T3 MANUAL OF OPERATIONS

TABLE OF CONTENTS

CHAPTER 16

THALLIUM CORE LABORATORY PROCEDURES

16.1 DATA ACQUISITION

16.1.1 Stress Test

The thallium-201 stress test should be performed within three days prior to discharge from the hospital. If this is not possible, the test may be performed within the five days following hospital discharge. If the patient is unable to exercise on a treadmill at hospital discharge, dipyridamole Thallium-201 imaging should be performed (see Section 16.1.1.2 for details). Thallium tests should be performed at least four hours prior to discharge as redistribution scans are required. If as part of the ancillary study "Additional Resting Thallium Imaging after Pre-discharge/Six-Week T3 Exercise Test" a 24-hour redistribution scan is going to be obtained, the thallium imaging test should be performed at least one day before discharge.

16.1.1.1 Hospital Discharge Exercise Treadmill Test

The patient will be exercising on a motor-driven treadmill using a modified Bruce protocol. The patient should continue to exercise until the completion of Stage II unless one of the following end points occurs: angina, decrease in systolic blood pressure greater than 10 mm Hg from control, and ST-segment deviation $\geq$ 1 mm from baseline. If none of these end points occurs, exercise will be terminated at the completion of Stage II of the modified Bruce protocol. At peak exercise, 2.0 to 2.5 mCi of thallium-201 will be injected via an intravenous line and flushed with 10 ml of saline. The patient will be encouraged to exercise for two more minutes.

16.1.1.2 Pharmacologic Stress (Dipyridamole)

Dipyridamole thallium-201 imaging should be performed if a patient is physically unable to exercise on a treadmill at hospital discharge. A dipyridamole thallium imaging test should also replace the six-week exercise treadmill test if a patient cannot ambulate sufficiently to perform the exercise treadmill test. Patients must stop medications containing xanthine/caffeine for 48 hours prior to this test. These medications include theophylline, aminophylline, cold and allergy tablets, coffee and soft drinks.

16.1.1.2.1 I.V. Dipyridamole Protocol

A total of 0.142 mg/kg/min of dipyridamole will be infused over a four-minute interval. After completion of the infusion the patient could, if able, perform light arm exercise such as lifting a 5-10 lbs weight. Thallium-201 (2.0-2.5mCi) is injected four minutes after completion of the infusion (eight minutes after the start of the procedure). Blood pressure and ECG are monitored each minute until TI-201 is injected.

16.1.1.2.2 Adverse Reaction

Aminophylline must be readily available to treat adverse reactions (chest pain and hypotension) to the dipyridamole. One hundred mg of aminophylline (IV push) should be given first. If symptoms persist, up to 250 mg can be given. Aminophylline must be given > 1 minute after TI-201 is injected to prevent an invalid study. If aminophylline must be given before the TI-201 injection at eight minutes, inject TI-201 early, wait one minute and administer the aminophylline.

16.1.1.2.3 Oral Dipyridamole Protocol

A dose of 375 mg of dipyridamole is ground up and given orally. Blood pressure and ECG are monitored at baseline and every ten minutes for 45 minutes. An injection of 2.0-2.5 mCi of TI-201 will be administered 45 minutes after dipyridamole is taken orally. Aminophylline is administered for adverse reactions in the same manner as described under IV dipyridamole protocol.

Note: Dipyridamole imaging is discouraged, since imaging after pharmacological stress is more equivalent to maximal treadmill exercise than the protocol submaximal predischarge exercise.

16.1.2 Imaging Protocol

Imaging should begin within five minutes after TI-201 is injected (exercise or pharmacologic stress.) The injection site is counted first for 15 seconds to ensure no extravasation of the thallium-201 dose occurred. Planar myocardial imaging will be performed in the left anterior oblique (best separation between right and left ventricle) projection with the patient supine. Subsequently, a left lateral view will be obtained with the patient on his/her right side and finally the anterior projection will be obtained with the patient lying supine. Each image will be obtained for time (eight to ten minutes) containing at least 600K counts per view using a general all-purpose collimator. In addition breast marker images will be obtained of each view on all female patients at stress, and delayed imaging times (see breast marker procedure.) The camera will be peaked using a 25% window on the 80 keV and 20% window on the 167 keV thallium-201 energy peaks. A 1.2 zoom should be used on large field of view cameras. If this zoom option is not available use no zoom. Acquire all studies using 128 X 128 matrix in word mode.
Images will be labeled with the patient's Name Code, ID

Number, and appropriately labeled as Initial, Delayed or 24 Hour with views identified.

