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**HIGHLIGHT**

**Alternative diagnoses in suspicion of PTE**

**Cervical tomography in sleep apnea**

**Crazy-paving pattern**

# A CIDADE MARAVILHOSA TE ESPERA DE BRAÇOS ABERTOS PARA NOSSO PRÓXIMO ENCONTRO

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Expediente

## BRAZILIAN THORACIC SOCIETY

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## EDITORIAL



## ORIGINAL ARTICLE

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# 2016 – a second step

Rogério Souza[1,2]

The role of the editorial board of a scientific journal goes beyond deciding what should or should not be published on the basis of scientific merit; it must include identifying needs in the area of interest so that the journal can serve as a major channel of communication, raising discussions and highlighting trends that will aid in achieving a better understanding of the field. This is perhaps a point that needs to be explored further in the JBP in the year we are now entering.

At the beginning of a new cycle, it is important to look back on failures and successes, always keeping in mind the goals set forth for the entire journey.[1] As we look back on 2015, we can see that it was a special year for the JBP. We celebrated our 40th anniversary! That is no trifle, nor has it been easy! From the accounts of former JBP editors, it is evident that the success of the journal is the direct result of the maturing of pulmonology as a specialty in Brazil and that the internationalization of the journal is a consequence of the increasing international visibility of a number of researchers working in the country.[2,3]

Another point for consideration is the pattern of citations to articles published in the JBP. In the past two years, the most-cited original articles were those related to diseases that are less prevalent, such as lymphangioleiomyomatosis,[4] pulmonary hypertension,[5] and congenital muscular dystrophy.[6] In contrast, the most-cited review articles were those related to clinical conditions that are more prevalent. This only underscores the ultimate goal of bringing the JBP ever closer to its readers, taking into account their diversity, including not only researchers interested in topics that are more specific but also those who have had a general education and use the JBP as a vehicle for continuing education. Therefore, in this past year, we placed an emphasis on review topics that are more general, such as the treatment of idiopathic pulmonary fibrosis,[7] the role of PET/CT in lung cancer,[8] and indications for lung transplantation.[9] In the same vein, there has been growing interest in the continuing education series on imaging in pulmonary medicine and on scientific methodology, both of which were initiated in 2015. The discussion of various radiological patterns[10] has been extremely educational and can be used as a reference by residents and graduate students. The same can be said about the series on methodology, which is intended to disseminate knowledge on the topics that are most relevant to the correct interpretation of a scientific article.[11]

These factors should contribute to increasing the number of citations to our journal in various databases, as well as to increasing the number of views and downloads of articles published on our website. That, in fact, will be one of the focal points of our activities during 2016. One means of improving access to the information conveyed in the JBP is to organize it in a way that will meet the expectations of its varied readership. Obviously, most readers access our articles via PubMed or PubMed Central. However, for our readers in Brazil, there is the possibility of organizing access by topics of interest or even via a program of continuing education based on the content published in the JBP. Such initiatives can be developed through our website.

Communication with the readership as a whole can be strengthened by focusing on individual interest in certain topics. This increases the visibility of articles that are specific to each topic, which has particular relevance for clinical conditions that are less prevalent.

Another very important point is that of publishing updates to several of the Brazilian Thoracic Association guidelines. This year, the journal will be publishing new COPD guidelines, with the aim of reflecting the great advancements that have been made in the field since the latest guidelines were published. Guidelines on other topics are also being developed, which makes the outlook for the coming months very positive.

Certain topics, such as instruction in general medicine and in medical specialties, as well as the profile of graduate programs in pulmonology in Brazil, deserve more attention and have been poorly covered by the various journals in the field of respiratory medicine. At a time when many medical schools are reformulating their curricula, it is appropriate to establish a forum for discussion about what should be considered the minimum requirements for a degree in general medicine. In parallel, it is necessary to revisit the discussion of what is the minimum knowledge required to be a specialist in respiratory medicine, in terms of fields of study as well as practical skills. The JBP can host such discussions and remain a permanent forum for the exchange of opinions and teaching strategies.

Because of the evolution of the various graduate programs in pulmonology that are currently available in Brazil, there is a need for more in-depth analysis so that it is possible to discuss potential collaborations and changes. There is a potential change in student and professor expectations in view of the current crisis in research funding. It is necessary to adapt to this situation, and, once again, the JBP can serve as a forum for the exchange of views on the current and future state of research in the field of respiratory medicine.

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We expect that, by setting up discussion forums, the JBP will assume an increasingly important role as a channel of communication in the field of respiratory diseases. It is our hope that, in the near future, we can open those discussions to the international community, as a means of broadening the parameters of comparison and allowing diversity to be a source of constant evolution in the concepts medical education that are applied in Brazil. Finally, let us hope that 2016 will take the JBP one step further in disseminating knowledge regarding respiratory medicine at all of its levels.

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EDITORIAL

# Ischemia/reperfusion-induced lung injury prevention: many options, no choices

Pedro Caruso[1,2], Susimeire Gomes[1]

The pulmonary parenchyma is prone to injuries caused by indirect insults, such as sepsis, pancreatitis, burn, blood transfusion, bypass surgery, intoxication, and ischemia followed by reperfusion (ischemia/reperfusion injury). Approximately 20% of all cases of acute respiratory distress syndrome (an extreme case of lung injury) are the result of an indirect insult to the lung parenchyma.[1] However, the exact incidence of lung injury caused by an ischemia/reperfusion insult remains unknown. In the clinical arena, there are frequent situations of ischemia/reperfusion insults to tissues other than the lungs. Vascular surgery, orthopedic surgery, mesenteric ischemia, trauma, renal ischemia, liver ischemia, and liver transplantation are well-known examples of ischemia/reperfusion insult, and it is not an overstatement to say that such insults are common in the clinical arena.

In the treatment of severe acute lung injury, the guiding principles are treatment of the main cause and the prevention of further lung injury, mainly through protective mechanical ventilation. However, because there is an interval between the ischemia/reperfusion insult and the occurrence of the lung injury, there is an opportunity to and interest in finding drugs to prevent or attenuate the lung injury. Many drugs and procedures have been tested in order to prevent the deleterious effect of the ischemia/reperfusion insult, including hyperbaric oxygen, iloprost, cyclosporine, levosimendan, ascorbic acid, preconditioning with hyperoxygenated solution, tempol (a membrane-permeable radical scavenger), melatonin, rapamycin, pyrrolidine dithiocarbamate, surfactant, inhaled nitric oxide, prion protein, creatine supplementation, catalase, ischemic conditioning maneuvers, and carbon monoxide. Most studies evaluating such drugs and procedures have tested them in small animals, using various models of ischemia/reperfusion, injury quantification scales, and time intervals from the ischemia/reperfusion insult to the injury analysis.

We read with interest the article by Takhtfooladi et al., entitled "Effects of N-acetylcysteine and pentoxifylline on remote lung injury in a rat model of hind-limb ischemia/reperfusion injury", which appears in this issue of the *Jornal Brasileiro de Pneumologia*.[2] The authors evaluated the protective effect of N-acetylcysteine and pentoxifylline on remote lung injury in a rat model of hind-limb ischemia/reperfusion insult and concluded that N-acetylcysteine and pentoxifylline protect against the consequent oxidative stress and histological damage to the lungs. We found it interesting that administration of the combination of N-acetylcysteine and pentoxifylline does not increase the protective effect. In other experimental studies, many drugs have been shown to minimize the lung injury caused by ischemia/reperfusion. Therefore, we would expect to see many clinical trials testing such drugs. However, the number of published clinical studies addressing the prevention of ischemia/reperfusion injury is disproportionally lower than is that of the experimental studies, and the clinical studies have produced controversial results. The effectiveness of cyclosporine in attenuating ischemia/reperfusion injury caused by percutaneous coronary intervention has been tested, as has that of remote ischemic conditioning in attenuating ischemia/reperfusion injury after living donor renal transplantation, and neither treatment was found to be effective.[3] The results obtained in clinical studies of N-acetylcysteine as an antioxidant have also been controversial. In one clinical study, N-acetylcysteine effectively attenuated tourniquet-induced ischemia/reperfusion injury following knee surgery,[4] whereas other studies have shown that N-acetylcysteine does not attenuate myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention[5] or hepatorenal injury in patients undergoing orthotopic liver transplantation.[6] In the clinical arena, pentoxifylline has been less extensively tested than has N-acetylcysteine, and the few studies evaluating the former, such as a study of pentoxifylline for the prevention of delayed graft function in recipients of deceased donor kidney grafts,[7] have reported disappointing results in terms of injury attenuation.

The study conducted by Takhtfooladi et al.[2] shows us that N-acetylcysteine and pentoxifylline both protect the lung parenchyma from the effects of an ischemia/reperfusion insult. Although this is an interesting finding, further studies are needed in order to test the hypothesis that N-acetylcysteine and pentoxifylline are able, in the clinical arena, to protect the lungs from ischemia/reperfusion injury or to attenuate such injury.

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ORIGINAL ARTICLE

# Effects of N-acetylcysteine and pentoxifylline on remote lung injury in a rat model of hind-limb ischemia/reperfusion injury

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Study carried out at the Young Researchers and Elites Club, Science and Research Branch, Islamic Azad University, Tehran, Iran.

## ABSTRACT

**Objective:** To investigate the effects of N-acetylcysteine (NAC) and pentoxifylline in a model of remote organ injury after hind-limb ischemia/reperfusion (I/R) in rats, the lungs being the remote organ system. **Methods:** Thirty-five male Wistar rats were assigned to one of five conditions (n = 7/group), as **follows:** sham operation (control group); hind-limb ischemia, induced by clamping the left femoral artery, for 2 h, followed by 24 h of reperfusion (I/R group); and hind-limb ischemia, as above, followed by intraperitoneal injection (prior to reperfusion) of 150 mg/kg of NAC (I/R+NAC group), 40 mg/kg of pentoxifylline (I/R+PTX group), or both (I/R+NAC+PTX group). At the end of the trial, lung tissues were removed for histological analysis and assessment of oxidative stress. **Results:** In comparison with the rats in the other groups, those in the I/R group showed lower superoxide dismutase activity and glutathione levels, together with higher malondialdehyde levels and lung injury scores ($p < 0.05$ for all). Interstitial inflammatory cell infiltration of the lungs was also markedly greater in the I/R group than in the other groups. In addition, I/R group rats showed various signs of interstitial edema and hemorrhage. In the I/R+NAC, I/R+PTX, and I/R+NAC+PTX groups, superoxide dismutase activity, glutathione levels, malondialdehyde levels, and lung injury scores were preserved ($p < 0.05$ for all). The differences between the administration of NAC or pentoxifylline alone and the administration of the two together were not significant for any of those parameters ($p > 0.05$ for all). **Conclusions:** Our results suggest that NAC and pentoxifylline both protect lung tissue from the effects of skeletal muscle I/R. However, their combined use does not appear to increase the level of that protection.

**Keywords:** Skeletal muscle; Ischemia; Reperfusion injury; Lung injury; Acetylcysteine; Pentoxifylline.

## INTRODUCTION

Re-establishing perfusion in a tissue after a period of ischemia worsens the initial ischemic injury. This process is known as ischemia/reperfusion (I/R) injury.[1] Such injury constitutes an important clinical event and is common in the lower extremities. Although restoration of blood flow can save the extremity, it can also result in multiple organ dysfunction syndrome.[2] For example, I/R of a lower limb leads to noncardiogenic pulmonary edema by means of pulmonary vasoconstriction, pulmonary hypertension, and increased alveolar membrane permeability.[3] Pulmonary dysfunction after I/R injury of a lower extremity continues to be a major cause of morbidity and mortality.[4] Previous studies have suggested that oxygen free radicals, inflammatory mediators, and, especially, neutrophils play an important role in the development of lung injury related to I/R in a lower limb.[5,6]

Various agents have been reported to reduce remote lung injury after hind-limb I/R in rats.[7-9] N-acetylcysteine (NAC) is an antioxidant that acts by increasing intracellular levels of glutathione, as well as by direct scavenging of reactive oxygen species (ROS) such as hypochlorous acid, hydrogen peroxide, superoxide, and hydroxyl radical.[10] Pentoxifylline, a nonspecific phosphodiesterase inhibitor, has been shown to improve tissue oxygenation and endothelial function as well as inhibiting pro-inflammatory cytokine production.[11] Pentoxifylline also inhibits cell proliferation and extracellular matrix accumulation.[12] Therefore, in the present study, we evaluated the possible involvement of oxidative stress in skeletal muscle I/R-induced lung injury in rats by examining the effects of pentoxifylline, NAC, and the combination of the two.

## METHODS

All experimental procedures were performed in accordance with established guidelines for the ethical treatment of experimental animals, and the study was approved by the Institutional Animal Care and Use Committee of the Islamic Azad University School of Veterinary Medicine, in the city of Tehran, Iran.

Thirty-five healthy adult male Wistar rats, 90-120 days of age and weighing 250-350 g, were purchased from the Pasteur Institute of Iran. The animals were housed in a temperature- and humidity-controlled environment

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(22 ± 1°C; relative humidity, 50 ± 5%), on a 12/12-h light/dark cycle, with ad libitum access to a commercial pellet diet and filtered tap water. The animals were randomly divided into five experimental groups of seven rats each: an I/R group, in which the animals were subjected to 2 h of hind-limb ischemia, induced by clamping the left femoral artery, followed by intraperitoneal administration of 2 mL of 0.9% saline solution and 24 h of reperfusion; a sham-operated (control) group, in which the animals were subjected to all surgical procedures except arterial occlusion and also received 0.9% saline (2 mL, i.p.); an I/R+NAC group, in which the animals were subjected to I/R, as described above, and received 150 mg/kg of NAC in 0.9% saline solution (i.p., in a total volume of 2 mL); an I/R+PTX group, in which the animals were subjected to I/R, as described above, and received 40 mg/kg of pentoxifylline in 0.9% saline solution (i.p., in a total volume of 2 mL); and an I/R+NAC+PTX group, in which the animals were subjected to I/R, as described above, and received a combination of NAC and pentoxifylline (at the doses listed above) in 0.9% saline solution (i.p., in a total volume of 2 mL).

The rats were weighed, after which they were anesthetized with a combination of ketamine hydrochloride 10% and xylazine hydrochloride 2% (i.m., 50 mg/kg and 10 mg/kg, respectively). The animals were placed on a warming pad, in dorsal recumbency, their thoraces and hind limbs immobilized with adhesive tape. After aseptic surgical preparation, 250 IU of heparin were administered via the jugular vein (in order to prevent clotting) and a skin incision was made on the medial surface of the left hind limb. After isolating the left femoral artery from the surrounding tissues, we induced ischemia by using a microvascular clamp to occlude the artery for 2 h. Throughout the period of ischemia, the animals were maintained in dorsal recumbency and remained anesthetized (additional doses given as necessary). Body temperature was monitored with a rectal thermometer. At the end of the period of ischemia, the clamp was removed and the surgical site was routinely closed with 4/0 polypropylene sutures. Animals in the control group underwent a similar surgical procedure, although without arterial occlusion. The rats subjected to ischemia then underwent 24 h of reperfusion. Throughout the periods of ischemia and reperfusion, the animals received noninvasive ventilatory support.

