Management of purulent pericarditis with intrapericardial fibrinolysis: a review.

Pascal Augustin, MD, Sigismond Lasocki, MD, PhD, Jean-Michel Maury, MD, Mathieu Desmad, MD, PhD, Philippe Montravers MD, PhD.

1. Department of Surgical Intensive Care, Hôpital Bichat-Claude Bernard, Assistance Publique - Hôpitaux de paris, Paris 7 University (Denis Diderot), Paris, France.

Correspondance: Pascal Augustin, Département d’Anesthésie et Réanimation, Hôpital Bichat Claude Bernard, 46, rue Henri-Huchard, 75877 PARIS Cedex 18 FRANCE.

e-mail: pascalaugustin@hotmail.com
Telephone: +33-6-79-68-93-64
FAX number: +33-1-40-25-88-48

Running head: fibrinolysis in purulent pericarditis
Abstract:

Purulent pericarditis remains a life-threatening pathology. There is no consensus on its medicosurgical management. Nevertheless, total pericardiectomy eradicates focus of infection and provides a better outcome than simple pericardial drainage. Because of high morbidity, intrapericardial fibrinolysis has been considered as a less invasive approach for prevention of persistent and constrictive pericarditis. Literature was reviewed using MEDLINE database. We evaluated the pathophysiological rationale, clinical efficacy, outcome, and complications of pericardial fibrinolysis. Experimental data demonstrate that fibrinoformation is observed in the first week after onset of the disease, and is an essential step in the evolution to constrictive pericarditis and chronic pericarditis. Seventy-five cases of fibrinolysis in purulent pericarditis have been analyzed. Among the 41 analyzable cases, only 2 treated by late fibrinolysis encountered failure requiring surgery. Only 1 serious complication was described. Despite the lack of definitive evidence, potential benefits of fibrinolysis outweigh its very low morbidity. Fibrinolysis is a promising and less invasive alternative to surgery in the management of purulent pericarditis. It should be applied as soon as possible with the aim to prevent both constrictive and purulent pericarditis. Nevertheless, in case of failure of fibrinolysis, total pericardiectomy remains an option allowing a complete eradication of infection.
Introduction

Purulent pericarditis (PP) was a common complication of pulmonary infection before the antibiotic era [1]. Despite medical progress, PP is still associated with high mortality attributed to early and late complications, chronic purulent pericarditis and constrictive pericarditis. These late complications may be prevented by early pericardiectomy known for its potential morbidity. Twenty years ago, intrapericardial fibrinolysis emerged as a promising and less invasive alternative to surgery. Nevertheless, there is no consensus about its indication in PP. History, pathophysiology, complications and surgical management of PP are briefly described. At the light of physiological and histological data, we reviewed the rationale of fibrinolysis in PP, the evidences of its efficacy, and all publications on indications, timing, results, and complications of this technique.

Definitions and etiologic classification

Purulent pericarditis is defined by a neutrophilic pericardial effusion infected by a bacterial, fungal, or parasitic agent. Tuberculous pericarditis are not PP but lymphocytic pericarditis, and will not be discussed. Classification of PP comprises 5 etiologic entities (Table 1) [1,2]. Purulent pericarditis arising from a pleuropulmonary infection was the main etiology in the early 20th century, before the advent of antibiotics [1,3]. Oesophageal and cardiothoracic surgeries, immunosuppressive therapy and chemotherapy have made emerge new predisposing conditions [2].

Diagnosis

When PP is suspected, the diagnosis is confirmed by pericardiocentesis guided by echocardiography yielding purulent fluid. It may have different clinical features according to the aetiology. In a context of pneumonia the diagnosis may be suspected when infection doesn’t
respond adequately to antibiotic treatment. In this case, echocardiography or computed tomography scan of chest may disclose thoracic complications such as pleural empyema or pericardial effusion [4,5] (figure 1). Interestingly, PP may have an insidiously subtle presentation, and classical pericardial signs can be absent until tamponade [2,6]. Pain chest or pericardial friction rub are observed in about 50% of cases [7]. These data are in agreement with autopsy series of Klacsmann showing that of 55 PP, only 10 had been discovered antemortem [1]. Indeed, before the advent of echocardiography, less than 20% of PP discovered at autopsy had been clinically suspected [1]. This poor index of suspicion results in underdiagnosis and late diagnosis at an advanced stage of the disease after onset of pericardial adhesions loculations [8].

