Intrapericardial Treatment of Autoreactive Myocarditis with Triamcinolon

Successful Administration in Patients with Minimal Pericardial Effusion

Bernhard Maisch[1], Arsen D. Ristić[1, 2], Petar M. Seferovic[2], David H. Spodick[3]

Abstract

A major clinical drawback in the treatment of autoreactive pericarditis is its inherent feature to relapse. Intrapericardial treatment with triamcinolone was reported to be efficient in patients with large, symptomatic autoreactive pericardial effusions, avoiding side effects of systemic treatment as well as compliance problems.

Intrapericardial treatment with 300 mg/m^2 triamcinolone was for the first time performed in patients with autoreactive myopericarditis and minimal pericardial effusions (75 to 110 ml). After 12 months of follow-up both patients are asymptomatic and there were no further recurrences of pericardial effusion. Pericardiocentesis in these patients was performed with the application of the PerDUCER® device, guided by pericardioscopy. This device has a hemispherical cavity at the top of the instrument connected with a vacuum-producing syringe. In this cavity the pericardium is captured by vacuum and tangentially punctured by the introducer needle. Pericardium that can be captured, must be up to 2 mm thin to fit into the hemispherical cavity. Pericardioscopy performed from the anterior mediastinum significantly contributed to the success of the procedures enabling visualization of the portions of the pericardium free of adipose tissue or adhesions, suitable for puncture with the PerDUCER®.

In conclusion, intrapericardial treatment of symptomatic autoreactive myopericarditis with minimal pericardial effusion was safely and efficiently performed in 2 patients. Pericardiocentesis was enabled by means of the PerDUCER® device, facilitated by pericardioscopy.

Key Words: Pericarditis · Pericardium · Pericardiocentesis

Erfolgreiche intraperikardiale Therapie von Patienten mit minimalem Perikarderguss mit Triamcinolon bei autoreaktiver Myoperikarditis

Zusammenfassung

Die Behandlung von Patienten mit autoreaktiver Perikarditis wird durch die hohe Rezidivrate kompliziert. Bisher erfolgte eine lokale intraperikardiale Behandlung mit Triamcinolon nur bei Patienten mit großen, symptomatischen Perikardergüssen, um die Nebenwirkungen einer systemischen Corticoidtherapie und die tägliche Medikamenteneinnahme zu vermeiden.

Hier wird erstmals über die intraperikardiale Therapie mit 300 mg/m^2 Triamcinolon bei zwei Patienten mit autoreaktiver Myoperikarditis und minimalem Perikarderguss (75 bis 110 ml) berichtet. Nach zwölf Monaten sind beide Patienten asymptomatisch und ohne Perikardergussrezidiv. Bei beiden Patienten wurde die Perikardpunktion mit dem neuen PerDUCER®-System unter perikardioskopischer Sicht durchgeführt. Dieses System verfügt über einen halbkugelförmigen Hohlraum an der Spitze, der mit einer Vakuumspritze verbunden ist. In dem halbkugelförmigen Hohlraum wurde das parietale Perikard durch das Vakuum angesaugt und fixiert und konnte anschließend durch eine aus dem Hohlkörper auszufahrende Nadel punktiert werden. Die Punktion mit dem PerDUCER® setzt voraus, dass die Dicke des Perikards 2 mm unterschreitet. Die mediastinale Perikardioskopie trug bei beiden Patienten wesentlich zum Erfolg der Prozedur bei, weil sie die Auswahl einer Perikardoberfläche ohne Adhäsionen und Fettgewebe erlaubte.

Damit konnte erstmals eine intraperikardiale Behandlung mit Triamcinolon bei zwei Patienten mit einer symptomatischen autoreaktiven Myoperikarditis und einem kleinen (< 110 ml) Perikarderguss unter simultaner Verwendung von mediastinaler Perikardioskopie und PerDUCER®-Punktionssystem dokumentiert werden.

