Direct Epicardial Mapping Can Differentiate Hibernating from Scarred Myocardium: A Validation Study with ^{18}F -FDG-PET

Christian Vahlhaus, M.D.,* Michael Schäfers, M.D.,†
Hans-Jürgen Bruns, Ph.D.,* Frauke Janssen, M.D.,*
Jörg Stypmann, M.D.,* Dieter Hammel, M.D.,‡ Hans H. Scheld, M.D.,‡
Otmar Schober, M.D., Ph.D., F.E.S.C.,†
Günter Breithardt, M.D., F.E.S.C., F.A.C.C.,*
and Thomas Wichter, M.D., F.E.S.C.*

From the *Department of Cardiology and Angiology, †Department of Nuclear Medicine, and ‡Department of Cardiothoracic Surgery, University of Münster, Münster, Germany

Aim: This study investigated the value of epicardial mapping immediately before CABG in the differentiation of hibernating from scarred myocardium in correlation to the noninvasive gold standard ^{18}F -FDG PET.

Methods and Results: In 35 patients with CAD, myocardial perfusion ($^{99\text{m}}\text{Tc}$ -Tetrofosmin-SPECT), viability (^{18}F -FDG-PET), and function (LVangiography) were assessed before CABG. 102 bipolar epicardial electrograms per patient ($n = 3570$ electrograms) were recorded simultaneously with a ventricular jacket array. Based on the scintigraphic and LV angiographic data at the site of each electrode with good myocardial contact ($n = 1963$), segments ($n = 492$, 14.1 ± 5.6 per patient; mean $\pm$ SD) were classified into three groups: hibernating ($n = 139$), scarred ($n = 104$), and control ($n = 249$). Regional mean bipolar voltage values were calculated for Receiver Operating Characteristic (ROC) analysis. Mean bipolar voltage was significantly lower in scarred when compared to hibernating myocardium. ROC curve analysis (area under the curve of 0.92 ± 0.47 , mean $\pm$ SE) for mean bipolar voltage to discriminate between hibernating and scarred myocardium revealed a sensitivity of 94% with a specificity of 83% at a cut-off value of 8.75 mV.

Conclusion: Hibernating myocardium can be differentiated correctly from scarred myocardium by direct epicardial mapping. In the future, hibernating myocardium may be detectable by body surface mapping techniques using inverse solutions.

A.N.E. 2002;7(4):349-356

hibernating myocardium; mapping

Myocardial hibernation, i.e., the active reduction of myocardial contractile function to preserve myocardial viability during myocardial ischemia,¹ is the most relevant cardioprotective phenomenon in patients with coronary artery disease considered for revascularization. In pigs, hibernating myocar-

dium, induced by gradual coronary artery occlusion, was characterized by preserved electrical activity (NOGA mapping): voltage was not affected in ischemic regions when compared with control regions.² In contrast, electrograms from infarct sites had smaller amplitudes and longer durations when

This study was supported by the Interdisciplinary Center for Clinical Research (IZKF; B1, BMBF-01KS 9604) and the German Academic Exchange Program (DAAD; 313/sf-ppp-kr).

Address for reprints: Dr. Christian Vahlhaus, Westfälische Wilhelms-Universität Münster, Medizinische Klinik und Poliklinik-Innere Medizin C-Albert-Schweitzer-Str. 33, D-48149 Münster, Germany. Fax: +49-251-83-47864; E-mail: Vahlhaus@uni-muenster.de

compared with control regions.³ Thus, preserved electrical activity in ischemic and dysfunctional myocardium may be a marker of the potential of functional recovery. Therefore, we investigated whether direct epicardial bipolar mapping is able to differentiate hibernating from scarred myocardium.

METHODS

Patients

Thirty-five patients (29 male, 6 female; age: 61 ± 9 years, mean $\pm$ SD) admitted for elective coronary artery bypass grafting (CABG) without valvular heart disease were prospectively enrolled in this study. All patients had undergone coronary angiography and biplane left ventricular angiography (global LV-EF range: 23-61.7%; $48.3 \pm 10\%$, mean $\pm$ SD) before admission because of angina ($n = 32$) and/or angina equivalents ($n = 12$) with a positive stress test. Twenty patients had a history of prior myocardial infarction. Only patients with regional left ventricular dysfunction were included. Patients with recent acute myocardial infarction, former CABG or PTCA, implanted pacemaker or ICD, complete left bundle branch block, or diabetes mellitus were not included.

The study protocol had been approved by the Ethical Review Board of the University of Münster, Germany. Patients gave written informed consent before entering the study.