At the end of the experimental period, all of the rats were euthanized with an overdose of pentobarbital (300 mg/kg, i.p.) and the lungs were removed *en bloc*. The left lungs were immersed in 10% formalin solution, and the right lungs were stored at −20°C for subsequent biochemical analysis. The lung tissue homogenate and supernatant samples were prepared as described by Yildirim et al.[13] Malondialdehyde levels, superoxide dismutase (SOD) activity, and glutathione levels were measured in the right lungs, whereas samples of the left lungs were submitted to histopathological evaluation under light microscopy.

Malondialdehyde levels were determined by thiobarbituric acid reaction, as described by Yagi.[14] In the thiobarbituric acid reaction test, malondialdehyde (or malondialdehyde-like substances) react with thiobarbituric acid to produce a pink chromogen with peak absorbance at 532 nm on a spectrophotometer. The tissue levels of malondialdehyde are expressed as nmol/g of tissue.

The SOD activity was determined according to the method devised by Winterbourn et al.,[15] assayed as inhibition of the photochemical reduction of nitroblue tetrazolium at 560 nm. The SOD activity is expressed as U/g of tissue.

Glutathione levels were determined by the method described by Ellman,[16] in which the level of glutathione is considered directly proportional to the rate of formation of the reduced chromogen, 5,5′-dithiobis(2-nitrobenzoic acid), as determined by measuring its absorbance at 412 nm. The results are expressed as nmol/g of tissue.

The left lung specimens were fixed in 10% buffered formalin, processed by standard techniques, and embedded in paraffin. Cross-sectional slices (5-µm thick) were taken from the middle zones of the lungs and mounted on slides. The slides were stained with hematoxylin and eosin, after which they were examined under light microscopy by a pathologist who was blinded to the groups. Lung injury was evaluated semiquantitatively with the classification system established by Koksel et al.[17]: grade 0, normal appearance; grade 1, mild-to-moderate interstitial congestion and neutrophil infiltration; grade 2, perivascular edema, partial destruction of the lung architecture, and moderate neutrophil infiltration; and grade 3, complete destruction of the lung architecture and dense neutrophil infiltration. A total of five slides from each lung sample were randomly screened, and the mean was accepted as the representative value of the sample.

All results are shown as mean ± standard deviation. The analytical results were evaluated using the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). Statistical analysis was done by analysis of variance. Values of $p < 0.05$ were considered statistically significant.

## RESULTS

As can be seen in Figure 1, the malondialdehyde levels were significantly higher in the I/R group than in any of the other groups ($p < 0.05$). In addition, the malondialdehyde levels were lower in the I/R+NAC+PTX group than in the I/R+NAC and I/R+PTX groups, although the differences were not statistically significant. The SOD activity was significantly lower in the I/R group than in the control group (Figure 2), whereas it was significantly higher in the I/R+NAC, I/R+PTX, and I/R+NAC+PTX groups than in the I/R group ($p < 0.05$). Although SOD activity was highest in the I/R+NAC+PTX group, there were no significant differences among the

I/R+PTX, I/R+NAC, and I/R+NAC+PTX groups in terms of SOD activity. Glutathione levels were also significantly lower in the I/R group than in the control group (Figure 3), whereas they were significantly higher in the I/R+NAC, I/R+PTX, and I/R+NAC+PTX groups than in the I/R group. Although glutathione levels were higher in the I/R+NAC+PTX group than in the I/R+NAC and I/R+PTX groups, the differences among those three groups were not significant. The mean histopathological lung scores are shown, by group, in Figure 4. The mean I/R group score was significantly lower than was that of the I/R+NAC, I/R+PTX, and I/R+NAC+PTX groups, although lung injury scores did not differ significantly among the three treated groups. As shown in Figure 5, interstitial inflammatory cell infiltration was markedly more pronounced in the lung samples from rats in the I/R group than in those from rats in the other groups. The lungs of I/R group rats also showed various signs of interstitial edema and hemorrhage.

## DISCUSSION

Peripheral artery clamping is routinely used during orthopedic surgery or trauma, in elective and emergency procedures. Lung damage has been shown to occur following transient arterial occlusion. The ischemic damage results from a decrease in the blood flow to an organ. When blood flow is restored, more pronounced damage, known as reperfusion injury, occurs. It has been suggested that oxidative stress plays a role in the development of I/R injury.[18] Various tissue markers of oxidative stress have been measured to evaluate the effects of I/R injury. It is known that ROS, which are potent oxidizing and reducing agents that can directly damage cellular membranes by lipid peroxidation, are overproduced during oxidative stress.[19] Peroxidation of endogenous lipids leads to the conversion of reduced glutathione to glutathione-disulfide.[20] Malondialdehyde is an end product derived from the peroxidation of polyunsaturated fatty acids and related esters. Therefore, tissue levels of malondialdehyde are a valid reflection of lipid peroxidation. Another line of cellular defense against free radicals is a system of three enzymes, SOD, catalase, and glutathione peroxidase. SOD catalyzes the conversion of superoxides to hydrogen peroxide, which is subsequently converted to water and oxygen by catalase or glutathione peroxidase. Because it plays such a key role in cellular defense against free

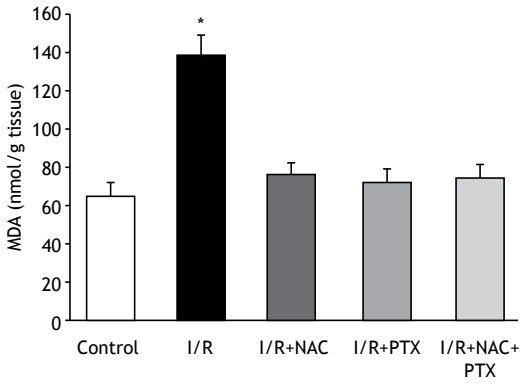


**Figure 1.** Malondialdehyde (MDA) levels in lung tissue after 2 h of hind-limb ischemia and 24 h of reperfusion. I/R: ischemia/reperfusion; NAC: N-acetylcysteine; and PTX: pentoxifylline. *p < 0.05 vs. all other groups.

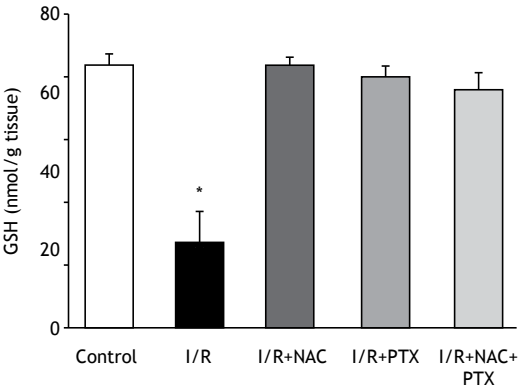


**Figure 3.** Glutathione (GSH) levels in lung tissue after 2 h of hind-limb ischemia and 24 h of reperfusion. I/R: ischemia/reperfusion; NAC: N-acetylcysteine; and PTX: pentoxifylline. *p < 0.05 vs. all other groups.

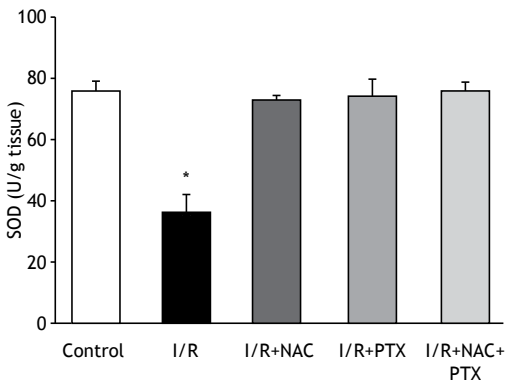


**Figure 2.** Superoxide dismutase (SOD) activity in lung tissue after 2 h of hind-limb ischemia and 24 h of reperfusion. I/R: ischemia/reperfusion; NAC: N-acetylcysteine; and PTX: pentoxifylline. *p < 0.05 vs. all other groups.

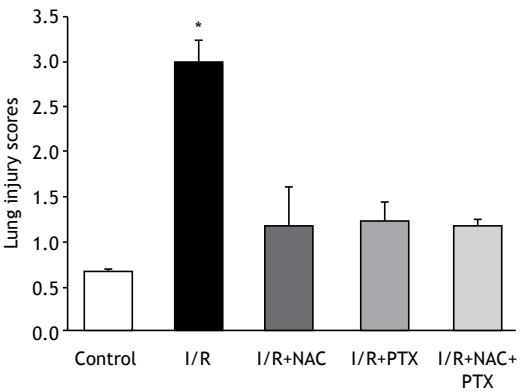


**Figure 4.** Histological lung injury scores after 2 h of hind-limb ischemia and 24 h of reperfusion. I/R: ischemia/reperfusion; NAC: N-acetylcysteine; and PTX: pentoxifylline. *p < 0.05 vs. all other groups.

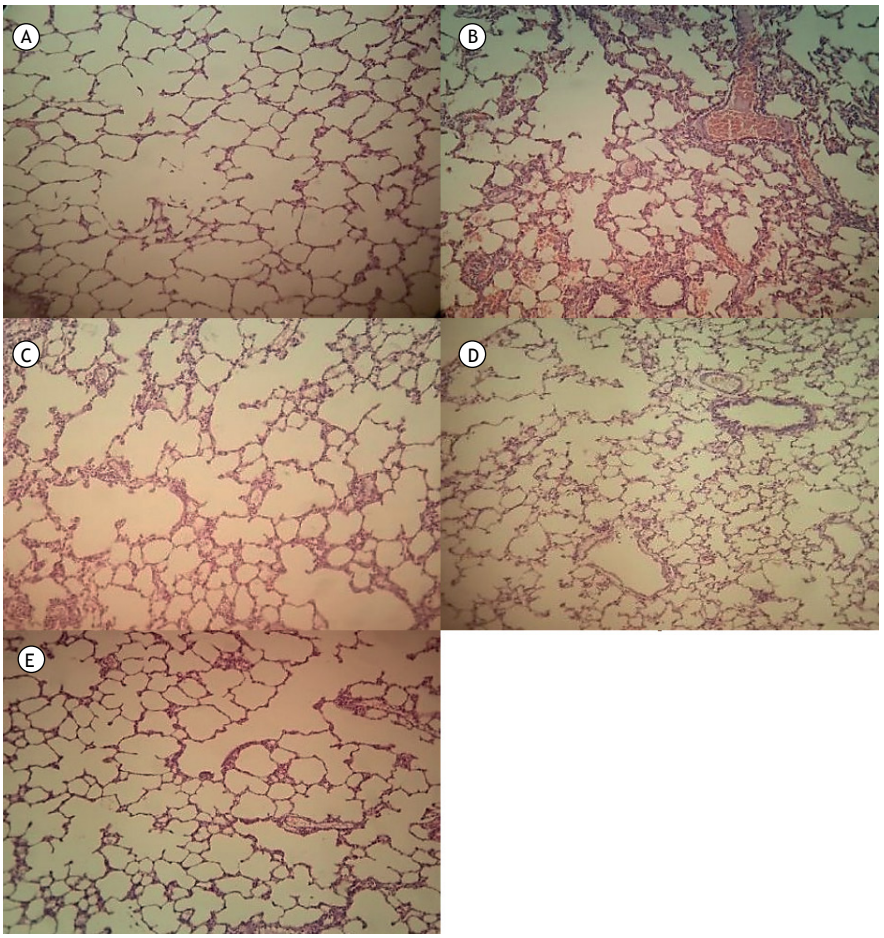


**Figure 5.** Lung tissue samples stained with hematoxylin and eosin (original magnification, ×100): (A) control group sample, showing no remarkable pathological changes; (B) ischemia/reperfusion (I/R) group sample, showing widespread histological changes such as edema, severe alveolar congestion, alveolar collapse, and inflammatory cell infiltration; and (C, D, and E, respectively) I/R+N-acetylcysteine, I/R+pentoxifylline, and I/R+N-acetylcysteine+pentoxifylline group samples, all showing fewer histological alterations (markedly less interstitial edema and inflammatory cell infiltration) in comparison with the I/R group sample.

radicals, SOD is also an important indicator of the oxidative state.[21]

The glutathione precursor NAC is a small molecule containing a thiol group, which has antioxidant properties, and is freely filterable with ready access to intracellular compartments.[22] The diversity of pharmacological applications of NAC is due mainly to the chemical properties of the cysteinyl thiol group of its molecule, the ability of reduced thiol groups to scavenge oxygen free radicals having been well established.[23-25] In addition, NAC has a variety of anti-inflammatory effects.[26,27] In previous rat studies, the administration of NAC at doses of approximately 400 mg/kg has been shown to protect organs against oxidative damage.[28,29] In the present study, we found that NAC administration after ischemia (prior to reperfusion) resulted in lower malondialdehyde levels, greater SOD activity, and higher glutathione levels in comparison with no treatment. In other words, NAC effectively attenuated the I/R-induced increase in the level of malondialdehyde.

Pentoxifylline is a methylxanthine derivative with multiple hemorheological properties. Pentoxifylline acts by increasing intracellular cyclic adenosine monophosphate on red blood cells, thus improving oxygen delivery to ischemic tissues, increasing cyclic adenosine monophosphate on polymorphonuclear leukocytes, and decreasing oxygen free radical production.[30-33] Recent reports suggest that pentoxifylline can enhance the chemotactic response of neutrophils, as well as inhibiting phagocytosis and superoxide production by neutrophils and monocytes.[34] Those findings have translated into clinical benefits, pentoxifylline having been used in order to attenuate I/R injury in patients with lung, intestinal, or kidney damage.[31] Previous studies have shown that supplementation with 50 mg/kg of pentoxifylline has the beneficial effect of reducing oxidative stress and inflammatory indices in I/R-induced spinal cord injury and fatty liver disease.[35,36] In the present study, pentoxifylline administration after ischemia (prior to reperfusion) resulted in lower malondialdehyde levels, greater SOD

activity, and higher glutathione levels in comparison with no treatment.

In conclusion, the significant I/R-induced increase in malondialdehyde levels, decrease in glutathione levels, and destructive appearance on histology of the lung suggest that skeletal muscle I/R-induced lung injury is mediated by oxidative reactions. The results of our study confirm that pentoxifylline and NAC are both protective against I/R injury. These effects might be, at least in part, due to the inhibition of ROS production. To our knowledge, this was the first study to compare the effects of these two substances on remote lung injury. We found that the antioxidant properties of pentoxifylline were comparable to those of NAC. However, we observed no additional effect when the two were administered in combination. Further studies are needed in order to determine the clinical importance of treatment with pentoxifylline and NAC, especially regarding the possible mechanisms other than ROS scavenging. Such treatments might prove effective for enhancing protection of the lungs after lower-limb I/R.