16.1.2.1 Delayed Imaging

Delayed images will be obtained two to three hours after exercise and four hours after pharmacologic stress. Images will be obtained using the same parameters as the initial images.

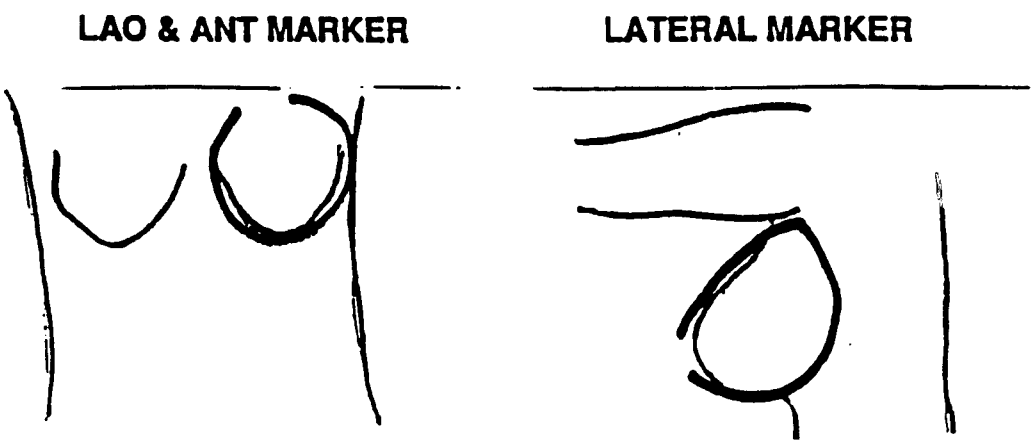
16.1.2.2 Breast Marker

Since breast tissue easily attenuates thallium-201 and causes defects on the images, all female patients will have images taken of a radioactive line source marker outlining the left breast on each view. Images should be acquired for 30 seconds and taken immediately after each view before the patient is moved. Views of breast marker will be obtained at delayed and 24 hour imaging. A cobalt-57 line source marker can be purchased or you can make up your own using 12-inch extension tubing with a stopcock. Fill the tubing with 20-40 uCi of TI-201 mixed in saline. Seal off the tube with tape and you have a line source marker that can be used for a week. The breast should be outlined as shown below.

16.1.2.3 Positioning the Breast Markers

1. LAO and Anterior views: Position the tubing around the periphery of the breast with the ends of the tubing at the top of the breast. Image for 30 seconds or longer if the marker is weak. You don't need to move the marker for the anterior view simply change the angle of the camera (see diagram below).
2. Lateral marker: Position the tubing to follow the breast outline paying particular attention to feel where the breast

tissue ends under the arm. Position the opening of the tubing anteriorly (see diagram below).



16.1.3 Study Interpretation at Clinical Site

The thallium-201 stress images will be qualitatively interpreted at the clinical site. The clinical site reading will be used to determine if patients have "failed therapy." Patients randomized to the conservative strategy will undergo angiography if they fail therapy for the first time with this test.

These qualitative results will be reviewed by Drs. Wackers and Zaret in the Core Laboratory, since the Core Laboratory will perform an independent qualitative analysis of data in addition to the quantitative analysis. In this way, uniform standardized reporting of results is assured, and errors in clinical unit performance will be detected and corrected in a timely manner.

16.2 DATA TRANSFER

Only original data will be stored on floppy disks or magnetic tape. A list of computer media that can be read by the Core Laboratory is given in Section 16.3.1. Each disk or tape will contain a recent flood

and bar phantom and the initial, delayed and 24-hour images labeled with the appropriate Name Code, ID Number and study type as outlined under imaging protocol. The outside of the floppy disk must be labeled: T3, with the patient's Name Code, ID Number, date of study, center name and number, and type of computer media, e.g., ADAC. The disk must be sent with a shipping form to the address below:

T3
Jennifer Mattera
Yale University School of Medicine
Department of Nuclear Cardiology
Fitkin 2, Room 5
333 Cedar St.
New Haven, Connecticut 06510

