Newer Aspects of Diagnostic and Therapeutic Management of Acute Idiopathic Pericarditis*. **

RUDOLPH E. FREMONT, M.D., F.C.C.P.
and BRUNO W. VOLK, M.D.
Brooklyn, New York

Acute pericarditis continues to present a challenge to the clinician from the point of view of etiology and differential diagnosis as well as treatment. Acute pericarditis occurring in the course of myocardial infarction, neoplastic diseases and advanced renal disease with uremia may be accepted as directly related to these disorders. It poses, however, an etiologic and differential diagnostic problem when it is encountered not only in the so-called idiopathic or non-specific form but even in the case of so-called rheumatic or primary tuberculous pericarditis. It has been noted by many observers f. i. how rarely isolated rheumatic pericarditis is followed by subsequent recurrence of acute rheumatic fever or any valvular defects. The diagnosis of so-called primary tuberculous pericarditis rests also usually on circumstantial evidence since bacteriological proof of tuberculosis is obtained only rarely. Clinically these three types of pericarditis resemble each other markedly. There are, however, considerable differences in treatment and also prognosis.

At times, the clinical picture of pericarditis resembles closely that of acute myocardial infarction. Whether it occurs in a middle-aged or older individual the differential diagnosis bears greatly upon the immediate and long term management.

1. Pericarditis: Etiologic and differential diagnostic considerations.

The dissatisfaction with the laboratory procedures currently available for this purpose have prompted a search for additional laboratory aids. Of these the fibrinogen polymerization (F.P.) test of Losner and Volk1 held particular promise. Having noted its highly specific nature in active rheumatic fever and arthritis2 we explored its usefulness in pericarditis and found it to be positive in a preliminary group of patients with acute rheumatic and non-specific pericarditis.3, 4 We have since followed a total of 20 patients with pericarditis with systematic serial studies of the F.P. test as well as the conventionally used acute phase reactants including the C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), plasma fibrinogen concentration and antistreptolysin-0 (ASO) titer. In cases where myocardial infarction had to be considered we have also employed the serum GO-transaminase test.

Our experience is summarized in Table I. Some of the observations recorded here have been reported elsewhere.5 The additional observations made since have confirmed the previous ones.

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*From the Cardiovascular Section of the Brooklyn Veterans Administration Hospital, the State University of New York, Downstate Medical Center, Brooklyn, New York, the Isaac Albert Research Institute of the Jewish Chronic Disease Hospital and the Department of Pathology, Albert Einstein College of Medicine, Brooklyn, N.Y.

Methods

The procedure used for the F.P. test is a modification of the method originally reported by Losner and Volk.\textsuperscript{1, 2} It has been described in detail elsewhere.\textsuperscript{5} The CRP determination was carried out according to the method of Tillet and Francis and that of the erythrocyte sedimentation rate (ESR) by the method of Wintrobe and Landsberg.\textsuperscript{7} The ASO titer was determined according to the procedure of Rantz and Randall\textsuperscript{8} and the SGO-transaminase by the method of Karmen et al.\textsuperscript{9} The plasma fibrinogen level was measured according to the clot density method of Losner and Volk\textsuperscript{10, 11} which is based upon the increasing optical density of coagulating plasma.

Results

Table I summarizes the data obtained in 20 patients with pericarditis. 15 of these had non-specific pericarditis which was acute in 12 and subsiding in three. Four suffered a relapse thus permitting the observations of a total of 16 acute and four subsiding episodes of idiopathic pericarditis. Three had so-called rheumatic pericarditis, i.e. pericarditis associated with rheumatic valvular disease. Two had presumptive tuberculous pericarditis.

One of these had early constrictive pericarditis, the other hemorrhagic pericardial effusion and evidence of old apical tuberculosis. Histological examination of the pericardium removed in the first patient showed granulomatous lesions consistent with tuberculosis. In neither patient did bacteriological examination of tissue and/or pericardial fluid yield tubercle bacilli.

The initial determination of the F.P. test gave consistently positive results in the acute phase of non-specific pericarditis correlating well with the uniformly accelerated ESR and the plasma fibrinogen concentration but poorly with the CRP and the antistreptolysin-O (ASO) titer.

The F.P. test was also positive in acute rheumatic pericarditis. It correlated well with the ESR, CRP and the plasma fibrinogen concentration, but poorly with the ASO titer.

In the presumable tuberculous group the F.P. test was negative as were all other tests except the ESR.

