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Unexplained In-Hospital Fever Following Cardiac Surgery

Natural History, Relationship to Postpericardiotomy Syndrome, and a Prospective Study of Therapy with Indomethacin versus Placebo

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SUMMARY In Part I of this study, the in-hospital course of 219 patients who had undergone a cardiac operation is analyzed. Fever ($\geq 37.8^\circ\text{C}$, rectal) was present after postoperative day 6 in 159 patients (73%) and was of unexplained cause in 118. Fever decay in the population of unexplained fever patients was exponential. All patients with unexplained postoperative fever were afebrile by postoperative day 19. In-hospital pericardial rub and pleuritic chest pain, widening of the mediastinum on chest film, and pleural effusion were not specifically associated with unexplained postoperative fever. In Part II, 67 patients with unexplained postoperative fever were given

indomethacin (100 mg per day) or placebo for 7 days by a randomized, double-blind protocol. Indomethacin resulted in a shorter duration of fever (2.4 vs 3.5 days, $P < 0.01$) and in a shorter duration of chest pain, malaise, and myalgias compared to placebo. Sixty-seven percent of the patients in Part I and all of the patients in Part II were contacted 2–8 months following hospital discharge. Five percent had experienced an illness that we considered to be acute pericarditis, but its occurrence was unrelated to whether the patient had had in-hospital unexplained postoperative fever, in-hospital rub or chest pain, or in-hospital administration of indomethacin.

FEVER AND CLINICAL SIGNS of a pleuropericardial process sometimes develop days to months after cardiac surgery, a combination of events widely referred to as the "postpericardiotomy syndrome."^{1, 2} Opinions about what constitutes postpericardiotomy syndrome — when it begins, its relationship to the more general problem of unexplained postoperative fever, and its clinical importance and natural history — are extremely diverse. The incidence of the syndrome has been reported to be as low as 1% and as high as 64%,^{3–10} and recommendations for therapy have differed widely.^{6–8, 11–15} Cardiologists and cardiac surgeons in our institution have frequently administered indomethacin to such patients when fever has been accompanied by pleuro-

pericardial pain, by a pericardial rub, or by malaise. Standards of practice have varied widely, however, because of uncertainty about the significance and course of unexplained postoperative fever and because the risk-benefit ratio of indomethacin administration under these circumstances has not been established.

The present study consists of two parts. In the *first*, we examine 1) the incidence and natural history of the unexplained fever that frequently occurs during the in-hospital postoperative period following a cardiac operation and the relationship of fever during this period to the clinical signs that have been used to diagnose the postpericardiotomy syndrome; 2) whether either unexplained fever or the clinical signs that have been used to diagnose the postpericardiotomy syndrome, when they occur during the in-hospital postoperative period, are related to the later development of pericarditis following hospital discharge. The *second* part of the investigation is a prospective, randomized study of the effectiveness of indomethacin compared to placebo in the therapy of unexplained in-hospital postoperative fever and its associated symptoms.

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Methods

In the present study, fever is defined as a rectal temperature of 37.8°C (100°F) or more. Fever is considered to be of infectious cause when cultures of blood, sputum, urine, wound swabs, or aspirated fluids are positive for bacteria, and are accompanied by evidence that the responsible physicians have considered the positive cultures to be of significance. Fever is considered to be drug-induced when there has been clinical suspicion of a specific drug as a cause of fever and discontinuation of the drug is followed by the prompt disappearance of fever. Fever occurring during the in-hospital postoperative period that is not categorized as being of infectious or drug origin is called unexplained postoperative fever unless some other specific cause (phlebitis, pulmonary embolism, pancreatitis, etc.) is demonstrated.

Part I

Of 291 consecutive adult patients, identified retrospectively, who had undergone cardiac surgery between November 1975 and March 1976 and who had survived the hospitalization during which the operation was performed, hospital records, reports of electrocardiograms, and reports of chest X-ray films were available for review in 219 (75%); these 219 patients constitute the study population for Part I.

In our institution, the pericardium is usually left open following cardiac operations. This is true in all patients who have had aortocoronary bypass procedures and in approximately 80% of patients who have had only valvular procedures.

Several drugs are administered routinely to patients undergoing cardiac operations. A semisynthetic penicillin is given for seven days, beginning the night before the operation. Hydrochlorothiazide and spironolactone are frequently prescribed at the time of the patient's discharge from the surgical intensive care unit and continued until the patient's postoperative weight is approximately the same as it had been preoperatively. Patients who have undergone aortocoronary bypass operations are given oral procainamide in divided daily doses beginning the day after operation and for five days thereafter. Appropriate substitutions are made if the patient has a history of hypersensitivity to these drugs.

