Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension: hemodynamic characteristics and changes

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Abstract

Objective: To see whether degree of pulmonary hypertension or severity of cardiac failure affect the success of pulmonary thromboendarterectomy (PTE) in chronic thromboembolic pulmonary hypertension. Methods: From May 1996 to June 1999, 33 patients, all in New York Heart Association (NYHA) class 3 or 4, were treated with PTE. Preoperative hemodynamic values were: central venous pressure (CVP) 8 ± 6 (1–23), mean pulmonary artery pressure (mPAP) 50 ± 10 (30–69), cardiac output (CO) 3.3 ± 0.9 (1.8–5.2), pulmonary vascular resistance (PVR) 1056 ± 344 (523–1659), and right ventricle ejection fraction (RVEF) 12 ± 5 (5–21). To establish whether some hemodynamic or cardiac variables correlate with surgical failure (early death or functional non-success), these patients were divided into a low risk or a high risk group for each variable: CVP (<9 or ≥9), mPAP (<50 or ≥50), CO (≥3.5 or <3.5), PVR (≥1100 or <1100), and RVEF (≥10 or <10). The duration of 3–4 NYHA class period (<24 or ≥24 months) was also included in the study. Results: Three patients (9.1%) died in hospital, one (3.0%) underwent lung transplant shortly after PTE, and in five cases (15.2%) mPAP and PVR at the 3-month follow-up examination corresponded with our definition of functional nonsuccess (mPAP and PVR decreased by less than 40% of preoperative values). One of the five functional nonsuccess patients underwent lung transplant 3 months after the operation and another died 17 months after the operation from a non-related cause. Thus PTE was successful in 24 patients and unsuccessful in nine. None of the hemodynamic variables considered was found to be associated with the disparate outcomes. At the 3-month examination, all surviving patients were in NYHA class 1 or 2 except for three in NYHA class 3. At 2 years, hemodynamic values were: CVP 2 ± 2 (0–4), mPAP 16 ± 3 (12–21), CO 5.0 ± 1.0 (3.4–6.5), PVR 182 ± 51 (112–282), and RVEF 35 ± 5 (26–40). All differences were significant with respect to baseline values (P < 0.001). Preoperative mPAP and RVEF values had a strict linear correlation ($R = 0.45; P = 0.014$). Conclusions: None of the variables considered was correlated with early death or functional nonsuccess. Neither preoperative severity of pulmonary hypertension nor degree of cardiac failure influenced the outcome of the operation. PTE leads to hemodynamic recovery even in very compromised patients.

Keywords: Chronic thromboembolic pulmonary hypertension; Pulmonary hemodynamic values; Cardiac failure; Pulmonary thromboendarterectomy; Lung transplantation

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTPH) is a rare disease but is the only type of pulmonary hypertension that can be successfully treated with conservative surgery. Although pulmonary thromboendarterectomy (PTE) is being more and more adopted as an alternative to lung transplantation for CTPH patients, some issues regarding its choice as a treatment for this pathology have not yet been adequately resolved. One of the major problems the surgeon has to deal with is the degree of pulmonary hypertension and the severity of cardiac failure in these patients. Several authors have described the characteristics of
CTPH [1,2] and the indications for PTE [3–7]. Others have described the early [8,9], mid-term [10,11] and long-term [12,13] results of PTE.

Little information is available, however, on the pre-surgery risk factors and on the predictors of mortality in these patients [14–18]. The aim of this study was to verify whether some hemodynamic and cardiac variables can jeopardize the successful outcome of PTE and whether, in these cases, lung transplantation should be the treatment of choice.

2. Materials and methods

2.1. Study

Since the aim of this study was to establish whether CTPH could be successfully treated with PTE regardless of the degree of pulmonary hypertension and the severity of cardiac failure, five hemodynamic and cardiac variables were measured: central venous pressure (CVP), mean pulmonary artery pressure (mPAP), cardiac output (CO), pulmonary vascular resistance (PVR), and right ventricle ejection fraction (RVEF). For each variable the patients were divided into two groups defined as low risk or high risk group: CVP (<9 or ≥9 mmHg), mPAP (<50 or ≥50 mmHg), CO (≥3.5 or <3.5 l/min), PVR (<1100 or ≥1100 dynes/s cm$^{-5}$), and RVEF (≥10 or <10 %). The duration of the 3 or 4 NYHA class period (<24 or ≥24 months) was also included in this study to verify its influence on the outcome of these patients (Table 1). Cut-points were chosen based on other clinical PTE studies [14–18].