In serial determinations extending over a period of up to 12 months

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|}
\hline
\textbf{Etiology} & \textbf{Total No. of Patients} & \textbf{No. of Patients with Abnormal CRP} & \textbf{No. of Patients with Abnormal ESR} & \textbf{No. of Patients with Abnormal F.P.} & \textbf{No. of Patients with Abnormal Fibr Conc.} & \textbf{No. of Patients with Abnormal CRP} & \textbf{No. of Patients with Abnormal ASO-Titer} \\
\hline
\textbf{Non.Spec.} & 15 & 12 & 13 & 12 & 9 & 14 & 9 & 1 \\
\textbf{"Rheum"} & 3 & 3 & 3 & 2 & 2 & 2 & 0 & 0 \\
\textbf{"TB"} & 2 & 0 & 2 & 0 & 2 & 0 & 0 & 0 \\
\hline
\end{tabular}
\caption{Incidence of Abnormal Laboratory Findings in Pericarditis as Related to Chest Pain and ACG Changes}
\end{table}

F.P.—Fibrinogen Polymerization
Fibr. Conc.—Plasma fibrinogen concentration (upper limit of normal 400 mgm%)
ESR—Corrected sedimentation rate
For details of patients with "Rheum." and "TB" pericarditis see text.
the F.P. test reflected closely the clinical course of idiopathic pericarditis. Similar observations were obtained in the three cases of rheumatic pericarditis of the series in agreement with our previous experiences.

There was also close correlation between the F.P. test and the clinical manifestations of pericarditis such as pain and between the F.P. test and the electrocardiographic changes as well. We have noted, furthermore, that the F.P. test remained positive until all clinical manifestations of activity of the disease had disappeared while the acute phase reactants usually reverted to normal at an earlier date. In several instances when the F.P. test remained positive for a prolonged period a recurrence of the acute pericarditis was observed and with it a return to abnormal of the acute phase reactants.

In contrast to the non-specific acute phase reactants the F.P. test was not affected by steroid therapy.

Of particular interest are two patients (S. R. Fig. 1, and L. R. Fig. 2 and 3) in whom a primary tuberculous pericarditis could not be ruled out entirely even though the clinical course and the laboratory findings including the F. P. test were quite consistent with the presence of non-specific pericarditis. Since in both cases the symptoms and findings did not respond to salicylates, steroid therapy was considered. In view of the positive PPD reaction it was felt advisable to try anti-tuberculous therapy first. As seen in Figs. 1 and 2 this regimen did not prove efficacious. Temperature, symptoms and signs did not improve and the F.P. test remained positive throughout this period. When these patients were

FIGURE 1: Graph demonstrating the correlation of the F.P. test, the acute phase reactants and the ASO titer with the temperature, chest pain, and the therapy used in a patient (S. R.) with recurrent idiopathic pericarditis. (Reproduced by courtesy of American Journal of Cardiology.)
then put on steroid treatment prompt improvement of all clinical findings occurred and the F.P. test became negative.

These cases seem to confirm the value of the F.P. test as a useful aid (1) for the diagnosis of the non-specific variety of acute pericarditis, (2) for the evaluation of the continued activity of the disease, and (3) for the efficacy of treatment.

As regards so-called rheumatic pericarditis the doubt appears justified whether cases of isolated pericarditis even when occurring in patients with a history of rheumatic fever or presenting the findings of inactive rheumatic valvular disease are truly rheumatic in nature. Clinically this appears only certain in the presence of simultaneous rheumatic myocarditis and endocarditis or other associated major manifestations of acute rheumatic fever.

A case of pertinent interest is that of J. G. (Fig. 4) representative of the three patients of this series carrying the diagnosis of rheumatic pericarditis. This patient gave a history of repeated attacks of rheumatic fever and exhibited the residual findings of minimal mitral regurgitation. The acute episode of pericarditis for which he was hospitalized behaved in regard to the clinical course, the serial laboratory tests including the F.P. test and the response to salicylate and steroid treatment exactly like the episodes of non-specific pericarditis.

![FIGURE 2: Graph demonstrating the correlation of the F.P. test, and the acute phase reactants and the ASO titer with the temperature, chest pain, and the therapy used in a patient (L. R.) with idiopathic pericarditis.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21329/)
The fact that the F.P. test is positive in the acute phases of all observed cases of non-specific and rheumatic pericarditis and reflects the course of this disease as consistently as it does in active rheumatic fever with and without carditis suggests an underlying mechanism common to both conditions which interferes with the normal polymerization process of fibrinogen.