Phone: (203) 785-4749

16.3 RADIONUCLIDE CORE LABORATORY

16.3.1 Computer Transcription Capabilities

The following are the current computer formats that can be transcribed by Yale University Radionuclide Core Lab:

ADAC	5 1/4 " & 8" Floppy and Mag tape
CDA (Siemens)	5 1/4 " Floppy & VAX Mag tape & Floppy
DEC Gamma 11	8" Floppy and Mag tape
Elscint	8" Floppy (F0 and F1 Format)
GE	Star 8" Floppy & Mag tape, Starcam Floppy
IBM	3 1/2" and 5 1/4" Floppy
MDS	8" Floppy and Mag tape
MicroVAX	TK50 Cartridge and 5 1/4" Floppy
Picker	5 1/4" and 8" Floppy, Mag tape
SIMIS	Floppy
Sopha	5 1/4" Floppy
Technicare	8" Floppy and Mag tape
Toshiba	8" Floppy
VAX	8" Floppy and Mag tape

16.3.2 Certification Process

To ensure quality and standardization of technique each center must be certified by the Yale University Radionuclide Core Lab. To become certified each center must send at least three planar stress TI-201 studies, a camera flood and a bar phantom. One normal study, one abnormal study and one female patient study with breast markers must be performed according to the T3 imaging protocol. If more than one camera and computer will be used for T3 patients, at least one patient study from each is required for certification. Certification

studies and the Radionuclide Core Lab survey form will be sent to Yale University Radionuclide Core Lab (address listed in Section 16.2). The Core Lab will review the studies and determine if (1) the Core Lab is able to read and process the studies, (2) the studies are of sufficient quality for quantification, and (3) the studies are performed according to protocol which ensures uniformity with the other participating centers. When all requirements are met a certification letter will be sent to the center. More detail concerning the certification process can be found in Chapter 5: Section E, T3 Thallium Core Laboratory Certification Requirements, of Volume II of the T3 Manual of Operations.

16.3.3 Data Processing

At Yale University the study will be logged in on arrival and transcribed to a common format for central processing. The study is checked for quality and completeness. The data will be processed using quantitative software which will generate circumferential profiles and quantitate initial, delayed and 24-hour defects by comparison to a normal data base. The generated graphs as well as images are printed on 8 x 10 photographic film and put in the Core Lab patient chart. The studies will be analyzed by Dr. Wackers and/or Dr. Zaret. The analysis form is filled out and sent to MMRI. In case of technical problems with the quality of the study, feedback will be given to the specific clinical site.

16.3.4 Quantification of Thallium-201 Stress/Rest Myocardial Perfusion Images

The quantification of thallium-201 images involves several steps: (1) interpolative background subtraction, (2) generation of circumferential profiles, and (3) quantification of exercise and resting defects by comparison with a normal data base.

16.3.4.1 Interpolative Background Subtraction

Because of the difference in regional distribution of thallium-201 in noncardiac structures, normalization of myocardial activity to

correct for cross-talk and scatter must be performed. After nine-point image smoothing, an elliptical reference region is positioned around the heart to enclose both right and left ventricles. The mean distance from the boundary of the reference region to the visible edge of the myocardium usually averages four pixels. This reference boundary is used for weighted bilinear interpolative background correction. Within the reference boundary, a cardiac background image is generated and is subtracted from the unsmoothed original images, resulting in two myocardial images normalized for differences in background.

16.3.4.2 Segmental Mapping

The left ventricle is outlined on the background-corrected initial image using a joystick, guided by visual inspection following the apparent edge of the left ventricle. This region of interest is also mapped onto the background-corrected delayed image by automated registration and cross-correlation. Both images are automatically rotated to correct for slight differences in positioning. Next, the apex on each view is marked to be used for superimposition of the normal lower limits of normal thallium-201 distribution (derived from a normal data base of 28 low likelihood patients). The geometric center of the region of interest over the left ventricle is determined and aligned with the center of a radial definition map that divides both left ventricles into 36 segments, each of a 10° angle.