In our study the definition of surgical failure was given whether we had an in-hospital or within 30 day mortality (early mortality) or when at the 3-month follow-up examination the mPAP and PVR values had gone down by less than 40% of preoperative values (functional non-success). The hemodynamic follow-up protocol has the first examinations yearly for 5 years.

Our very strict follow-up protocol, which foresees examinations at 3 months after the operation and then yearly for 5 years, yielded detailed data up to 2 years after the operation on which to conduct our analyses.

2.2. Inclusion and exclusion criteria

Patients were selected for PTE on the basis of combined clinical (only patients in New York Heart Association (NYHA) class 3 or 4), anatomical (lesions at the level of the main, lobar and segmental pulmonary branches), and hemodynamic (PVR >300 dynes/s cm$^{-5}$) characteristics. PTE was postponed for patients with a fair clinical status (NYHA class 2) or with an acceptable hemodynamic status (PVR <300 dynes/s cm$^{-5}$ due to still elevated cardiac output), while patients with exclusively distal lesions (segmental or sub-segmental pulmonary branches) were excluded from the PTE program.

2.3. Population

Between May 1996 and June 1999, 33 CTPH patients (18 male, 15 female; age at operation 48.0 ± 14.4 years, range 17–75) were referred to our center and treated with PTE. The majority of these patients (N = 21, 63.6%) presented with a positive history for venous thromboembolism (N = 9, 27.3%), in some instances associated with immunological disorders (N = 12; 36.3%). Almost half our population (N = 16; 48.4%) presented with antiphospholipid antibody syndrome, in two cases associated with Systemic Lupus Erithematosus. Despite detailed analyses, in eight patients (24.2%) no cause was found for CTPH.

All patients were in NYHA class 3 (N = 21; 63.6%) or 4 (N = 12; 36.4%) at the time of operation, with an average period in this condition of 27 ± 45 months (range 6–264) (Table 1).

2.4. Instrumental exams

The most important instrumental exams for accurate diagnosis of this disease are pulmonary ventilation/perfusion scintigraphy, pulmonary angiography, pulmonary spiral angio-CT scan and right heart hemodynamics. The preoperative hemodynamic values of our 33 patients are shown in Table 1. They show the very compromised status of some patients, with severe right cardiac failure as a consequence of extremely high values of pulmonary hypertension. In 15 patients (45.5%) PVR exceeded 1100 dynes/cm$^2$. The RVEF was lower than 10% in 11 patients (33.3%).

2.5. Surgical technique

The operation was always performed through two separate arteriotomies on both main intrapericardial pulmonary arteries following the standardized technique described by the University of California at San Diego (UCSD) group [10]. In one patient the procedure was attempted only on one side, because we were unable to find the dissection plane inside the pulmonary artery wall. Unlike the UCSD

Table 1

<table>
<thead>
<tr>
<th>Hemodynamic values before PTE for all patients (N = 33)$^{a}$</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>High risk (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP</td>
<td>8 ± 6</td>
<td>1–23</td>
<td>≥ 9 (14/33)</td>
</tr>
<tr>
<td>mPAP</td>
<td>50 ± 10</td>
<td>30–69</td>
<td>≥ 50 (17/33)</td>
</tr>
<tr>
<td>CO</td>
<td>3.3 ± 0.9</td>
<td>1.8–5.2</td>
<td>&lt; 3.5 (19/33)</td>
</tr>
<tr>
<td>PVR</td>
<td>1056 ± 344</td>
<td>523–1659</td>
<td>≥ 1100 (15/33)</td>
</tr>
<tr>
<td>RVEF</td>
<td>12 ± 5</td>
<td>5–21</td>
<td>&lt; 10 (11/29)</td>
</tr>
<tr>
<td>Months in NYHA 3–4</td>
<td>27 ± 45</td>
<td>6–264</td>
<td>≥ 24 (13/33)</td>
</tr>
</tbody>
</table>

$^{a}$ CVP, central venous pressure; mPAP, mean pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance; RVEF, right ventricle ejection fraction.
group we usually neither clamp the ascending aorta nor use cardioplegia because in our experience better cardiac protection is achieved by perfusing the arrested heart with cold blood while the left ventricle is vented through the right superior pulmonary vein.

