Intrapericardial Treatment of Inflammatory and Neoplastic Pericarditis Guided by Pericardioscopy and Epicardial Biopsy—Results from a Pilot Study

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Summary: From a registry of 136 patients undergoing pericardiocentesis, 14 patients with autoimmune and 15 patients with neoplastic effusions were selected. All underwent pericardioscopy, epicardial and pericardial biopsy with histologic, immunohistologic, and polymerase chain reaction/or in situ hybridization analysis for microbial DNAs and RNA. Pericardioscopy identified neoplastic effusions by the high occurrence of protrusions. Fibrin threads and layers and neovascularization were found in both groups. For identification of the inflammatory and neoplastic process, the combined analysis of the cytology of the effusion and epicardial biopsy evaluation proved to be most important. Epicardial biopsy demonstrated a slightly higher sensitivity for identifying neoplastic disorders in the pericardium than cytology alone. Pericardial biopsy was inconclusive. Intrapericardial administration of 1 g of crystalloid triamcinolone in autoreactive pericarditis prevented recurrence in 13 of the 14 cases after 3 months and in 12 of the 14 cases after 1 year. In neoplastic effusion, intrapericardial administration of 50 mg cis-platin for 24 h prevented recurrence of a hemodynamically relevant effusion after 3 months in all, and after 6–12 months in 14 of 15 patients. Mortality in neoplastic effusion due to noncardiac tumor progression was 47 and 80%, respectively, after 3 and 6 months, as can be expected in endstage neoplastic disease. This pilot study demonstrates that local drug application is feasible, lifesaving, and well tolerated by the patients. It opens perspectives for local drug application in other cardiac disorders as well.

Key words: pericardioscopy, pericardial effusion, epicardial biopsy, neoplastic pericardial effusion, triamcinolon, cis-platin

Introduction

The causes of pericardial effusion are manyfold.1, 2 Viral,3 bacterial,4 fungal or rickettsial infections, radiation,5 renal failure,6 severe heart failure, hypertrophic and dilated cardiomyopathy,7 or storage diseases may induce it. It is observed after cardiac surgery,8, 9 after trauma or transmural infarction,10 after post-transfusion,1 and in neoplastic disorders (reviewed in Refs. No. 2 and 23).

Echocardiography, computed tomography, and magnetic resonance imaging are all used by clinicians to assess the presence and size of pericardial effusion. Macroscopic evaluation was restricted to the pathologist or the surgeon until transcutaneous pericardioscopy12–14 and epicardial and pericardial biopsy12, 14–18 revealed macroscopic and microscopic evidence of inflammatory or neoplastic pericardial and epicardial injury. These methods add positively to the analysis routine assessment of the pericardial fluid for enzymes, density, and hemoglobin,19 and cells by cytochemistry. It facilitates epicardial15, 16 and pericardial biopsies,15–18 both of which are fairly new investigative techniques. Pericardioscopy and epicardial biopsies are obviously the prerequisite for polymerase chain reaction (PCR) assessment of microbiologic etiology.20–22

For the treatment of so-called idiopathic pericardial effusion, nonsteroidal antiphlogistics, colchicine, and prednisone or prednisolone have been used widely, sometimes in controlled, rarely in randomized, and never in double-blind, randomized multicenter trials (reviewed in Ref. No. 2). For this reason, we examined in this pilot project the acute and long-term effect of 1 g triamcinolon acetate in crystalloid form given intrapericardially for 24 h. In neoplastic pericardial dis-
malignant pericardial effusion may cause fatal tamponade or cardiac failure. Diagnostic measures\textsuperscript{23,24} may identify the underlying malignant growth when analyzed directly in the pericardial fluid or in the biopsies.

Whereas tamponade can be relieved by pericardiocentesis, surgical or transcutaneous pericardiotomy\textsuperscript{25} is the treatment course for preventing recurrence in addition to systemic application of antineoplastic drugs. Therefore, this report also focuses on the effect of an intrapericardial application with cis-platin in patients with large effusion or tamponade from malignant pericardial effusions.