**Complications**

Purulent pericarditis may be accompanied by tamponade and septic shock, the 2 early life threatening complications which have no specificity in this setting. On the contrary, the 2 late complications constrictive pericarditis and persistent/chronic PP, imply specific considerations and management [1,2].

Constrictive pericarditis is defined by thickening and fusion of pericardium causing low pericardial compliance with symptoms of chronic right heart failure. It may cause hemodynamic compromise with low cardiac outpout because of adiastoly with impaired cardiac filling. Pericardial fibrosis is caused by chronic or subacute pericardial inflammation which is associated with fibroblast proliferation and collagen deposition. In the largest meta-analysis of PP by Gaudelus that specially addressed to constrictive pericarditis, there were 19 cases (3.5%) of constrictive pericarditis beyond 524 published PP [9]. This frightened complication is specifically expected when no pericardiectomy has been performed [9].

Persistent pericarditis is defined by a chronic or recurrent purulent pericardial effusion. Because
chronic inflammation can cause fibrosis, persistent purulent pericarditis may be followed by constrictive pericarditis. Nevertheless, even if persistent and constrictive pericarditis may be associated, these entities have distinct clinical features. This late complication of PP is much more frequent than constrictive pericarditis but has rarely been classified as chronic purulent pericarditis. Therefore, its incidence cannot be precisely known. Many authors have well described adhesions, loculations of pericardial effusion, with persistence or recurrence of PP due to the presence of thick fibrin clots preventing complete evacuation of pus through pericardial drains [10-14]. In these cases, despite drainage and appropriate antibiotherapy PP, chronic purulent discharge persists several weeks until death due to septic shock or tamponade. At this stage, surgical management with pericardiectomy is challenging, with high morbidity because of pericardial adherences and impaired general status of patient. In fact, the real challenge should be to prevent chronic and constrictive pericarditis.

**Physiopathology of PP and of complications**

Few publications studied the physiological mechanisms of purulent pericarditis, but this pathology shares some pathophysiological similarities with empyema that has been widely studied. Clinical and experimental studies show that contiguous spread of lung infection causes pleural mesothelial barrier dysfunction [15]. First, activated mesothelial cells release vascular endothelial growth factor (VEGF) leading to exudative pleural effusion with pleural inflammation by increasing protein vascular permeability. The second step is bacterial invasion of pleural space that enhances inflammatory response by attracting leucocytes. By expressing tissue factor, activated leucocytes activate platelets and coagulation, both resulting in fibrinoformation [16]. Fibrin deposits are responsible of pleural adhesion, thickening and loculation of effusion, therefore preventing easy drainage and antibiotics diffusion. When
drainage is suboptimal, the pathologic process may relapse and progress. Finally, when the
process continues, subacute or chronic inflammation leads to fibrosis due to collagen secretion by
fibroblastic proliferation.

An experimental model in sheep argued for a very close pathophysiological process of PP leading
from pericardial inflammation to pericardial adhesions and fibrosis [17]. In addition of
demonstrating histological course of PP, this study provides timings of occurrence of the
essential steps of the disease. After a first inflammatory stage, fibrin strands appeared since the
third day. At 6 days, newly formed collagen fibrils were deposited throughout the interstitial
spaces and among the aggregated cells. At 2 weeks, intrapericardial fibrosis had produced focal
adhesions between the pericardial surfaces. At 1 month, extensive areas of the pericardial cavity
were obliterated [17]. Another experimental study showed comparable timings in histological
progression [18].