Schlüsselwörter: Perikarditis · Perikard · Perikardpunktion

[1] Department of Internal Medicine-Cardiology, Philipps University, Marburg, Germany,
[2] University Institute for Cardiovascular Diseases, Medical Center of Serbia, Belgrade, Yugoslavia,
[3] Cardiology Division, St. Vincent Hospital, University of Massachusetts Medical School, Worcester, MA, USA.

When using standard clinical, biochemical, and cytological methods, the etiology of the majority of acute and chronic/recurrent pericarditis cases remains unresolved and is classified as idiopathic [1]. Many of these cases will represent either viral infections, or autoreactive pericarditis, however. In the latter group, a significant therapeutic contribution can be made with local and/or systemic glucocorticoid treatment [2]. From the curative point of view, it is therefore essential to distinguish between these 2 major forms of "idiopathic" pericarditis.

The diagnosis of autoreactive pericarditis is established if an increased number of lymphocytes and mononuclear cells, as well as the presence of antibodies against heart muscle tissue (antisarcolemmal) are detected in the pericardial fluid [2, 3]. Active viral infection in these patients must be excluded (negative virus isolation, no IgM titer against cardiotropic viruses in pericardial effusion, and negative PCRs on major cardiotropic viruses (adenovirus, enteroviruses, cytomegalovirus, influenza, hepatitis B, herpes simplex, parvo B19). In addition tuberculosis and other bacterial infection must be also excluded by PCR and cultures.

The treatment of autoreactive pericarditis with small pericardial effusion includes: oral non-steroid antiinflammatory drugs, (e. g. aspirin 2 to 3 g/day, or ibuprofen 2 g/day) or colchicine (0.6 mg every 6 to 12 hours). However, in some patients the results of non-steroid antiinflammatory therapy are unsatisfactory, and in severely symptomatic patients treatment with glucocorticoids is needed. However, systemic application of clinically effective doses is very often related with significant side effects.

In patients with symptomatic autoreactive pericardial effusions, large enough to perform pericardiocentesis, intrapericardial instillation of glucocorticoids could avoid their systemic side effect and allows high local dose application. This concept has proven its long-term efficacy in our previous series of patients [2]. However, due to technical difficulties, this was not yet possible in patients with very small pericardial effusions (< 200 ml), without unacceptable increase of the risks of pericardiocentesis.

A novel concept for access to the pericardial space is offered by the introduction of the PerDUCER® device (Comedicus Inc., Columbia Heights, Minnesota, USA) [4, 5]. It includes: 1. subxiphoid access to the mediastinal space, 2. pericardial capture, puncture, and insertion of the guidewire. Puncture of the pericardium is enabled by a sliding introducer needle located inside of the body of the instrument that ends with a hemispherical side cavity. In this cavity the pericardium is captured by vacuum and tangentially punctured by the introducer needle.

Using this approach, additionally facilitated by pericardioscopy, we have successfully applied intrapericardial treatment with triamcinolone in 2 patients with autoreactive perimyocarditis and minimal pericardial effusion.

Methods

The diagnosis of autoreactive myopericarditis was established after a thorough clinical assessment, serial echocardiographic examinations, and cardiac catheterization with endomyocardial biopsy. Endomyocardial biopsies revealed myocarditis with negative PCRs for the following microbial genomes: influenza A/B, cytomegalovirus, enterovirus, adenovirus, herpes simplex virus, Ebstein Barr virus, parvo B19, borrelia burgdorferi, chlamydia pneumoniae, and mycobacterium tuberculosis. To exclude eventually coexisting malignant disease, pericardial fluid obtained during the pericardiocentesis is analyzed by cytology and immunocytochemistry and by the same PCR battery of tests as the endomyocardial biopsies, to reveal eventual active infection.

