Preoperative high-intensity training in frail old patients undergoing pulmonary resection for NSCLC

DOI 10.1515/med-2016-0079
received August 18, 2016; accepted September 6, 2016

Abstract: Thoracic surgery remains the better therapeutic option for non-small cell lung cancer patients that are diagnosed in early stage disease. Preoperative lung function assessment includes respiratory function tests (RFT) and cardio-pulmonary exercise testing (CPET). VO2 peak, FEV1 and DLCO as well as recognition of performance status, presence of co-morbidities, frailty indexes, and age predict the potential impact of surgical resection on patient health status and survival risk. In this study we have retrospectively assessed the benefit of a high-intensity preoperative pulmonary rehabilitation program (PRP) in 14 patients with underlying lung function impairment prior to surgery. Amongst these, three patients candidate to surgical resection exhibited severe functional impairment associated with high score of frailty according CHS and SOF index, resulting in a substantial mortality risk.

Our observations indicate that PRP appear to reduce the mortality and morbidity risk in frail patients with concurrent lung function impairment undergoing thoracic surgery. PRP produced improvement of VO2 peak degree and pulmonary function resulting in reduced postoperative complications in high-risk patients from our cases. Our results indicate that a preoperative training program may improve postoperative clinical outcomes in frail lung cancer patients with impaired lung function prior to surgical resection.

Keywords: Respiratory function tests; Non-small cell lung cancer; Thoracic Surgery; Pulmonary rehabilitation program; Frail patients; Aging

1 Introduction

Thoracic surgery remains the better curative option for non-small cell lung cancer treatment as chemotherapy is not satisfactory in terms of response rate and survival [1-6]. Despite improvements in diagnostic procedures [7-13], only a few patients are eligible for surgical treatment [14]. As lung cancer shares common risk factors with other respiratory diseases [15-19] abnormal pulmonary function is a frequent finding. Several functional and clinical assessments are required before surgery is decided upon. An algorithm proposed in clinical guidelines by Brunelli et al. represents a well-established tool for the assessment of cardiopulmonary reserve before lung resection in lung cancer patients [20]. The preoperative assessment of respiratory lung function, including respiratory function tests (RFT) and cardio-pulmonary exercise testing (CPET), is fundamental to predict the impact of surgical resection.
on the health status of the patient [21-23]. An integrated pre-operative evaluation of residual pulmonary function after surgical removal of lung parenchyma allows the definition of the treatment options and risks, to achieve the best therapeutic option [20]. According to this recommendation, VO2 peak evaluation, assessed using CPET, represents the best independent predictor of surgical complication rate [24]. CPET, indeed, is mandatory in the presence of any slight functional abnormalities, including forced expiratory volume in one second (FEV1) and/or diffusion lung capacity of CO (DLCO)<80% of the predicted value. However, other clinical assessments are required for final decision-making. Age, performance status, presence of co-morbidities and frailty indexes should also be considered for an accurate selection of patients suitable to surgery. Preoperative physiologic assessment serves to identify patients with elevated risk of peri-operative complications and long-term pulmonary disability in order to optimize peri- and post-operative management. A high-intensity preoperative pulmonary rehabilitation program (PRP) improved the degree of VO2, increased physical performance, reduced the perception of dyspnea and increased quality of life in patients with COPD and NSCLC undergoing surgical resection. [25-28]. These effects continue to be observed after surgery. Adherence to medical treatment and rehabilitation is important to achieve synergistic effects. In this study we have retrospectively assessed the impact of a preoperative high-intensity training program in frail and elderly patients undergoing thoracic surgery for lung cancer.

2 Material and methods

2.1 Patients

We retrospectively reviewed 14 patients (10 males – 4 females; median age 68±7,1 years) with Stage I/II NSCLC and underlying respiratory function impairment due to COPD who underwent a preoperative high-intensity training program. The criteria for operability and resectability were based on the preoperative staging test and the recommendations of the ERS/ESTS guidelines. All patients enrolled in this cohort were treated with long-term bronchodilators (beta-2 agonists and/or anticholinergics), with or without use of inhaled corticosteroids. Within the cases selected, we have evaluated three patients prior to surgical resection who exhibited severe respiratory function limitations associated with high score of frailty according to CHS and SOF index [29, 30], resulting in a considerable mortality risk focusing the impact of pulmonary training on mortality and morbidity risk.