Protocol

Preoperative Evaluation

The standard clinical procedure prior to CABG included physical examination, a standard 12-lead ECG recording, a respiratory function test, and a chest x ray. Preoperatively, patients underwent ^{99m}Tc -Tetrofosmin-SPECT and ^{18}F -FDG-PET for assessment of myocardial perfusion and myocardial viability, respectively.

Intraoperative Epicardial Mapping

Epicardial mapping was performed using a ventricular jacket array and a commercial recording system (CardioMapp™, Prucka Engineering Inc., Houston, TX, USA). The mapping unit consisted of a PC based system for recording, amplification, analog-to-digital conversion (ADC), and storage of bipolar electrograms from the ventricular jacket

Figure 1. Ventricular jacket array consisting of 102 gold-plated bipolar electrode pairs, arranged in 12 strips of printed copper layers on flexible plastic material: 6 strips with 10 pairs of electrodes and 6 strips with 7 pairs of electrodes.

array and four standard limb leads as a reference. The ventricular jacket array consisted of 102 gold-plated bipolar electrode pairs, arranged in 12 strips of printed copper layers on flexible plastic material: 6 strips with 10 pairs of electrodes and 6 strips with 7 pairs of electrodes (Fig. 1). Each electrode measured 1.5 mm in diameter. In vertical direction, the distance between electrode pairs was 13 mm with an interpole distance of 4 mm. In horizontal direction, the 12 electrode strips were connected with elastic fabric to fit the ventricular jacket array to different sizes of the heart.

After opening the chest and the pericardium, preparation of the left internal thoracic artery and connection of the right atrium and the aorta in the common way to the heart-lung machine, the ventricular jacket array was carefully fixed around both ventricles. Multiple registrations of 8.9-second duration were made while the patients were in stable sinus rhythm during partial normothermic cardiopulmonary bypass and before induction of ventricular fibrillation. Mechanical pulmonary ventilation was interrupted for the time of the recordings and the systolic blood pressure was set to about 100 mmHg. Signals were transmitted to a junction box and then conducted via shielded cables to the amplifier unit. They were separately band-pass filtered (0.2-300 Hz), amplified (dynamic input range ± 16 mV, gain 63), analog-to-digital converted (1 kHz sampling rate, 12-bit digital resolution, $7.8 \mu\text{V}$ least significant bit) and stored on a hard disk.

Segmental Myocardial Function

Biplane left ventricular cine angiograms were visually interpreted by two experienced readers. Left ventricular segmental function was assessed in relation to the position of the epicardial electrodes using a wall-motion score (0 = dyskinetic, 1 = akinetic, 2 = hypokinetic, 3 = normokinetic). The septum of the left ventricle could not be analyzed since no epicardial signal can be obtained intraoperatively by the ventricular jacket array.

Segmental Myocardial Perfusion and Viability

Segmental myocardial perfusion was measured using single photon emission tomography (SPECT) imaging starting 1 h after injection of 740 MBq ^{99m}Tc -Tetrofosmin (Myoview; Nycomed-Amersham, Amersham, UK) under resting conditions. Images were acquired using a two-headed camera, 24 projections per head, in a 64 x 64 matrix during a 180° orbit for 50 seconds per step with a zoom factor of 1.45 (E.Cam; Siemens Gammasonics Inc., Des Plaines, IL, USA). Images were reconstructed using filtered back projection with a Butterworth filter (cut-off 0.6, filter order 5). Segmental relative myocardial ^{99m}Tc -tetrofosmin-uptake was assessed.

Myocardial glucose utilization (MGU) was measured using positron emission tomography (PET) with ^{18}F -fluor-deoxyglucose (FDG) under hyperinsulinemic, euglycemic steady state conditions (clamp).⁴ Before the start of the PET scan, a cannula was inserted into a superficial forearm vein for injection of insulin and glucose as originally described by De Fronzo and coworkers.⁵ For withdrawal of arterialized venous blood samples, a second cannula was inserted into a superficial wrist or hand vein while the hand was heated using a heating pad at 50°C. The hyperinsulinemic, euglycemic clamp started with a constant infusion of 40 mU*minutes⁻¹ per m² of body surface area after priming with four times this infusion rate for the first 4 minutes, followed by two times this infusion rate for 3 minutes. During the whole PET scan, plasma glucose levels were measured in 5-minute intervals and a 20% D-glucose infusion was adjusted to maintain euglycemia.