While the patients are hospitalized on the cardiac surgical service, they are examined daily by surgical residents. In addition, each patient is followed by a cardiologist, who examines the patient every 1–2 days. White blood cell counts are performed every other day following the patient's release from the surgical intensive care unit. Most patients continue to have periodic electrocardiograms and chest X-ray films after the first postoperative week.

The usual duration of hospitalization following operation is 10–14 days. Ambulation is not delayed because of fever, chest pain, or the presence of a pericardial friction rub, but patients are usually observed in the hospital until fever has disappeared.

Follow-up was initiated 2–6 months following the patient's hospital discharge. Patients were contacted by telephone and were specifically questioned as to their general state of health, the occurrence of hospitalization since the time of their cardiac operation, the occurrence and nature of any form of chest pain, and the occurrence of febrile ill-

nesses. They were also asked whether a diagnosis of pericarditis had been suggested by their primary care physician, cardiologist, or cardiac surgeon and whether anti-inflammatory agents or antibiotics had been prescribed at any time following discharge.

On the basis of information obtained from the patient, pericarditis was diagnosed as having occurred during the follow-up period after hospital discharge if two or more of the following events occurred near the same time: pleuropericardial chest pain, the patient was told of a pericardial rub, or the institution of anti-inflammatory therapy.

Part II

Patients were prospectively identified as candidates for this portion of the study by two criteria: 1) if unexplained fever was present on the morning of postoperative day 7; or 2) if the patient had unexplained fever after postoperative day 3 and an order was written for indomethacin therapy. If a patient met the first criterion, the patient's cardiologist and cardiac surgeon were asked for permission for the patient to enter the study; if they agreed, informed consent was obtained from the patient. If a patient met the second criterion, and if all involved persons concurred, the prescribed indomethacin was withheld, and the patient was entered into the study.

Patients were excluded from the study if any of the following were present: 1) positive blood or urine cultures; 2) purulent sputum; 3) clinical suspicion of pneumonia or of wound, skin, or other infection; 4) clinical suspicion of another specific cause of fever (radiologic evidence of pulmonary atelectasis, in itself, was not considered a cause of fever); 5) a history of a hypersensitivity reaction to indomethacin; 6) a history of peptic ulcer disease, of gastritis, or of gastrointestinal bleeding.

Study patients were assigned by a randomized, double-blind protocol to receive either indomethacin, 25 mg by mouth four times daily for seven days, or placebo, one capsule, identical in appearance to indomethacin, four times daily for seven days.* The placebo capsules consisted of lactose (208 mg) and magnesium stearate (2 mg). If the patient was discharged prior to completion of the seven day course of the study drug, the remainder of the capsules were sent with the patient, and the patient was instructed to complete the course at home.

The seven day period during which indomethacin or placebo was administered will be referred to as the study period. While the patients were in the hospital, they were examined daily by one of the investigator-physicians. Particular attention was given to the presence or absence of chest pain, malaise, myalgias, or other complaints. Temperatures were recorded at least four times daily. All stools were checked for the presence of occult blood and hematocrits were measured every other day. If the patient was anticoagulated with warfarin, the prothrombin time was determined daily.

Seventy-two patients were entered into this prospective study of the effectiveness of indomethacin. The physicians caring for study patients complied with our request not to

*Both indomethacin and placebo were supplied by Merck Sharp & Dohme, West Point, Pennsylvania.

order glucocorticoids, aspirin or other anti-inflammatory agents during the study period. Acetaminophen and codeine (or other narcotic analgesics) were used as needed, and a record was kept of the amounts of these drugs administered to each patient.

All patients were contacted by telephone 2-7 months following hospital discharge and were specifically questioned as in Part I. In addition, they were asked if they had experienced any bleeding.

On the basis of information obtained from the patient, pericarditis was diagnosed as having occurred during the follow-up period following hospital discharge as in Part I.

Statistical Methods

The data were statistically analyzed by comparing proportions of patients by the chi-square test or, where expectations were too small to allow the use of the chi-square test, by Fisher's exact test. Group means were compared by Student's *t*-test and analysis of variance. Curve fitting was performed by regression analysis.

Results

Part I. Retrospective Study Of Unexplained Postoperative Fever

Fever Early In The First Postoperative Week

Two hundred and nineteen consecutive patients who were operated on between November 1975 and March 1976 and for whom adequate data for review were available constituted the study population; they ranged in age from 17 to 84 years (mean 55 years).

Fever early in the first postoperative week was virtually universal: 218 (99%) of the 219 patients were febrile. Causes of fever were not analyzed for this phase of the in-hospital period.