The concept of pericardiocentesis with the PerDUCER® includes a combination of vacuum suction and tangential puncture of the parietal pericardium. The construction of the device was previously described in detail [4, 5]. It contains a 21-gauge introducer needle located inside a stainless steel sheath, which ends with a plastic view tube and a hemispherical side hole cavity where the pericardium is captured by vacuum and tangentially punctured by an introducer needle. The size of the side hole determines the maximum thickness of the pericardium that can be captured and punctured, which is up to 2 mm for the present model of the device. The procedure includes 2 major steps: 1. subxiphoid access to the anterior mediastinal space, 2. pericardial capture, puncture, and insertion of the guidewire. The procedure is performed in the cardiac catheterization laboratory in local anesthesia.

To facilitate the positioning of the device in the mediastinal space, selection of the surface suitable for application of the PerDUCER® device was performed with the endoscopic guidance (AF 1101 Bl flexible endoscope, Karl Storz Co., Tuttlingen, Germany).

Intrapericardial treatment with triamcinolone assumed instillation of 300 mg/m^2 of crystalloid suspension, in a single dosage, diluted in 100 ml of normal saline over a 7F pigtail catheter introduced over a guidewire after pericardiocentesis. The triamcinolone solution was held for 24 hours in the pericardial space and than completely evacuated. After aspiration of all residual fluid the pigtail catheter was removed. Patients were followed clinically and echocardiographically for 12 months.

The study was approved by the local ethical committee and all patients have signed an informed consent before the procedure.

Results

Clinical history of both patients with autoreactive myopericarditis with minimal pericardial effusion, treated with intrapericardial instillation of triamcinolone is summarized below:

B. H., a 26-year-old male patient was admitted to our hospital with a flu-like illness and precordial pain. There were no pericardial rubs on auscultation. The electrocardiogram showed minimal ST segment elevation in leads 2, 3, and aVF. Creatine kinase upon admission was 469 IU/l (10.8% CK-MB) reaching a maximum of 635 IU/l 1 day later (11.8% CK-MB). Troponin I upon admission was 49.0 µg/l reaching a maximum of 61.6 µg/l on the next day. Echocardiography showed upper normal left ventricular diameters (LVEDD/LVESD = 56/40 mm) with basal hypocontractility and minimal pericardial effusion of Type B of Horowitz classification [6]. Coronary angiography revealed normal coronary arteries and left ventricular endomyocardial biopsy was performed. Pathohistology demonstrated active myocarditis according to the Dallas criteria (infiltrate of 78 lymphocytes/mm^2, necrosis and edema). PCR for cardiotropic viruses, borrelia burgdorferi, and chlamydia pneumoniae was negative in the myocardial specimens. Computed tomography of the chest showed normal pericardial thickness of up to 1.4 mm and small pericardial effusion of 1 cm thickness in the apical region (Figure 1).

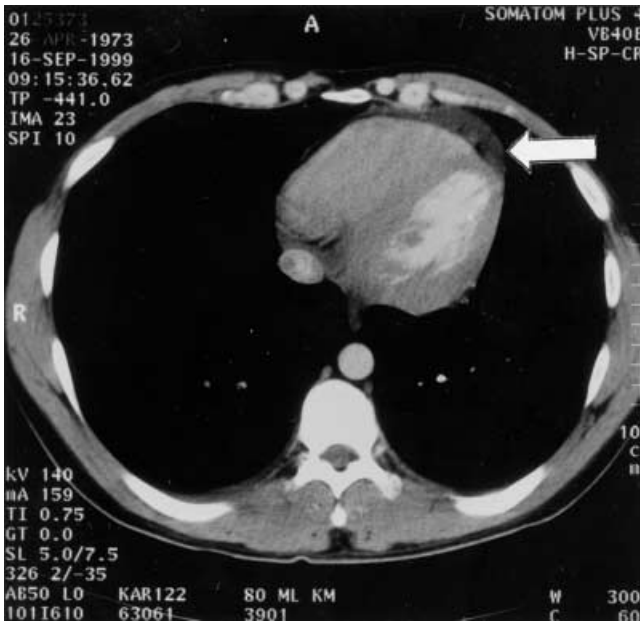

Figure 1
Very small pericardial effusion (white arrow) demonstrated by computer tomography before the pericardiocentesis with PerDUCER® device and application of intrapericardial treatment (Courtesy of Prof. K.-J. Klose, Director, Department of Radiology, Philipps University Marburg).