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# The Manchester Respiratory Activities of Daily Living questionnaire for use in COPD patients: translation into Portuguese and cross-cultural adaptation for use in Brazil

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## ABSTRACT

**Objective:** To translate The Manchester Respiratory Activities of Daily Living (MRADL) questionnaire into Portuguese and to create a version of the MRADL that is cross-culturally adapted for use in Brazil. **Methods:** The English-language version of the MRADL was translated into Portuguese by two health care researchers who were fluent in English. A consensus version was obtained by other two researchers and a pulmonologist. That version was back-translated into English by another translator who was a native speaker of English and fluent in Portuguese. The cognitive debriefing process consisted in having 10 COPD patients complete the translated questionnaire in order to test its understandability, clarity, and acceptability in the target population. On the basis of the results, the final Portuguese-language version of the MRADL was produced and approved by the committee and one of the authors of the original questionnaire. **Results:** The author of the MRADL questioned only a few items in the translated version, and some changes were made to the mobility and personal hygiene domains. Cultural differences regarding the domestic activities domain were found, in particular regarding the item "Do you have the ability to do a full clothes wash and hang them out to dry?", due to socioeconomic and climatic issues. The item "Do you take care of your garden?" was questioned by the participants who lived in apartments, being modified to "Do you take care of your garden or plants in your apartment?" **Conclusions:** The final Portuguese-language version of the MRADL adapted for use in Brazil was found to be easy to understand and easily applied.

**Keywords:** Activities of daily living; Questionnaires; Translations; Pulmonary disease, chronic obstructive.

## INTRODUCTION

Characterized by irreversible airflow obstruction, which is usually progressive, COPD worsens as a result of inhalation of smoke and noxious gases.[1] This disease, which is preventable and treatable, has various systemic manifestations, such as skeletal muscle dysfunction related to decreased exercise capacity, which, in association with dyspnea, tends to cause impairment of activities of daily living (ADLs).[2,3]

Impairment of ADLs in individuals with COPD can be assessed by the six-minute walk test, the six-minute walk distance being considered a good marker of functional capacity.[4] However, this test does not identify which activities are impaired, nor does it assess impairment of activities performed with the arms, which are invariably involved in ADLs.

There are few validated tools to assess impairment of ADLs in patients with COPD. The available instruments have little applicability in severely impaired patients[5] or show limited sensitivity to changes following interventions, such as pulmonary rehabilitation.[6]

Yohannes et al.[7] developed the Manchester Respiratory Activities of Daily Living (MRADL) questionnaire, which has been used as a physical disability scale in elderly patients with COPD[8] and consists of four domains: mobility (7 items); activities in the kitchen (4 items); domestic tasks (6 items); and leisure activities (4 items). The MRADL is aimed at assessing ADL impairment in patients with COPD. The scoring system ranges from 0 to 21, with the maximum score indicating no physical disability. The MRADL is an adapted composite of the Nottingham Extended Activities of Daily Living Questionnaire and the Breathing Problems Questionnaire.[7] The MRADL is valid, reliable, and reproducible, as well as being easy and rapid to complete (10 min), in addition to distinguishing between individuals with COPD and healthy elderly individuals and being sensitive to pulmonary rehabilitation.[7,8] It has good internal consistency (Cronbach's alpha coefficient = 0.91),[7] with low final scores indicating difficulties in ADLs.

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A score ≤ 7.5 is considered a predictor of mortality.[9] However, because the MRADL is an instrument originally developed in English, it should be translated into the target language and adapted to the social and cultural circumstances of the target country.[10-13]

In this context, the objective of the present study was to translate the MRADL into Portuguese and to create a version of the MRADL that is cross-culturally adapted for use in Brazil.

## METHODS

The study sample was intentionally comprised of 10 patients who had been diagnosed with COPD and were treated at the pulmonology outpatient clinic of the Federal University of Santa Catarina University Hospital, located in the city of Florianópolis, Brazil. The inclusion criteria were as follows: having previously been diagnosed with COPD by spirometry, in accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria[1] (post-bronchodilator $FEV_1$/FVC ratio < 0.70); having shown clinical stability in the signs and symptoms of COPD in the last four weeks; having been free from respiratory infection and COPD exacerbation in the last three months; and being able to understand the study procedures. Patients who had a respiratory disease other than COPD were excluded, as were those who had a systemic inflammatory disease and those who had a mental illness or a deficit in understanding or forming speech that would prevent them from answering the questions in the instrument. Symptoms and health status were assessed by the COPD Assessment Test (CAT),[14] and patients were evaluated for dyspnea on the basis of the modified Medical Research Council (mMRC) scale score,[15] which was used for the classification of disease severity.

The study was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (Protocol no. 800.310). The translation and cross-cultural adaptation of the MRADL were performed as described by Guillemin et al.[16] and Wild et al.[17] In Brazil, Felisbino et al. used this methodology to translate a chronic cough questionnaire into Brazilian Portuguese and adapt it for use in Brazil.[18]

The cross-cultural adaptation process was carried out, in phases, strictly in accordance with internationally accepted guidelines[17]: acquisition of permission for cross-cultural adaptation and acquisition of the rights of use of the MRADL from one of its original authors; translation of the MRADL from English into Portuguese; reconciliation; back-translation; review and harmonization of the back-translation; acquisition of approval from the author of the MRADL; review of the Portuguese-language version of the MRADL by experts; cognitive debriefing; and reconciliation/preparation of the final version.

First, the MRADL was translated from English into Portuguese by two bilingual researchers who participated in this study, and then a review committee met to produce a first Portuguese-language version. Subsequently, the major questions raised and difficulties encountered were discussed with the author of the questionnaire, and a second version was reached.

The second Portuguese-language version of the MRADL was back-translated into English by a translator who was a native speaker of English and fluent in Portuguese. The back-translation was then reviewed by the review committee, which produced a back-translated English version and a matching Portuguese-language version. The back-translated version was sent to one of the authors of the original MRADL for evaluation, and, once that had been approved, a third Portuguese-language version of the MRADL was produced. The third version was reviewed by an expert committee, which included a bilingual pulmonologist and two Brazilian translators who were fluent in English and performed the translation independently, and, subsequently, a fourth Portuguese-language version of the MRADL was produced. The fourth version was used in the cognitive debriefing process, with the questionnaire being administered to the study participants. Questions regarding and difficulties related to the text were addressed, and, at the end of this phase, a fifth version was produced. After reconciliation, the final Portuguese-language version of the MRADL was produced (Figure 1).

The cognitive debriefing process consisted of a preliminary test, i.e., a pretest to identify problems in the text of the questionnaire (complexity of the questions, imprecise wording, unnecessary questions, embarrassment or exhaustion caused to respondents, etc.)[19] and offer solutions to make it easier to understand. To that end, we chose 10 individuals with COPD, because they belonged to the population under study,[19,20] and administered the translated questionnaire to them in order to assess the clarity and precision of the terms; the form, break-down, and order of the questions; and the introduction to the questionnaire.[19] In this phase, the following elements were also investigated: reliability (the same results will always be obtained with the questionnaire, regardless of who administers it); validity (the data collected are necessary to the research); and operability (accessible vocabulary and clear meaning).[20] During the visit, the study was explained in detail, and individuals who agreed to participate gave written informed consent. In addition, anthropometric data were collected and spirometry was performed to diagnose COPD. In addition, the CAT and the mMRC scale were administered. The MRADL was administered to each participant by the same researcher. Individuals were informed that they should not worry about the accuracy of their responses, but rather just report what they understood, any problems related to the questions or statements on the questionnaire, and their level of acceptance of the questionnaire. During the administration of the MRADL, the researcher and the patient were alone. The researcher read the questions to the participant and re-read them if necessary but did not explain them.

Finally, in the reconciliation phase, the review committee and the expert committee met to produce

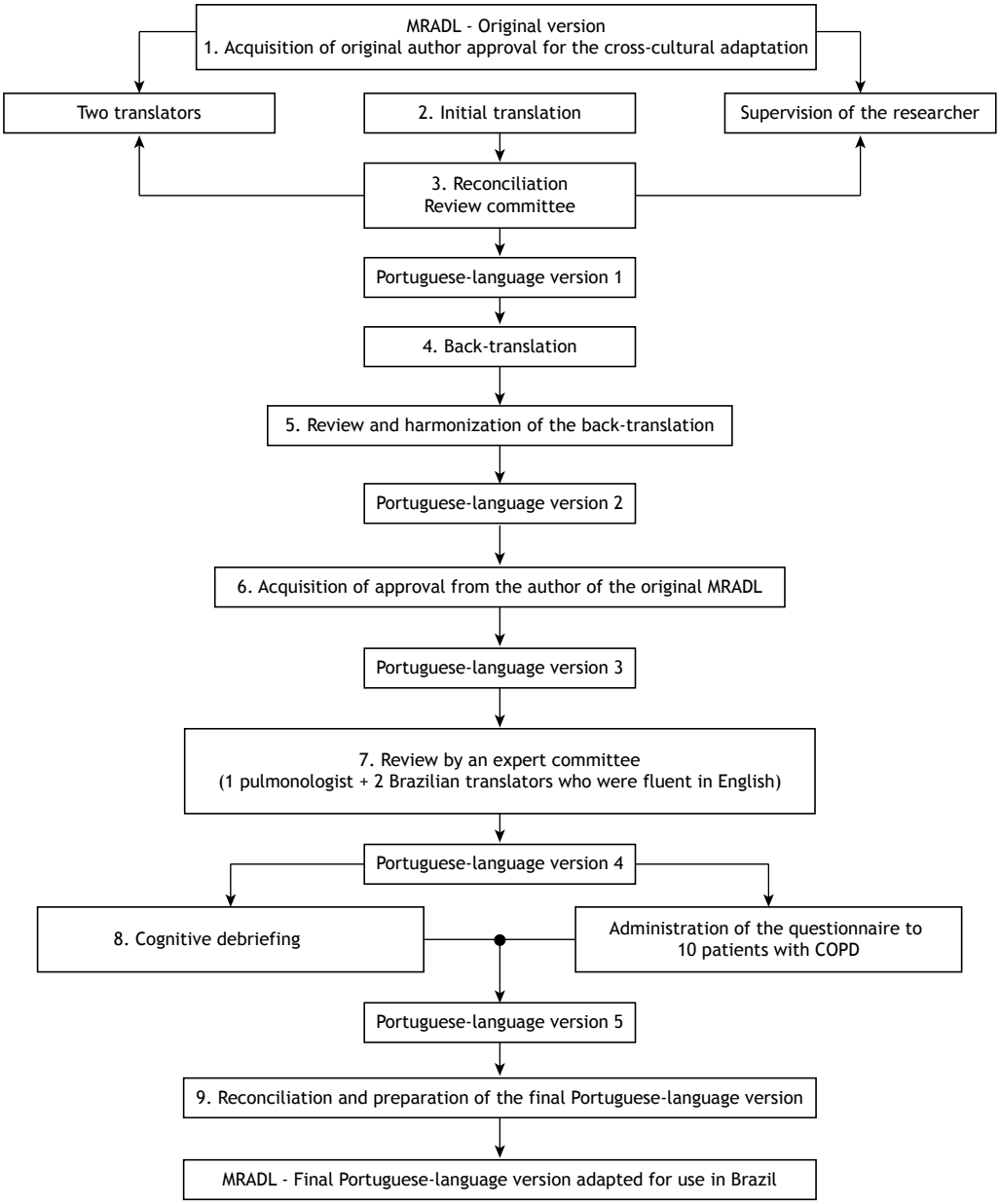


**Figure 1.** Summary of the process of translating the Manchester Respiratory Activities of Daily Living (MRADL) questionnaire into Brazilian Portuguese and creating a version of the MRADL that is cross-culturally adapted for use in Brazil.

the final Portuguese-language version of the MRADL. To that end, the instrument was analyzed item by item. The cognitive debriefing findings were discussed by the authors of this study and the author of the original questionnaire, and the relevant changes were made. Therefore, the final Portuguese-language version of the MRADL adapted for use in Brazil was produced. The phases of the study can be seen in Figure 1.

## RESULTS

Of the 10 patients interviewed in the cognitive debriefing phase, 7 were female, all were While, and all resided in the greater metropolitan area of Florianópolis. The general, anthropometric, and clinical characteristics of the participants are listed in Table 1.

During the MRADL translation phase, there were some questions raised and suggestions made for changes, with changes being made with the approval of the author of the MRADL. The item "Do you cross roads?" was changed to "Do you cross the street?" The item "Do you wash and dry yourself?" was changed to "Do you carry out personal hygiene (brush your teeth, wash your face, comb your hair)?", expanding the scope of the question to the ability of individuals to perform their personal hygiene in general. The items to which changes were made after the translation of

the original questionnaire can be seen in Table 2. In addition, in this phase, the item "Do you cross roads?" was questioned by the experts because "streets" and "roads" are considered to be the same type of route in Brazil, and the item was changed to "Do you cross the street?" "Do you wash and dry yourself?" was initially translated as "*Você se lava e se seca?*"; however, the translators discussed between themselves and questioned the author of the original questionnaire about the equivalence between that item and the item "Do you have a bath?", both of which were aimed at determining the patients' ability to bathe themselves. Nevertheless, "Do you have a bath?" means bathing in a bathtub, which is not very common in Brazil, where few people have a bathtub at home. Therefore, the item was changed to "Do you carry out personal hygiene (brush your teeth, wash your face, comb your hair)?", which can detect impairment of personal hygiene in general.

In the back-translation of the MRADL into English, the following items underwent changes: "Do you walk around outside?" was back-translated as "Do you go hiking outdoors?"; however, the author of the MRADL suggested that the item remain as in the original version. The item "Do you walk over uneven ground?", which was back-translated as "Do you walk on irregular terrain?", remained as in the original version because the author of the original questionnaire did not agree with using the word "terrain", arguing that it would alter the original meaning of the question. The domestic activities domain subheading was back-translated as "home chores", there being no change in its meaning in Portuguese. The back-translation of the item "Do you wash small items of clothing?" as "Do you wash small garments?" was discarded by the author of the original questionnaire because the term "garments" was considered inappropriate.

The review by the expert committee indicated some grammatical errors and offered conceptual suggestions, as well as questioning whether the item "Do you walk around outside?" was meant to refer to mobility (confidence in leaving home) or to physical activity (walking). The author of the MRADL explained that this item refers to both, as well as to social interaction, and therefore it was changed to "Do you walk outside the house?" The item "Do you do a full clothes wash?" was changed to "Do you have the ability to do a full clothes wash and hang them out to dry?" because of socioeconomic issues, because, in Brazil, not everyone has a washer, and because of climatic issues, taking into account that most people hang clothes on the clothesline to dry and do not have a dryer. The items to which changes were made after the review by the expert committee are listed in Table 3.

