Biomarkers, November 2005; 10(Supplement 1): S1–S9

Taylor & Francis
Taylor & Francis Group

Cardiovascular imaging to quantify the evolution of cardiac diseases in clinical development

GREGORY J. KLEIN[1] & JEAN-PHILIPPE THIRION[2]

[1]*Quantificare, Inc., Oakland, CA, USA and* [2]*Quantificare, S.A., Sophia Antipolis, France*

Abstract
Cardiovascular diseases are the leading causes of mortality in western countries, leading to the development of a large set of preventive and curative treatments. Medical imaging is the gold standard to evaluate both cardiac perfusion and cardiac function and can be used even before the advent of hard events to accurately assess treatment effects. This study reviews the different image modalities that can be used to evaluate the evolution of cardiac diseases, especially coronary artery diseases. It also reviews different techniques heavily relying upon image co-registration techniques and population model designs that enable accurate quantitative evaluation of cardiac perfusion and cardiac function through time. It will draw the pros and cons of the different imaging modalities in actual clinical trials: Gated or tagged MRI, MRI for perfusion, PET, SPECT, Gated SPECT, MUGA, Ultrasound. This study also details the latest advances in quantification of cardiac SPECT, which has wide use in clinical trials today.

Keywords: *Cardiac imaging, SPECT, perfusion, defect*

Introduction

Clinical hard events seen during the course of a drug or device trial are the classical end-points used for assessing efficacy of the therapy. For cardiac treatments, the usual class of clinical events is called 'Major Adverse Coronary Events' (MACE), which include patient deaths, new myocardial infarctions, heart failure and required re-intervention procedures. Another often used class of end-points is somewhat subjective and relies upon patient or investigator reporting of patient performance and/or perceived condition. These include angina scores, treadmill tests and quality of life ratings. Both of these classes of end-points have shortcomings. Hard events like the MACE criteria often require large numbers of patients and an extended timeframe to achieve results with statistical significance. Furthermore, they tend to be binary indicators for a given patient and give little information of relative gains or losses during a treatment period. The subjective end-points have the strong shortcoming that they can be influenced by investigator or patient bias, for example the well-known placebo effect for measures relying on patient self-reporting.

Medical imaging techniques in cardiology, such as magnetic resonance imaging (MRI), computed tomography (CT), ultrasound and nuclear techniques like single photon emission computed tomography (SPECT), positron emission tomography (PET) and multi-gated acquisition blood pool (MUGA) have now progressed to the

Correspondence: Gregory J. Klein, Quantificare, Inc., 375 Cavour Street, Oakland, CA 94618, USA. Email: gregory.klein@quantificare.com

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.1080/13547500500216934

point where they have become accepted primary and secondary efficacy end-points in clinical trials. Imaging techniques like these have a number of advantages over the other methods previously mentioned. They may be used to obtain objective, quantitative measures of treatment efficacy, not prone to investigator bias or the placebo effect. For each patient, they often can provide a scaled response, not just a binary indicator and, therefore, can provide a more detailed measure of effects and more sensitive assessment of dosage effects. They may also often be used in a compressed time scale, since changes can usually be detected in the image data before hard events occur.

This article will review the latest imaging techniques used in cardiology clinical trials. It will discuss important factors in image end-point selection and weigh the pros and cons of available imaging modalities. Finally, it will discuss some of the most recent advancements in quantitative assessment of cardiac SPECT, which is a technique offering a number of important advantages compared to other imaging modalities being applied to clinical trials.

Image-based end-points

Image-based end-points in cardiology can be classed into two main groups. The first of these are those techniques that image and allow quantification of anatomical structure. Anatomical structure for cardiac imaging is based primarily on image data that can resolve the boundaries of the left ventricle. Imaging modalities such as MRI, CT, ultrasound, SPECT and PET can all resolve the inner and outer boundaries of the left ventricle. Additional information can be obtained if separate images can be obtained for different phases of the cardiac cycle. Probably the most common end-point based on anatomical information is cardiac ejection fraction, 1 – (DV-SV)/DV, where DV equals the left ventricular volume at end diastole and SV equals the left ventricular volume at end systole. The gold standard for ejection fraction is now gated MRI, which can clearly show the boundaries of the left ventricle at a very high spatial and temporal resolution, though currently other imaging techniques are usually used because of practicality. Access to images at higher temporal resolution also makes possible other anatomical function measurements such as regional wall motion, peak filling rates and calculation of regional left ventricular stress and strain. Anatomical end-points possible using a single time frame include regional wall thickness, end-diastolic volume and myocardial mask.