16.3.4.3 Circumferential Profiles

Within each segment, thallium-201 activity can be displayed as a functional angle and presented as a circumferential profile. The circumferential profiles contain information about the relative distribution of thallium-201 activity, both on the initial image as well as on the delayed image. Profiles generated over the initial image and delayed image are each normalized to the segment with highest activity. In the process of visual analysis of thallium-201

images, an observer compares radioactivity in various myocardial segments to the segment with the highest activity, which intuitively is assumed to be normal. Experience acquired in reading many scans has taught the observer to appreciate a certain degree of diminished thallium-201 activity as being abnormal or a "defect." A similar process can be graphically displayed on thallium-201 distribution profiles in which the segment with maximal counts is displayed as 100% and all other segments are displayed as a percentage of this segment. By displaying the distribution profile with overlay of the lower limit of normal, excessively diminished activity is graphically demonstrated.

16.3.4.4 Quantitation of Defects and Reversibility

To demonstrate a change in relative thallium-201 distribution or filling-in of a defect, the circumferential profile of the delayed study can be displayed relative to the segment with maximal counts. When circumferential profiles of the initial and delayed images are each displayed in this way, the composite profiles show relative changes in distribution of thallium-201 over the time interval (Exhibit 16-1). Thus, in spite of the lower count rate usually present in the delayed image, the relative distribution of thallium-201 in the two studies can be compared. If no change in relative distribution of thallium-201 over time occurs, the two normalized distribution curves should be closely superimposable. This is usually the case in patients without defects or in patients who have a fixed defect. A defect is characterized by the area of the circumferential profile below the lower limit of normal. A reversible defect is characterized by a defect on the exercise profile and the absence of a defect or a smaller defect on the delayed circumferential profile. Defect size can be further quantitated by a "defect integral" (Exhibit 16-2), which describes both the extent (the number of data points below the lower limit of normal) and the severity (depth) of the defect. On three projections the left ventricle is divided into 15

segments. A defect size in each segment is computed as is the total defect size per view and for the entire study (Exhibit 16-3). For the T3 study, we propose to quantitate the exercise defects as well as the amount of reversibility compared with a lower limit of normal. Although analysis of thallium-201 washout is extremely useful, this value is dependent on many variables that may be difficult to control in a multicenter study. Therefore, we elected not to include this particular parameter in the quantitative analysis.

In summary, thallium-201 studies will be described as either normal, abnormal with a fixed defect, or abnormal with a reversible defect. The defects (D) will be quantitated as a defect integral using the definitions outlined below.

EMPIRIC DEFINITIONS (AREA UNDER LOWER LIMIT, %)

	Per View	Total 3 Views
Defect	> 1	> 3
Reversibility	> 3	> 9
Defect Size		
Small	1 < D < 5	1 < D < 15
Medium	5 < D < 10	15 < D < 30
Large	10 < D	30 < D
Reversibility		
Small	2 < R < 4	2 < R < 12
Medium	4 < R < 8	12 < R < 24
Large	8 < R	24 < R

16.4 OBTAINING THALLIUM SUPPLIES

Mallinckrodt, Inc. in St. Louis, Missouri has agreed to provide free thallium doses for (1) protocol pre-discharge studies, (2) ancillary study 24 hour re-injections, and (3) six-weeks maximal exercise ancillary T1-201 studies. An account will be opened at Millinckrodt to which the doses for T3 studies should be charged.

Before the account can be set up, the T3 Data Coordinating Center must submit for each Clinical Center the names of the Principal Investigator and the person who will order the thallium from

Mallinckrodt. If the nuclear medicine laboratory at a center already has an account with Mallinckrodt, the DCC will need that number. If a center does not have an account with Mallinckrodt, the DCC will need the hospital's NRC license number.

Each Clinical Center will receive an Information for Mallinckrodt Account Form (Exhibit 16-4). This form should be submitted promptly to the Data Coordinating Center. Data Coordinating Center staff will then submit the information to Mallinckrodt and the accounts will be set up.

After the account has been set up, Clinical Centers routinely stocking thallium made by Mallinckrodt, Inc. should call 1-314-895-2075 and report the name of the hospital, name of the patient, and hospital account number for thallium. The amount of the dose of the thallium will be credited to the account of the hospital.

Clinical Centers who do not routinely use thallium produced by Mallinckrodt, Inc. but wish to use it for a T3 patient should call 1-800-325-3688. The account number which should be used to bill thallium for these patients is C2903. Mallinckrodt, Inc. will express ship the thallium to the hospital, usually by the next day. Mallinckrodt recommends that the thallium be ordered at least 48 hours prior to the expected date of the test to be sure it will arrive in time.

