

CHAPTER 18

QUALITATIVE ANGIOGRAPHIC CORE LABORATORY PROCEDURES

18.1 SPECIFIC AIMS AND PURPOSES

The principal purposes of the Qualitative Angiography Core Laboratory are: 1) to identify and confirm certain angiographic end point(s); 2) to judge the suitability of patients for coronary angioplasty; and (3) to assess the outcome of coronary angioplasty in the T3B protocol. Specific aims are as follows:

1. To determine the extent of coronary narrowing (secondary T3B end point).
2. To detect the presence and extent of intracoronary thrombus and its response to therapy.
3. To evaluate the suitability of coronary lesions for PTCA.
4. To determine the outcome of PTCA.
5. To assess the quality of the cineangiographic technique.
6. To assist in the development of the study design and angiographic end point(s) of the protocol.
7. To train and certify T3 investigators.

18.2 SIGNIFICANCE OF THE QUALITATIVE ANGIOGRAPHIC CORE LABORATORY

The ability of t-PA to reduce the severity of coronary narrowing and the extent of angiographically-detectable intracoronary thrombus will be assessed visually by the Qualitative Angiographic Core Laboratory. Knowledge of the effects of this agent upon such end points will be of importance when analyzing the final outcome of the trial. For example, should t-PA not demonstrate a positive effect on the initial therapy composite primary end point, determination of the extent to which thrombus persisted, as determined from analysis of the placebo-treated group randomized to routine early angiography, will be of value in the interpretation of the results. Should t-PA be effective in improving clinical outcome, yet no effect be observed upon epicardial coronary artery narrowing, then an action upon the distal coronary circulation might be postulated.

The angiographic end point of extent and severity of coronary narrowing, the presence of intracoronary thrombus, and global left ventricular function could be obtained from clinic site interpretations alone. Such angiographic features, however, are subject to substantial inter- and intraobserver

variability. A Core Laboratory assessment assures the unbiased interpretation of these important end point(s) in a uniform and standardized fashion.

One of the comparisons to be made in T3 is the strategy of invasive versus conservative revascularization. Invasive Strategy includes ventricular and coronary cineangiography performed within 24 to 48 hours with revascularization, if indicated, while the Conservative Strategy entails angiography with revascularization only after failure of initial therapy. PTCA has been recommended as an efficacious therapy for patients with unstable angina and non-Q-wave myocardial infarction. Although the value of PTCA for such patients, and particularly those with multivessel disease, is not well established, acute ischemia in such patients can often be attributed to one severely narrowed coronary artery. By relieving significant coronary obstruction in this single "culprit" artery, PTCA has the potential for providing immediate clinical stabilization and rendering a severely ill patient asymptomatic. To what extent PTCA can accomplish this goal in either the short- or long-term is unclear and warrants investigation.

The Qualitative Angiography Core Laboratory will assume a major role in the refinement of guidelines for the performance of cardiac catheterization, coronary angioplasty, and coronary bypass surgery in T3B patients. The Core Laboratory will monitor the use of PTCA in the trial by reviewing angiograms of each patient randomized to Invasive Strategy. In addition to interpreting coronary anatomy, a judgment will be made as to the suitability of each patient for PTCA. Furthermore, if PTCA is performed, the outcome of the procedure will be assessed. The percent of coronary narrowing and perfusion status before and following the procedure, and the occurrence of any untoward events such as coronary dissection, embolization, or patients undergoing nonprotocol catheterization procedures would also be reviewed.

These efforts will ensure that PTCA is performed properly in patients assigned to Invasive Strategy. The outcome of a PTCA procedure is very much operator-dependent. Inappropriately performed PTCA, that is, PTCA that is associated with an unacceptably low success rate or high complication rate, could result in a negative treatment effect not because the intervention is ineffective, but because it was applied in an improper or inadequate manner. The Qualitative Angiographic Core Laboratory will participate in the certification of T3 PTCA operators and will monitor procedural outcome throughout the course of the trial.