A second class of image end-points is one that characterizes ventricular *tissue* function. Typically, these are imaged using nuclear techniques, such as SPECT and PET. The nuclear tracers have the advantage over other techniques in that they may be custom designed to characterize desired parameters of interest, for example blood flow (myocardial perfusion), tissue metabolism, tissue death or inflammatory response. Recent developments in tracer technologies for MRI, ultrasound and CT also show promise, particularly for quantifying myocardial blood flow. For characterization of treatments for coronary artery disease, image-based measurements of myocardial tissue blood flow is an extremely important imaging end-point. Imaging tracers to quantify regions of abnormally reduced myocardial perfusion, called myocardial perfusion defects, have now been used in many clinical trials using SPECT. Experimental results have also been obtained using gadolinium contrast-enhanced MRI or contrast-enhanced ultrasound to quantify myocardial perfusion. Another important end-point evaluating tissue function are markers of tissue

Table I. Summary of common anatomical and functional end-points used in cardiology.

	Imaging modalities used
Structural/anatomical end-points	
End-point	
Ejection fraction	planar X-ray ventriculography, MUGA, gated MRI, gated SPECT, gated PET, ultrasound, 3D ultrasound, gated CT
End diastolic volume	gated MRI, gated SPECT, gated PET, ultrasound, 3D ultrasound
Regional wall motion	MRI, ultrasound, gated SPECT, gated PET, 3D ultrasound
Myocardial mass	gated MRI, SPECT, PET, ultrasound, CT
Peak filling rate	ultrasound, MUGA
Regional wall stress and strain	tagged MRI, Doppler 2D and 3D ultrasound
Functional tissue end-points	
Myocardial perfusion (infarct size, infarct severity)	99m-Tc or 201-Tl SPECT, O2 or 82Rb PET, Gd-enhanced MRI, contrast ultrasound
Myocardial metabolism	FDG PET, 201-Tl SPECT, Gd-enhanced MRI
Myocardial infarction markers	SPECT, PET

metabolism, often called viability markers. PET imaging using the glucose-analogue tracer 18-FDG is the gold standard for assessing myocardial viability. SPECT imaging using 201-Thallium is also often frequently used as a viability marker in clinical trials.

Table I summarizes the main image-based cardiac end-points now in use in clinical trials and research, as well as the imaging modalities most commonly used to quantify them.

Modality comparison

Important factors in comparing modalities

A number of factors must be considered in judging the most appropriate imaging modality for a given task. Among these factors are the following:

Clinical relevance. The most important parameter to consider is whether the image data has documented clinical relevance for the medical therapy under consideration.

Practical issues. These include such parameters as the cost of the imaging study, the invasiveness and medical risk to the patient for the imaging procedure and the availability of the imaging technique at clinical centres.

Validation of the technique and acceptance by the scientific community. This includes such factors as the sensitivity and specificity and the reproducibility of the quantification technique. These can be very dependant on inherent imaging characteristics of each modality discussed next.

Inherent imaging characteristics. Many factors play a role in the ability of a particular imaging modality to provide a reliable quantitative endpoint. Certainly, the spatial and temporal resolution are important parameters. As previously discussed, the targeted aspect of the heart to be imaged is also important. In some cases, anatomical boundaries are important, in others, functional tissue parameters are more important. Also important for obtaining reliable measurements are some rather subtle factors

intrinsic to the image acquisition process. For example, whether the field of view is obtained simultaneously as a 3D volume, as in PET, or as a slice-by-slice series of 2D views, as in conventional ultrasound, can have a dramatic impact on the reproducibility of quantification techniques. Likewise, the amount of training required by an imaging technologist to obtain good images is also important. The time required to obtain a suitable image for quantification can also be an issue, since long acquisition times can bring about image artifacts due to patient motion.

Table II summarizes the important characteristics for the most common imaging techniques used in clinical trials. The relative advantages and disadvantages of each modality are summarized below.

MRI

MRI is now widely available in most clinical centres. MRI offers several advantages for imaging in cardiology. Images have extremely high spatial resolution for accurate identification of anatomical features. Temporal resolution can be very high, where a 10–20 minute acquisition can result in a full 3D volume of the heart divided into 8–16 time frames per cardiac cycle. These characteristics make MRI the current gold standard for ejection fraction calculations. In addition, specialized acquisition protocols for MRI can offer further advantages. Injection of a contrast agent during an acquisition, typically a gadolinium compound, can make MRI imaging capable of showing tissue perfusion and viability. The use of a specialized imaging technique called MRI tagging can create image data with landmarks that can be easily tracked to allow computation of myocardial stress and strain.