2.2 Pulmonary Rehabilitation Program

The high intensity training was conducted for 3 consecutive weeks. The program included respiratory exercises on the bench, mattress pad and wall bars. Rowing ergometer, treadmill and bicycle were used for upper and lower limb training. The starting exercise work load was set with 70% of the maximum score reached at the CPET and increased by 10 W according patient conditions.

2.3 Surgical technique

All patients underwent lobectomy associated with mediastinal lymphadenectomy. In one case, upper right lobectomy was performed by three-portal access Video-assisted thoracoscopic surgery (VATS). The other two lobectomies (upper right lobe and lower left lobe) were obtained by axillary vertical muscle – sparing thoracotomy.

2.3.1 Case 1

A 69-year old male, heavy smoker, with a medical history of pulmonary emphysema was referred to our department for the evaluation of a single nodule in right upper lobe. Pre-operative pulmonary function assessment showed a severe obstruction and moderate reduction in DLCO (FEV1: 1.070 L; FEV1%th: 29%; DLCO: 14.3 mL/mmHg/min; DLCO%th: 46%). A CPET was performed, resulting in a severe reduction in VO2 peak (VO2 peak: 13.6; VO2peak%th: 48%). The post-operative predictive value resulted in a significant risk of mortality and morbidity according to the SFAR score. The patient was admitted to a pulmonary rehabilitation program during the 3 weeks preceding the surgical treatment. A functional post-rehabilitative program reassessment was conducted reporting an improved lung function. The ppo-FEV1 and ppo-VO2 peak hugely increased (ppo-FEV1 vs post-rehabilitation ppo-VO2 peak: 25% vs 38%; ppo-VO2 peak vs post-rehabilitation ppo-FEV1: 25% vs 38%; pre-rehabilitation ppo-VO2 peak vs post-rehabilitation ppo-FEV1: 25% vs 38%). The post-operative predictive value resulted in a significant risk of mortality and morbidity according to the SFAR score. The patient was admitted to a pulmonary rehabilitation program during the 3 weeks preceding the surgical treatment. A functional post-rehabilitative program reassessment was conducted reporting an improved lung function. The ppo-FEV1 and ppo-VO2 peak hugely increased (ppo-FEV1 vs post-rehabilitation ppo-FEV1: 25% vs 38%; ppo-VO2 peak vs post-rehabilitation ppo-FEV1: 25% vs 38%). The post-operative predictive value resulted in a significant risk of mortality and morbidity according to the SFAR score. The patient was admitted to a pulmonary rehabilitation program during the 3 weeks preceding the surgical treatment. A functional post-rehabilitative program reassessment was conducted reporting an improved lung function.
risk: 24% vs 20%). Lobectomy by thoracotomy confirmed the diagnosis of squamous cell carcinoma. No perioperative complications were observed.

2.3.2 Case 2

A 66-years old male was referred to our hospital to undergo a VATS right upper lobectomy (Figure 1). Pre-operative pulmonary function assessment showed a severe obstruction and severe reduction in DLCO (FEV1: 0.910 L; FEV1%th: 32%; DLCO: 8.40; DLCO%th: 34%). Patient underwent CPET, which showed a moderate reduction in VO2 peak (VO2 peak: 15.7; VO2peak%th: 63%). Before VATS lobectomy the patient underwent a pulmonary rehabilitation program. All functional parameters improved (pre-rehabilitation ppo-FEV1 vs post-rehabilitation ppo-FEV1: 29% vs 45%; pre-rehabilitation ppo-VO2 peak vs post-rehabilitation ppo-VO2 peak: 53% vs 54% and pre-rehabilitation ppo-DLCO vs post-rehabilitation ppo-DLCO: 28% vs 32%). A reduction of mortality and morbidity risk assessed by SFAR index was achieved (pre-rehabilitation mortality risk vs post-rehabilitation mortality risk: 9% vs 6%; pre-rehabilitation morbidity risk vs post-rehabilitation morbidity risk: 24% vs 20%). Surgical procedure was performed safely without complications.