Abbildung 1
Sehr kleiner Perikarderguss (weißer Pfeil) im Computertomogramm vor der Perikardpunktion mit dem PerDUCER®-System und der intraperikardialen Therapie mit Triamcinolon (freundlicherweise zur Verfügung gestellt von Prof. K.-J. Klose, Direktor der Röntgenabteilung der Philipps-Universität Marburg.

Having in mind the young age of the patient and symptomatic, active, virus-negative perimyocarditis we assumed that intrapericardial corticosteroid treatment would have distinct advantages in comparison to systemic corticosteroid therapy. The above described pericardial puncture with combined mediastinal pericardioscopy and the PerDUCER® device was accomplished and a 7F intrapericardial catheter introduced (Figure 2). The amount of pericardial effusion was 110 ml. After evacuation of the effusion, 300 mg/m^2 of a diluted crystalloid suspension of triamcinolone was instilled and left in place for 24 hours. After 14 hours pericardial pain ceased.

The patient was discharged 2 days after the procedure on colchicine 1.5 mg/day orally. Electrocardiographic changes normalized within 3 weeks. Twelve months after the procedure, the patient is free of symptoms and of pericardial effusion. Myocardial contractil-

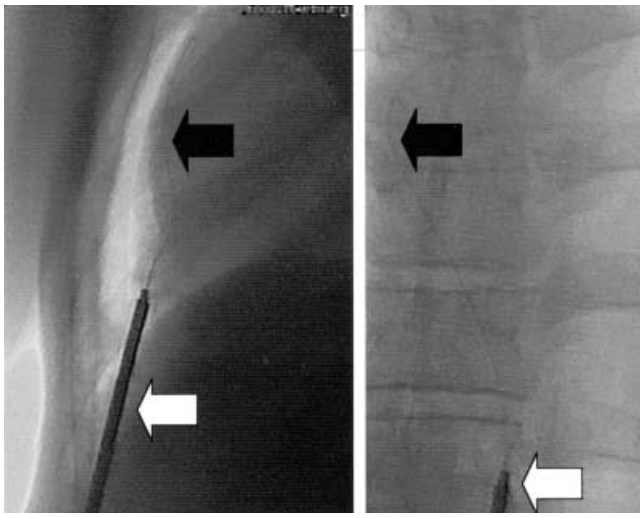

Figure 2
Successful pericardial access with the PerDUCER® device (white arrows). Intrapericardial position of the guide-wire is depicted with black arrows in the lateral view (left) and in the frontal view (right).

Abbildung 2
Erfolgreiche Perikardpunktion mit dem PerDUCER®-System (weiße Pfeile). Die intraperikardiale Lage des Führungsdrahts ist in der lateralen (links) und frontalen Ebene (rechts) durch schwarze Pfeile gekennzeichnet.

ity and left ventricular dimensions returned to normal (LVEDD/LVESD = 50/36 mm). No long-term side effects of corticosteroid treatment were observed.

The second patient we treated with the same protocol was G. H., a 59-year-old woman who presented with recurrence of chest pain, small pericardial effusion, and slightly impaired left ventricular contractility (LVEDD/LVESD = 46/29 mm) 6 months after the first episode of pericarditis and initial pericardiocentesis. Computed tomography of the chest showed normal pericardial thickness. Pathohistology of epicardial biopsies revealed a perimyocarditis, while cytology showed lymphocytic effusion. PCR examination for the cardiotropic viruses performed in both biopsies and effusion did not confirm active viral infection.