During the cognitive debriefing phase, participants raised some questions about the text. The item "Do you get in and out of the car?" was questioned by participants because some of them had difficulty in performing only one of these activities. However, the author of the original questionnaire suggested that the item remain in the questionnaire and that difficulty in performing only one of the activities be considered impairment. For the item "Do you bend over from standing?", it was necessary to explain and even simulate the movement, and the item was changed to "Do you bend over from standing position to pick up an object?" for better understanding. The item "Do you do the washing up?" was questioned by participants because, for cultural reasons, this activity is performed mostly by women in Brazil; however, the author of the MRADL suggested that the item remain in the questionnaire, because it refers to the ability of individuals to perform the activity, even if they do not do it frequently. The items "Do you wash small items of clothing?" and "Do you have the ability to do a full clothes wash and hang them out to dry?" remained in the questionnaire and should be taken into account even if patients use a washer, in which case the patients' ability to put clothes into and take them out of the washer to hang them on the clothesline should be

**Table 1.** General, anthropometric, and clinical characteristics of the participants.[a]

| Characteristic | Result |
|---|---|
| Gender, M/F | 3/7 |
| Smokers, yes/no | 4/6 |
| Age, years | 62.6 ± 9.9 |
| Weight, kg | 69.5 ± 13.5 |
| Height, m | 1.6 ± 0.1 |
| Smoking history, pack-years | 38.4 ± 38.8 |
| $FEV_1$, L | 1.2 ± 0.8 |
| $FEV_1$, % of predicted | 36.4 ± 14.4 |
| FVC, L | 2.1 ± 0.9 |
| FVC, % of predicted | 49.9 ± 11.5 |
| $FEV_1$/FVC, % | 54.4 ± 11.3 |
| CAT score | 18.3 ± 7.9 |
| mMRC dyspnea scale score | 1.4 ± 0.9 |

CAT: COPD Assessment Test; and mMRC: modified Medical Research Council. [a]Values expressed as n/n or mean ± SD.

**Table 2.** The Manchester Respiratory Activities of Daily Living questionnaire items to which changes were made after their translation into Brazilian Portuguese.

| Initial translation | Portuguese-language version 1 |
|---|---|
| "*Atravessa estradas?*" | "*Atravessa a rua?*" |
| "*Se lava e se seca?*" | "*Realiza higiene pessoal (escovar os dentes, lavar o rosto, pentear o cabelo)?*" |

**Table 3.** The Manchester Respiratory Activities of Daily Living questionnaire items to which changes were made after the review by the expert committee.

| Original English-language version | Modified English-language version |
|---|---|
| "Do you walk around outside?" | "Do you walk outside the house?" |
| "Do you do a full clothes wash?" | "Do you have the ability to do a full clothes wash and hang them out to dry?" |

assessed. Finally, the item "Do you manage your own garden?" was questioned by the individuals who lived in apartments and did not have a garden, and it was realized that some individuals in the sample would have a low total score. Therefore, that item was modified to "Do you take care of your garden or plants in your apartment?" The items to which changes were made after the cognitive debriefing can be seen in Table 4.

During the analysis of the latest provisional version of the MRADL, the author of the original instrument suggested that the following changes be made to its instructions: "This scale was elaborated" was changed to "This scale is designed" and "Circle the most appropriate response that best describes you" was changed to "Reply with one tick (√) that best describes you". The final Portuguese-language version of the MRADL can be seen in Chart 1.

## DISCUSSION

In the present study, the MRADL was translated into Portuguese and a version of the MRADL that is cross-culturally adapted for use in Brazil was created, with some caveats and changes.

There are some validated instruments to assess functional disability in patients with COPD; however, such instruments have little applicability in severely impaired patients.[21] That underscores the importance of the instrument translated in the present study, because the MRADL is aimed at assessing impairment of ADLs in individuals with COPD, as well as being able to detect overall impairment, even in severely ill individuals. The individuals included in the present study had a mean CAT score and a mean mMRC dyspnea scale score of 18.3 ± 7.9 and 1.4 ± 0.9, respectively, which demonstrates the severity of their disease, given that a CAT score ≥ 10 and an mMRC score ≥ 2 are indicative of high impact of symptoms.[1]

Among the available instruments that have been validated for use in Brazil, few assess impairment of ADLs specifically in patients with COPD.[15,21-23] One of the questionnaires developed specifically to assess impairment of ADLs in patients with COPD—the Pulmonary Functional Status and Dyspnea Questionnaire - Modified version—consists of three domains (influence of dyspnea on ADLs, influence of fatigue on ADLs, and change in ADLs after disease onset).[23] However, the instrument is not appropriate for assessing individuals who are elderly or severely impaired, because it includes questions regarding tasks that are more complex.

**Table 4.** The Manchester Respiratory Activities of Daily Living questionnaire items to which changes were made after the cognitive debriefing phase.

| Portuguese-language version 3 | Portuguese-language version 4 |
|---|---|
| *"Curva-se na posição em pé?"* | *"Curva-se na posição em pé para pegar um objeto?"* |
| *"Cuida do seu jardim?"* | *"Cuida do seu jardim ou plantas em seu apartamento?"* |

There are several predictors of prognosis for individuals with COPD, including lean body mass index, frequency of hospitalizations for acute exacerbations, and classification of symptoms.[24] The six-minute walk test is also widely used.[23] However, its use is limited because it does not assess functional capacity in patients who are more severely ill. The MRADL has proven useful in the assessment of physical disability as a predictor of mortality in elderly individuals with COPD,[24] which suggests that this instrument is more beneficial in clinical practice.

Of the patients interviewed in the cognitive debriefing phase, 70% were female, and all resided in the greater metropolitan area of Florianópolis. The region accounts for 18% of the total population of the state of Santa Catarina, which, in recent years, has shown low fertility rates and a trend toward growth in the number of elderly individuals; in addition, in Santa Catarina, the proportion of females in the elderly age group is higher than is that of males, a fact that can be explained by the greater exposure of men to a set of risk factors, such as alcohol use, smoking, and violence.[25] Therefore, the present study sample does not appear to be representative of the prevalence of COPD, which is higher in men.[26]

One of the difficulties found was an inability of respondents to differentiate among the response options for each ADL, because some of them reported not performing some activities because someone did that for them, and not because they were unable to perform them. Difficulties in interpreting the items assessed have also been identified in other studies, and such items need to be rephrased in order to be more easily understood.[21,22]

During the final reconciliation process carried out by the expert committee in order to prepare the final Portuguese-language version of the MRADL, it was suggested that a response option reading "not applicable" be included to minimize possible misinterpretations of responses, because, in Brazil, women make up more than 90% of all domestic workers, which shows that they predominate in this sector.[27] However, this suggestion was not accepted by the author of the original instrument, because the primary objective of the MRADL is to identify individuals severely affected by COPD and because the change would negatively affect the scoring system, making it difficult to quantify the results. A validation study is needed in order to assess the use of the MRADL, the scoring system applied, and the score by gender. Perhaps a different score should be considered for males, in order to reduce limitations in the items that comprise the "domestic activities" domain.

In a study aimed at performing a translation and cultural adaptation[21] of another measure of functional disability in patients with COPD, the London Chest Activity of Daily Living scale, an alternative scoring

**Chart 1.** Portuguese-language version of the Manchester Respiratory Activities of Daily Living questionnaire adapted for use in Brazil.
Este formulário foi elaborado para termos uma melhor compreensão sobre como seus problemas respiratórios podem afetar as suas atividades de vida diária.
Por favor, leia cada questão cuidadosamente e assinale com um "X" a alternativa que melhor descreve você:

| | Nunca | Com ajuda | Sozinho com dificuldade | Sozinho, facilmente |
|---|---|---|---|---|
| **MOBILIDADE** | | | | |
| Você: | | | | |
| Faz passeios a pé? | ---------- | ---------- | ---------- | ---------- |
| Sobe escadas? | ---------- | ---------- | ---------- | ---------- |
| Entra e sai do carro? | ---------- | ---------- | ---------- | ---------- |
| Caminha em terrenos irregulares? | ---------- | ---------- | ---------- | ---------- |
| Atravessa a rua? | ---------- | ---------- | ---------- | ---------- |
| Usa transporte público? | ---------- | ---------- | ---------- | ---------- |
| Se inclina a partir da posição em pé para pegar um objeto? | ---------- | ---------- | ---------- | ---------- |
| **NA COZINHA** | | | | |
| Você: | | | | |
| Pega algo que está em uma prateleira mais alta ou na altura de seus ombros? | ---------- | ---------- | ---------- | ---------- |
| Leva bebidas quentes de um cômodo para outro? | ---------- | ---------- | ---------- | ---------- |
| Lava a louça? | ---------- | ---------- | ---------- | ---------- |
| Faz um lanche quente para você? | ---------- | ---------- | ---------- | ---------- |
| **ATIVIDADES DOMÉSTICAS** | | | | |
| Você: | | | | |
| Realiza atividades domésticas em geral? | ---------- | ---------- | ---------- | ---------- |
| Lava peças pequenas de roupa? | ---------- | ---------- | ---------- | ---------- |
| Faz suas próprias compras? | ---------- | ---------- | ---------- | ---------- |
| Consegue lavar a roupa e estendê-la para secar? | ---------- | ---------- | ---------- | ---------- |
| Faz sua higiene pessoal (escovar os dentes, lavar o rosto, pentear o cabelo)? | ---------- | ---------- | ---------- | ---------- |
| Toma banho? | ---------- | ---------- | ---------- | ---------- |
| **ATIVIDADES DE LAZER** | | | | |
| Você: | | | | |
| Sai socialmente? | ---------- | ---------- | ---------- | ---------- |
| Cuida do seu jardim ou de suas plantas em seu apartamento? | ---------- | ---------- | ---------- | ---------- |
| Você precisa comer mais devagar do que gostaria?(*) | Muito mais devagar --------- | Mais devagar -------- | Um pouco mais devagar --------- | De maneira alguma --------- |
| Sua respiração deixa você acordado(a) durante a noite?(*) | A maior parte da noite ---------- | Por 1 ou 2 horas ---------- | Mais de ½ hora ---------- | Não ---------- |

Sistema de pontuação: Classificação das respostas: sozinho; sozinho com dificuldade; com ajuda; nunca
Escore:
0 – com ajuda; nunca (*muito mais devagar, mais devagar, a maior parte da noite, por 1 ou 2 horas).
1 – sozinho, facilmente; sozinho com dificuldade (*um pouco mais devagar; mais de ½ hora; não).

system was designed for the item "I do not perform this activity (because I have never needed to or it is irrelevant)." in order to disregard the questions for which the patient would score zero and prevent men completing the questionnaire from having a score that does not reflect their actual functional impairment, thereby identifying individuals who do not perform certain activities for reasons other than those related to the lung disease.

The study participants, according to the criteria used in the present study, were classified as patients with severe COPD (Table 1).[1] This made it impossible to assess the MRADL in terms of its applicability in individuals with mild disease. The objective of the present study was to translate the MRADL into Portuguese and to create a version of the MRADL that is cross-culturally adapted for use in Brazil. Although the MRADL is a self-report questionnaire, we chose to interview participants in order to receive their

suggestions. In order to test the applicability of the MRADL, as well as its reproducibility, a study is being conducted to assess its internal validity by determining interobserver and intraobserver variability.[28] A larger convenience sample will be used for those phases.[29]

The respondents' comments regarding the instrument were quite helpful. Their suggestions were relevant and essential to the changes made. Therefore, the MRADL has now been translated and adapted for use in Brazil. The final Portuguese-language version of the MRADL was found to be easy to understand and easy to administer, as well as being a useful instrument to assess the physical limitations and determine the prognosis of individuals with COPD.

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ORIGINAL ARTICLE

# Restrictive pattern on spirometry: association with cardiovascular risk and level of physical activity in asymptomatic adults

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Study carried out in the Laboratório de Epidemiologia e Movimento Humano – EPIMOV – Departamento de Ciências do Movimento Humano, Universidade Federal de São Paulo – UNIFESP – and at AngioCorpore – Instituto de Medicina Cardiovascular, Santos (SP) Brasil.

## ABSTRACT

**Objective:** To determine whether a restrictive pattern on spirometry is associated with the level of physical activity in daily life (PADL), as well as with cardiovascular disease (CVD) risk factors, in asymptomatic adults. **Methods:** A total of 374 participants (mean age, 41 ± 14 years) underwent spirometry, which included the determination of FVC and $FEV_1$. A restrictive pattern on spirometry was defined as an $FEV_1$/FVC ratio > 0.7 and an FVC < 80% of the predicted value. After conducting demographic, anthropometric, and CVD risk assessments, we evaluated body composition, muscle function, and postural balance, as well as performing cardiopulmonary exercise testing and administering the six-minute walk test. The PADL was quantified with a triaxial accelerometer. **Results:** A restrictive pattern on spirometry was found in 10% of the subjects. After multivariate logistic regression, adjusted for confounders (PADL and cardiorespiratory fitness), the following variables retained significance (OR; 95% CI) as predictors of a restrictive pattern: systemic arterial hypertension (17.5; 1.65-184.8), smoking (11.6; 1.56-87.5), physical inactivity (8.1; 1.43-46.4), larger center-of-pressure area while standing on a force platform (1.34; 1.05-1.71); and dyslipidemia (1.89; 1.12-1.98). **Conclusions:** A restrictive pattern on spirometry appears to be common in asymptomatic adults. We found that CVD risk factors, especially systemic arterial hypertension, smoking, and physical inactivity, were directly associated with a restrictive pattern, even when the analysis was adjusted for PADL and cardiorespiratory fitness. Longitudinal studies are needed in order to improve understanding of the etiology of a restrictive pattern as well as to aid in the design of preventive strategies.

**Keywords:** Spirometry; Hypertension; Motor activity; Sedentary lifestyle; Smoking.

## INTRODUCTION

Lung restriction is a multifactorial clinical condition, characterized by a reduction in lung volumes, and worsens with age. A restrictive pattern on spirometry is seen in approximately 12% of the general population.[1] The diagnosis of lung restriction requires the measurement of static lung volumes. However, a reduction in FVC, without bronchial obstruction, is commonly used as a proxy for lung restriction. Although it remains unclear whether a restrictive pattern has clinical relevance in the absence of respiratory symptoms, signs of pulmonary fibrosis, or other clinical changes, a different ventilatory strategy might be employed during exercise.[2] In addition, a restrictive pattern has been associated with various cardiovascular disease (CVD) risk factors, including obesity,[3] diabetes mellitus,[4] dyslipidemia,[5] and systemic arterial hypertension (SAH),[6] as well as with high mortality.[7]

Studies have shown that physical inactivity is associated with worse cardiorespiratory fitness and respiratory function.[8] Although previous studies have shown that a restrictive pattern on spirometry is associated with cardiovascular risk and disease,[9] there is little information about the possible confounding effect of the level of accelerometer-measured physical activity and of cardiorespiratory fitness, despite the fact that physical inactivity is associated with all of the aforementioned comorbidities.[9] A better understanding of the factors related to restrictive lung disease could enable primary care providers to intervene early and prevent problems associated with the abnormality. We hypothesized that a restrictive pattern is also associated with the level of physical activity in daily life (PADL), and that the associations between a restrictive pattern and CVD risk factors could be confounded by the levels of PADL and cardiorespiratory fitness. Therefore, we aimed to determine whether a restrictive pattern is associated with PADL and CVD risk factors in asymptomatic adults, even when the analysis of the latter is adjusted for PADL and cardiorespiratory fitness. A secondary objective was to assess the prevalence of this spirometric abnormality in a sample of the Brazilian population.