2.3.3 Case 3

A 65-year-old female with no significant past medical history was evaluated for the detection a single nodule in right lower lobe. Pre-operative diagnosis of adenocarcinoma was made by FNAB. Pulmonary function tests showed a moderate - severe obstruction with severe reduction in DLCO (FEV1: 1.293 L; FEV1%th: 52%; DLCO: 9.30; DLCO%th: 39%). Subsequently, CPET was performed, resulting in a moderate reduction in VO2 peak (VO2 peak: 16.04; VO2peak%th: 54%). Pulmonary rehabilitative training was carried out and the patient was evaluated after 3 weeks. Spirometry documented an improved lung function resulting in an increase of ppo-FEV1 and ppo-VO2 peak value (pre-rehabilitation ppo-FEV1 41% vs post-rehabilitation ppo-FEV1 51%; pre-rehabilitation ppo-VO2 peak vs post-rehabilitation ppo-VO2 peak: 43% vs 50%; ppo-DLCO value was unaltered after the training program. The improved pulmonary function resulted in reduction of mortality and morbidity risk assessed by SFAR index (pre-rehabilitation mortality risk vs post-rehabilitation mortality risk: 4% vs 1%; pre-rehabilitation morbidity risk vs post-rehabilitation morbidity risk: 15% vs 11%). Therefore the patient underwent lower left lobectomy by thoracotomy without experiencing complications (Figure 2).

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available from review by the Editor-in-Chief of this journal.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.
3 Discussion

Our cases indicate that a pre-operative pulmonary high-intensity program, in NSCLC patients undergoing surgical resection, improves physical performance even in frail patients with compromised lung function caused by COPD. Despite progress in understanding cancer biology [31-52] and a promising novel therapeutic approaches like cell-based therapy [53-56], just postulated in frail old patients [57,58], surgery remains the best option to offer patients. However, the presence of comorbidities such as cardiovascular and respiratory disorders [59-61] are limiting factors to perform surgery also in technically resectable lung lesions. Improvement in lung function, including several parameters such as FEV1, DLCO and VO2 peak, may lead to a reduction in mortality and morbidity risk. In fact, as is widely acknowledge, lung function assessment is the best independent factor able to predict patients’ outcomes following thoracic surgery. The integrated evaluation of ppoFEV1 ppoDLCO and ppoVO2 peak could offer to clinicians a reliable index of pulmonary function after surgical resection. In this scenario, high-intensity rehabilitation programs may represent fundamental tools, especially in older frail patients. In this subgroup, the impact of comorbidities (CHF, COPD, diabetes, chronic kidney failure) may result in a high risk of mortality. Also, pulmonary peri and post-operative complications (atelectasis, obstructive pneumonia, infections) occur more frequently in frail patients [22]. For this reasons, older patients undergoing pulmonary resection require a multidisciplinary pre-operative management. Smoking cessation and pulmonary rehabilitation program may represent the best approach to optimize surgical outcomes [26, 27]. Finally, the correct management should include a comprehensive geriatric assessment focused on the impact of comorbidities in order to optimize medical treatment. Further studies are required to confirm the impact of high-intensity rehabilitation programs also in elderly frail patient who present higher surgical risks.

Conflict of Interests: The authors declare that they have no conflict of interests.

References

[1] Comella P, Frasci G, De Cataldis G, et al. Cisplatin/carboplatin+etoposide+ vinorelbine in advanced nonsmall-cell lung cancer: a multicentre randomised trial. Gruppo Oncologico Campano Br J Cancer 1996; 74:1805-1811

[2] Comella P, Frasci G, Panza N, et al. Cisplatin, gemcitabine, and vinorelbine combination therapy in advanced non-small-cell lung cancer: a phase II randomized study of the southern Italy Cooperative oncology group. J Clinical Oncol 1999; 17:1526-34.