However, the MRI technology has a number of disadvantages. Perhaps the greatest is that it can only be used on a limited patient population. Currently, it is not advised that MRI imaging be used on patients with pacemakers or with implantable cardiac defibrillators due to the high magnetic fields used in MRI. Imaging with MRI often requires the patient to hold their breath for extended periods, which can further limit the available patient population, particularly for patients with severe heart disease. Other disadvantages include the high cost of MRI imaging and the high complexity in data analysis. Finally, for recent developments such as MRI perfusion imaging, the techniques are not yet viewed as being fully validated and are currently being treated as a research tool by most of the scientific community.

Ultrasound

Ultrasound is another technique offering high spatial and temporal resolution, much like MRI. A very important advantage of ultrasound is that it is extremely accessible

Table II. Characteristics of common imaging techniques using in cardiology and relative ratings of availability, cost and acceptance ($-$ =poor, 0 =average, $+$ =good, $++$ =excellent).

Image modality	Main application	Availability	Cost	Acceptance and reproducibility
SPECT	Defect size, ejection frac (EF)	$+$	$+$	$++$
PET	Viability	0	$-$	$+$
Ultrasound	EF, wall thickness	$++$	$++$	0
MRI	EF, wall thickness	$+$	$-$	$-$
CT	EF, wall thickness	$-$	$-$	$-$

and relatively inexpensive for most clinical sites. Ultrasound machines are usually portable and can be transported into a patient's room for more convenient imaging.

The main disadvantage of ultrasound is its lack of reproducibility due the 2D nature of the acquisition process and the high degree of variability that can be induced by a poorly trained imaging technician. Ultrasound data are acquired using a probe that is manually maneouvered by a technician. A series of 2D images are acquired in this fashion and the orientation of each acquired plane is completely a function of the position of a hand-held imaging probe. In order to calculate volumetric information, such as ejection fraction measures, geometric assumptions must be made and accuracy is extremely dependant on the training of the imaging technician.

Recent developments are making possible true 3D acquisition of ultrasound data using specialized imaging probes. These new devices may produce extremely accurate and reproducible data; however, the technology is still quite immature and needs considerable validation work before it can be used in clinical trials.

PET

PET is a technique that makes use of a radioactive tracer injected into the patient, then imaged with a camera called a tomograph, which detects the decaying radiotracers as they distribute into the various locations of the body. Although images from PET do not have quite the high spatial resolution of MRI, PET has the important advantage that it can image functional characteristics like perfusion and metabolism and can be used to obtain accurate quantitative values of these entities. Most other imaging techniques can only offer relative measurements of such quantities, where data generally must be normalized using the image regions where tissue is assumed to be normal. For this reason, PET is viewed as the gold standard for myocardial perfusion and metabolism measurements (Jadvar et al. 1999). PET also offers the advantage that it can simultaneously image both functional tissue data as well as anatomical data, for example measurements of perfusion and metabolism as well as ejection fraction.

Disadvantages of PET include the limited availability of PET imaging centres, the high cost compared to other imaging techniques, high complexity of obtaining quantitative measurements and the somewhat limited spatial resolution compared to some other imaging techniques like MRI, ultrasound or CT.

SPECT

SPECT is a nuclear imaging technique closely related to PET and, therefore, has similar advantages in that it can simultaneously image functional tissue and anatomical information. It relies upon isotopes that decay at a lower energy and can be detected using somewhat simpler imaging technology. Consequently, costs of SPECT are generally much less than for PET and the availability of SPECT is much larger than for PET in cardiology. Perfusion SPECT has widespread usage in the US. Over 6 million procedures were carried out in 2002. Furthermore, there has been a great base of validation data published for SPECT.

Disadvantages of SPECT include the relatively low spatial resolution compared to other techniques, moderate, but not low cost, complications in quantification due to the presence of considerable image noise and a difficulty in obtaining absolute quantification of tissue perfusion or other uptake values due to a lack of attenuation

correction. However, it is this author's opinion that when the pros and cons of SPECT are weighed against other imaging modalities, it is currently the most powerful and trusted imaging technique for use in cardiology clinical trials today.

