Review Article

Save or sacrifice the internal mammary pedicle during anterior mediastinotomy?

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Abstract:

Ligation and dissection of internal mammary vessels is the most under-estimated complication of anterior mediastinotomy. However, patients requiring anterior mediastinotomy may experience long survival that makes the development of ischemic heart disease throughout their life possible. Therefore, the un-judicial sacrifice of the internal mammary pedicle may deprive them from the benefit to have their internal mammary artery used as a graft in order to successfully bypass severe left anterior descending artery stenoses. We recommend the preservation of the internal mammary pedicle during anterior mediastinotomy, which should be a common message among our colleagues from the beginning of their training.

Key words:

Anterior mediastinotomy, coronary artery disease, internal mammary artery graft, lung cancer, mediastinal tumors

The anterior mediastinotomy proposed by McNeil and Chamberlain[1] is a reliable and well established diagnostic tool for the histological identification of anterior and superior mediastinal tumors and lymph nodes (LNs). Ligation of internal mammary vessels is the most underestimated complication among its potential complications since the primary end point of the procedure is the acquisition of sufficient tissue samples for histological identification of the mediastinal lesion. In most textbooks, the sacrifice of these vessels is considered an acceptable, meaningless maneuver that will provide a wider operative field facilitating the acquisition of adequate tissue samples. It is reported that "the internal mammary artery and vein are retracted or-rarely-divided and ligated."[2,3] It has also been stated that "occasionally it is necessary to ligate and divide these vessels to provide adequate exposure"[4] or "sometimes they must be divided to gain sufficient exposure"[5] or "the internal mammary artery and vein are usually ligated,"[6] or "if additional exposure is necessary, the internal mammary pedicle can be divided anteriorly."[7] In Thoracic Surgery Atlas by Mark Ferguson, on pages 142-143, the internal mammary vessels are shown ligated and divided by surgical clips.[4] However, some patients may have diseases associated with long survival and may be deprived from the benefit to have their left internal mammary artery (LIMA) used as a graft to bypass anterior descending artery stenoses provided that the aforementioned vessel has injudiciously been sacrificed during a previous anterior mediastinotomy procedure. In addition, adjuvant radiotherapy of the mediastinum will be required at a group of patients previously experienced anterior mediastinotomy. However, patients receiving adjuvant radiotherapy are at a greater risk of coronary artery disease (CAD) induction or aggravation. In the absence of data on this issue, we will try to evaluate its potential consequences based on the impact of LIMA graft on the outcome of patients with ischemic heart disease and on the background of the diseases requiring anterior mediastinotomy for tissue biopsy. Finally, alternative procedures for tissue biopsy will be provided.

Lima Graft and its Impact on Prognosis Of Patients Undergoing Coronary Artery Bypass Grafting (CABG)

Now-a-days, the LIMA to the left anterior descending (LAD) coronary artery graft is unanimously considered the method of choice during CABG.[8] A patent LAD is associated with significantly improved survival in patients suffering from ischemic heart disease. A study by Holzhey *et al*.[9] reported 90.2% 5-year survival and 85.5% 5-year freedom from major adverse cardiac events when a LIMA to LAD graft is used to bypass a completely stenotic coronary vessel. This study claims that a LIMA to LAD bypass is the treatment of choice for the management of patients with chronically completely occluded anterior descending arteries. When an *in situ* LIMA graft is used to bypass stenotic lesions of the LAD, the graft patency may reach up to 95% at 10 years, whereas right internal mammary