[3] Frasci G, Lorusso V, Panza N, Comella P, Nicorella G, Bianco A, De Cataldis G, Iannelli A, Bilancia D, Belfi M, Massidda B, Piagentini F, Comella G, De Lena M. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol. 2000 Jul;18(13):2529-2536

[4] Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine yields better survival outcome than vinorelbine alone in elderly patients with advanced non-small cell lung cancer. A Southern Italy Cooperative Oncology Group (SICOG) phase III trial. Lung Cancer 2001; 34(Suppl 4):S65-69

[5] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002; 346:92-98

[6] Piagentini FV, Caputo F, Mazzarella G, et al. Gemcitabine, ifosfamide and paclitaxel in advanced/metastatic non-smallcell lung cancer patients: a phase II study. Cancer Chemotherapy Pharmacol 2008; 61:803-807

[7] Brunese L, Greco B, Setola FR, Lassandro F, Guarracino MR, De Rimini M, Piccolo S, De Rosa N, Muto R, Bianco A, Muto P, Grassi R, Rotondo A. Non-small cell lung cancer evaluated with quantitative contrast-enhanced CT and PET-CT: net enhancement and standardized uptake values are related to tumour size and histology. Med Sci Monit. 2013 Feb 7;19:95-101

[8] Izzo A, Perrotta F, Cennamo A, Cerqua FS, Rinaldi L, Mazzella A, Grella E, Tranfa C, Bianco A, Stefanelli F, Mazzarella G. Spirometry in elderly laryngectomized patients: a feasibility study. Int J Surgery 2016 May 30. pii: S1743-9191(16)30144-3

[9] Del Giudice G, Bianco A, Cennamo A, Santoro G, Bifulco M, Marzo C, Mazzarella G. Lung and Nodal Involvement in NontuberculousMycobacterialDisease: PET/CT Role. Biomed Res Int. 2015, 353202

[10] Bianco A, Mazzarella G, Rocco D, Gasperi M, Di Marco R, Brunese L. FDG/PET uptake in asymptomaticmultilobar Chlamydia pneumoniae pneumonia. Med Sci Monit. 2010 Jun;16(6):CS67-70

[11] Maniscalco M, Bianco A, Mazzarella G, Motta A. Recent Advances on Nitric Oxide in the Upper Airways. Curr Med Chem. 2016 Jun 27. [Epub ahead of print]

[12] Maniscalco M, Vitale C, Vattrella A, Molino A, Bianco A, Mazzarella G. Fractional exhaled nitric oxide-measuring devices: technology update. Med Devices (Auckl). 2016 Jun 23;9:151-160

[13] Guarino C, Mazzarella G, De Rosa N, Cesaro C, La Cerra G, Grella E, Perrotta F, Curcio C, Guerra G, Bianco A. Pre-surgical bronchoscopic treatment for typical endobronchial carcinoids. Int J Surg. 2016 May 30; S1743-9191(16)30144-3

[14] Lang-Lazdunski L. Surgery for non small cell lung cancer. Eur Respir Rev. 2013 Sep 1;22(129): 382-404

[15] de Laurentiis G, Paris D, Melck D, Montusch P, Maniscalco M, Bianco A, Sofia M, Motta A. Separating Smoking-Related Diseases Using NMR-Based Metabolomics of Exhaled Breath Condensate. J Proteome Res. 2013 Mar 1;12(3):1502-1511
Preoperative training in frail patients

[16] Mazzarella G, Esposito V, Bianco A, Ferraraccio F, Prati MV, Lucariello A, Manente L, Mezzogiorno A, De Luca A. Inflammatory effects on human lung epithelial cells after exposure to diesel exhaust micron sub particles (PM1.0) and pollen allergens. Environmental Pollution, 2012. vol. 161, p. 64-69

[17] Mazzarella G, Ferraraccio F, Prati MV, Annunziata S, Bianco A, Mezzogiorno A, Liguori G, Angelillo IF, Cazzola M. Effects of diesel exhaust particles on human lung epithelial cells: an in vitro study. Respir Med. 2007 Jun;101(6):1155-1162

[18] Esposito V, Lucariello A, Savarese L, Cinelli MP, Ferraraccio F, Bianco A, De Luca A, Mazzarella G. Morphology changes in human lung epithelial cells after exposure to diesel exhaust micron sub particles (PM1(0.1)) and pollen allergens. Environmental Pollution. 2012 Dec; 171:162-167