Cardiopulmonary bypass lasted 233 ± 52 min (range 125–330). In three patients with heparin induced thrombocytopenia we applied a modified UCSD protocol [19] in which cardiopulmonary bypass was started after platelet inactivation with prostacyclin analogue (Iloprost Italfarmaco S.p.A. Italy). Iloprost infusion was started at a rate of 6 ng/kg per min. The dosage was doubled to 12 and 24 ng/kg per min respectively at 15-min intervals until the laboratory test showed complete platelet inactivation. Infusion was maintained at 24 ng/kg per min during the cardiopulmonary bypass and reduced to 6 ng/kg per min at the end of PTE. It was stopped after 6 h in the intensive care unit and overlapped with sodium danaparoid (Orgaran Organon, The Netherlands) for immediate post-operative anticoagulation.

Circulatory arrest, of a mean duration of 13 ± 8 min (range 1–33) per episode, was always performed with body temperature decreased to 17 ± 1°C (range 15–21). The number of circulatory arrests per patient was 2 ± 1 (range 1–3) with a total time per patient of 25 ± 13 min (range 6–58).

In two cases, when PTE was non-optimal and only a moderate lowering of pulmonary pressure was anticipated, a tricuspid repair for severe insufficiency was performed at the end of the procedure. None of the other tricuspid insufficiencies (nine mild; 14 moderate, four severe) was repaired.

2.6. Statistical analysis

In terms of descriptive statistics mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables were computed for each time-point. The baseline correlation between RVEF frequencies for categorical variables were computed for continuous variables and absolute and relative frequencies (nine mild; 14 moderate, four severe) was repaired.

3. Results

3.1. Early results

Post-operative course was characterized in three cases by immediate massive alveolar hemorrhage presumably due to a peripheral pulmonary vessel injury caused by PTE. In one case the site of airway bleeding was identified by intra-operative bronchoscopy and the corresponding pulmonary segmental artery was excluded with a suture. The hemorrhage was successfully controlled. In the other two cases the site of bleeding was not identified and an extra-corporeal membrane oxygenation device was started immediately with the aim of venting pulmonary circulation. This procedure was ineffective and both patients deceased respectively after 5 and 20 days of assistance. These two cases, plus a case of severe hemoptysis which began 3 days after a successful PTE, account for the in-hospital mortality in our experience (3/33; 9.1%).

In one other case it was not possible to wean the patient from the cardiopulmonary bypass at the end of the procedure due to right stone heart. We think that this was caused by severe systemic hypotension during the procedure induced by a high Iloprost dosage of 48 ng/kg per min. This was aggravated by the patient’s severe right ventricular hypertrophy. A right ventricular assist device was placed to facilitate cardiac recovery. After 5 days the device was successfully removed with excellent hemodynamic results. The patient is alive and well 2 months after the procedure.

In one patient we were unable to find the dissection plane and PTE was attempted only on one side. Hemodynamic values did not change and it was not possible to wean the patient from mechanical ventilation. The patient was put on an emergency lung transplant waiting list and a single lung transplant was performed 6 days later.

Post-surgical reperfusion edema was quite frequent (12/33; 36.4%), although never life-threatening. Treatment consisted of prolonged mechanical ventilation with high values of positive end-expiratory pressure alone in six patients or in association with nitric oxide in the other six. Mechanical ventilation lasted longer (11.1 ± 12.0 days; range 1–44) in the group with reperfusion edema than in the group without reperfusion edema (4.4 ± 4.1 days; range 2–20; P = 0.04).

Total length of stay in the intensive care unit was 10.5 ± 10.1 days (range 2–53) and the period between surgery and discharge from our division was 16.2 ± 10.8 days (range 5–58).