After pericardial access with the PerDUCER®, and evacuation of 75 ml of pericardial effusion, the patient received 300 mg/m^2 of triamcinolone intrapericardially. In a follow-up of 6 weeks the patient was asymptomatic with no pericardial effusion. Left ventricular ejection fraction on echocardiography has normalized. Six months after the procedure, she is also free of symptoms and had no more recurrences of pericardial effusion, as well as no side effects of corticosteroid treatment. Left ventricular diameters also improved (LVEDD/LVESD = 40/25 mm) in comparison to the initial assessment.

Discussion

A major clinical drawback in the treatment of autoreactive pericarditis is its inherent feature to relapse. Autoimmune mechanisms are most probably responsible for such recurrences. Local treatment with a high dose of crystalloid corticosteroid – triamcinolone – was proven to be highly efficient in patients with autoreactive pericarditis and large or moderate pericardial effusions (600 mg/m^2 of crystalloid triamcinolone in autoreactive pericarditis prevented recurrence in 13/14 cases [92.9%] after 3 months and in 12/14 cases [85.7%] after 1-year follow-up [2]). According to our further experience in additional 70 patients (unpublished data), doses of 300 mg/m^2 are equally efficient as the previously used higher doses and were therefore implemented in the 2 actual cases.

An important detail in application of this treatment is that intrapericardial application of concentrated triamcinolone is painful and therefore it must be covered by proper analgesia and the medication has to be instilled slowly, diluted in at least 100 ml of 37 °C warm normal saline. Less concentrated solutions of triamcinolone are also desired but could be implemented only in patients with pericardial effusions initially larger than 200 ml. In patients with initially very small effusions it is certainly essential to avoid hemodynamic compromise and even cardiac tamponade that could result after sudden intrapericardial instillation of volumes larger than 200 ml. Hemodynamic monitoring during the application of the intrapericardial treatment is a useful precaution measure.

Intrapericardial drug delivery was performed for decades in patients with neoplastic and uremic pericarditis. Recently, development of the PerDUCER®, as a novel instrument for pericardiocentesis in patients with very small or no pericardial effusion [4] reintroduced intrapericardial treatment as especially attractive option for the treatment of coronary disease, heart muscle diseases, and arrhythmias. However, despite the promising concept and good experimental efficiency, initial clinical application was only partially successful. In the study performed before bypass surgery in patients with

a normal pericardium, the PerDUCER® procedure was accomplished successfully in all of the 8 patients studied in the open-chest setting [4]. However, in an additional 4 patients studied before sternotomy for aortocoronary bypass, the pericardial access with the PerDUCER® could be achieved only in 2. Furthermore, in 5 patients with large to moderate pericardial effusions the procedure was not successful despite good mediastinal access and capture of the pericardium [5].

Apart from the appropriate selection of patients and exclusion of those with a thickened pericardium, one of the major reasons for the limited success of the procedure so far, could be the inability to avoid fat tissue or adhesions in positioning the device under standard fluoroscopic control. Having extensive personal experience with pericardioscopy [2, 3, 7] we applied the flexible percutaneous endoscope in the anterior mediastinal space for the inspection and selection of the pericardial surface so that pericardiocentesis with the PerDUCER® could be performed with no interposition of fat tissue. Addition of flexible endoscopy to the procedure certainly complicates and increases the costs of the procedure. However, we believe that its contribution was essential for the final success achieved in our 2 patients.

In addition to percutaneous access to the normal pericardium or to small pericardial effusions by the PerDUCER® there are several other concepts that are currently under investigation in animal models (transatrial [8, 9], transventricular [10], and Tuohy needle [11]). Despite very good safety and feasibility shown in these experimental studies, the procedures are certainly more invasive than the PerDUCER® concept and have not been applied in humans yet.