**Patients and Methods**

**Patients**

This report details our experience in 29 patients undergoing pericardioscopy and epicardial and pericardial biopsy. In 14 patients with autoimmune pericardial effusion, 1 g/24 h triamcinolone acetate was administered intrapericardially. In 15 patients, 50 mg/cis-platin was given intrapericardially. All patients were selected from our registry of 136 patients who had undergone pericardiocentesis puncture from 1989 to 1998 in our department. The patient cohort with autoreactive pericardial effusion (n = 14) comprised 5 male and 9 female patients, with an age range from 7 to 17 years. The neoplastic treatment group comprised 15 patients, 9 male, 6 female, with an age range from 47 to 78 years. In all patients, echocardiography was carried out from the parasternal, apical, and subxyphoid window. A prerequisite for both the puncture and the procedure was the echofree zone of > 4 to 5 mm in diastole in the subxyphoid view. Cardiac tamponade was present in 8 of 14 patients with autoimmune pericarditis and in 13 of 15 patients with neoplastic disorders.

**Methods and Pericardioscopy Procedure**

The diagnostic approach to the diagnosis of pericardial effusions is demonstrated in Figure 1.

Pericardiocentesis and pericardioscopy with optically guided biopsies from the epicardium and pericardium can be carried out as an emergency or elective measure, depending on the hemodynamic compromise derived from the effusion. Pericardiocentesis and pericardioscopy were carried out after local anesthesia in the subxyphoid region. Then a 1.4 mm cannula was advanced under radiographic control until pericardial fluid was aspirated. A teflon-coated exchange wire (Cordis) was then introduced, and the cannula was removed and exchanged for a 9F introducer set (Cordis). The length of the outer sheath was adapted to the length of the rigid pericardioscope minus 0.5 cm. A pigtail catheter was introduced and the pericardial fluid was removed gently by an electric suction syringe. Samples of the fluid were preserved for cytology, immunology, immunocytochemistry, bacteriology, virology, pathology, and the determination of standard laboratory parameters such as leukocyte count, Hb, HbE, protein content, and enzymes [lactose dehydrogenase (LDH), creatine kinase (CK), CK-MB, amylase]. Then 100–150 ml volumes of saline (37°C) were repeatedly injected into the pericardium and removed until the fluid from the pericardial sac was clear and permitted pericardioscopy. A flexible and a rigid instrument 110° or 180° angled pericardioscopes (Storz\textsuperscript{\textregistered}) were introduced. Videodocumentation (Sony Umatic) and photography (Ricoh) were performed. Representative images are demonstrated in Figure 2A and B.

**Epicardial Biopsies**

In all cases, an ACS 14 safety wire was introduced in the pericardial sac to allow rapid reintroduction of a pigtail cath-
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In case of perforation by the biopome and intrapericardial hemorrhage. Up to eight epicardial biopsies were taken with resterilizable biopomes (Schikumed) after selection of the biopsy site by pericardioscopy and x-ray control in biplane positions (posterior anterior and 90° left anterior oblique view). After the biopsy site was inspected by pericardioscopy, the next biopsy site was selected and biopsy was carried out. After the entire procedure, the pigtail catheter was left in place until cytologic and/or histologic examination of the samples had been carried out and the treatment strategy was decided upon. Representative histology is demonstrated in Figure 3A and B.

**Pericardial Biopsies**

Up to five pericardial biopsies were taken with biopomes from Schikumed, using established techniques. In principle, a 7F biopome sheath was advanced to the pericardial edge over a teflon guidewire until it reached the silhouette of the heart in the posterior anterior view. The wire was exchanged with the biopome. The biopome was then advanced and the branches were opened immediately after it had passed through the sheath.

**Patient Classification According to Investigative Methods**

When lymphocytes were the predominant cell population in the pericardial fluid, the patient was allocated to the lymphocytic autoreactive pericarditis group. Autoreactive predominantly antibody positive effusions had to be positive for antinuclear antibodies (ANAs) of the IgG and IgA isotype and cellularity in the fluid had to be minimal. Bacterial or fungal pericarditis was excluded from this analysis, as were patients with a positive PCR, in situ hybridization, or positive viral culture for one of the following cardiotropic agents: entero-, adeno-, cytomegalovirus, EBV, influenza virus, borrelia burgdorferi, or chlamydia pneumoniae. Bacterial pericarditis was diagnosed when the pericardial fluid contained bacteriae or acid fast bacilli either in the immediate smear analysis or in long-term culture.

**Results**

**Analysis of the Pericardial Fluid**

Of 136 patients treated over a period of 9 years, the patients and their laboratory parameters from the pericardial effusion
were selected for this comparative analysis from a registry on pericardial effusion undergoing pericardiocentesis. According to the criteria outlined in the “Patient” and the “Method” sections, either an autoimmune or a neoplastic effusion had to be present and confirmed by epicardial biopsy or cytology.