Fever After Postoperative Day 6

One hundred and fifty-nine patients (73%) were febrile at some time during their hospitalization after postoperative day 6. Fever was found to be of infectious cause in 35, appeared to be drug-related in six, and was unexplained in 118 (54% of the total).

The proportion of patients who had unexplained postoperative fever was not related to whether the cardiac operation that had been performed was a valvular operation or an aortocoronary bypass graft procedure (table 1). Only eight patients had had other types of cardiac operations.

The pyrexia of patients with unexplained postoperative fever tended to be low grade. Maximum temperatures

TABLE 1. Percentage of Patients with UPF after POD 6 Considered According to the Cardiac Operation That Had Been Performed

| | Number of operations | Number of patients with UPF |
|-----------------------------|----------------------|-----------------------------|
| Aortocoronary bypass grafts | 128 | 70 (55%) |
| Valvular operations | 93 | 54 (58%) |
| Open procedures | 88 | |
| Closed mitral valvotomy | 5 | |
| Other | 8 | 1 |

Abbreviations: UPF = unexplained postoperative fever; POD = postoperative day.

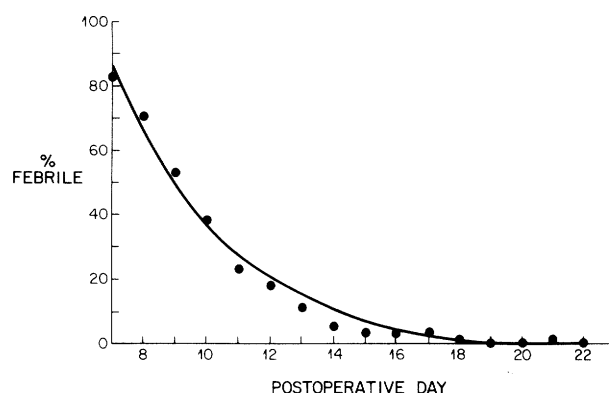


FIGURE 1. The decay of fever in the group of 118 retrospectively identified patients with unexplained postoperative fever after postoperative day 6. The percent of patients remaining febrile is plotted as a function of postoperative day beyond postoperative day 6. A patient is considered febrile if any temperature determination for a given day is $\geq 37.8^{\circ}\text{C}$. The % febrile on postoperative day 7 is 83%, rather than 100%, because in 17% of patients fever developed after postoperative day 7. The solid line is a best-fit (least squares) exponential curve ($r = 0.99$).

$\geq 38.9^{\circ}\text{C}$ (102°F) occurred in only seven of 118 patients with unexplained postoperative fever, whereas 14 of 35 patients with fever of infectious cause had maximum temperatures $\geq 38.9^{\circ}\text{C}$ ($P < 0.001$).

The course of fever in patients with unexplained postoperative fever is shown in figure 1. The curve relating percent of patients febrile to postoperative day (after postoperative day 6) is approximately exponential ($r = 0.99$) with a $T_{1/2} = 2.8$ days. All patients with unexplained postoperative fever were afebrile by postoperative day 19.

It is common, but not routine, on our cardiac surgical service for patients with unexplained postoperative fever to be treated with indomethacin. Of the 118 patients with unexplained postoperative fever, 54 had been treated with indomethacin at some time after postoperative day 6 and 62 had not; the rate of fever decay was no different in the former compared to the latter ($T_{1/2}$ 2.6 days vs 2.3 days).

The prevalence, during the second and third postoperative weeks, of various clinical signs that have been used by others to make a diagnosis of postpericardiotomy syndrome is shown for patients with unexplained postoperative fever in table 2 and compared to the prevalence of similar findings in patients who were afebrile after postoperative day 6. Pericardial rubs and pleuritic chest pain were noted after postoperative day 6 with approximately the same frequency in both groups. This was also true of the other clinical findings tabulated in table 2, with the exception of electrocardiographic ST-segment and/or T-wave abnormalities, which, though common in both groups, were more prevalent in patients with unexplained postoperative fever.

The prevalence of subsegmental or segmental atelectasis on chest X-ray films also was the same in patients with unexplained postoperative fever compared to patients who were afebrile. Of 100 of the former patients who had chest X-ray films taken after postoperative day 6, the chest X-ray films in 62 (62%) were interpreted as showing segmental or subsegmental atelectasis. Similar findings were present on the films of 24 of 44 (54%) afebrile patients with chest X-ray films taken after postoperative day 6.

