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ORIGINAL ARTICLE

Constrictive pericarditis: risks, aetiologies and outcomes after total pericardiectomy: 24 years of experience†

Gábor Szabó[a,b,†]*, Bastian Schmack[a,†], Cem Bulut[c], Pál Soós[b], Alexander Weymann[a], Susanne Stadtfeld[a] and Matthias Karck[a]

[a] Department of Cardiac Surgery, University of Heidelberg, Heidelberg, Germany
[b] Heart Centre, Semmelweis University, Budapest, Hungary
[c] Department of ENT, University of Heidelberg, Heidelberg, Germany

* Corresponding author. Department of Cardiac Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany. Tel: +49-6221-566246; fax: +49-6221-565585; e-mail: gabor.szabo@urz.uni-heidelberg.de (G. Szabó).

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Abstract

OBJECTIVES: Constrictive pericarditis is the result of a spectrum of primary cardiac and non-cardiac conditions. Few data exist on the preoperative risk specific to survival after pericardiectomy. This study was designed to compare the association of aetiology of constrictive pericarditis and other clinical variables, with long-term survival after total pericardiectomy.

METHODS: A total of 89 patients were studied, who underwent pericardiectomy for constrictive pericarditis at a single surgical centre between 1988 and 2012. Constrictive pericarditis was confirmed by the surgical report. Demographic, pre-, intra- and postoperative data and long-term outcome were investigated. Survival was assessed by the Kaplan-Meier method.

RESULTS: Aetiology of constrictive pericarditis was idiopathic in 49 patients (55%), prior cardiac surgery in 21 patients (23.6%), tuberculosis in 5 patients (5.6%), radiation treatment in 5 (5.6%), uraemia in 4 (4.5%), inflammation in 3 (3.5%) myocardial infarction in 2 (2.2%), and perioperative mortality was 7%. Seventy-five percent of patients were in New York Heart Association (NYHA) class III–IV, which status significantly improved in long-term survivors (95% in NYHA I–II). Idiopathic constrictive pericarditis had the best prognosis (5-year Kaplan-Meier survival: 81%) followed by post-surgical (50%) and post-radiation pericarditis (no survivors after 5 years). Tuberculosis, myocardial infarction and uraemia have survival rates comparable with idiopathic aetiology. In addition, preoperative NYHA class IV was associated with significantly lower long-term survival.

CONCLUSIONS: Long-term survival after pericardiectomy for constrictive pericarditis is related to underlying aetiology and overall clinical condition. The relatively good survival with idiopathic constrictive pericarditis emphasizes the safety of pericardiectomy in this subgroup.

Keywords: Pericardiectomy • Pericarditis • Constrictive/complications/surgery • Pericarditis • Retrospective Studies • Treatment outcome

INTRODUCTION

Constrictive pericarditis is a rare but challenging disease leading to restrictive heart failure in its final stages. Pericardial diseases were noted in the early middle ages by Avenzoar (1113–1162) who described serofibrinous pericarditis [1–3]. Later Lancisi (1654–1720) noted the clinical consequence of pericardial adhesions. In 1669, Richard Lower described a patient with dyspnoea and intermittent pulse. In 1873, Kussmaul coined the term ‘pulsus paradoxus’. In 1896, the concept of Pick’s disease was introduced, which represents patients with constrictive pericarditis who had concomitant ascites and hepatomegaly (‘pseudo cirrhosis’) [4].

Diagnosis of constrictive pericarditis includes typical clinical signs such as pulsus paradoxus, jugular venous pulse, pericardial knock (a third heart sound, often referred to as a rapid filling sound) and pericardial rub, as well as ECG abnormalities. Non-invasive imaging techniques, such as transthoracic and transoesophageal echocardiography and in the modern era, cardiac CT and MRI, became the ‘gold standard’ for their diagnosis. Invasive cardiac catheterization and pressure measurements reveal predominant ventricular filling in the first third of diastole. This phenomenon is caused by a rapid and abrupt stop to filling of the heart chambers in the mid- and late diastole, when the fixed and stiffened pericardial sac cannot stretch any further. This leads to the haemodynamic signs of dip (the rapid ‘y’-descent in the jugular venous pressure) and plateau during right heart catheterization. This phenomenon is called ‘square root sign’. As a consequence of these limitations, there is a diastolic equalization of pressures in the right atrium, right ventricle and pulmonary wedge pressure, which corresponds to the left heart diastolic pressure [4].

