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AN EVALUATION OF INTERNAL-MAMMARY-ARTERY LIGATION BY A DOUBLE-BLIND TECHNIC*

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K. ALVIN MERENDINO, M.D.,¶ AND ROBERT A. BRUCE, M.D.||

SEATTLE, WASHINGTON

CONSIDERABLE relief of symptoms has been reported for patients with angina pectoris subjected to bilateral ligation of the internal mammary arteries.¹⁻⁴ The physiologic basis for the relief of angina afforded by this rather simple operation is not clear. Allegedly, increased coronary flow is facilitated through collateral channels proximal to the site of ligation; these potential channels apparently do exist, as demonstrated by the injection studies of Battezzati et al.¹ and Kitchell, Glover and Kyle.² However, definitely increased coronary flow after bilateral internal-mammary-artery ligation has not been shown. Furthermore, this procedure does not afford protection to dogs after ligation of the anterior descending coronary artery.⁵

The influence of placebo therapy and its concomitant feature of enhanced professional interest by the physician have long been known to function beneficially in the relief of subjective symptoms, particularly in cases of angina pectoris.^{6,7} The present study was designed to evaluate the role of such factors after internal-mammary-artery ligation by observation of the effects of a "placebo" procedure consisting of parasternal skin incisions.

MATERIAL AND METHODS

Seventeen patients with angina pectoris attributed to coronary-artery disease were invited to participate in an experimental evaluation of internal-mammary-artery ligation. All patients were seriously limited by angina; the majority were unemployed. None had sustained a recognized myocardial infarction during the six months before operation. The patients were asked to keep a record of the number of anginal episodes and the number of nitroglycerin tablets used preoperatively and at periodic intervals after the operation. A standardized exercise-tolerance test⁸ in which the patient walked on a motor-driven treadmill at 1.7 m.p.h. on a 10 per cent grade was performed before and at least once after operation. The "respiratory efficiency" and blood pressure were determined and an electrocardiogram ob-

tained at rest, during exercise and during recovery. In the follow-up period the patients were periodically asked to estimate their degree of improvement in angina.

A reasonably optimistic attitude on the physicians' part was maintained. The subjects were informed of the fact that this procedure had not been proved to be of value, and yet many were aware of the enthusiastic report published in the *Reader's Digest*.⁹ The patients were told only that they were participating in an evaluation of this operation; they were not informed of the double-blind nature of the study.

To fulfill the objectives of this study, rigidly controlled conditions for the selection and evaluation of the patients were established. At the time of operation, which was performed under local anesthesia, the surgeon was handed a randomly selected envelope, which contained a card instructing him whether or not to ligate the internal mammary arteries after they had been isolated. The physicians following the patients postoperatively were not informed what was actually done in the operating room until the postoperative evaluations were completed. The patients were followed postoperatively for three to fifteen months.

SELECTION OF PATIENTS

By chance all 5 female patients in this study were included in the ligated group. As shown in Table 1, the numbers of patients with hypertension and cardiac enlargement were approximately equal in the two groups. However, the average age of sixty-four years in the ligated was significantly greater than the average of fifty-four years in the nonligated patients. There were no significant surgical complications. Two patients have died; 1 patient in the nonligated group died of a probable myocardial infarction eight months postoperatively, and 1 in the ligated group sustained a fatal proved myocardial infarction two months after internal-mammary-artery ligation.

EXERCISE TOLERANCE

The tolerance to a standardized exercise test is shown in Table 1. The duration before the onset of angina while the patient was performing the exercise test was greatly reduced in all** patients before operation. Since the follow-up periods (three to fif-

**One patient in the ligated group inadvertently was not exercised before surgery.

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teen months) are quite variable, the results of the postoperative exercise tests, as shown in Table 1, are the average durations of exertion before the onset of angina during the first six months of follow-up study.

NITROGLYCERIN CONSUMPTION AND SUBJECTIVE IMPROVEMENT

The patients were asked to keep a record of the number of anginal episodes they experienced during

TABLE 1. Patient Material and Clinical Evaluation in Ligated and Nonligated Groups.

GROUP	AVERAGE AGE	FEMALE PATIENTS	MALE PATIENTS	PATIENTS WITH HYPERTENSION	PATIENTS WITH CARDIOMEGALY*	AVERAGE EXERCISE TOLERANCE†		RANGE OF EXERCISE TOLERANCE‡	
						BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION
	yr.					min.	min.	min.	min.
Ligated	64	5	3	4	3	2.0	2.3	1-4½	1-5
Nonligated	54	0	9	4	2	2.8	3.8	¾-5	1-10

*+ to ++.