These experimental data clearly explain how PP evolves to persistent and constrictive
pericarditis. First, chronic/persistent purulent pericarditis is related to the absence of effective
drainage because of loculation and pericardial adhesion [19,20]. Secondly, constrictive
pericarditis is related to pericardial fibrosis which could be detected 2 weeks after the beginning
of the pathological process [17,18]. Furthermore, these studies shows that whatever the aetiology,
fibrinofibration is the essential step and a cornerstone in the pathogenesis of both
persistent/chronic and constrictive pericarditis. Thus, fibrin may be a therapeutic target in the
management of PP.
General management, surgery and fibrinolysis

1) General medicosurgical management

The management of PP requires a combined surgical and medical approach with drainage of purulent effusion and antibiotherapy. Antibiotic regimen is first empirical and must take into account Staphylococcus aureus, anaerobes and gram negative bacteria in case of abdominal or oesophageal origin [21,22]. In immunocompromised host or for a recently hospitalised patient, a high probability of Methicillin resistant Staphylococcus aureus must be considered [22]. Whatever the method applied, the goal of surgical management is to totally eradicate the focus of infection.

2) Surgery

Until 1941, the mortality of PP was estimated to be 100% in untreated cases. Pericardiostomy decreased mortality by about 50% and 30% when it was associated with antibiotics [19]. There is no consensus about the optimal method of pericardial drainage (table 2) [23]. Because of loculations and adhesions, simple evacuation by surgical or percutaneous drainage is known to be often associated with occurrence of constrictive pericarditis in the course of PP [23-25]. Beside, constrictive pericarditis, PP treated by simple drainage may evolve to a recurrence or persistence of PP leading to chronic pericarditis. To avoid these two complications, more invasive surgical treatments have been advocated. In retrospective series, partial pericardial resection, pericardial window, or total pericardiectomy showed a better outcome than simple pericardial drainage [23-25]. Majid published 13 cases of PP systematically treated with partial “preventive pericardiectomy”. With 1 death for 13 patients, outcome was better than reported in other investigations [23]. Corachan reported 4 deaths out of 5 patients treated with antibiotics and simple pericardiocentesis, whereas there were only 2 deaths out of 7 patients treated with
antibiotics associated with a surgical procedure consisting in a window pericardiectomy and manual breakdown of adhesions with a double pleural drainage left in situ [25]. Sethi et al. showed that compared to partial procedure, total pericardiectomy resulted in definitive eradication of pericardial focus of infection and avoided recurrence [20]. Taking together these data demonstrate the curative role of pericardiectomy by achieving a complete evacuation of purulent effusion. Indeed, systematic pericardiectomy prevents chronic and constrictive pericarditis by eradicating purulent collections, therefore avoiding pericardial fibrosis linked to chronic inflammation.

Despite these convincing data, physicians are still reluctant to perform a preventive radical surgery associated with potential serious complications. Nevertheless, this procedure could be easier in the first days after onset of disease, before apparition of adhesions, and some authors advocated a systematic early preventive pericardiectomy [26]. Indeed, early surgery may be performed before apparition of hemodynamic compromised. In fact, the operative mortality relates to the patients preoperative disability [27,28] and hemodynamic compromise caused by sepsis or cardiac compression rarely observed at an early stage.

3) Fibrinolysis

Intrapercardial fibrinolysis, a less invasive procedure, has been described as an alternative to surgery in the management of PP. Like pericardiectomy, this technique has a curative and a preventive role. The objective of fibrinolysis is to target fibrinoformation in order to optimise evacuation of the thick purulent fluid, and therefore to prevent both, chronic PP with relapses, and constrictive pericarditis.