3.2. Clinical-hemodynamical characteristics and surgical outcome

Surgical failure (early death or functional non-success)
occurred in nine cases: three early deaths, one emergency lung transplant, and five functional nonsuccesses. Functional nonsuccesses were defined as cases where the mPAP and PVR values went down by less than 40% of preoperative values. Of the functional nonsuccess cases, we decided to enroll one patient with no clinical improvement on a regular lung transplant waiting list and a double lung transplant was performed 7 months after PTE. Two showed an improvement in NYHA class respectively from 4 to 3 and from 3 to 2. One other patient did not improve clinically, but she refused any other therapeutic options such as lung transplantation and died 17 months after the PTE from a non-related cause. With this death the total mortality in our experience reached (4/33; 12.1%). The fifth nonsuccess patient, with a pre-PTE complete exclusion of one lung and major lesions on the other side, had re-occlusion of the occluded lung. In spite of the re-occlusion, she showed a significant improvement in NYHA class from 4 to 2, possibly due to improved hemodynamics on the other side, which was successfully treated.

This group of nine patients was compared to the 24 successful patients, by means of logistic regression (Table 2). None of the considered variables was found to be involved in the different outcomes: low risk and high risk groups showed no significant differences for any of the variables. ORs were close to 1 for mPAP, CO, PVR and RVEF; however the width of the confidence interval did not allow for conclusive results in this sample.

### 3.3. Longitudinal assessment

Excluding the emergency lung transplanted patient, 29 subjects entered our follow-up protocol. The cumulative survival at 1 and 2 years was respectively 90.9 ± 5.0 and 84.8 ± 7.5%. The mean follow-up of this group of patients was 15.9 ± 11.8 months (range 1–39) with ten patients having a follow-up of 2 years or longer.

Regression models showed a significant change with time of all the considered hemodynamic variables \( P < 0.0001 \). In all cases we observed a significant change 3 months after surgery, with a drop in CVP, mPAP and PVR, and an increase in CO and RVEF \( P < 0.0001 \). At 12 months a further decrease of mPAP was recorded \( P = 0.04 \) while all other variables remained stable. No further significant variation was observed at 2 years. At all time assessments, the difference was statistically significant with respect to pre-PTE values \( P < 0.001 \). Hemodynamic and cardiac values for the 23 cases available at 3-month follow-up were: CVP 2 ± 2 mmHg (range 0–6); mPAP 19 ± 6 mmHg (range 12–31); CO 5.6 ± 2.3 l/min (range 3.4–10.5); PVR 196 ± 39 dynes/s cm⁻² (range 150–242); and RVEF 30 ± 5% (range 25–37). For the ten cases available at the 2-year follow-up they were: CVP 2 ± 2 mmHg (range 0–4); mPAP 16 ± 6 mmHg (range 12–21); CO 5.0 ± 1.0 l/min (range 3.4–6.5); PVR 182 ± 51 dynes/s cm⁻² (range 112–282); and RVEF 35 ± 5% (range 26–40). The time course of mPAP is better illustrated in Fig. 1, where only complete cases are reported: the decrease was immediate at the first examination after the operation and remained stable over time as did the 5-fold decrease in the PVR value observed at the first examination (Fig. 2). RVEF recovered significantly (Fig. 3) 3 months after the operation, as a direct consequence of the reduction in mPAP, although more slowly and gradually. We found a linear correlation between these two variables, with \( R = 0.45 \) and \( P = 0.014 \) (Fig. 4).

Post-operative NYHA class had a similar but slower improving trend to RVEF values. By the 3-month examina-

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Table 2

<table>
<thead>
<tr>
<th>Low-risk events (%)</th>
<th>High-risk events (%)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP</td>
<td>36.8</td>
<td>14.3</td>
<td>0.29 (0.05–1.67)</td>
</tr>
<tr>
<td>mPAP</td>
<td>31.2</td>
<td>23.5</td>
<td>0.68 (0.14–3.16)</td>
</tr>
<tr>
<td>CO</td>
<td>28.6</td>
<td>26.3</td>
<td>0.89 (0.19–4.18)</td>
</tr>
<tr>
<td>PVR</td>
<td>22.2</td>
<td>33.3</td>
<td>1.75 (0.37–8.20)</td>
</tr>
<tr>
<td>RVEF</td>
<td>27.8</td>
<td>27.3</td>
<td>0.97 (0.18–5.23)</td>
</tr>
<tr>
<td>Months in NYHA 3–4</td>
<td>35.0</td>
<td>15.4</td>
<td>0.34 (0.06–1.97)</td>
</tr>
</tbody>
</table>

* CVP, central venous pressure; mPAP, mean pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance; RVEF, right ventricle ejection fraction; NYHA, New York Heart Association; OR, odds ratio; CI, confidence interval.