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†Gábor Szabó and Bastian Schmack contributed equally to this work.

The treatment of constrictive pericarditis includes medical and surgical treatment. Patients without symptoms or with slight symptoms may benefit from diuretics, avoiding the risks of the surgical approach. Otherwise surgical pericardiectomy is the treatment of choice, which leads to a reduction of the patient's symptoms. Nevertheless, the operative risk and late mortality vary from 5–10% and 15–70%, respectively, which depends on many factors [1–7].

The largest studies on patients with constrictive pericarditis treated surgically include the experiences of the Mayo Clinic, the Stanford University Medical Center and the Cleveland Clinic Foundation [5-7]. However it should be noted that these patient cohorts were reviewed over a period from the late seventies until the end of the past century. The longest experience of 24 years is presented by the Cleveland Clinic, followed by Stanford (15 years) and Mayo Clinic (10 years). Recently, three larger series have been published by the John Hopkins University, by Iran and by China [8–10]. Whereas the John Hopkins series more or less confirms the observations of the other major US centres, the studies from Iran and China represent a completely different distribution of aetiologies and associated outcomes.

Looking at the literature, no major series of surgically treated constrictive pericarditis cases from the European zone has been published. Therefore we retrospectively reviewed our database to better define the impact of aetiology on survival. Additionally, we sought to characterize how the aetiology of pericarditis is changing and its impact on outcomes. The present retrospective cohort represents 24 years of modern experience and is thereby comparable to the longest published experience to date.

PATIENTS AND METHODS

We retrospectively analysed the prospectively maintained Heidelberg Foundation of Multicentre Cardiac Surgical Database (HVMD), which consists of approximately 1500 pre-, intra- and postoperative items of the patients operated in Heidelberg. Between 1988 and 2012, we identified 89 patients diagnosed with constrictive pericarditis. The clinical records of the identified patients were reviewed for additional clinical data and operative descriptions. Follow-up was performed by telephone interview or written questionnaire.

Pericarditis aetiology was determined by the patient's history. Patients with a history of prior cardiac surgery were defined as having postoperative pericarditis. Patients with a history of prior chest radiation were defined as having post-radiation pericarditis. Additional possible aetiologies included infectious (bacterial or fungal) and infarction-related. Patients who could not be classified in any of these groups were considered to have idiopathic pericarditis.

All operations were performed via midline incision and median sternotomy. The primary surgical goal was total pericardiectomy, including the resection of the anterior pericardium between the two phrenic nerves, the basal aspect of the pericardium over the diaphragm, the posterior part of the pericardium lying on the left and right ventricles and the pericardium over the great arteries and both atria. In the patients who had thick, dense and constrictive pericardium over the pulmonary veins, pericardial resection was also performed beyond the phrenic nerves. In these patients, an effort was made to save the phrenic nerves as pediculated tissue.

The primary outcome examined was survival (in-hospital; 1-year; 5-year; up to actualized follow-up in November 2012). Institutional survival data were supplemented with data from the telephone interviews and written questionnaire. Secondary outcome measures included New York Heart Association (NYHA) clinical status, haemodynamics (central venous pressure) the need for cardiac re-operation, prolonged mediastinal drainage, stroke, renal failure, cardiac arrhythmias (atrial fibrillation, junctional rhythms, heart block) and infectious complications (sternal wound infection, pneumonia, septicemia) as well as laboratory values focusing on liver enzymes as markers of right ventricular congestion as a consequence of restrictive pathology.

STATISTICS

Unless otherwise indicated, all of the continuous variables are expressed as mean ± SD and the categorical variables as percentages. The χ^2 and Student's *t*- tests were performed as appropriate. The Wilcoxon signed rank test was used to compare the NYHA functional classes of patients preoperatively and postoperatively. Survival was calculated by the Kaplan-Meier method and survival comparisons were performed using the log-rank test. A P value < 0.05 was considered statistically significant.