artery graft 10-year patency ranges between 80% and 95% respectively.[10] As much as 80% of internal thoracic artery conduits have been proved to be free from failure in the third decade after CABG.[11] On the contrary, patency of a radial artery graft is significantly reduced ranging between 83% and 96% at 4-5 years.[12,13] Prognosis is further deteriorated in those patients receiving a saphenous vein graft since patency of vein grafts is dramatically reduced over time. It has been shown that, whereas 10-year LIMA graft patency is approximately 90%, that one of a vein graft is reduced to 70%.[14] Another study has documented 10-year patency rates of 85% for *in situ* LIMA grafts and of 61% for saphenous vein grafts.[15] This difference has a significant influence on both the patients' survival and their quality of life. Several studies have shown that the use of *in situ* LIMA grafts to bypass stenotic LAD lesions is associated with better long-term graft patency, less late myocardial infarctions, improved quality of life and longer survival.[16-19] Moreover, among patients with low ejection fraction (EF < 30%), the use of LIMA may significantly improve their survival. In a report by McCarron *et al*.,[20] 4-year freedom from death rate reached up to 77.1% of patients receiving a LIMA graft and 60.7% of those receiving other vessel grafts. This difference was found to be statistically significant (P = 0.026). The aforementioned results clearly demonstrate that the use of a normal LIMA graft bypassing the LAD during CABG determines in advance the patient's long-term prognosis.

Mediastinal Tumors and Diseases that May Require Anterior Mediastinotomy for their Histological Confirmation: Age at Presentation and Survival

- The diagnosis and staging of non-small cell lung cancer (NSCLC) requires an accurate histopathological diagnosis.[21] Anterior mediastinotomy is mainly performed for staging of lung cancer especially that one involving left upper lobe.[22] This approach indeed provides access to subaortic and aortopulmonary window areas (LN stations 5 and 6), superior left hilar elements, left upper pulmonary lobe and parietal pleura.[2,22,23] It may define whether a patient with a left upper lobe tumor should be referred to surgery or not, giving rise to minimal risk.[22] NSCLC is a disease of the elderly.[24] More than 50% of the patients is over 65-year-old and one-third of them is even more than 70-year-old on the time the diagnosis is made.[24,25] Whether a surgical or a multimodality treatment is performed, prognosis is poor. The study done by Wigle *et al*.[26] reported the following 5-year survival rates depending on the stage of the disease: stage I (2648 patients): 60-70%, Stage II (1097 patients): 40-50%, Stage IIIA (1241 patients): 25-40%, Stage IIIB (1327 patients): 2-15% and Stage IV (1427 patients): 1-10%. In another study including 2378 patients suffering from NSCLC, the 5-year survival rate after complete tumor resection was 50.2%; and the 5-year survival rate depending on stage was 72% for Stage IA, 59.8% for Stage IB, 47.8% for Stage II, 45% for Stage IIIA and 38.7% for Stage IIIB.[27] These differences show that various parameters such as sex, age, histological type, tumor differentiation, number of positive nodes, stage of the disease and complete tumor resection have an impact on patient's survival.