EXHIBIT 16-1

COMPOSITE PROFILES: RELATIVE CHANGES IN THE DISTRIBUTION OF THALLIUM-201 OVER TIME

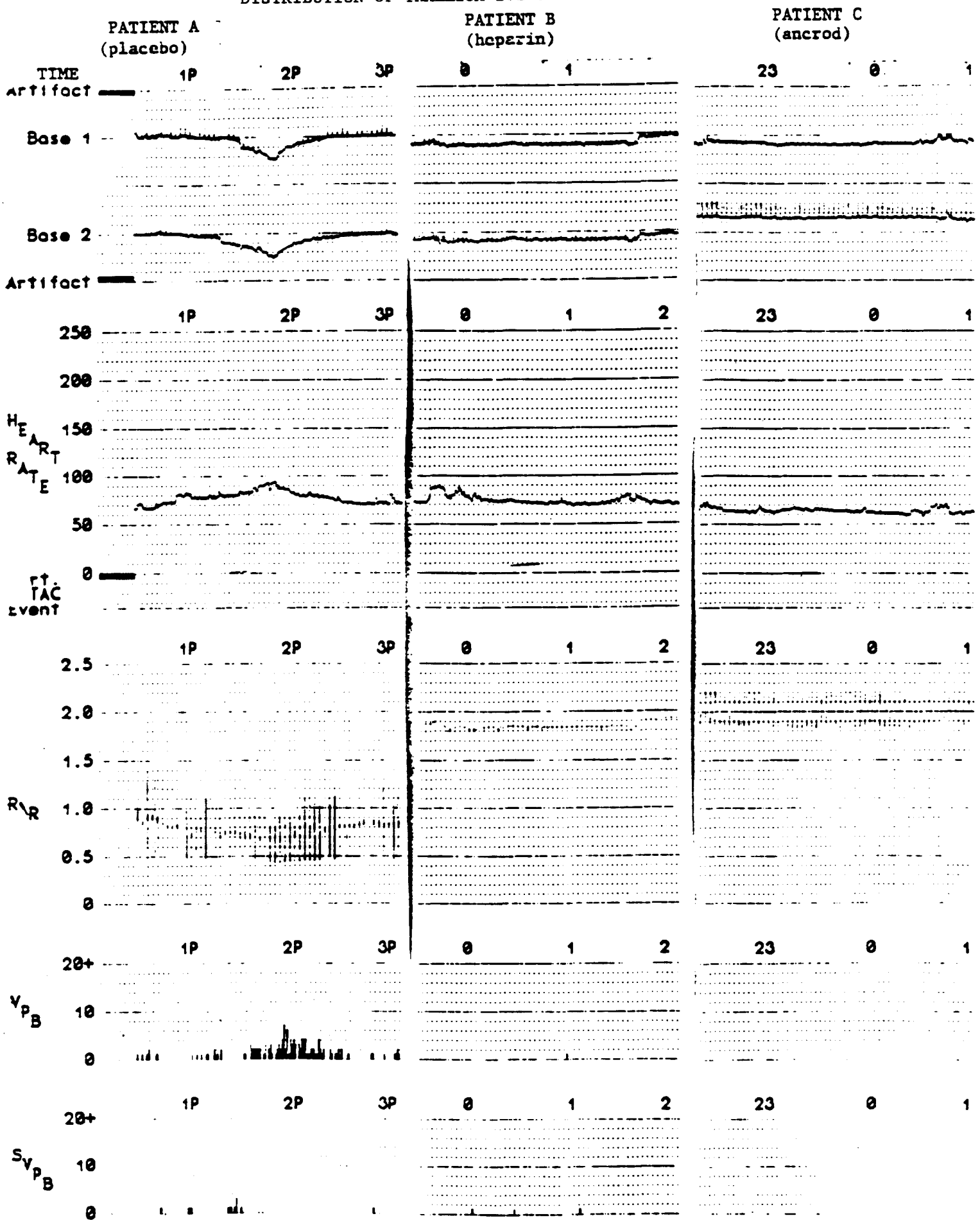


EXHIBIT 16-2

DEFECT INTEGRAL

(this portion represents only the peak of the episode)