†Standardized exercise test at 1.7 m.p.h. on 10% grade for 10 min., or until onset of chest pain.

‡Patient's estimate of improvement in angina afforded by operation.

Only 2 patients (Cases 4 and 14) demonstrated a significantly increased endurance after internal-mammary-artery ligation. They were able to walk for the full ten minutes of the test without angina, whereas before operation typical angina developed after four or five minutes; it is noteworthy that both were in the nonligated group. Because of the striking change in these 2 patients, the average increase in endurance postoperatively of those in the nonligated group (one minute) was somewhat greater than that of the ligated patients (three-tenths minute).

ELECTROCARDIOGRAPHIC EVALUATION

The standard 12-lead electrocardiograms taken with the patient resting were abnormal in 15 of the 17 patients (ST-segment and T-wave abnormalities in 7, old myocardial infarction in 5, and 1 each with left-bundle-branch block, peri-infarction block and hypertrophy of the left ventricle). The electrocardiograms were not significantly altered after operation.

Electrocardiographic (CB₅) changes during and immediately after exercise on the motor-driven treadmill were significantly abnormal in 4 patients in each group. With 1 exception these abnormalities were again demonstrated at the time of follow-up testing during the six-month period after surgery.

Case 14 reported marked improvement subjectively. He was able to complete the prescribed exercise test six weeks postoperatively without electrocardiographic changes or angina, whereas preoperatively there had been striking inversions of the T waves after only four minutes of exercise (Fig. 1). The internal mammary arteries in this patient were not ligated.

intervals of one or two weeks and to estimate the percentage of improvement afforded by the operation. The nitroglycerin consumption for the two groups is shown in Table 1. Before operation the average number of nitroglycerin tablets used was greater in the ligated group than in the nonligated patients (43 versus 30 tablets per week). The average reduction postoperatively in the number of nitroglycerin tablets was comparable in the two groups, however (34 per cent and 42 per cent).

The estimated degree of subjective improvement during the first six months is shown in Table 1. The average improvement was 32 per cent for the ligated patients and 43 per cent for those whose internal mammary arteries were not ligated. Five patients (3 ligated and 2 nonligated) noted no improvement whatsoever. If an arbitrary value of 40 per cent is taken as indicative of "significant" improvement, 5 patients in each group could be said to be "significantly" better during the first six months of follow-up study. The degree of improvement in some cases was extraordinary. One patient (Case 4), who had been unable to work because of his heart disease, was almost immediately rehabilitated and was able to return to his former occupation. He reported a 100 per cent improvement at six months and 75 per cent improvement after a year. His arteries were not ligated.

DISCUSSION

The evaluation of any therapeutic measure designed to alleviate subjective complaints is usually a difficult undertaking. This is particularly true when the relief of pain and discomfort is the end point. It has long been recognized that the syndrome of angina pectoris could be influenced by many factors,

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some of which are associated diseases, anxiety and the attitude of the physician in his relation to the patient. Thus, the total environment of the patient with angina pectoris must be considered while one is evaluating a new therapeutic agent. Placebo com-

nificantly better than placebo therapy and the concomitant features of enhanced interest in the patient and the desires of the patient and the physician for improvement.^{6,7,10,11}

The surgical procedures commonly used in the

TABLE 1 (Concluded).

RANGE OF EXERCISE TOLERANCE†	GROUP	ABNORMAL ELECTROCARDIOGRAM (PRECORDIAL LEAD) DURING & IMMEDIATELY AFTER EXERCISE‡		NITROGLYCERIN TABLETS TAKEN			ESTIMATED SUBJECTIVE IMPROVEMENT‡		
		BEFORE OPERATION	AFTER OPERATION	AVERAGE BEFORE OPERATION	AVERAGE AFTER OPERATION	AVERAGE DECREASE AFTER OPERATION	AVERAGE	>40%	NONE
min.	AFTER OPERATION	no. of patients	no. of patients	no./wk.	no./wk.	%	%	no. of patients	no. of patients
1-5	Ligated	4	4	43	25	34	32	5	3
1-10	Nonligated	4	3	30	17	42	43	5	2

*+ to +++.

†Standardized exercise test at 1.7 m.p.h. on 10% grade for 10 min., or until onset of chest pain.

‡Patient's estimate of improvement in angina afforded by operation.