The PET scan started 1 hour after the start of the clamp with a rectilinear scan to position the heart in the field of view, followed by a 20-minute trans-

mission scan to correct for attenuation. This was then followed by the measurement of MGU using injection of 370 MBq of the glucose analogue ^{18}F -FDG and a 23 frames dynamic emission scan (12 × 10, 4 × 30, 2 × 300, 4 × 600 second frames; ECAT EXACT 47 scanner; Siemens/CTI Inc., Nashville, TN, USA). Images were reconstructed with a Hanning filter (cut-off 0.5) in a 128 × 128 matrix. Parametric images of the regional MGU were calculated according to the Patlak plot, described elsewhere.^{6,7}

Analysis of the parametric images and correlation to the epicardial mapping data started with an automated contour finding algorithm of the left ventricular myocardium as described recently.^{8,9} On the defined contour of the left ventricular myocardium, the electrode mapping system was projected as an elastic net array using the sulcus interventricularis anterior (seen on the scintigraphic image as the antero-septal origin of the right ventricle), the sulcus interventricularis posterior (seen on the scintigraphic image as the infero-septal origin of the right ventricle) as well as the apex as guiding structures. Finally, for comparison with electrophysiological and LV angiographic findings, the relative tracer uptake in each electrode coordinate of the net was measured. If the segmental ^{99m}Tc -tetrofosmin-uptake was lower than 60% of the individual maximum, segments were classified as hypoperfused. If the segmental MGU was higher than 60% of the individual maximum, segments were classified as viable.

Signal Analysis

A total of 3,570 electrograms were sampled. Only electrograms with good myocardial contact ($n = 1963$, 56.1 ± 12.1 of 102 segments in each patient, mean $\pm$ SD) were analyzed. Electrode pairs without left ventricular contact were excluded (right ventricular: $n = 997$, overhanging at apical or atrial border: $n = 267$ on fatty epicardium: $n = 268$, with atrial far field signals: $n = 75$).

The recording with the highest signal-to-noise ratio was selected for single-beat analysis. In this recording of 8.9 second duration, one beat was manually selected from the limb lead for further analysis. A 200 ms window, centered around the maximum amplitude of the limb lead QRS complex, was chosen as "raw data set." Maximum and minimum amplitudes were automatically measured and the maximum amplitude range was cal-

Table 1. Characteristics of the Myocardial Regions: P < 0.05 versus control, Ý: P < 0.05 versus hibernating

Regions (n = 70)	Control (n = 34)		Hibernating (n = 18)		Scar (n = 18)	
	Mean	SD	Mean	SD	Mean	SD
Regional myocardial function (mean wall-motion score)	2.9	±0.3	2.0*	±1.0	0.9*Ý	±1.1
Regional myocardial perfusion (relative 99mTc-uptake)	0.74	±0.09	0.48*	±0.11	0.40*	±0.18
Regional myocardial viability (relative 18F-FDG-uptake)	0.87	±0.07	0.8	±0.09	0.49*Ý	±0.16
Mean bipolar signal duration [ms]	17.2	±5.3	16.3	±4.1	19	±7.5
Mean bipolar voltage [mV]	11	±4.4	12.7	±3.3	5.0*Ý	±4.1

culated. Time domain parameters were measured as described recently.¹⁰ In brief, the manually marked QRS onset of the limb lead was set as the reference time zero for all local epicardial electrograms. For the detection of amplitude variations in the onset and offset of bipolar deflections indicating local depolarization, a new highly sensitive method was developed.¹⁰ The time of local activation onset and offset was defined as the point where amplitudes exceeded a noise level calculated from samples before or after the activation peak, plus a variable threshold level T. The smaller values for this threshold level T were chosen, the more sensitive this algorithm detected amplitude variations in the onset or offset of local activation. Different threshold levels T were tested to find markers for onset and offset of both deflections.

Classification of Regions

A total of 70 regions were formed representing 492 of 1963 LV segments. In accordance with the individual angiographic and scintigraphic findings, regions were classified as hibernating (n = 18, dysfunctional, hypoperfused segments with normal glucose uptake), scarred (n = 18, dysfunctional, hypoperfused segments with a relative glucose uptake < 60%), or control (n = 34, normokinetic, normoperfused segments with normal glucose uptake). Regional mean values of myocardial viability, bipolar signal duration, and bipolar voltage were calculated for each patient based on the segmental data derived from the 70 classified regions. The minimal segmental perfusion value and the minimal segmental wall-motion score achieved in each classified region represented its regional myocardial perfusion and its regional myocardial function, respectively.