TABLE 2. Percentage of UPF and Afebrile Patients with Clinical Signs of a Pleuropericardial Process in the Second or Third Postoperative Week

| Clinical events* | UPF patients (118)† | | Afebrile patients (60)† | | P |
|---|---------------------|----|-------------------------|----|-------|
| | Number | % | Number | % | |
| Pericardial rub‡ | 10 (118) | 22 | 4 (60) | 13 | NS |
| Pleuritic chest pain‡ | 7 (118) | | 3 (60) | | |
| Both rub and pain‡ | 9 (118) | | 1 (60) | | |
| ECG ST-segment and/or T-wave abnormalities§ | 85 (95) | 89 | 30 (45) | 67 | <0.01 |
| Mediastinal widening on chest X-ray film¶ | 39 (54) | 72 | 12 (21) | 57 | NS |
| Pleural effusion on chest X-ray film¶ | 71 (100) | 71 | 30 (44) | 68 | NS |
| Leukocytosis** | 55 (118) | 47 | 27 (58) | 47 | NS |

*Occurring in-hospital on one or more days after postoperative day 6. UPF = unexplained postoperative fever.

†Numbers in parentheses refer to the number of patients at risk for the event, since not all patients had ECGs recorded, chest X-ray films taken, or white blood counts measured after postoperative day 6.

‡As recorded in daily progress notes in the medical record.

§ST-segment and/or T-wave abnormalities interpreted as "non-specific," "consistent with pericarditis," or "consistent with the postoperative state."

¶Chest X-ray film reports were inadequate to allow judgement about mediastinal widening. Therefore, films from 75 patients were randomly selected and shown to one of us (RAJ), who was blinded to the fever status of the patient.

**Taken from chest X-ray film reports of all patients who had films after postoperative day 6.

**A white blood cell count exceeding 10,000 on one or more days after postoperative day 6.

The age of patients with unexplained postoperative fever did not differ from that of afebrile patients (56 ± 1 (SEM) vs 55 ± 2 years). The average period of extracorporeal circulation and aortic cross clamping that had been required during the cardiac operation also did not differ in unexplained postoperative fever (96 ± 4 min and 36 ± 3 min, respectively) compared to afebrile patients (88 ± 6 min and 34 ± 4 min, respectively).

One hundred and forty-seven patients were contacted 2–6 months (mean 3.4 months) following hospital discharge. A total of seven patients (4.8%) had had evidence for an episode of pericarditis, which was recurrent in two, during follow-up (occurring 3 weeks to 5 months after discharge). Five of the patients were known to have been febrile during the episode of pericarditis. Table 3 shows that the occurrence of pericarditis during follow-up was not uniquely related to whether the patient had had unexplained postoperative fever or had been afebrile while in-hospital, or to whether a pericardial rub or pleuritic chest pain had been noted in-hospital.

Part II. Prospective Study of Indomethacin vs Placebo

Seventy-two patients, all adults, entered the study. Five were withdrawn: three because of subsequent evidence of an infection (two were on placebo and one on indomethacin); one patient (later found to have been on placebo) because of nausea suspected to be due to indomethacin; and one patient (later found to have been on placebo) because the study drug packet was misplaced at the time the patient was transferred to another floor in the hospital.

TABLE 3. Number of Patients in whom Pericarditis Developed during Follow-up Considered According to their In-Hospital Course

| In-hospital (after POD 6) | Number of patients contacted during follow-up | Number of patients with pericarditis during follow-up |
|---------------------------------------|---|---|
| UPF | 93 | 4 |
| Afebrile | 54 | 3 |
| Presence of rub and/or pleuritic pain | 33 | 3 |
| Absence of rub or pleuritic pain | 114 | 4 |

Of the remaining 67 patients, 34 were found to have received indomethacin and 33 placebo after the code was broken. The postoperative day on which patients were begun on the study drug were similar in both groups (fig. 2). The types of cardiac operations performed in patients receiving indomethacin compared to those receiving placebo are shown in table 4.

The duration of fever was briefer in the patients receiving indomethacin compared to those receiving placebo (fig. 3) (mean 2.4 ± 0.2 days vs 3.5 ± 0.3 days, $P < 0.01$), a finding that appears to conflict with the observation of Part I. All of the patients, whether they had received indomethacin or placebo, were afebrile by postoperative day 19.