Rationale of intrapericardial fibrinolysis

Fibrinolysis in PP follows the same rationale than in empyema. In the setting of empyema, surgical management has also better results than simple drainage. Many authors
attempted to demonstrate the efficacy of intrapleural fibrinolysis compared to simple drainage as a tool for prevention of persistent empyema requiring surgical debridement. Efficacy of fibrinolysis was demonstrated in empyema in a positive randomised controlled trial (RCT) and a meta-analysis [29,30]. In double blind RCT of Diacon et al., 44 patients received either placebo or streptokinase at an early stage of the disease, the day after chest drain insertion[29]. Authors found a better clinical outcome and less referrals to surgery in the fibrinolysis group. No bleeding event occurred. Unexpectedly, the largest RCT testing the efficacy of streptokinase in empyema was negative [31]. The group of 208 patients assigned to streptokinase treatment had the same rate of referrals to surgery than the group of 222 patients who received normal saline. No more hemorrhagic events occurred in the streptokinase group. Many comments on this study pointed out the heterogeneity of the population and the late timing of fibrinolysis, therefore suggesting that fibrinolysis may be useful in subgroups of younger patients treated earlier.

*Evidences of pericardial fibrinolysis efficacy*

Given the similarities shared between empyema and PP, fibrinolysis has been considered in PP in recent years, but in fact, the first cases of successful management of PP with fibrinolysis had been first reported in 1951 [10]. In these cases, patients had chronic purulent pericarditis persisting and relapsing despite surgical pericardiostomy and antibiotics. Fibrinolysis was applied with success at a late stage as a rescue treatment allowing a complete evacuation of purulent material. Forgotten for 30 years, it was “rediscovered” in 1984 by Bennet [11]. Since this paper, case reports and little series have been published with a great heterogeneity of protocols. In an experimental model of constrictive pericarditis following acute pericarditis in dogs, efficacy of fibrinolysis was demonstrated [18]. Fibrinolysis or normal saline was applied through pericardial drain daily from the third through sixth day after instillation of intrapericardial irritant mixture. Clinical and histological patterns of constrictive pericarditis were evaluated over a 60 day period.
All 11 animals assigned to normal saline group developed pericardial thickening and massive pericardial adhesions. Among them, 9 demonstrated clinical features of constrictive pericarditis. Half of the ten animals in the urokinase group did not demonstrate any sign of constriction and any histological changes in the pericardium. The 5 other of the fibrinolysis group manifested clinical signs of constriction. Pericardial thickening was significantly lower in the fibrinolysis group than in the control group. Clinical data on fibrinolysis in PP exist. All cases of fibrinolysis in PP available in the English-language literature are summarized in table 3. Among these studies, there’s only one small RCT that assessed the efficacy of this treatment in PP [44]. Unfortunately, the study population comprised both, tuberculous pericarditis and PP. As we mentioned, these two entities have not the same pathophysiology and prognosis. Among 94 patients, 34 suffered of PP, and 60 of tuberculous pericarditis. The study group received 200 000 Units of urokinase diluted in 20 ml of normal saline. Fibrinolysis promoted pericardial drainage with increased fluid drainage within the two hours following instillation of urokinase. Long term occurrence of pericardial constriction diagnosed at echocardiography was reduced compared to the control group (19% vs 57%). As expected, patients with PP were more likely to develop constriction than patients with tuberculous pericarditis. We can’t draw a firm and definitive conclusion from this study because no subgroup analysis was performed in the PP population and because it comprised only 34 patients with PP.

**Timing of fibrinolysis in PP**

There is no consensus on the appropriate timing of pericardial fibrinolysis (table 3). Two main options can be distinguished. Primary fibrinolysis is performed since the diagnosis of the disease as soon as the drain has been inserted. Rescue fibrinolysis is applied in rescue in case of recurrence or incomplete evacuation of pus. Among articles published, we found cases of failure only when fibrinolysis had been applied late, in rescue because of persistence of purulent effusion.
after many days of drainage. At this time thick loculations cannot be liquefied by fibrinolytic agent [36,38] (table 3). Furthermore, fibrinolytic agents can only dissolve fibrin, but hasn’t any effect on fibrosis present at a late stage but not at the beginning of the disease. The two experimental studies described above, indicate that pericardial fibrin influx increases in the first week and that fibrosis appears after about 2 weeks [17,18]. In addition of indicating that fibrinolysis may prevent acute pericarditis from progressing to constrictive pericarditis, the results of this study suggest that this treatment may be applied as soon as possible [17,18].