Statistics

Area under the curve (receiver operating characteristic analysis) is expressed as mean ± SE, all other data are reported as mean ± SD. Statistical analysis was performed using SPSS software (Version 10.0 SPSS Inc., Chicago, IL, USA). Data on patient characteristics, regional myocardial function, scintigraphic data, mean bipolar signal duration, and mean bipolar voltage data were subjected to a one-way analysis of variance (ANOVA) accounting for the regional classification: control, hibernating, and scarred. With ANOVA the effect of regional myocardial function on mean bipolar signal duration and mean bipolar voltage was analyzed. When significant differences were detected, individual mean values were compared using Tukey's post hoc test. A level of P < 0.05 was considered to represent significant changes between groups analyzed. Discriminant analysis was performed for mean bipolar signal duration and mean bipolar voltage to discriminate hibernating from scarred myocardium. The cut-off value at optimized sensitivity and specificity was estimated with receiver operating characteristic (ROC) analysis.

RESULTS

Regional myocardial function, regional scintigraphic data, and regional mean bipolar signal duration and voltage data are shown in Table 1.

Segmental Myocardial Function and Segmental Myocardial Perfusion

LV angiography disclosed 324 normokinetic (66%) and 168 dysfunctional (34%) of 492 LV segments. Regression analysis revealed a significant

Figure 2. Relation of segmental myocardial perfusion to segmental myocardial function. Regression analysis ($n = 492$) revealed a significant relation between regional myocardial function and blood flow ($y = 0.15x + 0.32$, $r = 0.65$, $P < 0.001$).

relation between regional myocardial function and perfusion ($y = 0.15x + 0.32$, $r = 0.65$, $P < 0.001$; Fig. 2, $n = 492$).

Regional Myocardial Function and Regional Mean Electrical Data

Regional wall-motion score was significantly lower in hibernating when compared to control regions and was further decreased in scarred regions (Table 1). Mean bipolar signal duration was not different in dysfunctional regions (dyskinetic: 20.0 ± 11.2 ms, akinetic: 18.8 ± 8.8 ms, hypokinetic: 17.3 ± 7.0 ms, mean $\pm$ SD) when compared to normokinetic regions (16.7 ± 8.1 ms; Fig. 3A; mean $\pm$ SD). With increasing regional myocardial function, mean bipolar voltage significantly increased [$P < 0.001$, ANOVA; dyskinetic: 6.3 ± 7.5 mV, akinetic: 7.4 ± 6.3 mV, hypokinetic: 10.4 ± 7.1 mV, normokinetic: 11.6 ± 7.0 mV; Fig. 3B; mean $\pm$ SD].

Regional Mean Electrical Data in Hibernating Myocardium

Mean bipolar signal duration and mean bipolar voltage in hibernating regions and control regions were comparable (Table 1; Figs. 4 and 5). In addition

in nonhibernating, nonscarred but ischemic segments mean bipolar signal duration (17.9 ± 8.3 ms, mean $\pm$ SD) and mean bipolar voltage (10.6 ± 7.9 mV, mean $\pm$ SD) was not different from control regions and from hibernating regions. While mean bipolar signal duration in scarred myocardium was not different from hibernating or control myocardium, mean bipolar voltage was significantly lower in scarred when compared to hibernating or control myocardium.

Figure 3. Boxplot distributions. (A) bipolar signal duration; and (B) bipolar voltage in dyskinetic ($n = 33$), akinetic ($n = 67$), hypokinetic ($n = 68$), and normokinetic ($n = 324$) segments. Data shown within each box correspond to 25th, 50th (median), and 75th percentile cut points for each group (error bars indicate the 95% confidence interval; *: $P < 0.05$ versus dyskinetic, Y: $P < 0.05$ versus akinetic).

Figure 4. Comparison of bipolar signal duration expressed as mean values from regions classified as control (n = 34), hibernating (n = 18), and scar (n = 18). Scatterplot is showing regional mean signal duration data, superimposed are mean values (black squares) and standard deviation (error bars).

Predictive Accuracy of Mean Bipolar Voltage in Detecting Hibernating Myocardium

Seventeen of 18 hibernating regions (94%) and 15 of 18 scarred regions (83%) were correctly predicted by their regional mean bipolar voltage. Regional mean bipolar voltage discriminated well between hibernation and scar. ROC curve (area under the curve: 0.92 ± 0.47 ; Fig. 6; mean $\pm$ SD) revealed a sensitivity of 94% with a specificity of 83% at a mean bipolar voltage cut-off of 8.75 mV.