Application of intrapericardial steroids was for the first time proposed by Zeman et al. [12] in 1997 for the treatment of rheumatoid pericardial tamponade. Further application was, however, mostly dedicated to uremic and dialysis-associated pericardial effusion. Buselmeier et al. [13] investigated the effect of local steroid instillation in 45 patients with uremic pericardial effusion through an indwelling pericardial drainage catheter. In these patients previous intensive dialysis and other attempts at control of the effusions were unsuccessful. The catheter was left in place for an average of 50 hours and the amounts of steroids injected were 200 mg of methylprednisolone sodium succinate and 80 to 1,250 mg of triamcinolone hexacetonide. Triamcinolone doses were administered in 4- to 6-hour intervals until the pericardial drainage was stopped. Before the removal of the catheter a final dose of 50 mg of triamcinolone was instilled. The procedure had immediate success rate of 97.8% regarding both pericardial pain and effusion production. During the follow-up of 1 to 54 months (mean 14 months) there was no recurrence of symptoms or pericardial effusion in 95.6% of patients. The procedure was safe, apart from the development of an asymptomatic internal mammary artery fistula in 1 patient. Another patient had resolution of her pericardial effusion but not of associated pericardial pain. One patient had a recurrence of her effusion 6 months after therapy.

Reversal of intractable uremic pericarditis by triamcinolone hexacetonide was also achieved in the study of Fuller et al. [14]. In 5 patients who developed intractable uremic pericarditis during a long-term hemodialysis intrapericardial treatment with 50 mg of triamcinolone hexacetonide was applied. The same doses were repeated every 4 to 6 hours until the pericardial fluid drainage was stopped. The average doses of triamcinolone administered were 370 mg. These 5 patients recovered and subsequently were observed from 1 to 15 months with no evidence of recurrent pericarditis.

In contrast to the previous 2 contributions, Quigg et al. [15] treated dialysis-associated pericardial effusion with the intrapericardial administration of single doses of 250 mg of triamcinolone. The same approach with administration of a single dose of triamcinolone was implemented in our study. The number of treated patients was small (5 patients receiving maintenance hemodialysis for end-stage renal disease) but in all patients a prompt hemodynamic and symptomatic improvement was maintained during the follow-up evaluation for 6 months to 6 years.

In addition to intrapericardial administration of triamcinolone after subxiphoid pericardiocentesis 100% therapeutic success was reported by Popli et al. [16] for the treatment of uremic pericardial effusion by local steroid instillation via subxiphoid pericardiotomy in 7 patients.

In both cases presented in this study, as well as in other 82 patients treated with triamcinolone intraperi-

cardially in our center and most of the other procedures reported in the literature there were no major complications. It must be, however, kept in mind that in the setting of high-dose glucocorticoid treatment an increased risk of infection and development of purulent pericarditis exists. Such an infection with staphylococcus aureus complicating intrapericardial steroid instillation in uremic pericarditis that led to purulent pericarditis requiring pericardiectomy was described by Feinroth et al. [17].

In conclusion, this study presents the first clinical application of intrapericardial treatment with triamcinolone of patients with autoreactive myopericarditis with minimal pericardial effusions (70 to 110 ml). Intrapericardial application of corticosteroid therapy in patients with autoreactive acute or recurrent pericarditis avoids side effects of systemic treatment as well as compliance problems. After 12 months of follow-up both patients are asymptomatic and there were no further recurrences of pericardial effusion. Pericardiocentesis in these patients was performed with the application of the PerDUCER® device, guided by pericardioscopy. This device is enabling puncture of the pericardium with very small or no pericardial effusion making use of a hemispherical cavity at the top of the instrument connected with a vacuum-producing syringe. In this cavity the pericardium is captured by vacuum and tangentially punctured by the introducer needle. Pericardioscopy performed from the anterior mediastinum significantly contributed to the success of the procedures enabling visualization of the portions of the pericardium free of adipose tissue or adhesions, suitable for puncture with the PerDUCER®.

Acknowledgements

The authors greatly appreciate the research fellowship grant from the European Society of Cardiology as well as the Twin Centres Grant from the World Heart Federation that enabled participation of Dr. A. D. Ristić in the study.