In absence of more convincing data, we advocate the use of systematic and early fibrinolysis before onset of pericardial loculations, adhesions, septa, and fibrosis [17,18].

**Optimal fibrinolytic dose and volume**

Streptokinase, urokinase and tissue plasminogen activator (tPA) have been used in pericardial fibrinolysis. A review provides a dose comparison between tPA and urokinase (UK). According to the different studies that compared efficacy of tPA and UK, authors found an equivalence of 36,000 units urokinase for 1 mg tPA. Most of studies in PP used streptokinase, but allergic risk suggests using urokinase or tPA [46]. Urokinase was used at a dose of 400,000 units in 4 cases and 200,000 in another, diluted in 20 ml of normal saline. BTS guidelines for the management of pleural infection propose instillation of SK 250,000 UI daily or twice daily, UK 100,000 UI daily, or tPA [47]. A reasonable dose of tPA 10 mg have been proposed in empyema [48]. There is no definitive data on the appropriate dose of these 3 fibrinolytic agents. Nevertheless, given the different regimens used in PP (table 3) and the doses proposed by BTS and ATS in empyema, reasonable options may be daily instillations of SK 250,000 UI, UK 200,000 UI or tPA 10 mg. Each instillation should be diluted in a volume of at least 20 ml of normal saline to ensure an adequate diffusion in pericardial space. Fibrinolytic agent must be retained in pericardial space by drain clamping for 2 to 4 hours. The treatment may be repeated
for 3 consecutive days to achieve adequate and complete pericardial drainage assessed on echocardiography.

**Failure and complications of fibrinolysis**

In case of failure of fibrinolysis resulting in incomplete drainage despite three consecutive instillations of fibrinolytic agent associated with adequate antibiotherapy, a surgical approach should be considered according to a multidisciplinary assessment. Given the patient prognosis, general status, and disability, radical pericardiectomy should be performed only if its benefit is believed to outweigh the potential drawbacks.

Three complications can theoretically occur. Nevertheless, complications of fibrinolysis in PP have exceptionally been reported. Even if allergy is a well known side effect of fibrinolysis with repeated instillation of streptokinase, treatment with urokinase or tPA greatly reduces this risk [46]. The second risk is major haemorrhage. Only one case of hemorrhagic tamponade after fibrinolysis has been described [35]. Nevertheless, this complication could be a direct consequence of PP and may not have been directly related to fibrinolysis. Indeed, fibrinolysis in PP has no systemic effect detected on coagulation laboratory tests [23]. The third risk is cardiac tamponade that could happen if the volume instilled is not evacuated by pericardial drain. The pressure-volume curve (figure 2) described in the experimental study published by Refsum et al., illustrates that an addition of a small amount of liquid may lead to cardiac compression [49]. This risk could be increased in case of late stage disease with low compliance because of pericardial fibrosis. Despite this theoretical risk, no tamponade due to intrapericardial instillation of fibrinolytic agent was described. In fact, just after drain insertion and pus evacuation, the fibrinolytic agent can be instilled with a volume inferior to the amount of purulent fluid drained. Therefore, we should never observe tamponade. Therefore, theoretical risks of allergy, major bleeding and tamponade should not restrain physicians to apply this technique.
Conclusion