Although we have not had an opportunity to observe the F.P. test in patients with bacteriologically proved tuberculous pericarditis or pleuritis we have found the F.P. test to be negative in a patient with constrictive pericarditis in whom tuberculous granulomata with caseation were discovered in the excised pericardium. This observation suggests that a negative F.P. test may indeed help to rule out acute rheumatic or non-specific pericarditis. However, no definite conclusion as to the value of the F.P. test in tuberculous pericarditis can be drawn until this procedure can be applied to bacteriologically verified cases.

The problem of differentiation of pericarditis from myocardial infarction may be solved by the combined use of the F.P. test and serum enzyme determination. This problem is particularly acute when the ECG fails to show the pattern of a typical transmural infarction with abnormal Q waves or in the cases where a pericardial friction rub appears in the course of acute myocardial infarction and persists unduly long (for more than 48 hrs.). Table II lists a number of conventional phase reactants, the F.P. test and Serum enzymes (SGO-Transaminase and Aldolase) and allows a comparison of their behaviour in non-specific pericarditis and myocardial infarction. It is evident that where differentiation is usually most difficult—that is between subacute pericarditis and atypical myocardial infarction—the combined determination of the F.P. test and of the serum enzyme levels constitutes a particularly useful laboratory aid.

In the occasional patient who develops an acute pericarditis superimposed upon a recent myocardial infarction—Dressler's post-infarction syndrome the utilization of the F.P. test in combination with the SGO-transaminase test should be helpful in the differential diagnosis since this syndrome has been related to non-specific pericarditis. Unfortunately the patients in whom we suspected this condition on clinical grounds were all on anti-

<table>
<thead>
<tr>
<th>Laboratory Data</th>
<th>Acute Myocardial Infarction</th>
<th>Pericarditis</th>
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<tbody>
<tr>
<td></td>
<td>Transmural</td>
<td>Atypical</td>
</tr>
<tr>
<td>E.S.R.</td>
<td>freq. elevated</td>
<td>freq. normal</td>
</tr>
<tr>
<td>C.R.P.</td>
<td>usually elevated</td>
<td>freq. normal</td>
</tr>
<tr>
<td>Fibr. Conc.</td>
<td>usually elevated</td>
<td>freq. normal</td>
</tr>
<tr>
<td>F.P. S. Enz.</td>
<td>negative</td>
<td>freq. elevated</td>
</tr>
<tr>
<td>Q Ekg. ST T</td>
<td>abnormal</td>
<td>usually normal</td>
</tr>
<tr>
<td></td>
<td>freq. elevated</td>
<td>norm., depr. or elev.</td>
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<td></td>
<td>freq. inverted</td>
<td>freq. inverted</td>
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F.P.—Fibrinogen Polymerization
Fibr. Conc.—Plasma Fibrinogen Concentration
S. Enz.—Serum Enzyme Level (SGO—Transaminase or S. Aldolase)
coagulant therapy. The resultant prolongation of prothrombin and clotting time makes it impossible to carry out the F.P. test since it prolongs the procedure beyond practical limits of time (often beyond eight hrs.).

2. Treatment of acute pericarditis.

a) Non-specific pericarditis.

The treatment of this condition is difficult to evaluate in many cases of mild to moderate degree in view of the self-limiting nature of the disease. Equivocal results have been reported not only with salicylates but also with a number of antibiotics including penicillin, streptomycin, achromycin, terramycin, alone or in combination. In more severe cases characterized by prolonged chest pain, a protracted febrile course and persistent pericardial effusion we have found the prompt administration of steroids most efficacious. This confirms the isolated reports by others. Very large doses may have to be used, occasionally as high as 80 mgm of prednisone daily. Steroid therapy does not necessarily prevent recurrences but it is equally effective, usually in smaller dosage, when these set in. The prolonged and relapse-prone course of non-specific pericarditis noted in some of our patients afforded us a particular opportunity to observe the effect of steroid therapy not only upon the clinical course but also upon the serial laboratory tests (Figs. 1 and 2).