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## METHODS

### *Participants and study design*

This was a cross-sectional study involving 374 participants, with a mean age of 41 ± 14 years (91 males and 283 females), selected from among those enrolled in an ongoing study—the Epidemiological Study of Human Movement and Hypokinetic Diseases. All participants underwent spirometry. The classic definition of a restrictive pattern on spirometry is low FVC in the presence of a normal $FEV_1$/FVC ratio. However, restrictive lung disease is characterized by a decrease in total lung capacity (TLC).[10] There are two gold standard methods for the determination of TLC: helium dilution; and plethysmography. Both methods are costly and time consuming in comparison with simple spirometry. Various epidemiological studies have used the Global Initiative for Chronic Obstructive Lung Disease spirometry criteria for identifying a restrictive pattern, including an FVC < 80% of the predicted value and a fixed ratio of $FEV_1$ to FVC (in absolute values) ≥ 70%.[7,11-13] To make our results comparable to those available in the literature, we decided to employ the latter definition. To calculate the predicted spirometric variables, we used reference values for the Brazilian population.[14] We collected demographic and anthropometric data, as well as data related to CVD risk factors. We also assessed PADL (with accelerometry), body composition, muscle function, and postural balance, as well as performing cardiopulmonary exercise testing (CPET) and administering the six-minute walk test. The inclusion criteria were being between 18 and 90 years of age and having no cardiac or pulmonary diseases. The exclusion criteria were having orthopedic problems, having a recent history of respiratory infections, having had angina (unstable or stable) in the last four weeks, having a recent history of myocardial infarction, and having undergone angioplasty or cardiac surgery in the last three months. The participants were informed of the potential risks and discomforts of the procedures proposed in the present study, and all gave written consent. The study was approved by the Human Research Ethics Committee of the Federal University of São Paulo (Protocol no. 186.796).

In the present study, we evaluated a convenience sample of volunteers who were recruited through postings disseminated via social networks and brochures distributed at universities in the region, as well as though announcements in local magazines and newspapers. During the initial clinical evaluation, we asked all participants to complete the Physical Activity Readiness Questionnaire,[15] in order to identify any contraindications to undergoing CPET. To investigate the history of asthma and exposure to pollutants, as well as to determine smoking status, we used a respiratory questionnaire based on that developed for the American Thoracic Society Epidemiology Standardization Project.[16] The risk of CVD was stratified according to the American College of Sports Medicine guidelines.[17] On the basis of the verifiable and self-report data collected, we investigated the major risk factors for CVD, including age (male ≥ 45 years; female ≥ 55 years); family history of premature coronary heart disease (confirmed myocardial infarction before 55 years of age in the father or before 65 years of age in the mother or in another first-degree relative); SAH; diabetes; dyslipidemia; and current smoking.

### *Procedures*

Spirometry was performed with a hand-held spirometer (Quark PFT; Cosmed, Pavona di Albano, Italy), in accordance with the criteria established by the American Thoracic Society.[18] We determined $FEV_1$, FVC, and the $FEV_1$/FVC ratio. After determining body weight and height, we calculated the BMI. Body composition was determined with a tetrapolar bioimpedance analyzer (310e; Biodynamics, Seattle, WA, USA), following the procedure described by Kyle et al.[19] Lean body mass and fat body mass were calculated using the regression equations developed for healthy individuals.[20]

The maximal symptom-limited exercise capacity was assessed during CPET with a ramp protocol on a treadmill (ATL; Inbrasport, Porto Alegre, Brazil). After 3 min at rest, the speed and inclination were automatically increased according to the estimated maximal oxygen consumption, the aim being to complete the test in approximately 10 min. Cardiovascular, respiratory, and metabolic variables were analyzed breath by breath with a gas analyzer (Quark PFT; Cosmed). Oxygen uptake ($VO_2$), carbon dioxide production ($VCO_2$), the rate of gas exchange ($VCO_2/VO_2$), minute ventilation, and heart rate were monitored throughout the test. The data were filtered every 15 s for further analysis. The peak $VO_2$ (in mL/min, mL/min/kg, and % of predicted) was defined as the average values in the last 15 s of the incremental exercise.

Functional exercise capacity was assessed by means of a six-minute walk test performed rigorously in accordance with the American Thoracic Society guidelines.[21] The six-minute walk distance was recorded in meters and in percentage of the predicted value.[22]

Postural balance was evaluated by collecting kinetic data on center-of-pressure (COP) dynamics during postural balance assessment on a force platform (400 BIOMEC; EMG System do Brasil, São José dos Campos, Brazil). The frequency of platform data acquisition was 100 Hz. Participants were instructed to remain as immobile as possible, and the COP area (in $cm^2$) was registered while each participant was standing with eyes open or eyes closed. Each condition was maintained for 30 s.

Muscle function was assessed by determining the peak torque (PT) of the quadriceps and biceps on an isokinetic dynamometer (Biodex; Lumex Inc., Ronkonkoma, NY, USA). The PT (in N m) was evaluated in two trials of 5 movements each at 60°/s. After a rest period of at least 3 min, participants performed two tests of isometric force (also in N m) against fixed resistance

in a 60° range of knee flexion. After another similar rest period, participants performed 30 movements at 300°/s to record the total work (in kJ). In all tests, the highest value was selected for analysis.

The level of PADL was assessed with an ActiGraph triaxial accelerometer (MTI, Pensacola, FL, USA), the use of which has previously been validated.[23] Participants were asked to wear the device on an elasticized belt over their dominant hip for 7 days. A valid day was defined as one on which a participant wore the device for at least 12 h. Participants were instructed to remove it for water-related activities, such as bathing and swimming, and at bedtime. The triaxial accelerometer measures the duration and intensity of physical activity. The device incorporates an inclinometer, which records the time spent lying, sitting, and standing. We analyzed the accelerometry data only for the participants who had used the device for at least 4 (valid) days. Physical activity in the sedentary, low intensity, moderate intensity, vigorous, and very vigorous strata were defined as described by Freedson et al.[24] The minimum PADL, in terms of quantity and intensity, was defined as 150 min/week of moderate to vigorous intensity.[25] Individuals who did not reach this level of PADL were considered physically inactive.

### *Statistical analysis*

We first conducted descriptive analysis of the data, including frequencies, histograms, measures of central tendency, and variability. To assess the association between a restrictive pattern on spirometry and the studied variables, we calculated unadjusted and adjusted odds ratios, together with the respective 95% confidence intervals. We then selected the most significant variables and performed a multivariate logistic regression analysis using a restrictive pattern as the outcome variable. The model was adjusted for age, gender, race, level of education (higher education or not), self-reported CVD risk factors (SAH, diabetes, dyslipidemia, smoking, obesity, and physical inactivity), body composition (fat body mass), peripheral muscle function (PT of the quadriceps and biceps), postural balance (COP area while standing with eyes open), and cardiorespiratory fitness (peak $VO_2$). Obesity was defined as a BMI > 29.9 kg/m$^2$. The probability of a type I error was set at 5%. Statistical analysis was performed with the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

Of the 374 subjects evaluated, 37 (9.9%) presented a restrictive pattern on spirometry and 6 presented an obstructive pattern ($FEV_1$/FVC ratio < 0.7). In comparison with rest of the sample, the 37 participants with a restrictive pattern were older. In addition, the proportions of females and obese individuals were greater among the participants with a restrictive pattern, who also had more CVD risk factors and used a higher number of medications. In the sample as a whole, the prevalence of SAH was 11%, the prevalence of self-reported dyslipidemia was 21%, the prevalence of self-reported diabetes was 0.07%, the prevalence of current smoking was 11%, and the prevalence of accelerometer-measured physical inactivity was 19%. The characteristics of the sample are described in Table 1. After being adjusted for confounders, the multivariate logistic regression indicated that the variables SAH, smoking, physical inactivity, dyslipidemia, and COP retained their significance as predictors of a restrictive pattern (Table 2).

## DISCUSSION

We found an overall prevalence of a restrictive pattern on spirometry of 10%. To our knowledge, this is first study to show an association between a restrictive pattern and PADL through accelerometry. A restrictive pattern was also associated with SAH, smoking, and dyslipidemia, even after the analysis was adjusted for PADL and cardiorespiratory fitness. In a multicenter, population-based study carried out in Spain,[26] the reported prevalence of a restrictive pattern was 12.7%, similar to that found in the present study. In another population-based study, conducted in the greater metropolitan area of São Paulo, Brazil, the prevalence of COPD was found to be 15.8%.[27] It can be hypothesized that the major initiatives that have targeted an obstructive pattern on spirometry, regardless of the definition of COPD employed, have missed an important public health target by not exploring the frequency of a restrictive pattern.

Previous studies have reported that individuals with a restrictive pattern on spirometry are at increased risk for all-cause and cardiovascular mortality.[28] In the present study, the strongest predictor of a restrictive pattern was SAH. In fact, the association between SAH and pulmonary function abnormalities has been previously described.[6] However, the mechanism of that association remains unknown.

It is known that SAH is associated with increased systemic and pulmonary vascular resistance, as well as with increased vessel stiffness. Given the highly vascular nature of the lung and the intimate anatomic coupling of vascular parenchymal elements, it is quite possible that a loss of elasticity of the pulmonary vascular tree would, independently of any pulmonary parenchymal change, adversely affect vital capacity and $FEV_1$. In the Normative Aging Study, Sparrow et al.[29] concluded that a reduction in FVC precedes the onset of SAH. Inflammation, on the other hand, seems to play a critical role in the development of SAH, because individuals with elevated levels of high-sensitivity C-reactive protein seem to be more likely to develop SAH during the first 5 years of follow-up.[30]

Another CVD risk factor directly associated with a restrictive pattern on spirometry was, as expected, current smoking. Classically, smoking history and the heaviness of smoking are associated with obstructive

**Table 1.** Characteristics of the 374 participants.[a]

| Characteristic | Pattern on spirometry | |
|---|---|---|
| | Normal (n = 337) | Restrictive (n = 37) |
| Age, years | 42 ± 15 | 47 ± 16* |
| Gender (%) | | |
| Female | 53.3 | 73.0** |
| Male | 43.8 | 27.0 |
| FVC, L | 3.92 ± 1.00 | 2.75 ± 0.85** |
| FVC, % of predicted | 98 ± 12 | 74 ± 9** |
| $FEV_1$, L | 3.21 ± 0.80 | 2.13 ± 0.64** |
| $FEV_1$, % of predicted | 98 ± 11 | 71 ± 6** |
| $FEV_1$/FVC, % | 82 ± 5 | 80 ± 5* |
| Race (%) | | |
| White | 59.7 | 57.1 |
| Black | 7.6 | 5.7 |
| Mulatto | 30.0 | 31.4 |
| Asian | 2.1 | 0.0 |
| Indigenous | 0.6 | 5.7* |
| Weight, kg | 75 ± 18 | 77 ± 20 |
| Height, cm | 165 ± 97 | 161 ± 98 |
| BMI, $kg/m^2$ | 27 ± 6 | 29 ± 7** |
| Fat body mass, % | 28 ± 8 | 33 ± 10* |
| Lean body mass, kg | 53 ± 12 | 50 ± 11 |
| Peak $VO_2$, mL/min | 2,383 ± 863 | 1,928 ± 814** |
| Peak $VO_2$, mL/min/kg | 32 ± 10 | 25 ± 10** |
| Peak $VO_2$, % of predicted | 100 ± 20 | 91 ± 19** |
| 6MWD, m | 605 ± 90 | 519 ± 118** |
| 6MWD, % of predicted | 105 ± 13 | 93 ± 17** |
| CVD risk factors (%) | | |
| Family history | 24.6 | 16.2 |
| Obesity | 26.1 | 40.5** |
| Hypertension | 9.5 | 21.6* |
| Dyslipidemia | 21.1 | 27.0 |
| Diabetes | 5.9 | 16.2* |
| Current smoking | 10.4 | 21.6* |
| Physical inactivity | 16.8 | 36.4* |
| Use of medications (%) | 26.7 | 43.2* |
| Occurrence of falls (%) | 5.3 | 18.9* |
| Higher education complete (%) | | |
| Yes | 40.2 | 27.0 |
| No | 59.7 | 72.9** |

$VO_2$: oxygen uptake; 6MWD: six-minute walk distance; and CVD: cardiovascular disease.[a]Values expressed as mean ± SD, except where otherwise indicated.

breathing patterns and with COPD. Smoking is also able to trigger the inflammatory pathway and cause profound histological changes. There is loss of elastic tissue and resistive material because the inflammatory process involves a tissue repair phase, in which the lung parenchyma is replaced by fibrotic tissue. Similar results were found by Twisk et al.,[31] who also reported that smoking was related to decreases in FVC and $FEV_1$.

Previous studies have reported that subjects with higher levels of PADL also have higher levels of $FEV_1$ and FVC.[8] However, that association has been poorly investigated in the general population. In the present study, accelerometer-measured physical inactivity was selected as an independent predictor of a restrictive pattern on spirometry. The biological plausibility of the influence of physical inactivity on the decline of lung function relies on the elevated levels of inflammatory mediators seen in physically inactive subjects. A low level of PADL has been associated with elevated plasma levels of interleukin-6 and C-reactive protein, independently of obesity.[32] In a review of 40 observational studies, Hamer[33] found that 27 of those studies reported that PADL was inversely associated with one or more inflammatory markers, and that those associations

**Table 2.** Multiple logistic regression analysis of risk factors for a restrictive pattern on spirometry.

| Factor | Adjusted model | | |
|---|---|---|---|
| | OR | 95% CI | |
| | | Lower limit | Upper limit |
| Age | 1.016 | 0.917 | 1.126 |
| Gender | 0.115 | 0.006 | 2.093 |
| CVD-related | | | |
| Obesity | 1.756 | 0.194 | 15.930 |
| SAH | 17.513* | 1.659 | 184.819 |
| Dyslipidemia | 1.896* | 1.127 | 1.988 |
| Diabetes | 3.549 | 0.382 | 33.011 |
| Current smoking | 11.699* | 1.564 | 87.504 |
| Physical inactivity | 8.176* | 1.439 | 46.461 |
| Fat body mass | 1.012 | 0.913 | 1.121 |
| PTQ | 1.015 | 0.991 | 1.039 |
| PTB | 1.012 | 0.929 | 1.101 |
| COP-EO | 1.347* | 1.056 | 1.718 |
| Peak $VO_2$ | 0.982 | 0.838 | 1.150 |
| 6MWD | 0.997 | 0.985 | 1.009 |
| Use of medications | 0.242 | 0.039 | 1.495 |

CVD: cardiovascular disease; SAH: systemic arterial hypertension; PTQ: peak torque of quadriceps; PTB: peak torque of biceps; COP-EO: center of pressure-eyes open; $VO_2$: oxygen uptake; and 6MWD: six-minute walk distance. *Significant, after adjustment for confounders, as a predictor of a restrictive pattern on spirometry.

remained significant even after being adjusted for measures of obesity.