18.3 CERTIFICATION PROCESS

For new Clinical Centers, a formal certification process will be initiated prior to patient recruitment. Each new operator will submit cineangiograms of five successful PTCA cases in addition to a record of his/her personal PTCA experience. Angiograms will be reviewed in terms of cine quality as well as angiographic and PTCA technique and the outcome of PTCA. This process has been employed successfully in TIMI II.

18.4 CARDIAC ANGIOGRAPHY

A uniform standardized protocol will be employed for performing left ventriculography and coronary cineangiography. A suggested sequence of angiography and projections is listed below.

1. Left Ventriculography
 - a. 35B RAO, 7, 9 or 10" modes
 - b. 60B LAO, 20B cranial (optional)
2. Native Coronary Arteriography (5, 6 or 7")
 - a. Left Coronary Artery
 - (1) LAO 40B / caudal 20B
 - (2) LAO 40B / cranial 25B
 - (3) LAO 90B
 - (4) RAO 25B / caudal 20B
 - (5) RAO 5B / cranial 40B
 - b. Right Coronary Artery
 - (1) LAO 60B
 - (2) RAO 35B
 - (3) LAO 30B / cranial 15B (optional)

When possible, left ventricular and coronary angiographic studies of T3 patients should follow this protocol. Minor variations of projections and additional views are acceptable to optimize visualization of coronary arteries.

18.5 INTERPRETATION AND REVIEW OF CINEANGIOGRAMS

18.5.1 Quality Assurance

Interpretation of each cineangiogram by the Core Laboratory will begin with an assessment of film quality. A film quality score will be assigned in order to monitor performance, detect deficiencies and identify trends. The results of these assessments will be made available to the Study Chairman, the Data Coordinating Center (DCC) and individual clinical sites. Variables to be

assessed include not only film quality but also angiographic technique, and are listed below.

1. Scoring System
 - a. Unacceptable - end point data unobtainable
 - b. Acceptable
 - c. Superior
2. Criteria for Film Quality
 - a. Radiographic contrast
 - b. Radiographic blurring
 - c. Radiographic mottle
 - d. Artifacts
3. Criteria for Angiographic Quality
 - a. Injection adequacy
 - b. Display of stenosis(es)
 - c. Vessel overlap
 - d. Requisite projections
 - e. Panning - Excessive or inappropriate
 - f. Collimation
 - g. Inclusion of all vessel segments

18.5.2 Angiographic End Points

Both the left ventriculogram and the coronary cineangiogram will be reviewed to determine certain angiographic end point (Exhibits 18-1 - 18-6). The left ventriculogram will be assessed visually to determine global and regional systolic function with attention directed to identifying regions of hypocontractility. Each major coronary arterial system will then be reviewed to determine certain anatomic characteristics as described in Exhibit 18-1. Following review of the ventriculogram, coronary angiogram, and the 12-lead electrocardiogram, a judgment will be made as to the identification of the culprit artery(ies): i.e., the artery(ies) most likely responsible for the acute ischemic syndrome. A judgment will also be made as to the anatomic suitability of the patient for either PTCA or CABG in accordance with the T3 guidelines. Should PTCA be performed, the cineangiographic results of the procedure will be assessed in terms of the degree of coronary narrowing following the procedure and the occurrence of any untoward event, such as artery closure, embolization and major dissection. These interpretations will be recorded on a standardized form (7F) and sent to the DCC.

Should discrepancies be noted between the Core Laboratory and clinic interpretations, the Core Laboratory will be notified and the cineangiogram will be re-read by a second Angiography Reader. Persistent discrepancies between the clinical site and the Core Laboratory will be adjudicated by a PTCA/Angiography Committee appointed by the Operations Committee. This mechanism of quality control was employed successfully in the TIMI II Trial.