- Hodgkin lymphoma is the most frequent type of lymphoma affecting the mediastinum. It is more frequent in women presenting two peaks of incidence, the first one between 15 and 35 years of age and the second one after the age of 55.[28] Most of the cases are diagnosed between the 2nd and 4th decade of life and the mean age at presentation is 37-year-old.[29] Patients' survival after treatment is excellent; in a multicenter randomized trial including 202 patients, 10-year survival was 92.9%.[30]
- Non Hodgkin lymphomas are less frequent. The mean age at presentation is 37-year-old[31] while T and B lymphoblastic lymphomas are mainly found in children.[29] Non Hodgkin lymphomas have significantly poorer survival than Hodgkin lymphomas; in a 141-patients study, the diagnosis was made at a mean age of 37-year-old and 3-year survival rate was 65%.[31]
- Thymomas are thymic epithelial tumors located primarily in the superior, anterior mediastinum. The mean age at diagnosis is between 49 and 51-year-old with no statistically significant impact of sex on the peak of incidence.[29,32,33] Patients' survival is excellent if the disease is diagnosed early. 5- and 10-year survival rates vary between 89.9-97% and 84.1-89% respectively.[32,33] In a recent report including 39 patients operated over a period of 16 years, 5-, 10- and 15-year survival rates were 91.6%, 75.1% and 60% respectively; patients with advanced disease (Stage III and IV) experienced 5- and 10-year survival rates of 70% and 35% respectively.[34]
- The group of mediastinal germ cell tumors includes several types of tumors that are primarily diagnosed through anterior mediastinotomy. They are mostly found in young adults; in a retrospective analysis of 129 patients treated for mediastinal germ cell tumors the mean age at presentation was 26 years.[35] Teratomas represent the most frequent entity of these tumors with a predilection for males and a peak incidence between the 2nd and the 4th decade of life.[29] Similarly, in a review including 530 patients with primary or metastatic testicular seminomas the mean age was 27 ± 8 years.[36] Both teratomas and seminomas are associated to good prognosis having 10-year survival rates of 90% and 70% respectively. On the contrary, non seminomatous germ cell tumors have a significantly worse outcome. At 5-year survival reaches up to 30-40%, whereas 8-year survival is 15%.[35]
- Sarcoidosis is a systemic inflammatory granulomatous disease affecting people of all ages and races characterized by hilar and mediastinal LN masses. Thoracic lymphadenopathy detected in up to 85% of cases.[37] Invasive exploration of the mediastinum is necessary for histological confirmation and exclusion of other malignant diseases. In a multicenter ACCESS trial including 736 patients from 10 US medical centers, the mean age at presentation ranged from 35 to 39 years.[38] Prognosis is good and 5-year mortality depends on the stage of the disease at the time the diagnosis is made: 0% for Stage I, 11% for Stage II, 18% for Stage III and 50% for Stage IV.[39]
- Anterior mediastinotomy after pre-operative imaging may also be used for parathyroidectomy. Approximately 2% of ectopic parathyroid glands causing primary hyperparathyroidism require a thoracic approach due to their mediastinal location. If the abnormal gland is successfully removed, the patients' calcium levels are normalized and patients have same survival rates as the general population.[40]