DISCUSSION

Direct epicardial mapping discriminated well between hibernating myocardium and scarred myocardium as defined by the noninvasive gold standard for assessing myocardial viability, ^{18}F -FDG-PET. Direct epicardial mapping had a good accuracy in detecting myocardial viability which is a prerequisite for predicting recovery of myocardial function following revascularization in chronic ischemic myocardium.

What New Methods Are Worthy of Investigation?

Several noninvasive methods for assessing myocardial viability are available including radionuclide techniques,^{11,12} dobutamine echocardiography,¹³ and contrast enhanced magnetic resonance imaging.¹⁴ While there is consensus that radionuclide techniques represent the noninvasive gold standard for detection of myocardial viability,¹¹ dobutamine echocardiography shows the highest specificity¹⁵ and the best accuracy of a positive test¹⁶ in predicting recovery of myocardial contractile function following revascularization. In regions of severely dysfunctional segments, even the transmural extent of viable myocardium can be assessed by contrast enhanced magnetic resonance imaging which is a strength of this method.¹⁴ However, these methods are sometimes impracticable due to claustrophobia, implanted pacemakers or defibrillators, due to low-image quality in patients with emphysema or those suffering from diabetes.

Following the first report on myocardial hibernation identified in patients with coronary artery disease undergoing coronary artery bypass sur-

Figure 5. Comparison of bipolar voltage expressed as mean values from regions classified as control (n = 34), hibernating (n = 18), and scar (n = 18). Scatterplot is showing regional mean bipolar voltage data, superimposed are mean values (black squares) and standard deviation (error bars; *: P < 0.01 versus control, P < 0.01 versus hibernation).

Figure 6. Plot of Receiver Operating Characteristic (ROC; area under the curve: 0.92 ± 0.47 , mean $\pm$ SE) for mean bipolar voltage to predict hibernation and scar. At a mean bipolar voltage of 8.75 mV, sensitivity was 94% with a specificity of 83%.

ger^{17,18} the therapy of patients with coronary artery disease and severe contractile dysfunction has been revolutionized.^{19,20} In patients with coronary artery disease and severe left ventricular dysfunction who demonstrated myocardial viability during dobutamine echocardiography, revascularization improved survival.²¹ Therefore, it is of utmost relevance to detect all hibernating regions in patients with chronically ischemic myocardium before performing revascularization. Refining established methods and developing new methods may improve sensitivity (and specificity) of viability detection. Simultaneously, but not at the expense of the diagnostic accuracy, simpler methods are needed to save time and money, increase patient acceptance, and reduce potential risks (i.e., of radiation).

Why Use an Epicardial Approach?

In pigs, hibernation did not affect endocardial voltage in hibernating myocardium² but in scarred myocardium³ when compared with control regions. But the scatter of endocardial ECG amplitudes was so high, that endocardial mapping failed in establishing cut of values that allow distinction between viable and nonviable areas.²² Ischemia is more severe in the subendocardial when compared to the epicardial layer. Myocardial infarct development starts from the subendocardial layer before

expanding in a transmural direction. Areas of subendocardial infarction and viable but dysfunctional myocardium in the midmyocardial and/or the epicardial layer may have low endocardial ECG amplitudes but normal epicardial ECG amplitudes. Even if the endocardial approach is better to perform in the clinical setting, the epicardial approach is the only one that allows the detection of hibernating myocardium with good accuracy.

The present study demonstrates that epicardial mapping is feasible for intraoperative viability assessment, at least on the free left ventricular wall in the absence of epicardial fatty tissue. Myocardial hibernation and scarred myocardium can be electrically differentiated by epicardial mapping. Therefore, epicardial mapping may be the basis for development of noninvasive electrocardiographic mapping. The present findings encourage further investigation of whether hibernating myocardium can also be differentiated from scarred myocardium using noninvasive body surface mapping techniques with inverse reconstruction.²³

Study Limitations

One limitation of the study is that not the entire left ventricle can be mapped from the epicardium. The septum was excluded from the analysis, since no epicardial signal can be obtained intraoperatively by the ventricular jacket array. Because of epicardial fatty tissue, not all segments could be included in the analyses. Mapping of inferior segments especially in the basal regions was performed in all patients of this study. Technical problems during bypass surgery may complicate basal-inferior mapping when lifting the heart is not tolerated.