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 e improvement Table 1. The for the ligated whose internal Five patients o improvement 40 per cent is improvement, id to be "sig- months of fol- ment in some (Case 4), who his heart dis- ated and was . He reported onths and 75 rteries were

parison, preferably by the double-blind technic, is a well recognized necessity in the final evaluation of medical therapy in angina pectoris.^{6,7} Numerous

therapy of coronary-artery disease have previously been "major" operations utilizing thoracotomy and accompanied by some morbidity and a definite mor-

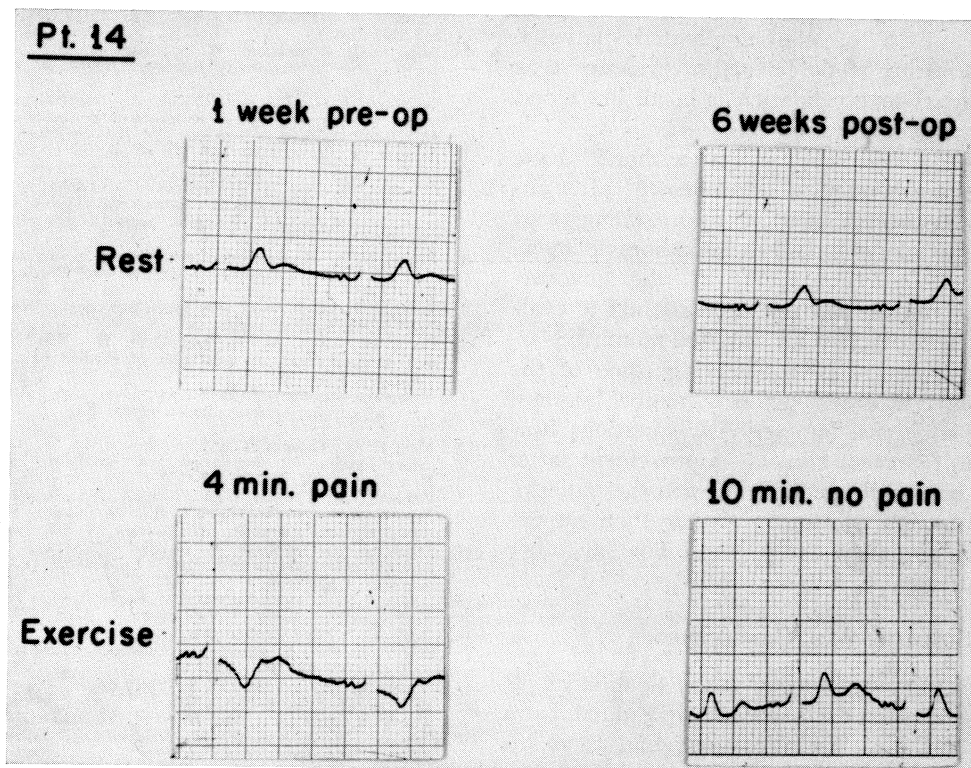


FIGURE 1. Precordial Electrocardiogram (CB₅) before and Six Weeks after Operation.

In the preoperative tracing there are striking inversions of the T waves after four minutes of treadmill exercise, when angina developed.

Six weeks postoperatively, the patient was able to tolerate ten minutes of exercise without chest pain or electrocardiographic abnormalities. The internal mammary arteries were not ligated.

measure de- its is usually rly true when e end point. syndrome of many factors,

drugs have been advocated as being beneficial in this syndrome, but very few have been shown to be sig-

ality. Thus, the evaluation of these operations has by necessity been deficient in excluding the factors

discussed above. With the advent of internal-mammary-artery ligation and its alleged benefit, a unique opportunity for applying the principles of a double-blind evaluation to a surgical procedure has been afforded. From the results in this rather small group of patients, bilateral skin incisions in the second intercostal space seem to be at least as effective as internal-mammary-artery ligation in the therapy of angina pectoris.

Fish, Crymes and Lovell¹² reported an initial period of marked improvement lasting from ten to sixty days after internal-mammary-artery ligation in 20 patients. Follow-up study on their patients failed to demonstrate sustained improvement, and the authors concluded that the operation did not produce significant relief of angina. In our patients, both ligated and nonligated, there was a tendency for subjective improvement to wane after several months, but it did not appear to be a consistent trend in all patients.

Simultaneously with our preliminary report of this study,¹³ Diamond, Kittle and Crockett¹⁴ reported a comparable double-blind study in which the internal mammary arteries of 13 patients were ligated and 5 had skin incisions only. These authors reported significant improvement in 10 of the ligated patients and all 5 of the nonligated patients. Adams's¹⁵ interesting study is further evidence that internal-mammary-artery ligation is in all likelihood a form of placebo therapy.

