its territory. The present study confirmed in a larger group of patients that strain abnormalities are

considerably more common in the presence of stenosis >50% and perfusion defects; that is, our results solidified the notion that there may indeed be a relationship between strain and the impact of stenosis. Moreover, this study was designed to determine the accuracy of this approach for the evaluation of the hemodynamic impact of stenosis against existing relevant reference standards. While planning this study, it quickly became apparent that identifying such a reference standard is not a trivial issue. This is because there is no noninvasive technique suitable for use in this setting that would provide reliable, definitive information needed to achieve this goal.

Although radionuclide myocardial perfusion imaging during vasodilator stress is routinely used to elucidate the impact of stenosis in patients with chest pain, it is an additional vasodilator stress test associated with significant additional radiation. Several recent studies have suggested the diagnostic performance of nuclear myocardial perfusion imaging may be worse than previously thought.⁵² Stress CT perfusion imaging has been increasingly gaining recognition as an alternative to nuclear myocardial perfusion imaging^{26,27,43,53–64} and can be easily performed in patients undergoing clinically indicated CTCA with minimal additional radiation, immediately and in the same setting. However, in our previous experience, the inability of most commercial scanners to image the entire heart in a single rotation and thus relying on sequential imaging with electrocardiographic gating frequently creates “slab artifacts” and contrast inhomogeneity, resulting in false-positive perfusion defects in myocardial areas supplied by normal arteries⁶⁵ and limiting the utility of stress CT perfusion as a reference standard for diagnosing ischemia in a clinical trial. To circumvent this limitation, we used a combination of SPDs with the presence of stenosis in the corresponding artery to define reference standard A, using 50% luminal narrowing as a cutoff, on the basis of well-established evidence that stenosis of a lower degree is unlikely to have hemodynamic or functional impact. Thus, only stenosis of at least that level that resulted in an SPD was considered significant for the purposes of this study.

Another possibility of a reference standard we considered was FFR measured during invasive coronary angiography. The problem with this approach was that it was impractical, as it would inevitably severely limit the number of patients we could evaluate and would bias the study population by excluding patients who are not considered to be at high enough risk to justify a referral for invasive angiography. A plausible alternative was the noninvasive fluid dynamics–based CT-FFR analysis,³² which could theoretically be performed in every study patient, because resting CT coronary angiographic images were available in all of them. Ultimately, we decided to limit CT-FFR analysis to patients with evidence of ≥25% luminal narrowing, because the likelihood of abnormal FFR is extremely low in the absence of at least minimally obstructive coronary disease. Also, because of the growing evidence that CT-FFR has limitations resulting in imperfect specificity, especially in patients with intermediate-grade stenosis,⁶⁶ we combined reduced FFR with the presence of a perfusion defect to define reference standard B. This allowed us to mitigate both false-positive perfusion defects caused by “slab artifacts” and potentially erroneous FFR determinations, by defining as hemodynamically significant only stenosis that resulted in a perfusion defect concomitant with CT-FFR < 0.80.

On one hand, these composite reference standards resulted in loss of arteries in which the impact of stenosis was judged as indeterminate because of discordance between the two component techniques and thus were not used for validation of strain abnormalities. On the other hand, however, this approach resulted in more robust reference standards than either one of the component techniques alone because of their inherent limitations. Nevertheless, we included in our report the results of the comparisons with the individual component techniques as well (Table 1) in order to be able to appreciate the improvement in accuracy that the use of the combined reference standards provided.

One might question the need for two combined reference standards in this study, rather than choosing one of the two. It is probably true that reference standard B is more relevant for hemodynamic significance of disease than reference standard A, because the former incorporates two functional markers of ischemia, whereas the latter uses one anatomic marker, namely, degree of stenosis, which is a necessary condition for ischemia but is also known to be not so well correlated with ischemia. Theoretically, we could have used reference standard B alone, which would have simplified our study somewhat but at the same time would have limited the sample size from 78 to 22. This is because CT-FFR analysis was performed only in a subset of patients with evidence of stenosis, because it did not make sense to perform this expensive analysis by an outside provider in patients with normal coronaries. Also the fact that both comparisons showed that the measures of diagnostic performance of our approach are similar in a sample of 22 patients and in the larger group of 78 support the notion that they are not due to a random effect of a small sample.

Assuming that strain abnormalities reflect significant stenosis, one may expect that this approach would result in the highest level of agreement with the reference technique that most closely reflects the hemodynamic impact of stenosis. Indeed, comparisons that included the presence of stenosis per se, namely, anatomic evidence only, did not fare as well as those that relied more on physiologic information, such as perfusion and FFR. Interestingly, of all comparisons, agreement was best with the composite reference standard B, supporting the hypothesis that resting strain may indeed reflect the impact of stenosis.

One might also question whether the hypothesis that resting regional LV strain would accurately differentiate significant from nonsignificant stenosis is realistic. Although we felt that this was a very legitimate question, it could not have been answered without conducting a study such as this one. We also believe that this may be the reason why the accuracy of this analysis just barely surpassed 0.80, which in fact is surprisingly high for a resting imaging technique in the context of ischemia detection. This is surprising because it means that the presence of a regional strain abnormality on echocardiographic images was associated with hemodynamically significant stenosis in >80% of cases. This may be due in part to the use of 3D strain analysis, which eliminates the loss of speckles as they move out of the imaging plane, which has been affecting two-dimensional strain measurements.