[19] Mazzarella G, Lucariello A, Bianco A, Calabrese C, Thanassoulas T, Savarese L, Fiumarella A, Esposito V, DE Luca A. Exposure to submicron particles (PM1.0) from diesel exhaust and pollen allergens of human lung epithelial cells induces morphological changes of mitochondria tonofilaments and rough endoplasmic reticulum. In Vivo. 2014 Jul-Aug;28(4):557-561

[20] Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculeri J-P, Varela Getal.on behalf of the European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J 2009; 34:17-41

[21] Damhuis RAM, Schütte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. Eur Respir J 1996; 9:7-10

[22] Beckles MA, Spiro SG, Colice GL, Rudd RM. The physiologic selection. Lung Cancer 2001;33 (Suppl 1):S9-S15

[23] Cattaneo F, Guerra G, Parisi M, Lucariello A, De Luca A, De Rosa N, Mazzarella G, Bianco A, Ammendola R. Expression of Formyl peptide Receptors in Human Lung Carcinoma. Anticancer Res. 2015 May;35(5):2769-74

[24] Cattaneo F, Guerra G, Parisi M, De Marinis M, Tafuri D, Cinelli M, Ammendola R. Cell-Surface Receptors Transactivation Mediated by G Protein-Coupled Receptors. Int J Mol Sci. 2014 Oct 29;15(11):19700-19728.

[25] A. Vatrella, S. Montagnani, C. Calabrese, R. Parrella, G. Pelaia, G.L. Biscione, N. Corcione, S.A. Marsico and Guerra G. Neuropeptide expression in the airways of COPD patients and smokers with normal lung function. J Biol Reg Homeos Ag 2010 Oct-Dec;24(4):425-432.

[26] Berra-Romani R, Raqeeb A, Torres-Jácome J, Guzman-Silva A, Guerra G, Tanzi F, Moccia F. The mechanism of injury-induced intracellular calcium concentration oscillations in the endothelium of excised rat aorta. J Vasc Res. 2012;49(1):65-76

[27] Perrotta F, Cerqua FS, Cammarata A, Izzo A, Bergamini C, Cucurci C, Guarino C, Grelle F, Forzano I, Cennamo A, Tafuri D, Rocco A, Bianco A, Mazzarella G. Integrated therapeutic approach to Giant Solitary Fibrous Tumor of the Pleura: Report of a case and review of the literature. Open Medicine Volume 11, Issue 1, 1 January 2016: 220-225

[28] Cattaneo F, Iaccio A, Guerra G, Montagnani S, Ammendola R. NADPH-oxidase-dependent reactive oxygen species mediate EGFR transactivation by FPRL1 in WKYMMv-stimulated human lung cancer cells. Free Radic Biol Med. 2011 Sep 15;51(6):1126-1136.

[29] Lodola F, Laferenza U, Bonetti E, Lim D, Dragoni S, Bottino C, Ong HL, Guerra G, Ganini C, Massa M, Manzoni M, Ambudkar IS, Genazzani AA, Rosti V, Pedrazzoli P, Tanzi F, Moccia F, Porta C. Store-operated ca(2+) entry is remodelled and controls in vitro angiogenesis in endothelial progenitor cells isolated from tumoral patients. PLoS One 2012 7(9):e42541.

[30] Dragoni S, Turin I, Laferenza U, Potenza DM, Bottino C, Glasnov TN, Prestia M, Ferulli F, Saitta A, Mosca A, Guerra G, Rosti V, Luinetti O, Ganini C, Porta C, Pedrazzoli P, Tanzi F, Montagna D, Moccia F. Store-operated ca(2+) entry does not control proliferation in primary cultures of human metastatic renal cell carcinoma. Biomed Res Int. 2014:739494.