It is of some interest that several authors¹⁻⁴ have reported a degree of clinical improvement after internal-mammary-artery ligation approaching that afforded by the more extensive intrathoracic operations designed to "revascularize" the myocardium.¹⁵⁻¹⁷ It is not the purpose of this study to evaluate operations¹⁸ other than internal-mammary-artery ligation; however, after observing some of the dramatic results afforded by only minor bilateral thoracic skin incisions, one seriously questions how much of the reported clinical improvement after thoracotomy is actually dependent upon the patients' psychologic reaction to surgery rather than an enhancement of coronary-artery blood flow or other physiologic alteration.

SUMMARY AND CONCLUSIONS

Effects of internal-mammary-artery ligation on 17 patients with angina pectoris were evaluated by a double-blind technic. Eight patients had their internal mammary arteries ligated; 9 had skin incisions

only. The patients were followed for three to fifteen months. During the first six months, 5 out of 8 of the ligated patients and 5 out of 9 of the nonligated reported "significant" subjective improvement. Striking improvement in exercise tolerance occurred in 2 patients whose internal mammary arteries were not ligated; 1 of these patients failed to demonstrate the abnormal electrocardiographic changes that occurred preoperatively with the same exercise test.

Internal-mammary-artery ligation probably has no effect on the pathophysiology of coronary-artery disease. The subjective benefit from this operation is more likely to be on a psychological basis, although any spontaneous improvement in collateral circulation cannot be excluded. The value of the usual clinical evaluation of any form of surgical therapy designed to relieve the symptoms of angina pectoris is considered highly speculative.

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ANTIBACTERIAL ACTIVITY OF SERUM OF NORMAL SUBJECTS AFTER ORAL DOSES OF DEMETHYLCHLORTETRACYCLINE, CHLORTETRACYCLINE AND OXYTETRACYCLINE*

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BOSTON

IN a previous paper from this laboratory, Kunin and Finland¹ reported that the new tetracycline antibiotic, demethylchlortetracycline, given to normal persons in single or repeated oral doses, produced much higher and better sustained levels of antibacterial activity in the serum than corresponding doses of tetracycline. The superior activity was demonstrated in comparisons employing standard strains of streptococcus, staphylococcus and *Bacillus cereus* in twofold dilutions of serum in broth, and also by comparison of the concentrations of antibiotic activity in serum as determined by an agar cup-plate diffusion method using *B. cereus* as the test strain and expressing the results in terms of activity of the same standard — either tetracycline or demethylchlortetracycline. The difference was considered to result from the greater activity of demethylchlortetracycline against the assay organisms and its longer half life (by about 44 per cent) in serum as compared with tetracycline.

In another study, reported by Sweeney and his associates,² demethylchlortetracycline was shown to be 25 per cent less active than chlortetracycline, but three times as active as either tetracycline or oxytetracycline against a strain of *Staphylococcus aureus* as measured in a turbidimetric test. After single oral doses of 250 mg. of these three antibiotics, average serum levels at one, three and six hours, as measured by the cup-plate method and expressed in terms of the antibiotic ingested, were highest after tetracycline, with the other two compounds yielding similar activity. The amount of tetracycline excreted in the urine during the first eight hours was also significantly greater than that of the other two analogues when expressed in terms of the antibiotic administered.

However, when the results obtained by Sweeney et al. were expressed as tetracycline equivalents, the highest average level in the serum at each interval was obtained with chlortetracycline, and the lowest with tetracycline, and those resulting from demethylchlortetracycline were intermediate. Antibiotic activity persisted in the serum for seventy-two and ninety-six hours after the single doses of demethylchlortetracycline, whereas none could be detected seventy-two hours after the ingestion of either tetracycline or chlortetracycline. The higher serum levels of tetracycline as compared with those of demethylchlortetracycline, when expressed in terms of the antibiotic ingested, were also noted in the data reported by Kunin and Finland,¹ as shown in Figure 1. These findings emphasize the importance of using the same standard of reference in comparing the activity of antibacterial agents.

The present paper deals with comparisons of the antibacterial activity resulting in the serum of the same normal subjects after ingestion of equivalent doses of demethylchlortetracycline, oxytetracycline and chlortetracycline.

MATERIALS AND METHODS

The antibiotics used in this study were provided in capsules, each of which contained 250 mg. of the respective hydrochloride. Demethylchlortetracycline§ was provided in two forms, one containing only lactose as a filler and the other having an equal amount of citric acid, which, in other studies, had been shown to enhance the serum levels of tetracycline.³⁻⁵ The chlortetracycline capsules¶ contained only lactose, but those of oxytetracycline|| contained equal amounts of glucosamine hydrochloride, which has been reported to enhance the serum levels of that drug.⁶

The subjects for this study were 8 normal young men ranging in weight from 68 to 86 (average, 73)

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