In our multiple regression model, adjusted for confounders, dyslipidemia was also selected as an independent predictor of a restrictive pattern on spirometry, an association that has not been extensively investigated. Yeh et al.[3] reported that individuals with metabolic syndrome have high serum levels of inflammatory markers, and that those increases seem to be related to the reduction in FVC. Accordingly, the authors found that reduced lung function presents before the development of metabolic syndrome. Restrictive lung disease has been associated with high levels of inflammatory mediators, such as C-reactive protein and fibrinogen.[12] Many pathological mechanisms (ranging from obesity to interstitial lung disease) can cause restrictive lung disease. The underlying mechanisms of the association between this type of metabolic disorder and impaired lung function remain unclear.

One interesting finding of the present study is that poor static postural balance was associated with a restrictive pattern on spirometry, regardless of age, gender, or comorbidities. Similar results have been obtained in patients with asthma or COPD.[34] Kayacan et al.[35] concluded that, in individuals with COPD, airflow obstruction and disease duration can reduce the conduction velocity of peripheral nerves and cause neurophysiological changes, such as balance deficits. That mechanism might be related to the systemic inflammation present in such individuals, as well as in those with a restrictive pattern. To our knowledge, ours is the first study to assess the correlations between measurements obtained on a force platform and spirometric indices in asymptomatic individuals. Clinically, it might be important to know that individuals with a restrictive pattern could be at increased risk of falls, which should be taken into consideration during the management of this condition. We believe that the inflammatory cascade can also affect postural balance, as can being physically inactive, being a smoker and having hypertension. However, because we did not assess inflammation, that falls into the realm of supposition. Therefore, such interactions should be investigated further.

Although diabetes has been shown to be associated with lower FVC[4] and vice versa,[36] that was not found to be the case in the present study. The self-report nature of the data regarding diabetes might have influenced our results, given that the prevalence of the self-reported diagnosis was below that previously reported for the region.[37] Nevertheless, those reports either did not consider the confounding effects of PADL and cardiorespiratory fitness or assessed PADL only by questionnaire.

In the present study, obesity was more prevalent among subjects with a restrictive pattern on spirometry than among the remaining participants. However, in the adjusted model, obesity was not selected as a significant predictor of a restrictive pattern. Although several studies have reported an association between obesity and poor lung function, they have not taken comorbidities or a low level of PADL into consideration as possible confounders. In addition, BMI is not the best variable to evaluate in investigating this association. We know that excess adipose tissue exerts a mechanical effect on the lungs, whereby fat tissue within the abdominal region reduces the capacity of the diaphragm to shift downward, thereby limiting lung inflation. We found it surprising that Scott et al.[38] observed no significant associations between

fat mass and lung function in males, nor was fat mass a significant predictor of lung function in either of the regression models employed in their study. Furthermore, systemic inflammation seems to have a greater impact on dynamic lung function than do the mechanical effects of obesity.[38]

Our study has certain limitations, one of which is related to the selection of subjects. Because we evaluated a convenience sample, our obese subjects might have shown above-normal cardiorespiratory fitness, which could have influenced the results, given that fitness is positively associated with lung function. In addition, this was a cross-sectional study, and we were therefore unable to determine the causes of a restrictive pattern on spirometry. Furthermore, the fact that the diagnoses of SAH, diabetes, and dyslipidemia were based on self-reported data might have resulted in those conditions being underdiagnosed in our sample. Moreover, we did not measure TLC, take chest X-rays, or obtain chest CT scans in order to diagnose true pulmonary restriction. Nevertheless, the participants were asymptomatic and had no history of exposure to known predisposing factors for restrictive lung disease. We believe that a restrictive pattern can be related to nonpulmonary diseases, given the association found with other factors, including systemic inflammatory mechanisms (such as SAH), physical inactivity, and dyslipidemia. Neither abnormal chest X-rays nor a history of pleural disease have been shown to be predictors of a restrictive pattern on spirometry. Although interstitial lung diseases clearly result in pulmonary restriction, they do not appear to be the main factor associated with a restrictive pattern on spirometry in a population.[7] Most other large epidemiological cohort studies have identified a restrictive pattern on the basis of the pre-bronchodilator values; we did not employ that methodology, which is another limitation of our study. However, our participants with a restrictive pattern did not show any sign or symptom of airflow obstruction or airway hyperresponsiveness. Another study, using pre-bronchodilator spirometry, reported that subjects with a restrictive pattern are at increased mortality risk.[1] Because we did not quantify the TLC, we can not affirm that participants with a reduction in FVC also had a lower TLC. Therefore, the reduction in FVC could be a nonspecific respiratory disorder.

We can conclude that a restrictive pattern on spirometry is common among asymptomatic adults. To our knowledge, this is the first study reporting an association between a restrictive pattern and PADL objectively measured. We also found that a restrictive pattern was associated with CVD risk factors, even after adjusting for PADL and cardiorespiratory fitness. There is a need for additional, longitudinal, studies in order to gain a better understanding of the etiology of a restrictive pattern on spirometry as well as to inform decisions regarding the design of preventive strategies.

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# Respiratory therapy: a problem among children and adolescents with cystic fibrosis

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## ABSTRACT

**Objective:** To evaluate the level of self-reported adherence to physical therapy recommendations in pediatric patients (6-17 years) with cystic fibrosis (CF) and to ascertain whether the different levels of adherence correlate with pulmonary function, clinical aspects, and quality of life. **Methods:** This was a cross-sectional study. The patients and their legal guardians completed a questionnaire regarding adherence to physical therapy recommendations and a CF quality of life questionnaire. We collected demographic, spirometric, and bacteriological data, as well as recording the frequency of hospitalizations and Shwachman-Kulczycki (S-K) clinical scores. **Results:** We included 66 patients in the study. Mean age, $FEV_1$ (% of predicted), and BMI were 12.2 ± 3.2 years, 90 ± 24%, and 18.3 ± 2.5 kg/m$^2$, respectively. The patients were divided into two groups: high-adherence (n = 39) and moderate/poor-adherence (n = 27). No statistically significant differences were found between the groups regarding age, gender, family income, and total S-K clinical scores. There were statistically significant differences between the high-adherence group and the moderate/poor-adherence group, the latter showing lower scores for the "radiological findings" domain of the S-K clinical score ($p = 0.030$), a greater number of hospitalizations ($p = 0.004$), and more days of hospitalization in the last year ($p = 0.012$), as well as lower scores for the quality of life questionnaire domains emotion ($p = 0.002$), physical ($p = 0.019$), treatment burden ($p < 0.001$), health perceptions ($p = 0.036$), social ($p = 0.039$), and respiratory ($p = 0.048$). **Conclusions:** Low self-reported adherence to physical therapy recommendations was associated with worse radiological findings, a greater number of hospitalizations, and decreased quality of life in pediatric CF patients.

**Keywords:** Cystic fibrosis; Patient compliance; Physical therapy modalities; Quality of life.

## INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disease characterized by chronic pulmonary infection, exocrine pancreatic insufficiency, and high concentrations of sweat electrolytes. Respiratory system changes constitute the primary cause of morbidity and mortality.[1-8] Data from the Cystic Fibrosis Foundation show that the life expectancy of individuals with CF was 37.8 years in 2012.[9]

The standard therapeutic approach to lung disease includes antibiotic therapy, airway clearance, physical exercise, mucolytics, bronchodilators, anti-inflammatory agents, nutritional support, and oxygen supplementation.[10,11] Outpatient treatment is provided by a multidisciplinary team every two or three months and is aimed at educating parents and patients regarding home treatment, monitoring disease progression, and improving treatment adherence, being adjusted as needed.[12]

Airway clearance techniques are considered essential components of the treatment of CF. In older children and adolescents, the use of techniques that prioritize their independence is encouraged.[13,14]

Flores et al.[15] studied 63 adult CF patients and showed that 40% had moderate to poor adherence to airway clearance therapies, a finding that was associated with the level of education and the severity of disease. The use of techniques preferred by patients was found to be associated with increased adherence, the level of agreement between physician-recommended therapy and self-reported adherence being highest for positive airway pressure.

In the pediatric population, poor treatment adherence is associated with patient dependence on their parents or caregivers to perform the recommended treatment techniques and a lack of understanding of the long-term implications of the disease.[16] The difficulty that parents have in establishing a treatment routine and the use of trial and error are barriers to treatment adherence, whereas anticipatory guidance provided by a multidisciplinary team can facilitate disease management.[17] Misconceptions, knowledge gaps, and errors regarding

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CF can have an impact on disease progression.[18] Few studies have examined adherence to therapy in patients with CF.[15,19,20]

A total of 2,669 patients are currently registered in the Brazilian CF Registry. Rio Grande do Sul ranks second among the Brazilian states with the highest number of CF patients, i.e., 356 individuals (13.3%). There are currently 1,918 pediatric patients (under 18 years of age) with CF in Brazil, pediatric patients accounting for 77.6% of all CF patients in the state of Rio Grande do Sul. The number of patients diagnosed with CF has increased annually since the advent of neonatal screening for CF by immunoreactive trypsin assay. Therefore, strategies to improve treatment adherence and prevent complications are increasingly necessary.[21]

The objective of the present study was to evaluate the level of self-reported adherence to physical therapy recommendations in pediatric CF patients and to ascertain whether the different levels of adherence correlate with lung function, clinical scores, and quality of life.

## METHODS

### Study design

This was a cross-sectional study of pediatric CF patients. The objective of the study was to evaluate the level of adherence to respiratory therapy.

### Study population

Patients with CF were recruited by the Pediatric Pulmonology Team of the *Hospital de Clínicas de Porto Alegre* (HCPA), located in the city of Porto Alegre, Brazil. The study sample consisted of children and adolescents in the 6- to 17-year age bracket diagnosed with CF in accordance with a consensus statement.[2]

The study sample was consecutively selected from among all patients being followed and meeting the inclusion criteria. Data were collected in the period between May and October of 2014. The study was approved by the Research Ethics Committee of the HCPA (Protocol no. 14-0157), and the parents or legal guardians of all participants gave written informed consent.

We included clinically stable patients, clinical stability being defined as no hospitalizations or changes in the maintenance therapy regimen for at least 30 days. Patients with neurological changes resulting in difficulty in completing the questionnaires were excluded.

### Measurements and instruments

After having accepted the invitation to participate in the study, patients and their parents or legal guardians gave written informed consent and headed for an area outside the ambulatory care environment.

Initially, patients (accompanied by their parents or legal guardians) completed a questionnaire regarding adherence to physical therapy recommendations, developed from a previous study[15] conducted at our referral center and consisting exclusively of objective questions, such as the following: "How many days a week and how many times a day do you perform physical therapy techniques for airway clearance?"; "How long does each session last?"; "What techniques do you perform?"; "What techniques do you like the most and what techniques do you like the least?"; "Who helps you?"; and "What are your reasons for not performing the recommended technique(s)?". Subsequently, patients completed a CF quality of life questionnaire previously validated for use in Brazil.[22] Both questionnaires were administered outside the ambulatory care environment by a professional who was not involved in the treatment of the patients. The patients themselves answered the questions, being helped by their parents or legal guardians when necessary.

Subsequently, a physical therapist who was a member of the treatment team answered the same questions, recording physical therapy recommendations for each patient.

A data collection form was used in order to gather information on the following: date; gender; age; ethnicity; family income; age at CF diagnosis; BMI; resting $SpO_2$; sputum bacteriology; lung function; frequency of hospitalizations in the previous year (information collected from the electronic medical records of the participants, the day on which the questionnaires were administered being used in order to mark the end of the one-year period); and Shwachman-Kulczycki (S-K) clinical scores.[23]

The pulmonary function test results used in the present study were those of the spirometry tests requested in routine clinical care. Spirometry was performed at the Pulmonary Physiology Clinic of the HCPA Department of Pulmonology, with the patient in the sitting position. A v4.31a spirometer (Jaeger, Würzburg, Germany) was used, and all tests were performed in accordance with the technical acceptability criteria recommended in the Brazilian Thoracic Association guidelines for pulmonary function testing.[24] Values of FVC, $FEV_1$, and $FEV_1$/FVC were recorded. All parameters were also expressed as a percentage of the predicted values for age, height, and gender.[25]

### Statistical analysis

Data were entered into a Microsoft Excel 2011 database, after which they were processed and analyzed with the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA).

On the basis of their answers to questions regarding adherence to physical therapy recommendations in the last two weeks, patients were divided into three groups: the high-adherence group (which included patients who always performed the airway clearance techniques recommended by the physical therapist and rarely failed to undergo the recommended number of sessions); the moderate-adherence group (which included patients who always performed the airway clearance techniques recommended by the physical

therapist but often failed to undergo the recommended number of sessions); and the poor-adherence group (which included patients who never or almost never performed the airway clearance techniques recommended by the physical therapist and never or almost never underwent the recommended number of sessions). For analysis purposes, the high-adherence group was compared with the moderate/poor-adherence group.

Quantitative data were expressed as mean and standard deviation or as median (interquartile range). Qualitative data were expressed as frequency and proportion.

Continuous variables were compared by the independent sample t-test. Ordinal variables or continuous variables without normal distribution were compared by the Wilcoxon signed-rank test. Qualitative data were analyzed with the chi-square test, Yates' correction or Fisher's exact test being used when necessary. The kappa coefficient of agreement was used in order to assess the level of agreement between physician-recommended therapy and self-reported adherence. All statistical tests were two-tailed, and the level of significance was set at $p < 0.05$.

In order to calculate the sample size, proportions between the high-adherence and moderate/poor-adherence groups were taken into consideration. For an expected 40% proportion of patients with moderate/poor adherence[15]—a total amplitude of 0.25 and a 95% confidence interval being used—the minimum sample size was calculated to be 59.[26]

## RESULTS

During the study period, the HCPA Pediatric Pulmonology Team followed a total of 109 patients with CF. Of those, 72 were between 6 and 17 years of age. Of those 72 patients, 66 were included in the study and evaluated. Two patients were excluded from the study: one was excluded because of pulmonary exacerbation requiring hospitalization, and the other was excluded because the parents did not allow the patient to participate in the study. Another 4 patients failed to return for follow-up during the study period.

On the basis of self-reported adherence, patients were divided into two groups for analysis: the high-adherence group (comprising 39 patients and accounting for 59% of the sample as a whole); and the moderate/poor-adherence group (comprising 27 patients and accounting for 41% of the sample as a whole).