[31] Dragoni S, Laferenza U, Bonetti E, Reforgiato M, Poletto V, Lodola F, Bottino C, Guido D, Rappa A, Pareek S, Tomasselli M, Guarerra MR, Cinelli MP, Aronica A, Guerra G, Barosi G, Tanzi F, Rosti V, Moccia F. Enhanced Expression of Stilm, Orai, and TRPC Transcripts and Proteins in Endothelial Progenitor Cells Isolated from Patients with Primary Myelofibrosis. PLoS One 2014 Mar 6;9(3):e91099.
[40] Dragoni S, Reforgiato M, Zuccolo E, Poletto V, Lodola F, Ruffinatti FA, Bonetti E, Guerra G, Barosi G, Rosti V, Moccia F. Dysregulation of VEGF-induced pro-angiogenic Ca2+ oscillations in primary myelofibrosis-derived endothelial colony forming cells. Exp Hematol. 2015 Dec;43(12):1019-1030. e3.

[41] Zuccolo E, Bottino C, Difazio F, Poletto V, Codazzi AC, Mannarino S, Campanelli R, Fois G, Marsega GL, Guerra G, Montagna D, Laforenza U, Rosti V, Massa M, Moccia F. Constitutive store-operated Ca2+ entry leads to enhanced nitric oxide production and proliferation in infantile hemangioma-derived endothelial colony forming cells. Stem Cells Dev. 2016 Feb 15;25(4):301-319.

[42] Poletto V, Dragoni S, Lim D, Biggiogera M, Aronica A, Cinelli M, De Luca A, Rosti V, Porta C, Guerra G, Moccia F. Endoplasmic Reticulum Ca2+ Handling and Apoptotic Resistance in Tumor-Derived Endothelial Colony Forming Cells. J Cell Biochem. 2016 Oct;117(10):2260-71. doi: 10.1002/jcb.25524.

[43] Corbi G, Bianco A, Turchiarelli V, Cellurale M, Fatica F, Daniele A, Mazzarella G, Ferrara N. Potential Mechanisms Linking Atherosclerosis and Increased Cardiovascular Risk in COPD: Focus on Sirtuins. Int J Mol Sci. 2013 Jun 17;14(6):12696-713.

[44] Negro E, Scudiero O, Sarnataro D, Mazzarella G, Sofia M, Bianco A, Daniele A. Adiponectin affects lung epithelial A549 cell viability counteracting TNFa and IL-18 toxicity through AdipoR1. Int J Biochem Cell Biol. 2013 Jun;45(6):1145-53.

[45] Negro E, Daniele A, Scudiero O, Ludovica Monaco M, Rovizzio F, D'Agostino B, Mazzarella G, Bianco A. Adiponectin in asthma: implications for phenotyping. Curr Protein Pept Sci. 2015;16(3):182-187.

[46] Bianco A, Mazzarella G, Turchiarelli V, Rosti V, Corbi G, Scudiero O, Sofia M, Daniele A. Adiponectin: an attractive marker for metabolic disorders in Chronic Obstructive Pulmonary Disease (COPD). Nutrients, 2013, 15(10), 4115-4125.

[47] Daniele A, De Rosa A, Negro E, Scudiero O, Capasso M, Mascillo M, de Laurentiis G, Oriani G, Sofia M, Bianco A. Adiponectin oligomerization state and adiponectin receptors airway expression in chronic obstructive pulmonary disease. Int J Biochem Cell Biol. 2012 Mar;44(3):563-569.

[48] Negro E, Scudiero O, Monaco ML, Palmieri A, Mazzarella G, Costagliola C, Bianco A, Daniele A. New insight into adiponectin role in obesity and obesity-related diseases. Biomed Res Int. 2014; 2014:658913.

[49] Negro E, Imperlini E, Scudiero O, Monaco ML, Politto R, Mazzarella G, Orrù S, Bianco A, Daniele A. Differentially expressed and activated proteins associated with non small cell lung cancer tissues. Respir Res. 2015 Jun 24;16:74. doi: 10.1186/s12931-012-0057-1.

[50] Cardarella S, Johnson BE: The impact of genomic changes on treatment of lung cancer. Am J Respir Crit Care Med 2013, 188:770-775.

[51] Wu JY, Vlastos AT, Pettle MF, Caligo MA, Bianco A, Krause KH, Laurent GJ, Irmlinger-Junger I: Aberrant expression of BARD1 in breast and ovarian cancers with poor prognosis. Int J Cancer 2006, 118:1215-1226.