The institution of this regimen leads to prompt improvement of the symptoms and normalization of the temperature usually in 24 to 48 hours. Within a short period the acute phase reactants return also to normal. The F.P. test, however, remains positive for a longer period. To discontinue steroids at this point—or even to reduce the dosage gradually—in the belief that the disease process has been already materially affected leads, however, to a quick relapse. This is well indicated not only by the prompt return of the temperature but also of chest pain and even physical signs. Only when the F.P. test has turned negative and has remained so for at least two weeks is it advisable to reduce the steroids in the manner usually

FIGURE 3A

Figure 3A: Cardiac silhouette before steroid therapy shows increase in size and abnormal configuration due to massive pericardial effusion.—Figure 3B: Cardiac silhouette 2 weeks after institution of steroid therapy.
recommended for a high dosage regimen. The F.P. test thus furnishes
guidance for the management of this disease. When relapses occur follow-
ing eventual discontinuation of steroids both the acute phase reactants
and the F.P. test become positive again. The latter will serve again as
the more valuable guide for the therapeutic regimen. It should be pointed
out that patients may be ambulated and even returned to moderate activity
as soon as the steroids have exerted their full effect.

b) Rheumatic Pericarditis
Our observations on the treatment of so-called rheumatic pericarditis
confirm the adequacy of salicylate therapy in most cases as noted by others.
Steroid administration may be required in patients intolerant of salicylates
and/or suffering from a more severe form of this disease. Our experience
again supports the value of the F.P. test as a reliable guide to the efficacy
of therapy in rheumatic pericarditis (J. G. G. Fig. 4).

c) Tuberculous Pericarditis
In cases where tuberculous etiology cannot be ruled out with certainty
the advisability of steroid therapy may be questioned. However, it has
been used with success not only in pleurisy of probable or proved tuberc-
ulous nature \(^{16,17}\) but also in proved tuberculosis pericarditis.\(^{16,17}\) Voegtlin\(^{17}\)
reported on the excellent response of tuberculous pericarditis with massive
effusion and tamponade to cortisone after triple anti-tuberculous therapy
had failed to halt the rapid reaccumulation of pericardial and pleural fluid.
The effusions disappeared within eight days of cortisone administration.
No pulmonary parenchymal lesion appeared. The cortisone treatment did
not prevent the early onset of constrictive pericarditis in one patient.

While primary tuberculous pericarditis, that is without obvious con-
comitant lesions elsewhere is quite rare, the prophylactic use of isoniazid
(INH) is advisable in cases of non-specific pericarditis where there is

\[\text{FIGURE 4: Graph demonstrating the correlation of the F.P. test, the acute phase reactants and the ASO titer with the chest pain, and the therapy used in a patient (J. G.) with rheumatic pericarditis.}\]
reasonable suspicion of a tuberculous cause. This was done in two our patients. One of these (S.R.) (Fig. 1) suffered numerous recurrences following the first episode which occurred during war imprisonment. The other (L.R. (Fig. 2) had mild to moderate symptoms but persistent massive hemorrhagic pericardial effusion. Both had a second strength positive PPD reaction. However, the temperature, symptoms and signs did not respond to antituberculous treatment. All findings, clinical and laboratory cleared promptly after prednisone treatment was started. Prolonged follow-up observations failed to reveal evidence of tuberculosis. Thus both cases could be considered to have non-specific rather than tuberculous pericarditis.

SUMMARY

Comparative serial studies of the fibrinogen polymerization test, with several acute phase reactants such as the C-reactive protein, the erythrocyte sedimentation rate and plasma fibrinogen concentration, and also the antistreptolysin-O titer were carried out to explore their relative usefulness, for the differential diagnosis of non-specific rheumatic and tuberculous pericarditis.

A consistently positive F.P. test indicated the presence, and mirrored the course, of rheumatic and idiopathic pericarditis, while it was negative in tuberculous pericarditis. Of the acute phase reactants only the ESR was abnormal to a comparable degree in all conditions studied. It seems, therefore, that the F.P. test can serve as a valuable aid in the diagnosis of idiopathic pericarditis.

The F.P. test appears, furthermore, of value for the differential diagnosis between atypical myocardial infarction and acute nonspecific pericarditis, particularly, when used concomitantly with the serum GO-transaminase or aldolase tests.

The treatment of pericarditis is discussed and the value of steroid therapy in non-specific and rheumatic pericarditis of severe degree is emphasized.

The F.P. test has a particularly useful criterion for the efficacy of therapy since it appears not to be suppressed by salicylate or steroid therapy and reflects the activity of the disease.

RESUMEN

Se ha llevado a cabo una serie de estudios comparativos de la prueba de la polimerización del fibrinógeno con varios reactantes de fase activa tales como el reactivo C de proteína; también se estudió la sedimentación de los eritrocitos, la concentración de los eritrocitos, la concentración en el plasma del fibrinógeno, así como el título de la antistreptolisina-O esto se ha hecho con el objeto de averiguar su relativa utilidad, para el diagnóstico diferencial de la pericarditis no específica y de la pericarditis tuberculosa.