Other modalities

Numerous other imaging modalities also exist that are not discussed in detail in this paper. CT, for example, is becoming a powerful technique capable of producing extremely high resolution images for use in calculating ejection fraction, perfusion values using contrast media and data to obtain calcium scores of coronary arteries. However, cardiac CT is still viewed by most as immature technology. Furthermore, the X-ray dose to a patient during a single cardiac CT scan can be quite high. Intravascular ultrasound (IVUS) is another powerful imaging technique in widespread usage for the specialized application of visualizing and quantifying coronary artery blockages. Planar X-ray angiography still has widespread use for this application as well.

Recent advances in cardiac SPECT

Cardiac SPECT is a clear example of an image-based modality suitable for use as an efficacy measure in clinical trials. Numerous references now point to the fact that SPECT perfusion and/or gated SPECT functional imaging can be used for risk stratification, for prediction of patient outcome and for improved patient management. Benefits of information derived from SPECT examinations have been shown in patients in stable condition, with unstable angina and after acute myocardial infarction. The following are recent examples for patients at risk (Ladenheim et al. 1986, Berman et al. 1995, Heller et al. 1995, Dakik et al. 1998, Hachamovit ch et al. 1998, 2002, 2003, Mandalapu et al. 1999, Allman et al. 2002) and for post-myocardial infarction survival (Travin et al. 1995, Miller et al. 1998, Gibbons et al. 2000, Spinelli et al. 2003).

Furthermore, SPECT has considerable past precedence in clinical trials. Examples of past usage include the following examples in angiogenesis or myogenesis therapies (Udelson et al. 2000, Vale et al. 2001, Assmus et al. 2002, Simons et al. 2002, Strauer et al. 2002, Fuchs et al. 2003, Grines et al. 2003, Kastrup et al. 2003, Perin et al. 2003, Stamm et al. 2003), in thrombolytic therapies (Mahaffey et al. 1999, Schomig et al. 2000, Baran et al. 2001, Dong et al. 2002, Kastrati et al. 2002, Kopecky et al. 2003) and in laser therapies (Frazier et al. 1995, 1999).

Until recently, the state of the art for quantification of SPECT image data was to use a 'semi-quantitative expert rated' approach. In this approach, four views of the heart are generally presented to an expert reader: a long axis view and three short axis views. These views are divided into 17 segments. For each imaging study, the expert grader rated the perfusion level of each segment on a 5-point scale where 4 represents no perfusion and 0 represents normal perfusion. This technique has the advantage that it makes use of the experience of an expert reader; however, reproducibility for the quantitative technique can be low unless extreme efforts are made to monitor and train the reader to ensure consistent gradings.

Recent advancements in image processing have made possible completely automated quantification of SPECT perfusion defect size and severity (Garcia et al. 1990,

Germano et al. 2000, Slomka et al. 2001, 2004). By aligning all imaging in 3D to a population model computed from scans obtained from normal subjects and by normalizing image intensities using a linear regression between regions of the image representing normal cardiac tissue and the corresponding location in the population model, a statistical analysis can be made of each heart image. Resulting parameters include an automatically calculated region of significant defect area and a quantitative value for the severity of the defect (Itti et al. 2004). Perhaps more importantly, access to methods that allow accurate spatial resolution between image data obtained at two time points, baseline and follow-up, allow precise calculation of the perfusion gains and losses that occur during a treatment period. It has been shown that using this type of technology can improve the reproducibility of quantification and reduce the number of patients required in a trial to obtain statistical significance by a factor of two (Klein et al. 2004).

Concluding remarks

Medical imaging has now progressed to the point where it can serve as a valuable primary and secondary end-point in clinical trials. For cardiology applications, SPECT currently has great precedence in past clinical trials. Other evolving technologies such as contrast enhanced MRI and CT, PET and 3D ultrasound will present new opportunities for use in clinical trials, offering increased accuracy of therapeutic effect in a reduced timeframe.

References

Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. 2002. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. Journal of the American College of Cardiology 39:1151–1158.

Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N, Grunwald F, Aicher A, Urbich C, Martin H, et al. 2002. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation 106:3009–3017.

Baran KW, Nguyen M, McKendall GR, Lambrew CT, Dykstra G, Palmeri ST, Gibbons RJ, Borzak S, Sobel BE, Gourlay SG, et al. 2001. Double-blind, randomized trial of an anti-CD18 antibody in conjunction with recombinant tissue plasminogen activator for acute myocardial infarction: limitation of myocardial infarction following thrombolysis in acute myocardial infarction (LIMIT AMI) study. Circulation 104:2778–2783.