RESULTS

From 1988 to 2012, 89 patients with constrictive pericarditis underwent total pericardiectomy. The mean age was 57.9 ± 15.6 years and 74 patients (83%) were male. Concomitant cardiovascular risk factors included coronary heart disease (n = 40; 45%), hypertension (n = 42; 47%), diabetes mellitus (n = 19; 21%), obesity (n = 53; 60%) and smoking history (n = 24; 27%).

The main aetiology of constrictive pericarditis was idiopathic in more than half of the cases (n = 49; 55%), followed by post-cardiotomy (n = 21; 23.6%). Further aetiologies included post-radiation, post-tuberculosis, uraemic, inflammatory and post-infarction cases (Table 1).

Diagnostic methods included echocardiography and cardiac catheterization.

Total pericardiectomy was performed via midline sternotomy in all cases. Twenty-three patients (25.8%) had undergone at least one previous sternotomy. The mean procedural time was 211 ± 101 min. Thirty-five patients (39.3%) needed cardiopulmonary bypass support with a mean cardiopulmonary bypass time of 51 ± 53 min. Concomitant cardiac surgical procedures

Table 1: Aetiology of constrictive pericarditis

Constrictive pericarditis aetiology	
Patients total, *n*	89
Idiopathic, *n* (%)	49 (55.0)
Post-cardiotomy, *n* (%)	21 (23.6)
Post-radiation, *n* (%)	5 (5.6)
Post-tuberculosis, *n* (%)	5 (5.6)
Uraemic *n* (%)	4 (4.5)
Inflammatory, *n* (%)	3 (3.5)
Post-infarction	2 (2.2)

were performed in 26 cases (29.2%), which included bypass surgery in 9 patients (10.1%), single valve surgery in 12 patients (13.5%), multiple valve surgery in 3 cases (3.3%) and congenital surgery in 2 cases (2.2%).

Pre- and postoperative NYHA classifications are shown in Fig. 1. Preoperatively, most of the patients were in NYHA class III–IV, which improved significantly to NYHA class I–II.

The comparison of pre- and postoperative central venous pressure values showed a significant drop of nearly 50% (Fig. 2).

Overall survival is shown in Fig. 3A, with 7% perioperative mortality and over 60% survival after 20 years. Subgroup analysis with respect to survival indicated that female patients have a worse survival rate than males (Fig. 3B). Survival rates were also clearly associated with preoperative NYHA classification (Fig. 3C). Worse NYHA classification was related to reduced survival. Survival rates were also dependent on the underlying aetiology: while idiopathic, post-inflammatory—including tubercular and uraemic—pericarditis showed a quite favourable outcome, post-cardiotomy patients had a markedly reduced survival. The worst outcome was shown in patients after radiation (Fig. 3D). Idiopathic constrictive pericarditis had the best prognosis (5-year Kaplan-Meier survival: 79.6%) followed by post-surgical (47.7%, $P < 0.05$) and post-radiation pericarditis (no survivors after 5 years, $P < 0.05$).

Pre- and postoperative laboratory values including liver enzymes and bilirubin had no impact, preoperative cardiovascular risk factors and concomitant operations had no significant impact on survival (data not shown).

DISCUSSION

In the present study we reported the 24-year experience of a single European centre regarding contemporary indications, risk factors and outcomes. We have shown that mid- and long-term outcome is strongly influenced by aetiology, namely that post-cardiotomy and more pronounced post-radiation patients have a reduced life expectancy after pericardiectomy.

To date, six large-scale studies have been published [6–10]. Even if these studies are considered relatively large, the incidence of constrictive pericarditis remains not more than a dozen cases per year in large centres. Constrictive pericarditis is a rare and serious disease; postoperative in-hospital mortality ranges from 4.4–11%, which is considerably higher than for routine bypass or valve surgery [6–10]. In our experience, in-hospital mortality was 7%, which is in line with previous cohorts.

A major finding of our series was that the aetiology of constrictive pericarditis influences not only short-term but also long-term outcome following pericardiectomy. Idiopathic and inflammatory pathogenesis was associated with the best in-hospital and long-term survival rates, while radiation-induced constrictive pericarditis showed very poor prognosis. In our series, none of the patients survived over 5 years. The survival curve of post-cardiotomy patients is between that of the idiopathic patients and that of the post-radiation patients. These tendencies are nearly identical to the major US series [5–8].