We found that we could not confidently distinguish complaints of chest pain related to the median sternotomy incision from pleuritic and nonpleuritic chest pains of other types (none of the patients was thought to have postoperative angina). Consequently, chest pains were considered together. Chest pain was present at the beginning of the study period in 10 patients who received indomethacin and in 13 patients who received placebo. Malaise or generalized myalgias were prominent initial symptoms of nine patients on indomethacin and of eight on placebo. The duration of symptoms in patients who complained initially of chest pain, malaise or myalgias (singly or in combination)

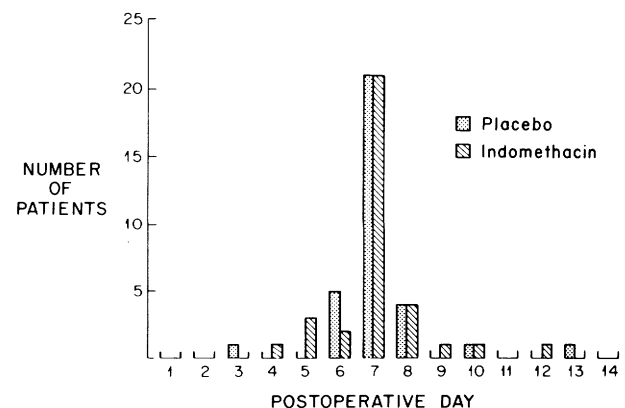


FIGURE 2. The postoperative day on which patients with unexplained postoperative fever entered the randomized study of indomethacin vs placebo. In the majority of cases, entry was on postoperative day 7.

TABLE 4. *Types of Cardiac Operations Performed in Indomethacin and Placebo Groups*

| Type of operation | Number of patients Indomethacin group | Number of patients Placebo group |
|--------------------------------|---|--|
| Aortocoronary bypass procedure | 23 | 16 |
| Valve replacement | 9 | 16 |
| Other | 2 | 1 |

is plotted in figure 4. Symptoms were of briefer duration in patients receiving indomethacin than in those receiving placebo (symptoms in one of 13 indomethacin patients vs eight of 16 placebo patients persisted more than two days; $P < 0.02$).

Indomethacin and placebo groups did not differ with regard to the persistence of pericardial rubs during the study period. Rubs were noted in 12 patients on indomethacin and persisted more than two days in three; rubs were noted in 18 patients on placebo and persisted more than two days in three.

The briefer duration of both fever and symptoms in patients receiving indomethacin compared to placebo could not be accounted for by differences in the administration of acetaminophen or of other analgesic agents (indomethacin group, 1.22 ± 0.53 g acetaminophen and 71.5 ± 29.6 mg codeine per patient; placebo group, 1.02 ± 0.21 g acetaminophen and 106.0 ± 37.0 mg codeine per patient).

The follow-up period ranged from two to eight months (mean 4.3 months). None of the patients became febrile again during the first two weeks after hospital discharge. In four patients, evidence of an episode of pericarditis subsequently developed (three weeks to six months following discharge). Three of these patients had received indomethacin during the study period, and one had received placebo.

No complications of indomethacin therapy were detected. In the in-hospital study period and the follow-up period

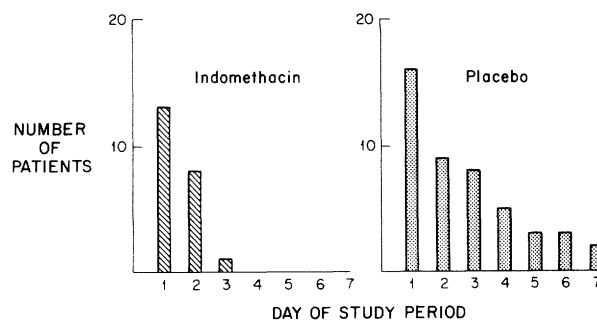


FIGURE 4. *A comparison of the duration of symptoms (number of patients with chest pain, malaise, myalgias — singly or in combination — shown on the ordinate) in patients who received indomethacin compared to those who received placebo.*

combined, three patients had a single bleeding episode, all of whom were taking oral anticoagulants. Two of these patients had received placebo. The bleeding episode in the one patient who had received indomethacin occurred two months after the study period.

Thirteen patients in the indomethacin group and 20 patients in the placebo group were given oral warfarin postoperatively. No difference existed between the indomethacin and placebo groups with regard to the number of patients in whom the prothrombin time exceeded the therapeutic range ($1\frac{1}{2}$ –2 times control) for at least one day of the study period (four indomethacin patients, four placebo patients). A sudden increase in the prothrombin time occurred in one patient on oral anticoagulants soon after hospital discharge; the study drug administered to this patient was placebo. The average daily warfarin dose (which is prescribed according to the prothrombin time each day while the patient is in the hospital) during the first four days of the study period did not differ between indomethacin and placebo patients who were receiving warfarin (5.9 ± 0.7 mg vs 5.5 ± 0.7 mg).