Purulent pericarditis managed with simple pericardial drainage may evolve to constrictive and persistent PP. Despite the lack of definitive evidence, intrapericardial fibrinolysis may be an alternative to pericardiectomy as a treatment of PP and for prevention of persistent PP and constrictive pericarditis. Clinical and experimental data demonstrate that irreversible fibrosis occur after two weeks of evolution. Therefore, as diagnosis is often delayed, fibrinolysis should be applied as soon as possible to ensure the best efficacy. Even if complications could theoretically occur, they have exceptionally been reported in available literature. Thus, physicians should not be reluctant to apply this promising technique. Nevertheless, in case of failure of pericardial fibrinolysis, total pericardiectomy should be considered to avoid persistent and constrictive pericarditis.
List of abbreviations:
Purulent pericarditis = PP
Randomised controlled trial = RCT
TF = Timing of fibrinolysis
TT = treatment
No = Number of patients
R = Fibrinolysis in rescue
P = Primary fibrinolysis
ND = Not determined in the article
SK = Streptokinase
SD = Streptodornase
yrs = years
U = Units
UK = Urokinase
hrs = hours
Intraperic = Intrapericardial
ATB = Antibiotic
TTE = Transthoracic echocardiography
TEE = Transesophageal echocardiography
Tissue plasminogen activator = tPA
Urokinase = UK
Competing interest:

P Augustin: No competing interests
S Lasocki: No competing interests
JM Maury: No competing interests
M Desmard: No competing interests
P Montravers: No competing interests
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40. Reznikoff CP, Fish JT, Coursin DB. Pericardial infusion of tissue plasminogen


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FIGURE LEGEND:

Figure 1:
CT of chest with visible left alveolar pneumonia, complicated by empyema (E) (arrow), and circumferential pericardial effusion (PE) (arrows).

Figure 2:
Pericardial pressure volume curve.

Figure 3:
Flow diagram describing algorithm proposed for diagnosis and management of purulent pericarditis. *: in relation with etiologic classification (table 1); **: if no hemorrhagic complication of pericardial drainage; †: if catheter/drain is permeable
Table 1. Classification of purulent pericarditis according to source of infecting organism.

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<th>Description</th>
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<tr>
<td>I.</td>
<td>Infection by contiguous spread from a pleural, mediastinal or pulmonary focus</td>
</tr>
<tr>
<td>II.</td>
<td>Infection by contiguous spread of intracardiac infections</td>
</tr>
<tr>
<td>III.</td>
<td>Infection following a systemic bacteremia</td>
</tr>
<tr>
<td>IV.</td>
<td>Infection with contiguous spread from a postoperative infection</td>
</tr>
<tr>
<td>V.</td>
<td>Infection following a subdiaphragmatic suppurative lesion</td>
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Table 2. Different surgical modalities of pericardial effusion evacuation

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<tbody>
<tr>
<td>I.</td>
<td>Subxiphoid percutaneous catheter</td>
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<tr>
<td>II.</td>
<td>Subxiphoid tube drain</td>
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<tr>
<td>III.</td>
<td>Subxiphoid tube or percutaneous catheter and fibrinolysis</td>
</tr>
<tr>
<td>IV.</td>
<td>Pericardial window and pleural drain</td>
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<tr>
<td>V.</td>
<td>Partial pericardiectomy with pericardial tube</td>
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<tr>
<td>VI.</td>
<td>Anterior interphrenic pericardiectomy</td>
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<tr>
<td>VII.</td>
<td>Total pericardiectomy</td>
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Adapted from Majid [23]
Additional data files.

Table 3: Articles published in English on pericardial fibrinolysis for PP: Protocols and outcome
Suspicion of PP
predisposing condition* + fever or pericardial

Significant pericardial effusion? YES

Echography-guided pericardiocentesis

Aspiration of purulent effusion?
With tube drain or catheter No

Alternative diagnosis

Immediate instillation of fibrinolytic**
diluted in 20 - 50 ml of normal saline
clamp tube for 2 - 4 hours
3 consecutive days

Residual effusion?

NO Persistent purulent discharge ?^ YES

Consider fibrinolysis again

Considering surgery NO

Persistent purulent discharge ?^ YES

Consider surgery or fibrinolysis again

Consider surgery NO

drain withdrawal + follow up

NO

Fig. 3
Additional files provided with this submission:

Additional file 1: Table 3annals.doc, 76K
http://ccforum.com/imedia/1620765023441759/supp1.doc