18.6 SUBMITTING ANGIOGRAMS/ANGIOPLASTY FILMS

Once patients are enrolled, T3B angiograms and angioplasty films should be sent as soon as clinically appropriate with the left ventriculogram, copies of the qualifying or ischemic and baseline ECGs and the T3B Shipment Log (Exhibit 18-7) to the Qualitative Angiography Core Laboratory. Film canister/container labels will be provided by the DCC. Canister/containers should be labeled with patient's ID number, NAME CODE, Clinical Center, date/time of procedure and the procedure performed (i.e., diagnostic angiogram or PTCA).

Submit films to: Paula E. Ferreira, R.N.
T3B Qualitative Core Lab
Rhode Island Hospital
593 Eddy Street
APC Building, Room 981
Providence, Rhode Island 02902

Address labels will also be provided by the DCC.

18.7 CORE LAB PROCEDURES

All films and accompanying materials will be logged in when received. A T3 angiographer will evaluate all materials submitted, review and interpret films and document their findings on T3 form 7F. This form will then be forwarded to the Data Coordinating Center.

18.8 FILM TURN-AROUND TIME

Films will be retained by the Core Lab no more than 20 working days before returning them to the clinical sites. Films needed emergently can be obtained overnight by calling Paula Ferreira, R.N., at (401) 277-4214 or (401) 277-5324 (answering machine).

EXHIBIT 18-1

END POINTS TO BE DETERMINED BY QUALITATIVE
ANGIOGRAPHY CORE LABORATORY

1. Global and regional left ventricular systolic function.
2. Location of coronary narrowing.
3. Severity of coronary narrowing.
4. Morphology of coronary narrowing.
5. Coronary perfusion status (Exhibit 18-2).
6. Presence and extent of intracoronary thrombus (Exhibit 18-3).
7. Presence and extent of coronary collateral circulation (Exhibit 18-4).
8. Identification of the ischemia-related artery.
9. Anatomic suitability for PTCA.
10. Outcome of PTCA (Exhibit 18-5).

EXHIBIT 18-2

T3 PERFUSION GRADE

- Grade 0 No perfusion No antegrade flow beyond the point of occlusion.
- Grade 1 Penetration without perfusion The contrast material passes beyond the area of obstruction, but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run.
- Grade 2 Partial perfusion The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.
- Grade 3 Complete perfusion Antegrade flow into the bed distal to the obstruction occurs as promptly as into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed in the same vessel or the opposite artery.

EXHIBIT 18-3

ASSESSMENT OF INTRACORONARY THROMBUS

- Grade 0 No thrombus present. No cineangiographic characteristics suggestive of thrombus.
- Grade 1 Possible thrombus present. Angiography demonstrates characteristics such as reduced contrast, density, haziness, irregular lesion contour or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus.
- Grade 2 Thrombus present - small size: Definite thrombus with greatest dimensions $\leq 1/2$ vessel diameter.
- Grade 3 Thrombus present - moderate size: Definite thrombus but with greatest linear dimension $> 1/2$ but less than 2 vessel diameters.
- Grade 4 Thrombus present - large size: As in Grade 3 but with largest dimension ≥ 2 vessel diameters.

EXHIBIT 18-4

CORONARY ARTERY COLLATERAL CIRCULATION ANGIOGRAPHIC ASSESSMENT

- Grade 0 No collaterals present, angiography fails to reveal evidence of collateral vessels.
- Grade 1 Minimal collaterals present, evidence of minimal to partial filling of the recipient artery.
- Grade 2 Well-developed collaterals. Evidence of collateral circulation with near complete to complete filling of recipient artery.

EXHIBIT 18-5

PTCA OUTCOME

- Full Improvement:
- a) . Post-PTCA < 60% stenosis.
 . and \geq 20% decrease in stenosis.
 . and perfusion grade 3.
 - b) . Post-PTCA < 60% stenosis.
 . and \geq 20% decrease in stenosis.
 . and change in perfusion grade from 0 or 1 to 2.
- Partial Improvement:
- a) . Post-PTCA < 60% stenosis or \geq 20% decrease in stenosis.
 . and perfusion grade 0 or 1 improves to 2 or 3.
 or perfusion grade 2 improves to 3.
 or perfusion grade 3 remains 3.
- No Improvement - All Others, e.g.
- a) . Post-PTCA stenosis \geq 60% and < 20% decrease in stenosis.
 - b) . Post-PTCA stenosis < 60% or \geq 20% decrease in stenosis but perfusion grade worse.