Berman DS, Hachamovitch R, Kiat H, Cohen I, Cabico JA, Wang FP, Friedman JD, Germano G, Van Train K, Diamond GA. 1995. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. Journal of the American College of Cardiology 26:639–647.

Dakik HA, Kleiman NS, Farmer JA, He ZX, Wendt JA, Pratt CM, Verani MS, Mahmarian JJ. 1998. Intensive medical therapy versus coronary angioplasty for suppression of myocardial ischemia in survivors of acute myocardial infarction: a prospective, randomized pilot study. Circulation 98:2017–2023.

Dong J, Ndrepepa G, Schmitt C, Mehilli J, Schmieder S, Schwaiger M, Schomig A, Kastrati A. 2002. Early resolution of ST-segment elevation correlates with myocardial salvage assessed by Tc-99m sestamibi scintigraphy in patients with acute myocardial infarction after mechanical or thrombolytic reperfusion therapy. Circulation 105:2946–2949.

Frazier OH, Cooley DA, Kadipasaoglu KA, Pehlivanoglu S, Lindenmeir M, Barasch E, Conger JL, Wilansky S, Moore WH. 1995. Myocardial revascularization with laser. Preliminary findings. Circulation 92:II58–65.

Frazier OH, March RJ, Horvath KA. 1999. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. New England Journal of Medicine 341:1021–1028.

Fuchs S, Satler LF, Kornowski R, Okubagzi P, Weisz G, Baffour R, Waksman R, Weissman NJ, Cerqueira M, Leon MB, Epstein SE. 2003. Catheter-based autologous bone marrow myocardial injection in no-option patients with advanced coronary artery disease: a feasibility study. Journal of the American College of Cardiology 41:1721–1724.

Garcia EV, Cooke CD, Van Train KF, Folks R, Peifer J, DePuey EG, Maddahi J, Alazraki N, Galt J, Ezquerra N, et al. 1990. Technical aspects of myocardial SPECT imaging with technetium-99m sestamibi. American Journal of Cardiology 66:23E–31E.

Germano G, Kavanagh PB, Waechter P, Areeda J, Van Kriekinge S, Sharir T, Lewin HC, Berman DS. 2000. A new algorithm for the quantitation of myocardial perfusion SPECT. I: technical principles and reproducibility. Journal of Nuclear Medicine 41:712–719.

Gibbons RJ, Miller TD, Christian TF. 2000. Infarct size measured by single photon emission computed tomographic imaging with (99m)Tc-sestamibi: a measure of the efficacy of therapy in acute myocardial infarction. Circulation 101:101–108.

Grines CL, Watkins MW, Mahmarian JJ, Iskandrian AE, Rade JJ, Marrott P, Pratt C, Kleiman N. 2003. A randomized, double-blind, placebo-controlled trial of Ad5FGF-4 gene therapy and its effect on myocardial perfusion in patients with stable angina. Journal of the American College of Cardiology 42:1339–1347.

Hachamovitch R, Berman DS, Kiat H, Cohen I, Friedman JD, Shaw LJ. 2002. Value of stress myocardial perfusion single photon emission computed tomography in patients with normal resting electrocardiograms: an evaluation of incremental prognostic value and cost-effectiveness. Circulation 105:823–829.

Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. 1998. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 97:535–543.

Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. 2003. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 107:2900–2907.

Heller GV, Herman SD, Travin MI, Baron JI, Santos-Ocampo C, McClellan JR. 1995. Independent prognostic value of intravenous dipyridamole with technetium-99m sestamibi tomographic imaging in predicting cardiac events and cardiac-related hospital admissions. Journal of the American College of Cardiology 26:1202–1208.

Itti E, Klein G, Rosso J, Monin JL, Gueret M, Meignan M, Thirion JP. 2004. Assessment of myocardial reperfusion after myocardial infarction using automatic three-dimensional quantification and template matching. Journal of Nuclear Medicine 45:1981–1988.

Jadvar H, Strauss HW, Segall GM. 1999. SPECT and PET in the evaluation of coronary artery disease. Radiographics 19:915–926.

Kastrati A, Mehilli J, Dirschinger J, Schricke U, Neverve J, Pache J, Martinoff S, Neumann FJ, Nekolla S, Blasini R, et al. 2002. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. Lancet 359:920–925.

Kastrup J, Jorgensen E, Ruck A, Tagil K, Hesse B, Ruzyllo W, Glogar D, Gyongyosi M, Bother H, Dudek D, et al. 2003. Gene therapy with phVEGF-A165 in severe ischemic heart disease: The euroinject one trial. Presented at American College of Cardiology 52nd Annual Scientific Session, Chicago, IL.