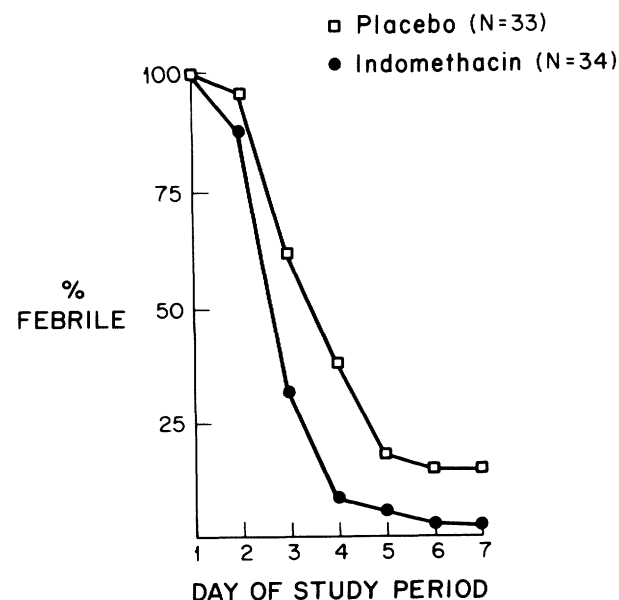


FIGURE 3. *The duration of fever following the institution of study drug in patients who received indomethacin compared to those who received placebo.*

Discussion

Part I of this investigation shows that unexplained fever in the in-hospital postoperative period following cardiac surgery is commonplace — 54% of our patients who had undergone a cardiac operation had unexplained postoperative fever after postoperative day 6. Unexplained postoperative fever is self-limited, however. When the percentage of patients with unexplained postoperative fever remaining febrile was plotted against time (days after postoperative day 6), the relationship was found to be unimodal and approximately exponential: between one-fifth and one-fourth of the patients became afebrile each day.

A possible objection to the finding of unimodal fever decay in the population of patients with unexplained postoperative fever is that one-half of the patients with unexplained postoperative fever had received indomethacin. Perhaps the use of indomethacin had obscured detection of a subgroup of patients whose fever otherwise would have followed a different course. However, in Part II of the study, a small but randomly selected group of patients with unexplained postoperative fever who were prospectively identified and not treated with indomethacin also exhibited unimodal fever decay (fig. 3). Hence, the unimodal decay of

fever in patients with unexplained postoperative fever in Part I is unlikely to be attributable to the fact that one-half of them had received indomethacin.

The postpericardiotomy syndrome has been said to be manifested by fever and by various signs of a pleuropericardial process: a pericardial rub; chest pain resembling that of acute pericarditis of other causes; electrocardiographic ST-segment and T-wave abnormalities; an abnormal cardiac silhouette on plain chest X-ray; pleural effusion(s); leukocytosis.^{1-6, 11, 16-18} But considering those patients with unexplained postoperative fever who had pericardial friction rubs, chest pain, or other signs of a pleuropericardial process as a separate subpopulation and designating them as having postpericardiotomy syndrome is not supported by the results of Part I of the present study. The unimodal fever decay in the population of patients with unexplained postoperative fever does not suggest that the unexplained postoperative fever population is composed of a number of subpopulations wherein fever is of a different cause in each, but that fever in the unexplained postoperative fever population is the result of a single process. The term "post-pericardiotomy syndrome" could just as easily be used to describe all of the patients with unexplained fever in the second or third postoperative week, or none of them; and there are two reasons why the latter might be preferable.

First, we did not find that pericardial friction rubs and pleuritic chest pain during the second and third postoperative weeks were specifically associated with fever. Thirteen percent of patients in Part I of this study who were afebrile during the second and third postoperative weeks had pericardial rubs, chest pain, or both, during this period. Admittedly, our results in this regard are based on a retrospective review of medical records. But this would seem more likely to have produced a falsely low estimate of the prevalence of rubs and chest pain in afebrile patients. Other findings that have been used as criteria for postpericardiotomy syndrome (table 2) also were not specifically associated with fever during the second and third postoperative week in the present study. Roses et al.⁹ have also found that pericardial rubs, chest pain, leukocytosis, and pleural effusions are not uniquely associated with fever during the in-hospital postoperative period. Second, neither unexplained postoperative fever nor the presence of pericardial rubs (or chest pain) in the second and third postoperative weeks were predictive of acute pericarditis during the follow-up period.

These observations do not necessarily mean that unexplained postoperative fever is unrelated to a pleuropericardial process, but they do suggest that the cause of unexplained postoperative fever is probably unrelated to the cause of pericarditis in some patients after hospital discharge. Late pericarditis occurred in only a small number of patients, and it is probably for them that the term "post-pericardiotomy syndrome" should be reserved. Studies of the incidence of the postpericardiotomy syndrome, which have come to widely differing conclusions when patients in the second and third postoperative week are included,⁹⁻¹⁰ yield similar results if the diagnosis is applied only to patients developing pericarditis after hospital discharge. In our study, for example, the incidence of pericarditis following hospital discharge was 5% in Part I and 6% in Part II.