**Table 1.** General characteristics of pediatric patients with cystic fibrosis, by level of adherence to respiratory therapy.[a]

| p | Moderate/poor adherence (n = 27) | High adherence (n = 39) | Variable |
|---|---|---|---|
| 0.139 | 12.9 ± 3.6 | 11.7 ± 2.8 | Age, years |
| 0.372 | 0.33 (1) | 0.25 (3) | Age at diagnosis, years[b] |
| 0.179 | 10/17 | 21/18 | Male/Female, n/n |
| 0.336 | 18.7 ± 3.1 | 18.0 ± 2.0 | BMI, kg/m$^2$ |
| | | | Sputum bacteriology[c] |
| 0.791 | 20 (74.1) | 30 (76.9) | MSSA |
| 0.483 | 2 (7.4) | 5 (12.8) | MRSA |
| 0.715 | 14 (51.8) | 22 (56.4) | *Pseudomonas aeruginosa* |
| 0.290 | 7 (25.9) | 6 (15.3) | *Burkholderia cepacia* |
| 0.222 | | | Family income[c] |
| | 11 (40.7) | 24 (61.5) | < 3 × the national minimum wage |
| | 6 (22.2) | 7 (17.9) | 3-5 × the national minimum wage |
| | 9 (33.3) | 7 (17.9) | > 5 × the national minimum wage |
| 0.184 | 74.2 ± 12.8 | 78.8 ± 14.1 | Total S-K score |
| 0.030 | 12.0 ± 4.8 | 15.0 ± 5.9 | S-K radiological findings domain, score |
| | | | Quality of life score domains, score |
| 0.019 | 72 ± 21.1 | 84.3 ± 15.9 | Physical |
| 0.088 | 68.3 ± 16.5 | 81.4 ± 14.8 | Vitality |
| 0.002 | 69.4 ± 16.6 | 82.2 ± 12.6 | Emotion |
| 0.180 | 76.7 ± 30.2 | 86.5 ± 15.6 | Eating |
| 0.000 | 55.0 ± 24.7 | 82.4 ± 14.9 | Treatment burden |
| 0.036 | 70.0 ± 18.9 | 87.6 ± 14.1 | Health perceptions |
| 0.039 | 67.5 ± 19.4 | 78.2 ± 17.3 | Social |
| 0.155 | 78.3 ± 27.0 | 87.2 ± 18.2 | Body image |
| 0.158 | 76.6 ± 19.5 | 88.8 ± 16.1 | Social role |
| 0.964 | 73.3 ± 37.8 | 74.0 ± 32.3 | Weight |
| 0.048 | 64.4 ± 21.0 | 75.3 ± 18.1 | Respiratory |

MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; and S-K: Shwachman-Kulczycki. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Value expressed as median (interquartile range). [c]Values expressed as n (%).

Table 1 presents the general characteristics of the CF patients in the present study, by level of self-reported adherence to respiratory therapy. There were no statistically significant differences between the groups regarding age, gender, family income, or total S-K clinical scores. When the "radiological findings" domain of the S-K clinical score was analyzed separately, scores were found to be significantly lower in the moderate/poor-adherence group than in the high-adherence group ($p = 0.030$).

The moderate/poor-adherence group had significantly lower scores for the quality of life questionnaire domains emotion ($p = 0.002$), physical ($p = 0.019$), treatment burden ($p < 0.001$), health perceptions ($p = 0.036$), social ($p = 0.039$), and respiratory ($p = 0.048$).

Table 2 shows pulmonary function test results and frequency of hospitalizations (number of hospitalizations in the last year and number of days hospitalized in the last year) in the CF patients studied, by level of self-reported adherence to respiratory therapy. There were no statistically significant differences between the groups regarding lung function variables. However, the mean number of hospitalizations in the last year and the mean number of days hospitalized in the last year were significantly higher in the poor/moderate-adherence group than in the high-adherence group ($p = 0.004$ and $p = 0.012$, respectively).

Table 3 shows self-reported reasons for not performing the recommended physical therapy techniques for airway clearance. Feeling tired and not liking the recommended technique were reported significantly more often in the moderate/poor-adherence group than in the high-adherence group ($p = 0.002$ for both); in contrast, having some other engagement was reported significantly more often in the high-adherence group than in the poor/moderate-adherence group ($p < 0.001$).

Of the 66 patients studied, 52 (78.8%) were supervised by their mothers, 25 (37.9%) were supervised by their fathers, and 4 (6.1%) were supervised by a physical therapist, whereas 26 (39.4%) performed the recommended techniques without supervision. When answering the question regarding assistance when performing the recommended physical therapy techniques for airway clearance, patients were allowed to select more than one response (i.e., more than one supervisor). There were no statistically significant differences between the groups regarding the aforementioned variable.

The most commonly used respiratory therapy techniques were coughing (in 97%), huffing (in 86.4%), expiratory positive airway pressure (EPAP) delivered through a mask (in 84.8%), positive expiratory pressure (PEP) on water seal (in 18.2%), and slow exhalation to residual volume with an open glottis (in 4.5%).

There was agreement between physician-recommended therapy and self-reported adherence for EPAP mask (kappa = 0.63; $p < 0.001$) and PEP on water seal (kappa = 0.54; $p < 0.001$), The level of agreement between physician-recommended therapy and self-reported adherence was not significant for huffing, coughing, and slow exhalation to residual volume with an open glottis.

## DISCUSSION

The present study included 66 pediatric CF patients followed by the HCPA Pediatric Pulmonology Team in order to evaluate the level of adherence to physical therapy recommendations. This was the first study to evaluate adherence to respiratory therapy in pediatric CF patients in Brazil. To that end, we used a questionnaire developed from a previous study conducted under the auspices of the HCPA Program for Adults with CF. Of the sample as a whole, 59% were in the high-adherence group and 41% were in the moderate/poor-adherence group.

Flores et al.[15] studied 63 patients enrolled in the HCPA Program for Adults with CF (mean age, 23.1 years) in order to evaluate adherence to respiratory therapy techniques. They found high adherence in 60% of the sample as a whole and moderate/poor adherence in 40%, findings that are similar to ours. This allows us to assume that, during childhood, patients develop a treatment adherence pattern that remains throughout adolescence and adulthood.

In our study, there were no differences between the high-adherence and moderate/poor-adherence groups

**Table 2.** Lung function and hospitalizations in pediatric patients with cystic fibrosis, by level of adherence to respiratory therapy.[a]

| p | Moderate/poor adherence (n = 27) | High adherence (n = 39) | Variable |
|---|---|---|---|
| 0.433 | 2.8 ± 1.3 | 2.6 ± 0.9 | FVC, l |
| 0.657 | 93.6 ± 21.1 | 95.9 ± 20.1 | FVC, % of predicted |
| 0.535 | 2.2 ± 1.1 | 2.1 ± 0.7 | $FEV_1$, l |
| 0.352 | 86.6 ± 22.8 | 92.3 ± 24.8 | $FEV_1$, % of predicted |
| 0.326 | 80.2 ± 11.4 | 82.8 ± 9.4 | $FEV_1$/FVC |
| 0.354 | 95.0 ± 13.6 | 97.9 ± 10.9 | $FEV_1$/FVC, % of predicted |
| 0.421 | 97.6 ± 1.7 | 98.0 ± 1.7 | Resting $SpO_2$, % |
| 0.004 | 1.4 (1.3) | 0.5 (0.8) | No. of hospitalizations in the last year[b] |
| 0.012 | 29.5 (38.5) | 8.5 (16.3) | No. of days hospitalized in the last year[b] |

No.: number. [a]Values expressed as mean ± SD. [b]Values expressed as median (interquartile range).

**Table 3.** Reasons for not performing the recommended physical therapy techniques for airway clearance.[a]

| Variable | Moderate/poor adherence (n = 27) | High adherence (n = 39) | p |
|---|---|---|---|
| Lack of time | 10 (25.6) | 13 (48.1) | 0.059 |
| Cannot be bothered | 1 (2.5) | 5 (18.5) | 0.038 |
| Feels tired | 1 (2.5) | 8 (29.6) | 0.002 |
| Does not like it | 1 (2.5) | 8 (29.6) | 0.002 |
| Cannot find any motivation | 0 (0.0) | 4 (14.8) | 0.024 |
| Other engagements | 31 (79.4) | 8 (29.6) | 0.000 |

[a]Values expressed as n (%).

regarding age, age at diagnosis, family income, total S-K clinical scores, sputum bacteriology, BMI, or lung function. However, when the "radiological findings" domain of the S-K clinical score was analyzed separately, scores were found to be significantly lower in the moderate/poor-adherence group. Arias Llorente et al.[27] evaluated adherence to treatment in a sample of 34 CF patients (including adult and pediatric patients) and found that S-K clinical scores were significantly higher in those who showed greater adherence to physical therapy recommendations. Flores et al.[15] found significantly lower S-K clinical scores and lung function in the group of patients who showed high adherence to physical therapy recommendations. This difference is due to the fact that adult patients present with disease that is more severe and therefore require greater adherence to treatment.

In our study, the high-adherence group showed higher scores for the quality of life questionnaire domains emotion, physical, treatment burden, health perceptions, social, and respiratory. A study conducted at the *Hospital de Clínicas de Campinas*, in the city of Campinas, Brazil, evaluated the quality of life of pediatric patients with CF and showed that patients with lower S-K clinical scores (< 70) had lower scores for the quality of life questionnaire domains social, respiratory, and digestive.[28]

In the present study, the most commonly used respiratory therapy techniques were coughing, huffing, and EPAP mask. The level of agreement between the two questionnaires was highest for EPAP and PEP on water seal. In contrast, Flores et al.[15] found that active cycle of breathing was the most commonly used technique in adults with CF (79.4%). This difference between pediatric/young patients and adult patients is probably due to the fact that the former require adult supervision in order to perform respiratory therapy techniques, and EPAP mask is easy to use and provides greater patient autonomy. A randomized study conducted at 12 CF centers in Canada showed that EPAP mask was superior to high-frequency chest wall oscillation in patients followed for one year. The number of pulmonary exacerbations was nearly twice as high in those who used high-frequency chest wall oscillation, and those who used EPAP less often required antibiotics.[29]

In 2010, Modi et al.[30] studied 153 patients (mean age, 14 years) in order to evaluate adherence to respiratory therapy. Patients completed a daily telephone diary and reported their level of adherence every four months. Of the sample as whole, 37% were assigned to the high-adherence group, 49% were assigned to the moderate-adherence group, and 14% were assigned to the poor-adherence group. The type of airway clearance technique was the only predictor of adherence, and high-frequency chest wall oscillation was the technique preferred by patients, being associated with greater adherence. The levels of adherence in the aforementioned study are not comparable to those in ours, given that the data collection instruments were different; nevertheless, the technique preferred by patients was associated with greater adherence in both studies.

In 2009, Bucks et al.[31] evaluated 38 adolescents with CF, analyzing the factors that had an impact on treatment adherence. According to the authors, nonadherence to respiratory therapy was associated with the way in which patients judged their personal need for treatment.

In the present study, the most common reasons for not performing the recommended physical therapy techniques for airway clearance included having other engagements, feeling tired, and not liking the technique (the first in the high-adherence group and the last two in the moderate/poor-adherence group). Flores et al.[15] found that the most common reason for not performing the recommended physical therapy techniques for airway clearance was lack of time. This difference might be due to the lifestyle of adults, who are encouraged to have social and work activities. In the study by Arias Llorente et al.,[27] self-reported adherence to physical therapy was 41.2%, being the lowest among all treatments studied. The most common reason for not performing physical therapy was lack of time. Adherence was greater among the patients who had more than one option of physical therapy technique to choose from.

The limitations of the present study are primarily related to the cross-sectional design and the inclusion of pediatric/young patients covering a wide age range and having different levels of understanding, as well as to the fact that adherence to physical therapy recommendations was self-reported, which is generally associated with higher adherence scores. The fact that the questionnaire regarding adherence to physical therapy recommendations used in the present study has yet to be validated might have biased the study

results. Future studies should examine parental education level and psychological aspects.

In conclusion, the present study showed that 59% of the pediatric CF patients studied had high adherence to physical therapy recommendations, whereas approximately 41% failed to follow such recommendations, other engagements and tiredness being the most common reasons for not performing the recommended techniques for airway clearance. These findings indicate a problem that deserves attention and provide the basis for strategies to improve patient adherence to physical therapy recommendations. Low self-reported adherence to physical therapy recommendations was associated with worse radiological findings, a greater number of hospitalizations, and decreased quality of life. There was no association between adherence to physical therapy recommendations and lung function.

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# Alternative diagnoses based on CT angiography of the chest in patients with suspected pulmonary thromboembolism

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## ABSTRACT

**Objective:** To determine the prevalence of alternative diagnoses based on chest CT angiography (CTA) in patients with suspected pulmonary thromboembolism (PTE) who tested negative for PTE, as well as whether those alternative diagnoses had been considered prior to the CTA. **Methods:** This was a cross-sectional, retrospective study involving 191 adult patients undergoing CTA for suspected PTE between September of 2009 and May of 2012. Chest X-rays and CTAs were reviewed to determine whether the findings suggested an alternative diagnosis in the cases not diagnosed as PTE. Data on symptoms, risk factors, comorbidities, length of hospital stay, and mortality were collected. **Results:** On the basis of the CTA findings, PTE was diagnosed in 47 cases (24.6%). Among the 144 patients not diagnosed with PTE via CTA, the findings were abnormal in 120 (83.3%). Such findings were consistent with an alternative diagnosis that explained the symptoms in 75 patients (39.3%). Among those 75 cases, there were only 39 (20.4%) in which the same alterations had not been previously detected on chest X-rays. The most common alternative diagnosis, made solely on the basis of the CTA findings, was pneumonia (identified in 20 cases). Symptoms, risk factors, comorbidities, and the in-hospital mortality rate did not differ significantly between the patients with and without PTE. However, the median hospital stay was significantly longer in the patients with PTE than in those without (18.0 and 9.5 days, respectively; p = 0.001). **Conclusions:** Our results indicate that chest CTA is useful in cases of suspected PTE, because it can confirm the diagnosis and reveal findings consistent with an alternative diagnosis in a significant number of patients.

**Keywords:** Pulmonary embolism/diagnosis; Pulmonary embolism/epidemiology; Angiography.

## INTRODUCTION

Pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT) are part of the spectrum of venous thromboembolism. The annual incidence of PTE is 100-200 cases/100,000 population,[1,2] and the overall 30-day mortality rate ranges from 6.7% to 11.0%,[3-5] reaching 30.0% in the absence of treatment.[6] Autopsy-based studies suggest that these figures are underestimated.[7] The underdiagnosis of PTE might be due, at least in part, to the wide variability in the clinical presentation of PTE and to the fact that the findings are often nonspecific. The clinical findings consistent with suspected PTE are dyspnea, chest pain, hemoptysis, and tachypnea that have an acute onset. In situations that are more dramatic, in which much of the pulmonary circulation is affected or there is a history of significant cardiopulmonary disease, there can be signs of clinical instability, such as hypotension, signs of low cardiac output, and significant hypoxemia.[8] The presence of risk factors for PTE in combination with a suggestive clinical picture reinforces the clinical suspicion of PTE.