In overall, the majority of mediastinal tumors referred for anterior mediastinotomy, excluding NSCLC, occur in younger ages. According to de Montpréville's *et al*. study,[41] the frequency of these tumors and the mean age at the time of presentation were as following: 169/420 patients had NSCLC with a mean age of 59-year-old, 36/420 patients had small cell lung carcinoma with a mean age of 60-year-old, 62/420 patients had sarcoidosis with a mean age of 39-year-old, 18/420 patients had tuberculosis with a mean age of 46-year-old, 45/420 patients had lymphoma with a mean age of 39-year-old, 5/420 patients had thymoma with a mean age of 51-year-old and 12/420 patients had other diagnoses with a mean age of 45-year-old. Moreover, it is clear that some of the mediastinal tumors are associated with good to excellent prognosis. Therefore, some of these patients will have long enough survival to be candidates to experience ischemic heart disease requiring coronary revascularization in the future.

Impact of Adjuvant Radiotherapy on the Development of CAD

Radiotherapy of the mediastinum is applied in patients suffering from NSCLC with N2 disease or other primary mediastinal or breast malignancies. However, mediastinal irradiation also affects coronary arteries resulting in CAD. CAD development, the incidence of which ranges from 5.5% to 12%, requires 3-29 years. The coronary ostia are affected due to their relatively central location within the radiation field. Atherosclerosis progression of the coronary vessels is accelerated by radiotherapy.[42] Patients receiving radiotherapy of the mediastinum during their treatment for Hodgkin lymphoma are expected to have long survival, so they may develop ischemic heart disease due to both aging and the effects of radiation on their native coronary vessels. Increased cardiac related mortality and morbidity rates should be expected, especially if the dose of delivered radiation exceeds 30 Gy.[43,44] Several long-term series of patients undergoing radiotherapy reported more deaths because of second malignancies and CAD than because of their Hodgkin lymphoma.[42] Heidenreich *et al*.[45] reported abnormal stress echo and/or nuclear scintigraphy findings in 21% of the 294 patients irradiated in the mediastinum for Hodgkin lymphoma whose disease was in complete remission at the time of cardiac evaluation. Coronary angiograms revealed significant coronary vessels stenosis in 1/3 of the patients. Thus, the authors concluded that patients with history of mediastinal radiotherapy for Hodgkin disease should be under strict cardiac surveillance. According to Rademaker *et al*.,[28] 8 out of 9 patients receiving radiotherapy for Hodgkin lymphoma developed significant coronary lesions and most of them were completely asymptomatic. It should be noted that 5 of these patients presented other risk factors for atherosclerosis as well, such as hypertension, diabetes and high blood cholesterol levels. The presence of significant lesions and silent ischemia may lead to myocardial infarction and is associated with increased cardiac related mortality. In a report of 7033 patients successfully treated for Hodgkin disease and a mean follow-up of 11.2 years, the standardized mortality ratio secondary to myocardial infarction was 3.2 for those who were treated with mediastinal irradiation.[46] We may conclude that the adjunction of mediastinal irradiation in the treatment protocols of these patients may accelerate the development of CAD. The same could happen in those few patients with NSCLC irradiated in the mediastinum that may achieve a relatively prolonged survival. Cardiac complications can be prevented both by managing cardiovascular risk factors and also by lowering the total radiotherapy dosage.[42]

On the other hand, internal mammary arteries affection by radiotherapy also raises our concern. Although isolated case reports demonstrate increased fragility and early failure of the graft under these circumstances, most of the studies on this issue support the use of internal mammary arteries in patients who had their mediastinum irradiated in the past.[47] Therefore, the internal mammary artery graft is still valid after radiotherapy and maintains its advantages with regard to long survival.

Alternative Methods of Biopsy of Mediastinal Tumors and LNs with Internal Mammary Artery Preservation

Several, more or less invasive, approaches other than anterior mediastinotomy are available in order to obtain the necessary tissue samples. The extended cervical mediastinoscopy, which is an extension of the classic one, offers the possibility to evaluate both the anterior and the middle mediastinum taking samples even at the level of the pulmonary hilum. Not only LNs stations 2, 3, 4 and 7 but also LNs stations 5, 6, 8 and 10 are accessible when this procedure is performed.[48,49] A procedure called Transcervical Extended Mediastinal Lymphadenectomy is a modification of the aforementioned procedure allowing the performance of complete mediastinal lymphadenectomy.[48-51] Its sensitivity of 95.7% and its negative predictive value of 97.6% make some authors to consider this approach as the "gold standard" for mediastinal restaging of patients with NSCLC receiving neoadjuvant treatment.[48-51] The anterior and middle mediastinum is accessed through a 5-8 cm collar incision and resection of all nodal tissue down to the level of paraesophageal nodes follows (station 8).[49,51] Although the operation is technically demanding and long lasting (mean time 161 min), there is no mortality in large series of patients and morbidity is of the order of 11.3%. Major complications include temporary (2.3%) or permanent (0.8%) recurrent laryngeal nerve palsy.[50]

The anterior mediastinoscopy constitutes another alternative procedure, which is a modification of the anterior mediastinotomy where the costal cartilage is not removed.[7] The mediastinoscope is inserted through the selected intercostal space (2nd, 3rd or 4th) in an oblique direction either laterally[52] or medially[41] to the internal mammary vessels. In the last case, the incision is very small approximating 1.5-2 cm and both the intercostal muscles and the endothoracic fascia are vertically divided at the border of the sternum. The operation can be carried out even under local anesthesia. A recent study Rendina *et al*.[53] reported that this procedure provided histological identification in all of the 46 patients with mediastinal tumors or enlarged LNs in wom it was performed. Moreover, their hospital recovery lasted only up to 24 h.