Others have reported the incidence of pericarditis following hospital discharge after cardiac surgery to be 4-10%.^{5, 19, 20}

The suggestions for possible causes of postpericardiotomy syndrome have included immunologic mechanisms,^{5, 18, 21-24} an inflammatory reaction to blood in the pericardial space,²⁵ reactivation of a latent virus infection,²⁶ an inflammatory reaction due to the starch powder on surgical gloves,²⁷ and a combined effect of surgical trauma to the pericardium and hypoalbuminemia.¹⁴ However, these etiologic studies have allowed admixture of patients with in-hospital pleuropericardial findings and patients with post-discharge acute pericarditis — processes that the present study suggests are unrelated. This distinction should be taken into account in future etiologic studies as well as in those that examine whether the postpericardiotomy syndrome is related to surgical techniques^{28, 29} or to late complications of cardiac surgery, such as the patency of aortocoronary bypass grafts.^{3, 30}

The cause of unexplained postoperative fever is unknown. Operative mediastinal trauma, blood in the mediastinum or pleural spaces, or an inflammatory reaction produced by mediastinal or chest drainage tubes seem the most likely possibilities. One or more of these same processes is also the likely cause of the pericardial rub and the widening of the mediastinal silhouette that are frequently present during the first two or three postoperative weeks.

The results of Part II of the present study show that indomethacin shortens the duration of unexplained postoperative fever. In Part I, which is retrospective, the duration of fever in the group of patients with unexplained postoperative fever who had been treated with indomethacin was the same as in the group of patients with unexplained postoperative fever who had not. The most likely explanation for the apparent discrepancy between Part I and Part II with regard to the effect of indomethacin is that the clinicians in our institution tend to administer indomethacin to those patients with the most persistent fever. Hence, when patients with unexplained postoperative fever are grouped retrospectively according to indomethacin therapy and the fraction of patients remaining febrile each day after a given postoperative day is determined, the fact that the patients treated with indomethacin have already had fever for a longer period offsets the effect of indomethacin in reducing the duration of fever — an effect of indomethacin that Part II, the prospective study, shows to be real.

Indomethacin has both anti-pyretic and anti-inflammatory properties^{31, 32} and reduction in the duration of unexplained postoperative fever may be simply a consequence of its anti-pyretic effect. That reduction in the duration of unexplained postoperative fever is a consequence of the anti-inflammatory property of indomethacin seems more likely, however. Differences in the number of patients who were afebrile in the indomethacin and placebo-treated groups did not occur until forty-eight hours after the study drug was begun. Also, patients who had been treated with indomethacin did not have a relapse of fever when the study period was over. Admittedly, the latter outcome is a possible consequence of simply suppressing fever for seven days, since only 15% of the placebo group were febrile at the end of the study period.

Patients treated with indomethacin also had a shorter

duration of the symptoms — chest pain, myalgias, and malaise — that were present in almost one-half of the patients with unexplained postoperative fever who were identified prospectively. Chest pain in many of the patients was pleuritic in nature, although we could not confidently separate incisional pain due to the median sternotomy from nonincisional pleuritic pain. Sacks and Kanarek have shown in a controlled study that indomethacin is effective in relieving pleuritic chest pain of pulmonary origin.³² Moreover, case reports have been published suggesting a beneficial effect of indomethacin in acute pericarditis of a variety of causes.^{33, 34}

An interaction of indomethacin with the anticoagulant effect of warfarin was not detected in this study, although the numbers of patients involved were not large. Also, the number of clinically apparent bleeding episodes in anticoagulated patients that were treated with indomethacin compared to those that were treated with placebo did not differ. These findings are in agreement with a recent study of indomethacin vs placebo in normal human volunteers wherein an interaction of indomethacin and warfarin could not be demonstrated.³⁵ Although indomethacin affects prostaglandin synthesis by platelets,³⁶ this effect appears to be of doubtful clinical importance from the standpoint of bleeding complications resulting from its short-term use.

The side effects of indomethacin that have been common in patients on longer-term therapy, headache, awkwardness, and gastrointestinal distress, for example,^{31, 37} did not occur in this study. Also not encountered in the present study, but a potential complication of indomethacin therapy in postoperative patients and one that we have occasionally encountered in clinical practice, was the masking of an underlying infectious cause of fever.