Klein GJ, Thirion JP, Hendel R. 2004. Reduced variability in myocardial perfusion defect severity measures using 3D template-based methods. Journal of Nuclear Medicine 45.

Kopecky SL, Aviles RJ, Bell MR, Lobl JK, Tipping D, Frommell G, Ramsey K, Holland AE, Midei M, Jain A, et al. 2003. A randomized, double-blinded, placebo-controlled, dose-ranging study measuring the effect of an adenosine agonist on infarct size reduction in patients undergoing primary percutaneous transluminal coronary angioplasty: the ADMIRE (AmP579 Delivery for Myocardial Infarction REduction) study. American Heart Journal 146:146–152.

Ladenheim ML, Pollock BH, Rozanski A, Berman DS, Staniloff HM, Forrester JS, Diamond GA. 1986. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. Journal of the American College of Cardiology 7:464–471.

Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, Eisenberg PR, Bolli R, Casas AC, Molina-Viamonte V, et al. 1999. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. Journal of the American College of Cardiology 34:1711–1720.

Mandalapu BP, Amato M, Stratmann HG. 1999. Technetium Tc 99m sestamibi myocardial perfusion imaging: current role for evaluation of prognosis. Chest 115:1684–1694.

Miller TD, Hodge DO, Sutton JM, Grines CL, O'Keefe JH, DeWood MA, Okada RD, Fletcher Jr WO, Gibbons RJ. 1998. Usefulness of technetium-99m sestamibi infarct size in predicting posthospital mortality following acute myocardial infarction. American Journal of Cardiology 81:1491–1493.

Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, Rossi MI, Carvalho AC, Dutra HS, Dohmann HJ, et al. 2003. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation 107:2294–2302.

Schomig A, Kastrati A, Dirschinger J, Mehilli J, Schricke U, Pache J, Martinoff S, Neumann FJ, Schwaiger M. 2000. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus thrombolysis for occluded coronary arteries in patients with acute myocardial infarction study investigators. New England Journal of Medicine 343:385–391.

Simons M, Annex BH, Laham RJ, Kleiman N, Henry T, Dauerman H, Udelson JE, Gervino EV, Pike M, Whitehouse MJ, et al. 2002. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: double-blind, randomized, controlled clinical trial. Circulation 105:788–793.

Slomka PJ, Nishina H, Berman DS, Kang X, Friedman JD, Hayes SW, Aladl UE, Germano G. 2004. Automatic quantification of myocardial perfusion stress-rest change: a new measure of ischemia. Journal of Nuclear Medicine 45:183–191.

Slomka PJ, Radau P, Hurwitz GA, Dey D. 2001. Automated three-dimensional quantification of myocardial perfusion and brain SPECT. Computer Medical Imaging Graph 25:153–164.

Spinelli L, Petretta M, Acampa W, He W, Petretta A, Bonaduce D, Cuocolo A. 2003. Prognostic value of combined assessment of regional left ventricular function and myocardial perfusion by dobutamine and rest gated SPECT in patients with uncomplicated acute myocardial infarction. Journal of Nuclear Medicine 44:1023–1029.

Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, Schumichen C, Nienaber CA, Freund M, Steinhoff G. 2003. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet 361:45–46.

Strauer BE, Brehm M, Zeus T, Kostering M, Hernandez A, Sorg RV, Kogler G, Wernet P. 2002. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 106:1913–1918.

Travin MI, Dessouki A, Cameron T, Heller GV. 1995. Use of exercise technetium-99m sestamibi SPECT imaging to detect residual ischemia and for risk stratification after acute myocardial infarction. American Journal of Cardiology 75:665–669.

Udelson JE, Dilsizian V, Laham RJ, Chronos N, Vansant J, Blais M, Galt JR, Pike M, Yoshizawa C, Simons M. 2000. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 improves stress and rest myocardial perfusion abnormalities in patients with severe symptomatic chronic coronary artery disease. Circulation 102:1605–1610.

Vale PR, Losordo DW, Milliken CE, McDonald MC, Gravelin LM, Curry CM, Esakof DD, Maysky M, Symes JF, Isner JM. 2001. Randomized, single-blind, placebo-controlled pilot study of catheter-based myocardial gene transfer for therapeutic angiogenesis using left ventricular electromechanical mapping in patients with chronic myocardial ischemia. Circulation 103:2138–2143.