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Fig. 1. Mean pulmonary artery pressure before PTE and at the 3, 12, and 24-month follow-up examinations for the ten patients with a follow-up of 2 years or longer. The differences between before and after PTE values are statistically significant at all intervals with \( P < 0.0001 \) at complete case analysis.
tion none of the patients remained in NYHA class 3 or 4 (6 NYHA 1; 4 NYHA 2), but it took 24 months for all patients to get to NYHA class 1 ($P \leq 0.004$).

4. Discussion

CTPH is a serious disease that results in death from progressive and intractable cardiac failure. Although infrequent, its recognition is very important because surgical treatment with PTE can be curative. With PTE offering reduced mortality rates (slightly less than 10% [10] in the UCSD group) and leading to good functional results and restoration of normal daily activity, the matter of whether it is a valid surgical option for all CTPH patients, is an important one. It is also a tempting alternative to lung transplantation in view of the paucity of donors.

The debate over which patients to treat with PTE has so far hinged on whether it can have a successful outcome regardless of the degree of pulmonary hypertension or the severity of cardiac failure or whether in the most compromised patients, heart-lung or lung transplantation is a better treatment. The results of the Chicago group [15] indicated that patients with severe hemodynamic disease ($mPAP > 50$ mmHg and $PVR > 1100$ dynes/s cm$^{-5}$) suffered significantly higher operative mortality than less compromised patients (37 vs. 8% $P < 0.01$ for $mPAP$; 41 vs. 6% $P < 0.01$ for $PVR$).

Our results, in contrast, indicate that neither poor pre-operative hemodynamic values nor the duration of the disease play a role in the outcome of PTE. Both the degree of pulmonary hypertension and the severity of cardiac failure in our patients were very advanced. Seventeen (51.5%) patients had a $mPAP$ higher than 50 mmHg, and 15 (45.5%) patients presented a $PVR$ higher than 1100 dynes/s cm$^{-5}$. Cardiac function was so compromised that 11 (33.3%) patients had a RVEF lower than 10%. None of the variables taken into consideration, however, was found to correlate with early death or functional nonsuccess. No correlation was found either between the severity of pulmonary hypertension or the degree of cardiac failure and outcome or between duration of the disease and outcome. Although interesting, our results cannot be considered reliable, as measured by the 95% CI, due to the uncertainty of our estimate in 33 patients. Longitudinal analysis indicated that lowering of pulmonary pressure and cardiac recovery are still possible in patients with a very compromised hemodynamic status even if the disease has been present for a long time.

Our experience suggests that the most important step towards a successful outcome is the patient selection based on the distribution of the pulmonary arterial obstruction. In addition to pulmonary angiography, pulmonary spiral angio-CT scan was found to be very useful for this purpose. Patients with lesions limited only to the segmental or sub-segmental branches are not good candidates for PTE. In this case the risk of airway bleeding due to a peripheral
pulmonary vessel injury during PTE is very high. According to Dartevelle [18], video-assisted angioscopy improves the quality and degree of PTE in cases of distal lesions. This approach may be very useful but only for patients with proximal lesions extending to distal branches. We believe that patients with only distal lesions must be listed for transplantation. However, complete recovery of cardiac function after PTE even in very compromised cases has led us to choose double lung transplantation instead of heart-lung transplantation for these patients.

While patients were never turned down for PTE because of hemodynamic status, eight patients with exclusively distal lesions were transferred to the lung transplant waiting list during the time of the study. Three underwent double lung transplantation, three remain listed, and two died while listed. In two other cases, lung transplantation was performed after an unsuccessful PTE.

In our experience, having an active lung transplant program in the same center with the same surgeons was a substantial advantage, as it was possible to offer patients affected by CTPH all the surgical options and in the case of unsuccessful PTE an effective surgical alternative.

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References


Appendix A. Conference discussion

Dr W.P. Dembtskys (Del Mar, CA): My associate, Dr Pat Daily, was the original describer of this technique. These are very difficult patients. We certainly do agree that this should represent an alternative to transplantation and, hopefully, these patients can be identified more and more in the future.