Some regions classified as scarred myocardium have markedly high mean bipolar voltage values (Fig. 5). With the mapping technique used in the present study bipolar signal were measured at the epicardial surface representing the integrity of maybe only a thin epicardial layer. In contrast, regional classification was based on PET findings representing a transmural summation of metabolic activity. Thus, segments with epicardial viability may have been classified as scarred myocardium.

REFERENCES

1. Heusch G, Schulz R. Hibernating myocardium: A review. *J Mol Cell Cardiol* 1996;28:2359–2372.
2. Fuchs S, Kornowski R, Shiran A, et al. Electromechanical

- characterization of myocardial hibernation in a pig model. *Coron Artery Dis* 1999;10:195-198.
3. Callans DJ, Ren JF, Michele J, et al. Electroanatomic left ventricular mapping in the porcine model of healed anterior myocardial infarction: Correlation with intracardiac echocardiography and pathological analysis. *Circulation* 1999;100:1744-1750.
4. Bolli R, Zhu WX, Thornby JI, et al. Time course and determinants of recovery of function after reversible ischemia in conscious dogs. *Am J Physiol* 1988;254:H102-H114.
5. Knuuti MJ, Nuutila P, Ruotsalainen U, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 1992;33:1255-1262.
6. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;237:E214-E223.
7. Gambhir SS, Schwaiger M, Huang SC, et al. Simple noninvasive quantification method for measuring myocardial glucose utilization in humans employing positron emission tomography and fluorine-18 deoxyglucose. *J Nucl Med* 1989;30:359-366.
8. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. *J Cereb Blood Flow Metab* 1985;5:584-590.
9. Biedenstein S, Schafers M, Stegger L, et al. Three-dimensional contour detection of left ventricular myocardium using elastic surfaces. *Eur J Nucl Med* 1999;26:201-207.
10. Stegger L, Biedenstein S, Schafers KP, et al. Elastic surface contour detection for the measurement of ejection fraction in myocardial perfusion SPET. *Eur J Nucl Med* 2001;28:48-55.
11. Bruns HJ, Janssen F, Schäfers M, et al. Signal characteristics of multichannel epicardial electrograms in chronic ischemic and scarred myocardium: Electromechanical mismatch indicates viability in regions of myocardial dysfunction. *Basic Res Cardiol* 2001;96:98-105.
12. Heyndrickx GR, Millard RW, McRitchie RJ, et al. Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. *J Clin Invest* 1975;56:978-985.
13. Walton S. Radionuclide techniques for myocardial viability and hibernation. *Heart* 1999;81:6-7.
14. Narula J, Dawson MS, Singh BK, et al. Noninvasive characterization of stunned, hibernating, remodeled and nonviable myocardium in ischemic cardiomyopathy. *J Am Coll Cardiol* 2000;36:1913-1919.
15. Cigarroa CG, deFilippi CR, Brickner ME, et al. Dobutamine stress echocardiography identifies hibernating myocardium and predicts recovery of left ventricular function after coronary revascularization. *Circulation* 1993;88:430-436.
16. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;343:1445-1453.
17. Perrone-Filardi P, Pace L, Prastaro M, et al. Assessment of myocardial viability in patients with chronic coronary artery disease: Rest-4-hour-24-hour 201Tl tomography versus dobutamine echocardiography. *Circulation* 1996;94:2712-2719.
18. La Canna G, Rahimtoola SH, Visioli O, et al. Sensitivity, specificity, and predictive accuracies of noninvasive tests, singly and in combination, for diagnosis of hibernating myocardium. *Eur Heart J* 2000;21:1358-1367.
19. Rahimtoola SH. Coronary bypass surgery for chronic angina-1981. A perspective. *Circulation* 1982;65:225-241.
20. Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. *Circulation* 1985;2:V123-V135.
21. Elsasser A, Schlepper M, Klovekorn WP, et al. Hibernating myocardium: An incomplete adaptation to ischemia. *Circulation* 1997;96:2920-2931.
22. Gunning MG, Chua TP, Harrington D, et al. Hibernating myocardium: Clinical and functional response to revascularization. *Eur J Cardiothorac Surg* 1997;11:1105-1112.
23. Afridi I, Grayburn PA, Panza JA, et al. Myocardial viability during dobutamine echocardiography predicts survival in patients with coronary artery disease and severe left ventricular systolic dysfunction. *J Am Coll Cardiol* 1998;32:921-926.
24. Oster HS, Taccardi B, Lux RL, et al. Electrocardiographic imaging: Noninvasive characterization of intramural myocardial activation from inverse-reconstructed epicardial potentials and electrograms. *Circulation* 1998;97:1496-1507.