In a series of 313 patients from the Mayo Clinic between 1936 and 1990, the overall mortality was 14% (in NYHA class IV it was 46%; in Class III, 10%; in Class I and II, 1%) [5]. In another series of 135 patients evaluated at the Mayo Clinic from 1985 to 1995, the 30-day perioperative mortality was 6%. In the late survival analysis (10 years of follow-up) independent predictors of late survival were age, NYHA class and previous radiation. Again, independent predictors of late cardiac-related deaths were previous radiotherapy, NYHA class III–IV, symptoms and age. Previous radiotherapy was the most powerful predictor of all outcome measures [5]. In the Cleveland Clinic Foundation series with 163 patients between 1977 and 2000, the perioperative overall mortality was 6%. This corresponds to a perioperative mortality of about 5–7.6% in recent studies [5–15]. The most frequent cause of death in the perioperative period of the Cleveland Clinic Foundation series was low output heart failure, as described in most other previous studies [5–8, 12]. Idiopathic constrictive pericarditis had the best prognosis with 7-year Kaplan-Meier survival of 88%, followed by post-surgical constrictive pericarditis with 66% and post-radiation constrictive pericarditis with 27%. In the current series of the John Hopkins University, the survival rates were almost identical to those of the Cleveland Clinic, emphasizing worse outcome after irradiation and cardiotomy [8].

Interestingly, the studies from the Asian zone [9, 10] showed a completely different distribution of aetiologies. Tuberculosis was

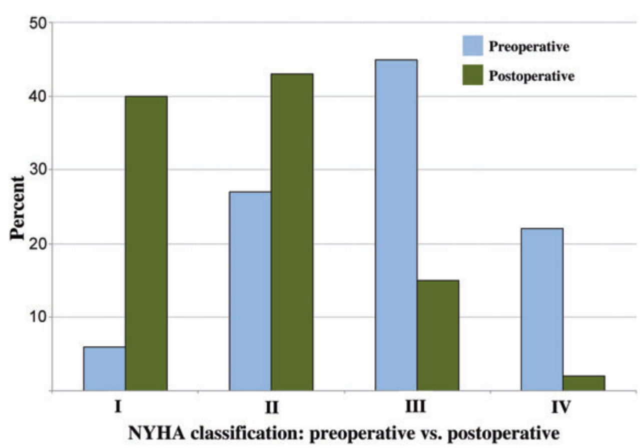

Figure 1: NYHA Classification. Pre- and postoperative NYHA classification is shown. It should be noted that the majority of the patients were in NYHA III–IV before the operation and moved towards NYHA I–II postoperatively.

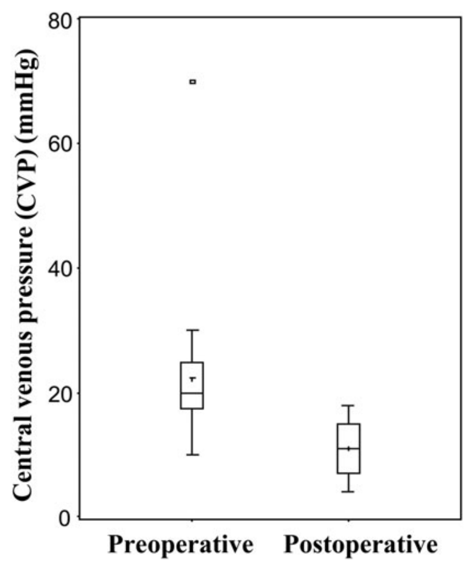

Figure 2: Central venous pressure. Pre- and postoperative central venous pressure (median, mean ± SD, 25 and 75 percentile) showed a significant improvement after total pericardiectomy.

