Appendix E1: Automated Image Analysis

Image analysis was performed by using custom software developed in the Matlab environment (MathWorks, Natick, Mass) and included image segmentation and registration.

For each section, after manual placement of a single point inside the LV cavity in a single frame, the best frame for endo- and epicardial detection was selected automatically (Fig E1). In this reference frame, first, the endocardial boundary was automatically detected (Fig E2, *A* and *B*) (16). Unlike previously used techniques that are mostly based on thresholding of pixel intensity, our approach is based on the assumption that the normal distributions of noise in the blood pool and that in the myocardium are different. This assumption allows us to use a region-based level-set technique to partition the heart into maximally homogeneous regions, taking into account local noise patterns. From a mathematic point of view, we first define a curve, *C*, as the zero-level set of an implicit real function φ with values in the image domain Ω:

$$C = \{(x, y) \in \Omega: \varphi(x, y) = 0\}.$$

This curve *C* undergoes an evolution in time to minimize the following functional *F*:

$$F(I,C) = \varepsilon \cdot \text{length}\left(C\right) - \int_{\Omega_i(C)} \log p(I)\, dxdy - \int_{\Omega_o(C)} \log p(I)\, dxdy\,,$$

where *I* is the gray-level intensity image; $\Omega_i(C)$ and $\Omega_o(C)$ are the regions inside and outside *C*, respectively; $\varepsilon \cdot \text{length}(C)$ is a regularization term (28), and *p(I)* represents the probability density distribution of the gray levels in the images, which can be reasonably approximated with a Gaussian distribution:

$$p(I) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left[-\frac{1}{2}\left(\frac{I - \mu}{\sigma} \right)^2 \right],$$

where μ and σ are the mean and variance of *I*, respectively.

The final step of endocardial border detection was boundary regularization, which was achieved by using curvature motion (29), which does not allow excessive curvature, and was designed to automatically include the papillary muscles in the LV cavity (Fig E2, *B*). We then used the classical edge-based level-set model (30) to search the image from the endocardium outward and identify the epicardial boundary (Fig E2, *C*). The equation that drives the evolution is the Malladi-Sethian model for active contour evolution (30), with the previously computed endocardium contour as the initial condition. Then, the epicardial boundary was also regularized with modified curvature motion.

Nonrigid image registration was achieved by means of a multiscale extension of two-dimensional normalized cross correlation to compensate for cardiac translation and deformation as a result of out-of-plane motion. To this effect, we defined a first template image of the LV in the reference frame, and five additional template images were created by resizing this template to different degrees (1 pixel difference each). Then, cross correlation between each consecutive frame and each of the six templates was calculated, and the new size and position of both endo- and epicardial boundaries were determined by finding the largest cross-correlation peak among the six combinations. Subsequently, contour adaptation was performed as a final step of boundary refinement by again using the edge-based level-set model (Fig E3). Templates were updated for each consecutive frame to take into account the changes in pixel intensity occurring during the passage of the contrast material bolus.

References

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Table E1. Results of Comparisons between Perfusion Indexes Derived from Automatically and Manually Generated Contrast Enhancement Curves

	Linear Regression Analysis*			Bland-Altman Analysis of Intertechnique Differences	
Parameter	*r*	*a*	*b*	Bias	Standard Deviation
Amplitude					
Stress	0.90	0.89	4.8	0.25	6.5
Stress in LV cavity	0.92	1.05	–0.0013	0.0030	0.015
Stress/rest	0.87	0.88	0.22	0.016	0.55
(Stress in LV cavity)/(rest in LV cavity)	0.75	0.76	0.48	0.070	0.68
Slope					
Stress	0.94	0.88	0.46	–0.18	0.88
Stress in LV cavity	0.94	1.05	–0.0017	0.00029	0.0080
Stress/rest	0.81	0.78	0.57	0.0069	1.10
(Stress in LV cavity)/(rest in LV cavity)	0.72	0.93	0.26	0.14	0.89
Amplitude · slope					
Stress	0.90	0.83	38	–17	104
Stress in LV cavity	0.90	0.88	0.00030	0.00000	0.0020
Stress/rest	0.83	0.90	0.32	–0.10	4.10
(Stress in LV cavity)/(rest in LV cavity)	0.72	0.88	0.55	0.21	2.10

*With Pearson correlation coefficient ($y = ax + b$ and r).

Table E2. Results of ROC Analysis for Perfusion Indexes Obtained on a Segment-by-Segment Basis with Both the Automated and Manual Techniques against Quantitative Coronary Angiography as a Reference Standard and Also against Visual Interpretation as a Reference

	Against Coronary Angiography*		Against Visual Interpretation	
Parameter	Automated	Manual	Automated	Manual
Amplitude				
Stress (myo)	0.70	0.71	0.60	0.63
Stress (myo/LV cavity)	0.58	0.59	0.71	0.75
Stress (myo)/rest (myo)	0.58	0.58	0.67	0.70
Stress (myo/LV cavity)/rest (myo/LV cavity)	0.55	0.55	0.65	0.68
Slope				
Stress (myo)	0.71	0.70	0.61	0.60
Stress (myo/LV cavity)	0.54	0.54	0.73	0.73
Stress (myo)/rest (myo)	0.56	0.58	0.69	0.67
Stress (myo/LV cavity)/rest (myo/LV cavity)	0.53	0.57	0.71	0.72
Amplitude · slope				
Stress (myo)	0.72	0.73	0.61	0.64
Stress (myo/LV cavity)	0.59	0.60	0.73	0.78
Stress (myo)/rest (myo)	0.59	0.58	0.64	0.65
Stress (myo/LV cavity)/rest (myo/LV cavity)	0.56	0.57	0.69	0.74

Note.—Data are AUCs calculated on a segment-by-segment basis. Myo = myocardium.

*At coronary angiography, luminal narrowing greater than 50% was considered to indicate significant stenosis.

Table E3. Intertechnique Comparisons against the Quantitative Coronary Angiography Reference Standard: κ Statistics Calculated on a Segment-by-Segment Basis for the Automated and Manual Techniques, Side-by-Side with Visual Interpretation

Parameter	Automated Technique	Manual Technique
Amplitude		
Stress (myo)	0.73	0.71
Stress (myo/LV cavity)	0.64	0.64
Stress (myo)/rest (myo)	0.60	0.59
Stress (myo/LV cavity)/rest (myo/LV cavity)	0.62	0.60
Slope		
Stress (myo)	0.74	0.73
Stress (myo/LV cavity)	0.62	0.59
Stress (myo)/rest (myo)	0.62	0.60
Stress (myo/LV cavity)/rest (myo/LV cavity)	0.60	0.62
Amplitude · slope		
Stress (myo)	0.74	0.74
Stress (myo/LV cavity)	0.62	0.62
Stress (myo)/rest (myo)	0.60	0.57
Stress (myo/LV cavity)/rest (myo/LV cavity)	0.62	0.59

Note.—Data are κ coefficients. The κ coefficient for hypoenhanced myocardium at visual interpretation was 0.58. The calculated κ coefficients were judged as follows: 0–0.20 = low agreement, 0.21–0.40 = moderate agreement, 0.41–0.60 = substantial agreement, 0.61–0.80 good agreement, and >0.80 = excellent agreement. Myo = myocardium.