EXHIBIT 18-6

QUANTITATIVE EVALUATION OF LEFT VENTRICULAR FUNCTION

QUANTITATIVE EVALUATION OF LEFT VENTRICULAR FUNCTION

RAO Projection

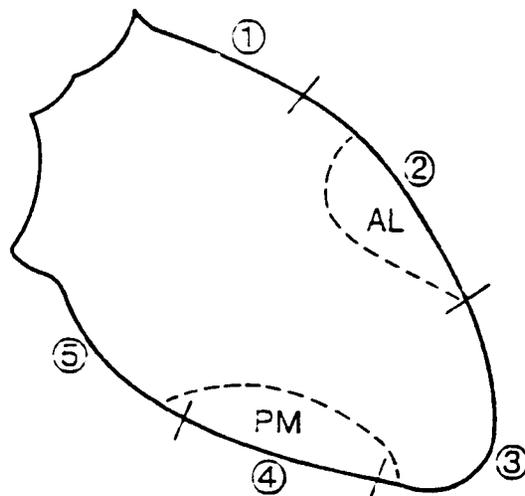


Figure 10-4 Nomenclature for identifying the left ventricular segments in the right anterior oblique projection as set forth by the American Heart Association in Circulation, 51:5-40, 1975. 1 = Anterobasal, 2 = Anterolateral, 3 = Apical, 4 = Diaphragmatic, 5 = Posteroobasal, AL = Anterolateral, PM = Posteroobasal.

LAO Projection

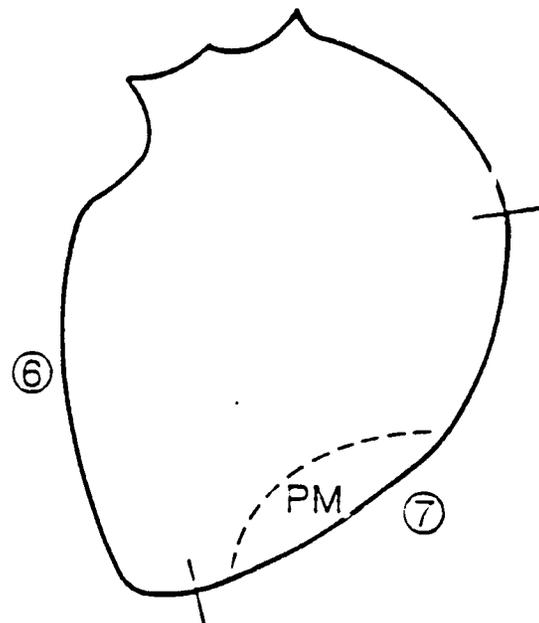


Figure 10-5 Nomenclature for identifying the left ventricular segments in the left anterior oblique projection as set forth by the American Heart Association in Circulation, 51:5-40, 1975. 6 = Septal, 7 = Posterolateral.

TIMI IIIB QUALITATIVE CORE LAB SHIPMENT SHEET

CLINICAL CENTER _____ - _____ - _____

DATE _____ / _____ / _____

NAME CODE	TIMI III I.D.#	DATE OF CINEANGIOGRAM	TIME OF CINEANGIOGRAM	ECG'S (CHECK IF INCLUDED)				COMMENTS (FOR CORE LAB USE)
				LV (CHECK IF INCLUDED)	QUALIFYING OR ISCHEMIC (SUBMIT 1)	AND	BASELINE	
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EXHIBIT 18-7

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T3 MANUAL OF OPERATIONS

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* This version is identical to the draft dated 7/01/91, with the exception of page 18-4, which has been revised.