Selection was also made on the ground of available follow-up data for 12 months for the patients with autoimmune and for at least 3 months for the patients with neoplastic effusion. All patients in the autoimmune group received intrapericardial treatment with triamcinolone (n = 14). In the group with neoplastic pericardial effusion, tumor etiology was bronchus carcinoma in seven patients (six oat cell carcinoma, one epitheloid cell carcinoma), breast cancer in three, adenocarcinoma of the colon or the esophagus in two, ovarian carcinoma, Hodgkin’s lymphoma, and non-Hodgkins lymphoma in one patient each. All 15 tumor patients received cis-platin intrapericardially.

Female patients prevailed in the autoimmune pericardial effusion group; their ages ranged between 17 and 71 years, with the majority between the ages of 17 and 60 years. In the neoplastic effusion group, the opposite was the case: male preponderance and an emphasis on patients beyond 50 years of age (Table I).

Serious effusion prevailed in autoimmune disease, whereas in neoplastic disease hemorrhagic fluid was more commonly found. Elevated LDH, when compared with serum values, was found more frequently in neoplastic disease, as was monocytosis. In contrast, lymphocytosis in the effusion prevailed in the autoimmune group of patients (Table I).

Macroscopic Evaluation by Pericardioscopy

The following criteria were evaluated regularly: presence of fibrin threads or a fibrin network at the epicardium, neovascularization or vascular injections, and protrusion. Figure 2A demonstrates a fibrin layer on the otherwise smooth epicardial surface and the small lesion due to epicardial biopsy. Figure 2B demonstrates tumor-related protrusion in a case of bronchus carcinoma. As outlined in Table II, fibrin threads, neovascularization, or increased vascular injections were similarly found in both groups of patients, although it appeared that the neovascularizations were more pronounced in neoplastic disease (graded data not shown). Protrusions were limited to neoplastic disorders and to tuberculous pericarditis (data not shown) and did not show in autoimmune pericarditis. When compared, autoimmune effusion protrusions were the only specific and sensitive parameter to distinguish one group from the other.

Comparative Analysis of Cytology, Epicardial Biopsy and Pericardial Biopsy

To assess the value of cytology and epicardial and pericardial biopsy in both disease groups, the number of positive patients for each method was evaluated (Table III). A trend could be demonstrated that in neoplastic disease epicardial biopsy was more sensitive than analysis of the pericardial fluid by cytology. A representative histologic example of bronchus carcinoma is given in Figure 3A. Both methods proved to be complementary for the final diagnosis. In autoimmune pericarditis, the inflammatory infiltrate (Fig. 3B) was detected regularly in the epicardial biopsy and lymphocytes, or mononuclear cells were found to a similar extent in the pericardial fluid. Pericardial biopsy did not prove truly informative except in one patient with neoplastic disease.

Intrapericardial Administration of Triamcinolone: Acute Effect and Recurrence Rate

When viral etiology and neoplastic cells were excluded from the pericardial fluid or epicardial biopsy and the diagnosis of autoimmune (lymphocytic) pericardial effusion was

<table>
<thead>
<tr>
<th>Parameters/effusion</th>
<th>Autoimmune (n = 14)</th>
<th>Neoplastic (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrin threads (%) positive</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>Vascular injections in epicardium (%) positive</td>
<td>64</td>
<td>93</td>
</tr>
<tr>
<td>Protrusions (%) positive</td>
<td>7</td>
<td>88</td>
</tr>
</tbody>
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*p < 0.01 by chi-square analysis using Yates’ correction factor.
confirmed, 1 g triaminicolone in a crystalloid suspension was given intrapericardially for 24 h over the pigtail catheter which had been left in place after pericardiocentesis for the 24 h needed for this analysis.

Intrapericardial triaminicolone was tolerated well by all patients. Intermittent glucose intolerance with blood glucose levels up to 215 mg% was seen in three patients, in whom diabetes was not known previously. Assessment after 3 months gave a recurrence of the effusion in one patient and after 12 months in two patients (14%). One of the two patients had received colchicine 0.5 mg 3 times per day orally, the other patient was treated with a nonsteroidal antiphlogistic (ibuprofen) for 3 months. After 3 months there was recurrence in the one patient (7%) despite additional treatment with colchicine, and after 12 months their was recurrence after colchicine had been stopped previously in both patients. In one of these patients, a second pericardiocentesis and triaminicoloneacetate administration intrapericardially had to be performed, and prolonged azathioprin and prednisone treatment was given orally thereafter. The patient with the second recurrence in the 12-month follow-up responded well to oral colchicine. Mortality and recurrences are outlined in Table IV. The 80% mortality in neoplastic pericardial effusion after 6 months clearly shows that the spreading of pericardial tumor is a late feature in terminal neoplastic disease.