The anterolateral mediastinotomy, which is in our opinion one of the most valid alternative methods, can be performed via an incision made along the selected intercostal space. The mediastinum is accessed through an intercostal space

without costal resection. The internal mammary vessel bundle is identified and preserved. Its major disadvantages lie in the extensive muscle dissection required and in the opening of the pleural cavity which requires chest tube drainage.

In recent years, video assisted techniques for biopsy of mediastinal tumors and LNs have become popular. These include both video-assisted mediastinoscopy (VAM) and video assisted thoracoscopy (VATS) assisted mediastinotomy. The first one is carried out through a standard cervical mediastinoscopy approach.[54] LNs of stations 2, 4 and 7 can be easily accessed and resected. Right hilar LNs can also be accessed.[48] Among 126 patients undergoing VAM, Jedlicka *et al*.[55] reported histological confirmation rate of 75% with no mortality. On the contrary, Venissac *et al*.[56] documented positive histological findings in 238/240 patients undergoing VAM. Among patients with lung cancer, post-thoracotomy definition of the disease stage confirmed the results of VAM approach in 93.6% of the cases. Morbidity is low (0.85-4%) and includes vascular injuries, hemothorax, air embolism and injury of lung parenchyma or pulmonary hilum.[56,57] Hunt *et al*.[58] has proposed a VATS assisted mediastinotomy approach. In those patients, who suffer from lung cancer with involvement of different structures that may not be accessible by a single procedure, a combination of VAM and VATS may be extremely useful for the evaluation of the resectability of the tumor.[59]

Transbronchial fine-needle aspiration (FNA) and computed tomography (CT) guided FNA or core biopsy is other alternatives. The first one has sensitivity ranging between 60% and 90% provided that the diameter of the LN detected on CT images is over 1 cm.[60] Bleeding and pneumothorax are the most frequent complications occurring in 2-5% of patients.[61] If it is guided by endoscopic or endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA), its utility increases. The sensitivity of EBUS-TBNA for benign or malignant mediastinal lesions ranges from 88% to 95%, its specificity is 100%, its negative predictive value ranges from 85% to 93% and its accuracy ranges from 93% to 97%. Hence, EBUS-TBNA is a safe, minimally invasive technique to access mediastinal and hilar LNs and set a diagnosis. However, surgical evaluation such as mediastinoscopy is required in case of negative findings.[62] Rarely, apart from pneumothorax EBUS-TBNA may be complicated with mediastinal infectious complications which is a severe one.[63,64] CT guided biopsy of LNs is primarily applied for the determination of the disease stage in lung cancer patients. It is less frequently used for the histological confirmation of tumors of the mediastinum due to their proximity to major mediastinal vascular structures. Its sensitivity may reach up to 98%.[65] However, it is associated with iatrogenic pneumothorax in 14-34% of cases.[66,67] Contraindications to the performance of CT guided biopsy include chronic obstructive pulmonary disease, diffuse lung parenchyma disease, limited pulmonary reserves, arterio-venous malformations and previous pneumonectomy.[23,67]

Conclusions

Ligation and dissection of the internal mammary artery during anterior mediastinotomy is surprisingly considered a meaningless event having no further impact on patients' survival in most textbooks. In this review, we reported that the majority of the diseases of the mediastinum requiring histological identification via anterior mediastinotomy mostly affects young and middle-aged adults but for those suffering from lung cancer. Moreover, apart from patients with lung cancer and rare mediastinal tumors related to unfavorable outcomes (non-Hodgkin lymphomas, non seminomatous germ cell tumors), all the others may achieve a long survival after treatment. This fact will allow the development of ischemic heart disease in some of them. The effects of radiotherapy used in the treatment protocols for patients presenting with malignant diseases may further enhance this possibility. Hence, sacrificing the internal mammary artery during anterior mediastinotomy, may deprive some patients from the advantages of the aforementioned vessel regarding the treatment of their ischemic heart disease. Therefore, preservation of the internal mammary pedicle via the application of alternative approaches to diagnose tumors and LNs of the mediastinum should become common sense to all the thoracic surgeons from the beginning of their training.

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