ADULT CARDIAC

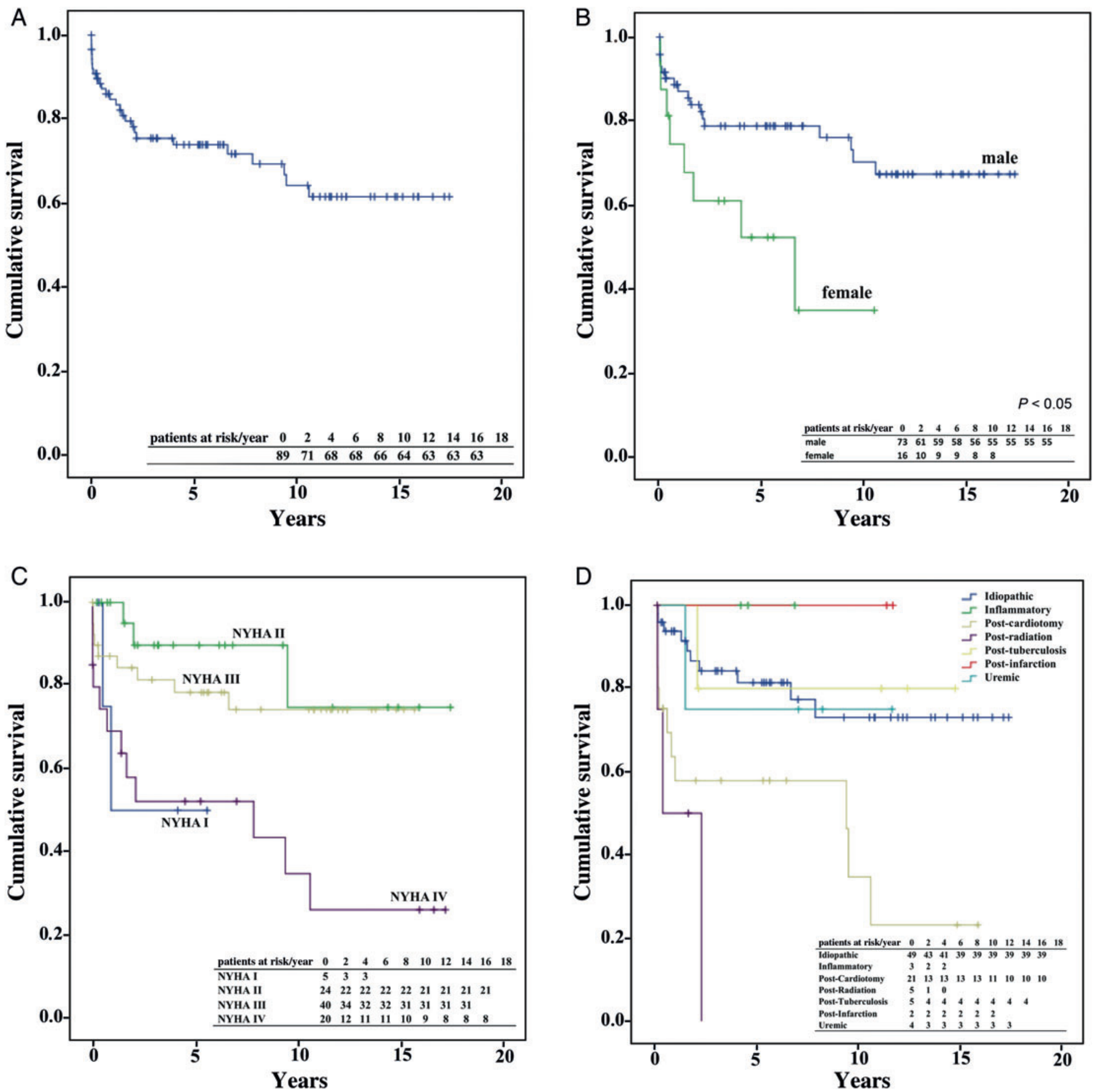

Figure 3: Survival calculation. (**A**) Kaplan-Meier survival curve of the complete patient cohort. (**B**) Kaplan-Meier survival curves in male and female patients showed a significant survival benefit in males ($P < 0.05$). (**C**) Kaplan-Meier survival curves showed an association with preoperative NYHA classification. (**D**) Kaplan-Meier survival curves demonstrate reduced survival in patients with post-cardiotomy or post-radiation in comparison to other aetiologies ($P < 0.05$).

one of the leading causes of constrictive pericarditis beside idiopathic cases: the role of post-cardiotomy and post-radiation cases can almost be disregarded. Accordingly, these centres reported excellent survival rates above 95% in the short term.