The results of the present study allow several recommendations to be made for the management of patients with unexplained postoperative fever. First, unexplained postoperative fever is self-limited and in itself does not require treatment. Second, patients with unexplained postoperative fever, whether or not clinical signs of a pleuropericardial process are present, should follow the usual postoperative ambulation schedule, unless their condition otherwise warrants restriction of activity. All patients who have undergone a cardiac operation would be observed for signs of cardiac compression from collections of mediastinal blood or fluid, but patients with unexplained postoperative fever do not appear to be at special risk in this regard. Third, patients who, from the standpoints of cardiopulmonary status, wound healing, and ambulatory ability, are ready for hospital discharge by the tenth postoperative day need not be kept in the hospital simply because of persistent fever. If the fever is low-grade ($< 38.9^{\circ}\text{C}$) and if evidence for infectious causes of fever has been lacking despite careful search, the patient may be discharged with instructions to record rectal temperatures at home. Patients who remain febrile at home (after the fifteenth postoperative day, for example, when only 5% of patients with unexplained postoperative fever are still febrile, fig. 1) should be re-evaluated for infectious, drug-related, or other causes of fever.

Finally, unexplained postoperative fever is sometimes associated with an unusual degree of subjective morbidity, and such patients may be effectively treated with indomethacin. The short-term use of indomethacin involves

relatively little risk, even for anticoagulated patients. Hence, indomethacin has practical advantages compared to glucocorticoids and, possibly, compared to aspirin as well. Although a seven day course of indomethacin was utilized in this study (Part II), a shorter course may prove to be just as effective and even less likely to mask other causes of fever.

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The Bruit of Carotid Stenosis Versus Radiated Basal Heart Murmurs Differentiation by Phonoangiography

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SUMMARY Phonoangiography, quantitative analysis of arterial bruits, has been shown to provide accurate noninvasive diagnosis of uncomplicated carotid arterial stenosis, but had not been tested where cervical bruits from other sources were present. In this study, 27 carotid bruits in 15 consecutive patients with carotid bruits and basal heart murmurs were analyzed by phonoangiography. Tape recordings were made over the base of the heart and along the course of the carotid arteries in the neck; spectral analysis was performed as previously described. The spectral shape of the basal heart murmurs was recognizable and amplitude decreased with distance from the

heart, although a secondary, lower amplitude, maximum often occurred over the carotid bifurcation. Intrinsic carotid bruits, by contrast, were always maximal over the bifurcation, and although they radiated both proximally and distally, were not detectable over the chest wall. In quantitative terms, the correct diagnosis as to the presence and extent of carotid stenosis was made in 25 of 27 cases (92%) despite the presence of a radiated murmur. Phonoangiography is capable of accurate differentiation of radiated murmurs from intrinsic carotid bruits and of quantitation of the latter even in the presence of radiated sounds.

ATHEROSCLEROTIC STENOSIS OF THE CAROTID BIFURCATION is a well recognized, treatable disease that accounts for 18% of strokes tabulated in the Harvard Cooperative Stroke Registry.¹ It is present in fully 50% of patients with transient cerebral ischemic attacks symptomatically involving the carotid artery territory.² The extent of carotid artery stenosis is usually assessed by X-ray angiography, a technique of established accuracy but with the disadvantage of being an invasive test with varying degrees of morbidity. Phonoangiography³⁻⁶ has proved a useful noninvasive method to detect stenosis of the carotid bifurcation when a bruit is present. Unlike many other noninvasive methods for carotid stenosis, it indicates the site and extent of stenosis.⁴ This technique has been used heretofore only for characterizing isolated carotid artery bruits; the phonoangiographic features of cardiac murmurs and of bruits arising from more proximal vessels have not been reported in detail. The present report describes phonoangiographic findings in patients with basal heart

murmurs which radiate to the carotid bifurcation and examines differences in those with and without significant stenosis at the carotid artery bifurcation.

Materials and Methods

The 15 consecutively studied patients in this study had bruits arising from the bifurcation of the carotid artery as well as basal systolic murmurs. Each patient was suspected by the referring physician of having carotid stenosis and had a unilateral or bilateral phonoangiogram within 48 hours of a transfemoral carotid arteriogram. Each test was performed and interpreted without knowledge of the results of the other test, i.e., the physician who read the phonoangiogram did not know the results of the arteriogram where the latter was performed first, and vice versa.

Bruits and murmurs were recorded with the recumbent patient in a quiet room, in a manner described previously.³⁻⁶ The signal from a skin surface piezoelectric displacement transducer (Hewlett-Packard 21050B) was preamplified and stored on magnetic recording tape. Recordings were made over the second right intercostal space, 1 cm below, and 1 cm above the suprasternal notch. The recording microphone was then placed over the right or left common carotid artery, 1-2 cm above the clavicular insertion of the sternocleidomastoid muscle. Further recordings were made at close intervals along the course of the common and internal

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