TIME	HR	ST ABSOLUTE	BASELINE	ST DEV	SLOPE
1:32.5P1	83	-1.13	-0.09	-1.04	0.25
1:33.0P1	84	-1.13	-0.09	-1.04	0.25
1:33.5P1	84	-1.25	-0.09	-1.16	0.37
1:34.0P1	83	-1.25	-0.09	-1.16	0.37
1:34.5P1	83	-1.25	-0.09	-1.16	0.37
1:35.0P1	84	-1.25	-0.09	-1.16	0.25
1:35.5P1	84	-1.25	-0.09	-1.16	0.25
1:36.0P1	87	-1.38	-0.09	-1.29	0.13
1:36.5P1	87	-1.50	-0.09	-1.41	0.00
1:37.0P1	87	-1.63	-0.09	-1.54	0.00
1:37.5P1	87	-1.50	-0.09	-1.41	0.12
1:38.0P1	85	-1.50	-0.09	-1.41	0.37
1:38.5P1	85	-1.38	-0.09	-1.29	0.25
1:39.0P1	89	-1.38	-0.09	-1.29	0.13
1:39.5P1	89	-1.38	-0.09	-1.29	0.00
1:40.0P1	90	-1.50	-0.09	-1.41	0.25
1:40.5P1	90	-1.63	-0.09	-1.54	0.00
1:41.0P1	90	-1.75	-0.09	-1.66	-0.13
1:41.5P1	90	-1.75	-0.09	-1.66	-0.13
1:42.0P1	90	-1.75	-0.09	-1.66	-0.13
1:42.5P1	90	-1.63	-0.09	-1.54	-0.12
1:43.0P1	91	-1.75	-0.09	-1.66	0.00
1:43.5P1	91	-1.88	-0.09	-1.79	-0.12
1:44.0P1	93	-2.00	-0.09	-1.91	-0.25
1:44.5P1	93	-2.13	-0.09	-2.04	-0.25
1:45.0P1	92	-2.13	-0.09	-2.04	-0.12
1:45.5P1	92	-2.25	-0.09	-2.16	-0.13
1:46.0P1	86	-2.25	-0.09	-2.16	-0.25
1:46.5P1	86	-2.13	-0.09	-2.04	-0.12
1:47.0P1	92	-2.13	-0.09	-2.04	-0.25
1:47.5P1	92	-2.25	-0.09	-2.16	-0.25
1:48.0P1	94	-2.25	-0.09	-2.16	-0.25
1:48.5P1	94	-2.25	-0.09	-2.16	-0.38
1:49.0P1	94	-2.25	-0.09	-2.16	-0.25
1:49.5P1	94	-2.25	-0.09	-2.16	-0.13
1:50.0P1	90	-2.00	-0.09	-1.91	-0.13
1:50.5P1	90	-1.88	-0.09	-1.79	0.00
1:51.0P1	88	-1.75	-0.09	-1.66	0.00
1:51.5P1	88	-1.50	-0.09	-1.41	-0.25
1:52.0P1	87	-1.50	-0.09	-1.41	-0.13
1:52.5P1	87	-1.38	-0.09	-1.29	-0.12
1:53.0P1	87	-1.38	-0.09	-1.29	0.00
1:53.5P1	87	-1.25	-0.09	-1.16	-0.13
1:54.0P1	87	-1.25	-0.09	-1.16	-0.13
1:54.5P1	87	-1.13	-0.09	-1.04	-0.12
1:55.0P1	86	-1.00	-0.09	-0.91	-0.13
1:55.5P1	86	-1.00	-0.09	-0.91	0.00
1:56.0P1	86	-1.00	-0.09	-0.91	0.12
1:56.5P1	86	-1.00	-0.09	-0.91	0.00

EXHIBIT 16-3

DEFECT SIZE

CHAN	ONSET	END	DUR.	HR-5	HR-2	ONSET HR	MAX HR		
1	1:27.5P1	2:06.5P1	0:39.0	80	80	83	94		
	MAX ST/ABS	BASE HR	MAX ST/DIFF	HR	PRODUCT	INTEGRAL	HR @ 1ST > 1mm		TYPE
	-2.25	75	-2.16	92	-84.4	48.71	84		I B

EXHIBIT 16-4

INFORMATION FOR MALLINCKRODT ACCOUNT

Clinical Center Name _____

Center Number _____

Principal Investigator _____

Person who will order T1-201 _____

Mallinckrodt account number (if applicable) _____

NRC license number _____