The reduced survival rates in post-cardiotomy and post-radiation cases are not completely understood. Unfortunately the retrospective analysis of the clinical data cannot explain the pathophysiological background, either in our series or in others.

Radiation-induced heart disease (RIHD) is a serious side-effect of radiotherapy for intrathoracic and chest wall tumours. The threshold dose for development of clinically significant RIHD is believed to be lower than previously assumed. RIHD becomes clinically apparent 10–15 years after radiation exposure. Chronic manifestations of RIHD include accelerated atherosclerosis, cardiomyopathy and valve abnormalities. Reducing exposure of the heart during radiotherapy is the only known method of preventing RIHD and there are no approaches to reverse RIHD once it occurs [16]. We might speculate that, in case of post-radiation, the disease is not restricted to the pericardium alone but also affects the myo/endocardium. Interstitial fibrosis and microvascular dysfunction may reduce ischaemic tolerance and exercise capacity. In the early postoperative period this may lead to prolonged low out syndrome and subsequent death. In the mid-term, progressive heart insufficiency may occur, followed by rapid deterioration of such patients. Reviewing our clinical records, post-radiation patients died because of cardiac insufficiency and not because of recurrence or secondary new onset of malignancies.

The impairment of survival in post-cardiotomy patients maybe explained, at least partly, by the fact that structural heart disease requiring previous cardiac surgery may implicate reduced myocardial function—or at least reduced functional reserve—that precludes a portion of this subgroup from benefiting from surgical treatment [7].

It should be also noted that, beside the aetiology of constrictive pericarditis, the overall clinical status of the patient might substantially influence postoperative outcome. In our experience, preoperative NYHA stage was clearly associated with survival rates ranging from over 80% long-term survival (NYHA II) to below 50% (NYHA IV). Due to the low number of our patients, we observed a bias in the NYHA-associated analysis, as two patients died in the NYHA I group within one year. Interestingly, both patients had irradiation, which emphasizes that radiation-associated pathophysiology may have a deeper impact on postoperative cardiac function, independent of the actual clinical status. As mentioned above, other studies also found that NYHA staging is a strong prognostic factor for survival in patients after pericardiectomy for constrictive pericarditis. Although early- but also long-term survival rate is reduced in high-risk patients (NYHA IV), survivors experience a marked improvement in their clinical status—improved by up to two classes—which is in consensus with other reports [5, 7, 8]. This implies that patients in NYHA IV can be operated at increased risk, with the prospect of improvement. However, how far real survival benefit can be achieved by the surgical option remains unclear, as no corresponding dataset exists about conservatively treated patients.

An interesting finding of the present series is that female gender was associated with markedly lower survival rates (less than half). To our best knowledge, this is the first report that describes this phenomenon. The underlying pathomechanisms remain unclear. It is well known that female gender is associated with higher risk of certain cardiovascular procedures. Gender differences exist in outcomes—particularly early mortality—for percutaneous interventions (PCI) and coronary artery bypass graft surgery (CABG) [17]. Female CABG patients appear to have higher perioperative mortality and cardiac morbidity, although studies of neurological outcomes in female CABG patients have produced equivocal findings. Women undergoing CABG tend to consume more hospital resources than men, in terms of blood transfusion, mechanical ventilation and length of intensive care unit and overall hospital stay. With regard to valve surgery, women appear to have worse outcomes than men if the surgery is combined with a CABG operation [18]. Early mortality differences were reduced—but not consistently eliminated—after adjustment for comorbidities, procedural characteristics and body habitus. Power to detect gender differences after multivariate adjustment was limited by declining mortality rates and small sample size. Gender was an independent risk factor for complications after both CABG and PCI. Women experience greater complications and earlier mortality after revascularization. In the present series of pericardiectomy patients, we have some limitations, primarily due to the relatively small overall size of this cohort, which precludes investigating confounding factors with regard to gender issues. Therefore, future exploration of gender differences is required in the context of constrictive pericarditis.