We found with hundreds of these patients now, that the preoperative presence of extreme degrees of hypertension do correlate with survival, especially in those patients where the pulmonary vascular resistance cannot be reduced. If you start with a moderate elevation of pulmonary vascular resistance and then are unable to reduce it, the liability is less. But in the extreme degrees that you’ve been working with here, if you cannot reduce the pulmonary hypertension, you’re faced with an insoluble problem that’s not always predictable by the pulmonary arteriogram. Have you found that to be the case as well?

Dr D’Armini: Yes, this is correct. In fact in our experience in two patients with extreme hypertension, in spite of a good indication, PTE was ineffective and in one case we were unable to wean the patient from mechanical ventilation. However, because our center also has an active lung transplantation program, we were able to resolve the problem by doing an emergency single lung transplant on this patient and an elective double lung transplant on the other.

We also put on our lung transplantation waiting list patients with distal lesions who could not be enrolled for PTE. In fact, the only three patients who died after PTE were those with peripheral lesions. Reviewing their documentation later we saw that the lesions had been too distal to be successfully treated with PTE. At the moment we have eight patients who were turned down for this technique, three of whom have received a double lung transplant. Before the beginning of the PTE program, we performed one heart-lung transplant in a patient affected by CTPH because we were concerned about the patient’s very compromised right cardiac function. Now, in the light of the good cardiac recovery after PTE, in patients turned down for PTE we perform double-lung transplantation.
remove proximal obstructions, that seem to have distal obstructions that are persistent and may actually represent in situ thrombosis of the lung, much as you can see with pulmonary venous disease. It’s almost the same histopathology. Have you seen that?

Dr D’Armini: Yes, we had this experience with one of functional non-success patients, a woman with complete occlusion of one pulmonary artery. And at the first follow-up examination, her right pulmonary artery was closed again. I have no explanation for this. The patient had an inferior vena cava filter, PTE went well, and the anticoagulation protocol was appropriate.

A 1996 [20] article by the San Diego group reported a higher percentage of rethrombosis in patients with unilateral occlusion, which they suggested to be attributed to the concomitant presence of a postobstructive arteriopathy.

Dr Dembitsky: Yes, we have definitely seen that, and it seems to be more common with unilateral.

Dr S. Ramanathan (Birmingham, UK): My question is, what is your anticoagulant protocol after this and what is the target INR you are aiming at? That’s question number one.

The second is, are they on any other medications apart from oral anticoagulants to reduce the pulmonary artery pressure?

The third question is, during this timeframe of your study, what is the proportion of patients who have primary pulmonary hypertension?

Dr D’Armini: In answer to the first question, we put all patients on anticoagulants, and we take INR to between 2.5 and 3.5. However, in the subgroup of patients with antiphospholipid syndrome we take INR higher, to between 3.5 and 4.5.

Answering the second question we normally do not use any other medication to reduce the pulmonary artery pressure, except sometimes a diuretic for a brief period after PTE.

As to the third question, patients affected by primary pulmonary hypertension are referred to our center because we have a lung transplantation program. In the same period (May 1996–June 1999) we put ten of these patients on the lung transplantation waiting list and four of these were successfully transplanted.

Appendix B

The Pavia Thromboendarterectomy Program Study Group is also composed by: Nicoletta Barzaghi (Intensive Care Unit, Director Antonio Braschi), Silvia Serafini and Marisa Barone (Thromboembolism Unit, Director Edoardo Ascari), Franco Recusani, Colomba Falcone, Stefano Ghio, Laura Scelsi and Claudia Raineri (Division of Cardiology, Director Luigi Tavazzi), Isa Cerveri and Massimiliano Beccaria (Institute of Respiratory Disease, Director Lucio Casali), Raffaella Passera (Radiodiagnostic Unit, Director Andrea Villa), Roberto Dore (Institute of Radiology, Director Rodolfo Campani), Eloisa Arbustini and Patrizia Morbini (Institute of Pathology, Director Umberto Magrini), Patrizio Vitulo and Tiberio Oggionni (Division of Pulmonology, Director Albino Rossi), I.R.C.C.S. Policlínico San Matteo, and by Carlo Aprile (Nuclear Medicine Unit, Director Carlo Aprile), I.R.C.C.S. Fondazione Maugeri.