[52] Zhang YQ, Bianco A, Malkinson AM, Leoni VP, Frau G, Rosa ND, Andrade PA, Versace R, Boulvain M, Laurent GJ, Atzori L, Irmlinger-Junger I: BARD1: An independent predictor of survival in non-small cell lung cancer. Int J Cancer 2012, 131: 83-94.

[53] Moccia F, Dragoni S, Lodola F, Bonetti E, Bottino C, Guerra G, Laforenza U, Rosti V, Tanzi F. Store-dependent Ca2+ entry in endothelial progenitor cells as a perspective tool to enhance cell-based therapy and adverse tumour vascularisation. Curr Med Chem 2012 Dec 1;19(34):5802-5818.

[54] Moccia F, Lodola F, Dragoni S, Bonetti E, Bottino C, Guerra G, Laforenza U, Rosti V, Tanzi F. Ca2+ Signalling in Endothelial Progenitor Cells: A Novel Means to Improve Cell-Based Therapy and Impair Tumour Vascularisation. Curr Vasc Pharmacol 2014 Jan;12(1):87-105.

[55] Moccia F, Zuccolo E, Poletto V, Cinelli M, Bonetti E, Guerra G, Rosti V. Endothelial progenitor cells support tumour growth and metastatization: implications for the resistance to anti-angiogenic therapy. Tumour Biol. 2015 Aug;36(9):6603-6614.

[56] Moccia F, Zuccolo E, Poletto V, Turin I, Guerra G, Pedrazzoli P, Rosti V, Porta C, Montagna D. Targeting Stim and Orai proteins as an alternative approach in anticancer therapy. Curr Med Chem. 2016 Jun 7. [Epub ahead of print].

[57] Berra-Romani R, Avelino-Cruz JE, Raqeeb A, Della Corte A, Cinelli M, Montagnani S, Guerra G, Moccia F, Tanzi F. Ca2+-dependent nitric oxide release in the injured endothelium of excised rat aorta: a promising mechanism applying in vascular prosthetic devices in aging patients. BMC Surg 2013 Oct 8;13(Suppl 2):S40.

[58] Moccia F, Dragoni S, Cinelli M, Montagnani S, Amato B, Rosti V, Guerra G, Tanzi F. How to utilize Ca2+ signals to rejuvenate the reparative phenotype of senescent endothelial progenitor cells in elderly patients affected by cardiovascular diseases: a useful therapeutic support of surgical approach? BMC Surg 2013 Oct 8;13(Suppl 2):S46.

[59] Bianco A, Mazzarella G, Bresciani M, Piacco G, Sipetri MA. Virus-induced asthma. Monaldi Arch Chest Dis 2002;57:188-190.

[60] Corbi G, Bianco A, Turchiarelli V, Cellurale M, Fatica F, Daniele A, Mazzarella G, Ferrara N. Potential mechanisms linking atherosclerosis and increased cardiovascular risk in COPD: focus on Sirtuins. Int J Mol Sci. 2013 Jun 17;14(6):12696-713.

[61] De Simone G, Aquino G, Di Gioia C, Mazzarella G, Bianco A, Mazzarella G, Ferrara N. Potential mechanisms linking atherosclerosis and increased cardiovascular risk in COPD: focus on Sirtuins. Int J Mol Sci. 2013 Jun 17;14(6):12696-713.

[62] De Simone G, Aquino G, Di Gioia C, Mazzarella G, Bianco A, Calcagno G. Efficacy of aerobic physical retraining in a case of combined pulmonary fibrosis and emphysema syndrome: a case report. J Med Case Rep. 2015 Apr 19;9:85.

[63] Kim ES, Kim YT, Kang CH, Park IK, Bae W, Choi SM, Lee J, Park YS, Lee CH, Lee SM, Yim JJ, Kim YW, Han SK, Yoo CG. Prevalence of and risk factors for postoperative pulmonary complications after lung cancer surgery in patients with early-stage COPD. Int J Chron Obstruct Pulmon Dis. 2016 Jun 16;11:1317-26. doi: 10.2147/COPD.S105206.