References

1. Permanyer-Miralda G, Sagrista-Sauleda J, Soler-Soler J. Primary acute pericardial disease: A prospective series of 231 consecutive patients. Am J Cardiol 1985;56:623–30.
2. Maisch B, Pankuweit S, Brilla C, et al. Intrapericardial treatment of inflammatory and neoplastic pericarditis guided by pericardioscopy and epicardial biopsy – results from a pilot study. Clin Cardiol 1999;22:Suppl 1:I17–22.
3. Maisch B, Bethge C, Drude L, Hufnagel G, Herzum M, Schönian U. Pericardioscopy and epicardial biopsy-new diagnostic tools in pericardial and perimyocardial disease. Eur Heart J 1994;15:Suppl C:68–73.
4. Macris PM, Igo SR. Minimally invasive access of the normal pericardium: Initial clinical experience with a novel device. Clin Cardiol 1999;22:Suppl 1:I36–9.
5. Seferovic PM, Ristić AD, Maksimovic R, et al. Initial clinical experience with PerDUCER®: Promising new tool in the diagnosis and treatment of pericardial disease. Clin Cardiol 1999;22:Suppl 1: I30–5.
6. Horowitz MS, Sehultz CS, Stinson EB, et al. Sensitivity and specificity of echocardiographic diagnosis of pericardial effusion. Circulation 1974;50:239–46.
7. Maisch B, Drude L. Pericardioscopy-a new diagnostic tool in inflammatory diseases of the pericardium. Eur Heart J 1991;12:Suppl D:2–6.
8. Verrier RL, Waxman S, Lovett EG, et al. Transatrial access to the normal pericardial space: a novel approach for diagnostic sampling, pericardiocentesis, and therapeutic interventions. Circulation 1998;98:2331–3.
9. Waxman S, Moreno R, Rowe KA, et al. Persistent primary coronary dilation induced by transatrial delivery of nitroglycerin into the pericardial space: a novel approach for local cardiac drug delivery. J Am Coll Cardiol 1999;33: 2073–7.
10. March KL, Wood M, Mehdi K, et al. Efficient in vivo catheter-based pericardial gene transfer mediated by adenoviral vectors. Clin Cardiol 1999;22:Suppl 1:I23–9.
11. Laham RJ, Simons M, Hung D. Subxyphoid access of the normal pericardium: a novel drug delivery technique. Catheter Cardiovasc Interv 1999;47:109–11.
12. Zeman RK, Scovern H. Intrapericardial steroids in treatment of rheumatoid pericardial tamponade [letter]. Arthritis Rheum 1977;20:1289–90.
13. Buselmeier TJ, Davin TD, Simmons RL, et al. Treatment of intractable uremic pericardial effusion. Avoidance of pericardiectomy with local steroid instillation. JAMA 1978;240:1358–9.
14. Fuller TJ, Knochel JP, Brennan JP, et al. Reversal of intractable uremic pericarditis by triamcinolone hexacetonide. Arch Intern Med 1976;136:979–82.
15. Quigg RJ Jr, Idelson BA, Yoburn DC, et al. Local steroids in dialysis-associated pericardial effusion. A single intrapericardial administration of triamcinolone. Arch Intern Med 1985;145:2249–50.
16. Popli S, Ing TS, Daugirdas JT, et al. Treatment of uremic pericardial effusion by local steroid instillation via subxiphoid pericardiotomy. J Dial 1980;4:83–9.
17. Feinroth MV, Goldstein EJ, Josephson A, et al. Infection complicating intrapericardial steroid instillation in uremic pericarditis. Clin Nephrol 1981;15:331–3.

Address for Correspondence:
Prof. Dr. Bernhard Maisch, Director, Department of Internal Medicine – Cardiology, University, Baldingerstraße 1, D-35033 Marburg, Germany, Phone (+49/6421) 286-6462, Fax -8954, e-mail: BerMaisch@aol.com