Una polimerización del fibrinógeno (FP) persistentemente positiva refleja la evolución de la pericarditis reumática e idiopática en tanto que cuando es tuberculosa la prueba FP es negativa.

De los reactantes en fase aguda, sólo la velocidad de la sedimentación globular fué anormal en grado comparable entodos los padecimientos estudiados. Parece por tanto, que la reacción FP puede servir como una ayuda de valor para el diagnóstico de la pericarditis idiopática.

La reacción FP parece además, ser de valor para el diagnóstico diferencial entre el infarto atípico del miocardio y la pericarditis aguda no específica en particular cuando se usa al mismo tiempo con las pruebas de transaminasa GP o aldolasa en el suero.

Se diserta sobre el tratamiento de la pericarditis y sobre el valor de los esteroides en el tratamiento de la pericarditis no específicas y reumáticas y de grave evolución, siendo esto lo que se recalca.

La prueba FP proporciona un criterio de utilidad para la eficacia del tratamiento puesto que parece que no se suprime por el uso de salicilatos o esteroides y refleja la actividad de la enfermedad.

RESUME

Une série d'études comparatives du te de la polymérisation du fibrinogène avec plusieurs réactions des processus aigus tels que la protéine réactive C, le taux de sédimentation de l'érythrocyte, la concentration plasmatique fibrinogène, et aussi le titre antistreptolysine O, furent poursuivies pour explorer leur utilité relative, dans le diagnostic différentiel des périкарdistis rhumatismales, non-spéciﬁque, et tuberculose.

Un test de la polymérisation du fibrinogène nettement positif indiquait la présence de l'évolutio rhumatismale et idiopatique, tandis qu'il était négatif dans la périкарdisite tuberculose. Sur les réactions des processus aigus, seul le taux de sédimentation érythrocytaire fut anormal à un degré comparable dans tous les états étudiés. Il semble alors que le test de la polymérisation du fibrinogène
puisse servir comme un moyen appréciable dans le diagnostic de la péricardite idiopathique.

Le test de la polymérisation du fibrinogène apparaît, ensuite, valable pour le diagnostic différentiel entre l'infarctus myocardique atypique et la péricardite aiguë non spécifique, particulièrement quand il est utilisé en même temps que les tests de l'alldose ou de la transaminase du sérum.

Le traitement de la péricardite est discuté, et l'auteur souligne la valeur de la corticothérapie dans les péricardites non-spécifiques et rhumatismales graves.

Le test de la polymérisation du fibrinogène fournit un critère particulièrement utile pour apprécier l'efficacité du traitement depuis qu'il semble ne pas être supprimé par le traitement salicylés ou par les stéroïdes, et reflète l'activité de l'affection.

ZUSAMMENFASSUNG

Es wurden vergleichende Reihenuntersuchungen des Fibrinogen-Polymerization-Testes (F.P.) durchgeführt mit verschiedenen rasch verlaufenden Reaktionen wie z.B. dem C-empfindlichen Protein, der Blutsenkung, der Plasma-Fibrinogen-Konzentration und auch dem Antistreptolysin-Titer zur Erklärung des relativen Wertes bei der Differentialdiagnose von unspezifischen rheumatischen und tuberkulösen Perfikarditiden.

Ein übereinstimmender positiver F.P.-Test zeigt, das Vorliegen und spiegelt den Verlauf einer rheumatischen und idiopathischen Perikarditis, wohin gegen der negativ ausfällt bei den rasch verlaufenden Reaktionen war nur die BSG in vergleichbarem Grade in allen untersuchten Fällen verändert. Es scheint daher, als könne der F.P.-Test als ein wertvolles Hilfsmittel gelten bei der Erkennung der idiopathischen Perikarditis.

Der F.P.-Test scheint darüber hinaus von Bedeutung für die Differentialdiagnose zwischen atypischen Myocardinfarkten und akuter unspezifischer Perikarditis, besonders wenn er zusammen mit dem Serum-GP-Transaminase-Test (Aldolase-Test) gebräucht wird.

Es wird die Behandlung der Perikarditis besprochen und der Wert der Steroid-Therapie bei unspezifischer und rheumatischer Perikarditis von ziemlicher Schwere betont.

Der F.P.-Test liefert ein besonders nützliches Kriterium für die Wirksamkeit der Therapie, da er augenscheinlich nicht beeinträchtigt wird durch Salicylate oder Steroid-Therapie und die Aktivität der Erkrankung wieder gibt.

REFERENCES