**Discussion**

It is obvious that assessment of the pericardial fluid allows a clear-cut differentiation between neoplastic and idiopathic pericardial effusion by cytology. The yield is improved by epicardial biopsy. Both methods, when applied alone or, even better, when carried out together can establish a firm diagnosis. This specific diagnosis permits specific intrapericardial anti-neoplastic treatment with cis-platin in high concentrations in the pericardial space. Although 80% of the patients did not survive 6 months due to tumor progression at other locations, the recurrence of a life-threatening effusion was very unlikely and thus found in one patient only. In contrast to systemic treatment, local application of cis-platin is well tolerated. Therefore, in neoplastic effusion, intrapericardial cis-platin application is the treatment of choice.

The entity defined here as autoimmune pericardial effusion probably comprises idiopathic pericardial effusion in many previous publications of other authors too numerous to be quoted here. This is primarily due to the fact that advanced molecular diagnostic methods such as PCR for microbial RNAs or DNAs, or immunohistochemistry for the characterization of epicardial infiltrate or for immunoglobulin binding in situ, or for anticardiac antibodies in the pericardial fluid have not been available. When viral persistence in the epicardium and the pericardial fluid is not detected, intrapericardial instillation of a crystalloid long-lasting triaminicolone suspension can be applied safely. From our experience, 1 g triaminicolone i.p. will exert its local effect for at least 4 to 6 weeks. It prevents

**TABLE III** Differentiation between autoimmune and neoplastic pericardial effusion by cytology and epicardial and pericardial biopsy (% positive)

<table>
<thead>
<tr>
<th>Parameters/effusion</th>
<th>Autoimmune (n = 14)</th>
<th>Neoplastic (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid: &gt; 3500 lymphocytes/mm³</td>
<td>64</td>
<td>13a</td>
</tr>
<tr>
<td>Fluid: AMLAs positive for IgG, IgM, and IgA</td>
<td>86</td>
<td>27a</td>
</tr>
<tr>
<td>Cytology diagnostic for inflammation or malignancy, respectively</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>Epicardial biopsy diagnostic for inflammation or malignancy</td>
<td>93</td>
<td>80</td>
</tr>
<tr>
<td>Pericardial biopsy diagnostic for inflammation or malignancy</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>PCR in fluid or biopsy positive for enteroviral RNA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PCR in fluid or biopsy positive for CMV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PCR in fluid or biopsy positive for EBV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PCR in fluid or biopsy positive for <em>borrelia Burgdorferi</em></td>
<td>0</td>
<td>0</td>
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*a<0.01 by chi-square analysis using Yates' correction factor.

Abbreviation: RNA = ribonucleic acid. Other abbreviations as in Table I.

**TABLE IV** Recurrence and mortality of autoimmune and neoplastic pericardial effusion after intrapericardial drug treatment

<table>
<thead>
<tr>
<th>Parameters/pericardial effusion</th>
<th>Autoimmune (n = 14)</th>
<th>Neoplastic (n = 15)</th>
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<tbody>
<tr>
<td>3-month recurrence rate (%)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>12-month recurrence rate (%)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>3-month mortality rate (%)</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>6-month mortality rate (%)</td>
<td>0</td>
<td>80</td>
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</table>
recurrence of symptoms and effusions very effectively but with serious side effects. Under these conditions, intrapericardial treatment will become the treatment of choice in inflammatory pericardial and perhaps myocardial disorders.

**Perspectives**

These two examples of local drug therapy are only prototypes of future treatment strategies for pericardial, myocardial, and even coronary disorders. This study could be carried out only when sufficient pericardial effusion was present to permit pericardial puncture without risking hemorrhage.

With new devices on the horizon, such as the PerDucer® (Comedicus), which will allow pericardial puncture without any effusion to be present due to the suction exerted on the pericardial layer, a completely new avenue in the local pericardial and myocardial drug treatment has been opened. Local anti-inflammatory treatment in myocarditis, intrapericardial antineoplastic treatment in small effusion, i.p. application of growth hormone in patients with heart failure and of cytokines and mediators of angiogenesis will become routine methods in the very near future. Local drug treatment has the unique advantage of little systemic side effects, thus improving the quality of the patients’ lives and of a high concentration at the site of application, where it is really needed.

**Acknowledgment**

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**References**