Limitations

One limitation of strain measurements is that they rely on tracking ultrasound speckles in the myocardium throughout the cardiac cycle. Although doing so in the 3D space eliminates the

problem of out-of-plane motion, the ability to accurately track these speckles depends largely on image quality, which is not always optimal and is well known to be affected by body habitus and other factors. Although every effort was made in this study to verify correct tracking, at times this can be difficult to achieve when image quality is limited. Because patients in this study were enrolled independently of the quality of their echocardiographic images, we can reasonably assume that suboptimal tracking is probably another likely factor that played into the limited intertechnique agreement. Similarly, the quality of cardiac CT images depends on the patient's body mass. Accordingly, the feasibility of our approach, which is based on fusion of these images, may be limited in obese patients.

In addition, cardiac arrhythmias may affect the quality of the 3D echocardiographic data sets and result in "stitch" artifacts, which limit the ability to perform accurate speckle-tracking analysis. Furthermore, it is likely that similar to the well-known limited ability of radionuclide perfusion imaging to detect "balanced ischemia" in patients with severe triple-vessel disease, strain abnormalities may be difficult to detect visually in the presence of globally reduced myocardial strain. We do not have a large enough number of such patients in this study to determine this with certainty.

Finally, one might question our choice to detect strain abnormalities qualitatively by visual assessment of the color-coded strain maps, rather than by quantitative analysis. In our recent pilot study, our attempts to define them quantitatively in terms of absolute strain value resulted in missing many of the visible abnormalities because of the large size and the location of the segments relative to the size and the location of the defects.²³ For this reason, we felt that qualitative visual assessment of the high-resolution strain-encoded parametric images was best to detect strain abnormalities.

CONCLUSIONS

Fusion of CTCA and 3DE-derived data allows direct visualization of each coronary artery and myocardial strain in its territory without the need to mentally coregister them within the complex 3D anatomy of the heart. In this study, resting strain abnormalities were considerably more common in the territories of coronary arteries stenosis >50% and perfusion defects. In addition, regional resting strain showed good agreement with two composite reference standards designed to boost their reliability for determining hemodynamic or functional impact of stenosis in patients with chest pain. In the future, this methodology may prove a radiation-free alternative to vasodilator stress perfusion imaging, with implied reduced risks to patients, simplicity, and cost savings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

3D	Three-dimensional
3DE	Three-dimensional echocardiography
CT	Computed tomographic
CTCA	Computed tomographic coronary angiography
CT-FFR	Fractional flow reserve from resting cardiac computed tomographic images
FFR	Fractional flow reserve
LAD	Left anterior descending coronary artery
LV	Left ventricular
SPD	Stress perfusion defect

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HIGHLIGHTS

- We studied patients with chest pain.
- CT angiography fusion with 3D echocardiography derived resting myocardial strain.
- Strain abnormalities correlated with perfusion defects on vasodilator stress CT.
- Strain abnormalities correlated with reduced noninvasive fractional flow reserve.
- Image fusion may help determine the hemodynamic impact of coronary artery disease.

Figure 1. Schematic diagram of the study design (see text for details). *CAD*, Coronary artery disease.

Figure 2.

Example of combined 3D displays obtained in a patient with no significant stenosis. The two snapshots depict (from *left to right*) the anterior and inferior views with fairly uniform resting longitudinal strain (*top*) and subendocardial perfusion during vasodilator stress (*bottom*).

Figure 3.

Example of combined 3D display of longitudinal strain and coronary arteries (*right*) obtained in a patient with an intermediate grade stenosis. Although reduced FFR by CT-FFR was noted in distal portion of the LAD (*left*), no obvious strain abnormality was seen in any of the LV walls (*right*).

Figure 4.

Example of combined 3D displays obtained in a patient with a hemodynamically significant mid-LAD stenosis, confirmed by CT-FFR analysis for a large portion of the artery (*left*). An extensive resting strain abnormality was noted in the antero-septal and septal walls, depicted by the red-orange-yellow area (*right*).

Figure 5.

Example of combined 3D displays obtained in another patient with a hemodynamically significant stenosis in the left circumflex coronary artery, confirmed by CT-FFR analysis (*left*). An extensive resting strain abnormality was noted in the lateral wall (*middle*), concomitant with a vasodilator subendocardial SPD in the same area of the myocardium (*right*).

Diagnostic accuracy of resting strain abnormalities against two reference standards for hemodynamically or functionally significant coronary stenosis (A and B defined below), as well as against their individual components

Table 1

Reference	Sensitivity	Specificity	PPV	NPV	Accuracy
(1) Stenosis >50% on CTCA	0.68	0.71	0.92	0.32	0.71
(2) SPD	0.67	0.80	0.82	0.63	0.75
(1) + (2)= reference A	0.71	0.81	0.92	0.47	0.79
(3) Abnormal CT-FFR	0.79	0.70	0.88	0.54	0.73
(2) + (3)= reference B	0.83	0.81	0.91	0.67	0.82

Reference standard A was defined as a combination of stenosis >50% on CTCA and vasodilator stress subendocardial perfusion defect. Reference standard B was defined as a combination of abnormally low CT-FFR (<0.80) and vasodilator stress subendocardial perfusion defect. See text for additional details and rationale. *NPV*, Negative predictive value; *PPV*, positive predictive value.

Table 2

Contingency table of agreement between repeated analyses of strain abnormalities (see text for details)

	Repeat analysis	
	Normal	Abnormal
First analysis		
Normal	38	3
Abnormal	6	13