LIMITATIONS

This is the first contemporary study that summarizes a European experience of treating constrictive pericarditis over the past 24 years. However, there were a few limitations that warrant mention. As the incidence of constrictive pericarditis is quite low, the total number of patients remains limited. Nevertheless, this cohort is comparable with the largest studies published to date. The limited number of patients also restricted statistical analysis: therefore the results of the survival analysis could not be extended by multivariate analysis of the subgroups. However it should be noted that other published data also do not contain such analysis.

CONCLUSIONS

In conclusion, treatment of constrictive pericarditis by pericardiectomy effectively relieves symptoms and has a favourable long-term outcome. Nevertheless, risk assessment and decision-making about treatment options should take into account the underlying aetiology and overall clinical status.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr S. Cebotari *(Hannover, Germany)*: The authors present a large single-centre series on the treatment of constrictive pericarditis. This is quite a rare disease in western Europe, so it is a study of 89 patients. The main outcome of the study is that these patients improve after the operation, their clinical status is improved.

So, to question number 1. In my opinion, the diagnosis of constrictive pericarditis is a very complex and difficult issue. You mentioned that echocardiography and cardiac catheterization were used in your patients. Unfortunately, I didn't see any data regarding cardiac MRI or CT scan and my question is: were they used in your patients and what do you think about these methods of diagnosis?

Dr Szabo: Echocardiography and cardiac catheterization were performed in all of the patients. Particularly in the earlier phase, the late '80s and beginning of the '90s, there were no CT and MRI scans available in these patients. In a more recent portion of the cohort, of course, we also performed CT and MRI. In fact, this has become the 'gold standard' to diagnose these patients or confirm the diagnosis, which is achieved by echocardiography.

Dr Cebotari: Secondly, I saw that you used cardiopulmonary bypass during the surgical procedure, I think in 30 patients. Is this is a predictive factor which increased mortality in these patients and did any of your patients require circulatory support in the intensive care unit (I mean ECMO)?

Dr Szabo: The reason for using cardiopulmonary bypass was mainly associated with the need for additional cardiac surgery procedures. We had a subset of patients—29 patients—who had coronary bypass, valve surgery or other surgery; these are mainly the patients who had cardiopulmonary bypass. There were only a very few patients in this cohort who had total pericardiectomy alone and required cardiopulmonary bypass. In this population, survival was not influenced, either by the use of cardiopulmonary bypass or the requirement for additional cardiac surgery procedures.

Dr Cebotari: And the ECMO usage postoperatively?

Dr Szabo: Only one or two patients required extracardiac support by ECMO in this cohort. I didn't mention it in the paper; I will put it in later.

Dr Cebotari: Now to question number 3. All of you probably know that increase in bilirubin acts like a surrogate for cardiac insufficiency and elevation of the liver enzymes speaks in favour of decreased hepatic perfusion and increased hepatic congestion. Several groups documented that increase in elevated bilirubin can be predictive of mortality in pericardectomy, which we also experienced in our patients. And, surprisingly for me, I didn't see this trend documented in your patient population. Could you comment on that?

Dr Szabo: Yes. In fact, we also performed this kind of analysis which, however, is not included in the presentation because of the time limits. We looked at the survival rates independent of bilirubin and other liver enzymes, collected before the operation, immediately after the operation and also at discharge. And, surprisingly, we didn't see any clear trend in the case of bilirubin or other liver enzymes. Although it's clear there is right ventricle congestion that results in liver dysfunction and an elevation of enzymes, in our cohort this is not a predictive variable.

Dr Cebotari: Finally, you documented the highest mortality in patients with pericarditis after radiation. I think that radiation influences not only the pericardium but also can induce myocardial fibrosis and restrictive cardiomyopathy. In your opinion should we do some more preoperative investigations in these patients, such as myocardial biopsy, in order to redirect them for transplantation or maybe assist devices?

Dr Szabo: That's a very, very good question. I absolutely agree that, most probably, not only the pericardium but also the myocardial structure is altered after radiation. And here new diagnostic tools would be necessary to investigate what the myocardial structure really looks like: for example, MRI texture analysis. Two of the patients who died were actually in quite good clinical shape but, because of the radiation, they had a very poor outcome. So this is a patient group which should be treated very carefully and the decision to operate—or not—has to be made, based on the entire clinical picture.