The clinical suspicion of PTE should be investigated by specific tests that vary according to the clinical status of the patient. The use of chest CT angiography (CTA) has increased sharply in recent years, and this imaging test has been used as the first-line tool for suspected cases of PTE in various institutions.[9-11] A safe, noninvasive imaging test that allows direct detection of the intra-arterial pulmonary thrombus, CTA is rapidly performed, results generally being available within 24 h. Reported rates of CTA sensitivity range from 64% to 100%, whereas those of CTA specificity range from 89% to 100%.[12-14] Chest CTA results are positive for PTE in 6.6-60.0%, depending on the criteria used for CTA referral.[9,15-21]

In parallel with the recognition of the importance of chest CTA in the diagnosis of PTE, its excessive and sometimes unnecessary use raises concerns about cost-effectiveness issues and about adverse effects related to intravenous contrast use and high radiation rates.[22] A potential

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advantage of CTA is identification of an alternative diagnosis when no findings of PTE are detected. Alternative diagnoses, such as pneumonia, cancer, pleural effusion, heart failure, COPD exacerbation, etc., or incidental findings, such as benign nodules, adenopathy, and granulomatous disease scarring, have been reported in 25.4% to 70.0% of chest CTA results.[9,15-21] The risks, benefits, and costs associated with the investigation of such findings need to be further elucidated, given that the investigation has therapeutic consequences in less than 5% of cases.[20] In addition, the role played by chest CTA in the absence of PTE in making alternative diagnoses that were missed by simple tests, such as chest X-ray, has not been fully investigated.[18-20]

The objective of the present study was to investigate the contribution of chest CTA findings to identifying alternative diagnoses to PTE that would explain the clinical picture of the patient and that were missed on chest X-ray.

## METHODS

This was a cross-sectional, retrospective study carried out in the Department of Radiology of the *Hospital de Clínicas de Porto Alegre* (HCPA), a general university hospital located in the city of Porto Alegre, Brazil. The HCPA has an operational capacity of 845 beds, of which 87 are ICU beds and 47 are ER beds; there are also 35 operating rooms. In 2012, the HCPA had 33,585 admissions and 594,942 outpatient visits. The HCPA uses an online medical record system (known as the Hospital Management Applications Web) that was developed in-house and, in September of 2009, was integrated into the Radiology Information System and into a system for the management and storage of medical images (Picture Archiving and Communication System). In parallel, an image and information management system (IMPAX®; Agfa HealthCare, Mortsel, Belgium) was employed as a technological option for performing the tasks of transmission, storage, and retrieval of medical images.

The study was approved by the HCPA Research Ethics Committee. Given the retrospective nature of the study, informed consent was not required. The authors signed a confidentiality agreement for the use of data. Between September of 2009 and May of 2012, 663 chest CTAs were performed for various reasons. We included all cases involving adult patients (≥ 18 years of age) referred to the Computed Tomography Division of the HCPA for chest CTA for suspected PTE. We excluded cases referred from the outpatient clinic for investigation of chronic pulmonary hypertension, as well as cases in which chest CTA was ordered for reasons other than the investigation of PTE (Figure 1).

Patient demographic and clinical data, such as age, gender, race, smoking history, symptoms at the time of suspicion of PTE, presence of risk factors for PTE, and comorbidities, as well as the health care setting from which the patient was referred at the time of suspicion, length of hospital stay, and clinical outcome (discharge or death), were obtained from the electronic medical records of the HCPA. The medical records were reviewed for the presence of clinical pretest probability scores for PTE. The Geneva score, in its original version,[8] was calculated retrospectively.[8]

Chest CTA images were obtained with a 16-detector helical CT scanner (Brilliance® CT; Philips Healthcare, Best, the Netherlands). All images were viewed on a workstation, with the image storage and transmission systems mentioned above, by two independent radiologists, trained to interpret CTAs. Discordant interpretations were resolved by consensus.

Chest CTAs were classified as positive, negative, or inconclusive for PTE. Scans were considered positive for PTE if they revealed filling defects within the pulmonary artery or any of its branches. For positive scans, PTE was classified as central (up to the first branch of the segmental artery), peripheral (beyond the first branch of the segmental artery), or diffuse (central and peripheral). In the presence of adequate opacification of the pulmonary vascular bed, with no filling defects, scans were considered negative for PTE. All CTAs were reviewed for the presence of other abnormal pulmonary and extrapulmonary findings.

Alternative diagnoses were reviewed on the basis of clinical and imaging findings, by two pulmonologists. Findings suggestive of an alternative diagnosis were defined as CTA abnormalities that could explain the symptoms (such as dyspnea, chest pain, hypoxemia, and tachycardia). The following criteria were used to establish the alternative diagnoses: 1) pneumonia—presence of cough, expectoration, and systemic findings (tachycardia, leukocytosis or leukopenia, and fever) associated with new pulmonary infiltrate; 2) decompensated heart failure—a clinical diagnosis of heart failure and radiological signs of heart enlargement and pulmonary edema or pleural effusion; 3) pleural

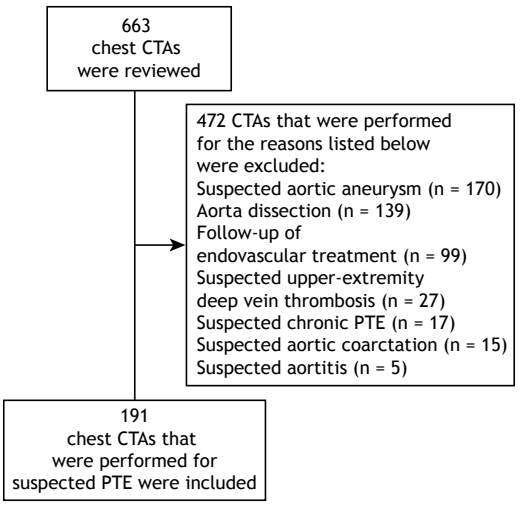


**Figure 1.** Flowchart of the patients included in the study. CTA: CT angiography; and PTE: pulmonary thromboembolism.

effusion due to other causes—signs of at least moderate pleural effusion that was not associated with heart failure; 4) lymphangitic carcinomatosis or progression of cancer—a histological diagnosis of lung cancer with radiological signs of interstitial involvement (with or without pleural effusion or enlarged mediastinal lymph nodes) or an increase in the lung tumor relative to the previous scan; 5) noncardiogenic pulmonary edema—radiological signs of pulmonary edema, including interstitial infiltrate, confluent consolidation, ground-glass attenuation associated with septal thickening, and/or unilateral or bilateral pleural effusion, in the absence of heart failure and in the presence of one or more conditions that explained the edema; 6) connective tissue disease-related lung disease—a previous diagnosis of connective tissue disease (rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis) with pleural and pulmonary involvement attributed to the connective tissue disease itself, including interstitial pulmonary infiltrate, consolidation, pulmonary nodules, pleural effusion, and pulmonary hypertension; and 7) atelectasis—signs of atelectasis (opacity and reduced lung volume) of at least one lung lobe, with significant ventilatory impairment. In addition, we reviewed the respective chest X-rays, together with the chest X-ray reports and the related notes contained in the medical records, and we determined whether the same alterations had been previously detected on chest X-rays.

Taking into account the prevalence of alternative diagnoses made on the basis of chest CTA findings in previous studies[9,15-21] and the high prevalence of tuberculosis in Brazil, we calculated that, in order to obtain an expected proportion of alternative diagnoses of 60% and achieve a power of 80%, at a level of significance of 5% (two-tailed test), the sample size would have to be 188 patients.

Data were entered into a Microsoft Excel spreadsheet and were analyzed with the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were presented as mean and standard deviation or as median and interquartile range. The prevalence of PTE, abnormal CTA findings, and alternative diagnoses was expressed as absolute numbers or as absolute numbers and proportions. The groups of patients with and without PTE were compared with the independent sample t-test or the Mann-Whitney test, depending on data distribution. Categorical variables were compared with Pearson's chi-square test. A value of $p < 0.05$ was considered statistically significant.

## RESULTS

A total of 191 patients were included in the study. The mean age was 59.3 ± 17.1 years, and women predominated. Of those, 113 patients (59.2%) were referred from the emergency room at the time of suspicion, whereas 71 (37.2%) were referred from the ward and 7 (3.7%) were referred from the ICU. The major clinical characteristics of the patients are shown in Table 1.

The demographics, symptoms, risk factors, comorbidities, length of hospital stay, and survival of the 191 patients are shown in Table 2, stratified by the presence (n = 47) or absence (n = 144) of PTE. The most common clinical complaints leading to referral for CTA in the 191 patients were sudden dyspnea, in 75.4%; chest pain, in 33.0%; and cough, in 25.1%. Less common complaints were anxiety (in 9.4%), syncope (in 6.3%), and hemoptysis (in 3.1%), there being no difference between the groups with and without PTE (6.4% vs. 2.1%; $p > 0.05$). The most common risk factors for PTE were cancer and previous hospitalization. The most common comorbidities were systemic arterial hypertension, diabetes, COPD, and previous stroke. There were no significant differences in demographic variables, symptoms, or risk factors between the patients with and without PTE ($p > 0.05$). There was a trend toward a higher prevalence of PTE in patients in whom suspicion was raised in the ward than in those in whom suspicion was raised in the emergency room (31.0% vs. 21.6%; $p = 0.09$). Patients with PTE had longer hospital stays than did those without (median: 18 days vs. 9.5 days; $p = 0.0001$). Among the 191 patients, mortality was 13.6%, being 12.8% and 13.9% in the groups with and without PTE, respectively ($p > 0.05$).

An objective, systematic evaluation of pretest probability of PTE, using a clinical score, was found in 14 of the 191 medical records (7.3%). The Geneva score, calculated retrospectively, was 5.9 ± 3.2 points in the patients with PTE and 5.0 ± 2.6 in the patients without PTE ($p = 0.06$). In a three-level stratification of clinical risk probability, 26.2% of the patients were classified as having low risk, 70.2% were classified as having intermediate risk, and 3.7% were classified as having high risk. There were no significant differences in risk stratification between the patients with and without PTE ($p = 0.07$).

A review of the chest CTAs identified six scans of poor technical quality. However, those six allowed a

**Table 1.** Characteristics of 191 patients undergoing CT angiography for suspected pulmonary thromboembolism.[a]

| Characteristic | Result |
|---|---|
| Age, years | 59.3 ± 17.1 |
| Gender | |
| Male | 128 (67.0) |
| Female | 63 (33.0) |
| White race | 169 (88.5) |
| Smoking history | 89 (46.6) |
| Smoking history, pack-years[b] | 59.3 ± 17.1 |
| Health care setting where the suspicion was raised | |
| Emergency room | 113 (59.2) |
| Ward | 71 (37.2) |
| ICU | 7 (3.7) |

[a]Values expressed as n (%) or mean ± SD. [b]n = 78

**Table 2.** Comparison of characteristics between patients with positive and those with negative CT angiography results for pulmonary thromboembolism.[a]

| Characteristic | All patients (N = 191) | Patients with positive CTA results for PTE (n = 47) | Patients with negative CTA results for PTE (n = 144) |
|---|---|---|---|
| Age, years[b] | 59.3 ± 17.1 | 60.3 ± 17.2 | 58.9 ± 17.2 |
| Female gender | 128 (67.0) | 28 (59.6) | 100 (69.4) |
| Smoking | 89 (46.6) | 18 (38.3) | 71 (49.3) |
| Symptoms | | | |
| Sudden dyspnea | 144(75.4) | 36 (76.6) | 108 (75) |
| Chest pain | 63 (33) | 17 (36.2) | 46 (31.9) |
| Cough | 48 (25.1) | 11 (23.4) | 37 (25.6) |
| Expectoration | 27 (14.1) | 7 (14.9) | 20 (13.9) |
| Anxiety | 18 (9.4) | 3 (6.4) | 15 (10.4) |
| Syncope | 12 (6.3) | 5 (10.6) | 7 (4.9) |
| Hemoptysis | 6 (3.1) | 3 (6.4) | 3 (2.1) |
| Risk factors | | | |
| Cancer | 49 (25.7) | 9 (19.1) | 40 (27.8) |
| Hospital admission in the last 3 months | 48 (25.1) | 10 (21.3) | 38 (26.4) |
| Being bedridden for more than 3 days | 31 (16.2) | 6 (12.8) | 25 (17.4) |
| Obesity | 31 (16.2) | 9 (19.1) | 22 (15.3) |
| Decompensated heart failure | 28 (14.7) | 5 (10.6) | 23 (16.0) |
| COPD exacerbation | 16 (8.4) | 3 (6.4) | 13 (9.0) |
| Recent surgery | 25 (13.1) | 9 (19.1) | 16 (11.1) |
| Previous DVT | 13 (6.8) | 4 (8.5) | 9 (6.3) |
| Previous PTE | 11 (5.8) | 2 (4.3) | 9 (6.3) |
| Intravenous catheter | 9 (4.7) | 1 (2.1) | 8 (5.6) |
| Paralysis of the lower limbs | 4 (2.1) | 2 (4.3) | 2 (1.4) |
| Fracture | 4 (2.1) | 1 (2.1) | 3 (2.1) |
| Comorbidities | | | |
| Systemic arterial hypertension | 89 (46.6) | 24 (51.1) | 65 (45.1) |
| Diabetes mellitus | 39 (20.1) | 12 (25.5) | 27 (18.8) |
| COPD | 35 (18.3) | 6 (12.8) | 29 (20.1) |
| Stroke | 28 (14.7) | 9 (19.1) | 19 (13.2) |
| Ischemic heart disease | 19 (9.9) | 4 (8.5) | 15 (10.4) |
| Thyroid disease | 17 (8.9) | 4 (8.5) | 13 (9.0) |
| Renal failure | 14 (7.3) | 3 (6.4) | 11 (7.6) |
| Diffuse connective tissue disease | 13 (6.8) | 2 (4.3) | 11 (7.6) |
| Asthma | 9 (4.7) | 0 (0.0) | 9 (6.3) |
| Outcomes | | | |
| Length of hospital stay, days[c] | 11.0 (4-22) | 18.0 (8-35) | 9.5 (3-19)* |
| Death | 26 (13.6) | 6 (12.8) | 20 (13.9) |

CTA: CT angiography; PTE: pulmonary thromboembolism; and DVT: deep vein thrombosis. [a]Values expressed as n (%). [b]Values expressed as mean ± SD. [c]Values expressed as median (interquartile range). *p = 0.0001; other results, p > 0.05.

conclusive interpretation. Abnormal findings were observed in 167 cases. A diagnosis of PTE was made in 47 patients (24.6%), and, in most cases, the thrombi were peripheral, being located either on the right side or bilaterally (Table 3). Among the 47 patients with PTE, 31 had other abnormal findings on CTA. The most common findings were atelectasis, in 31.9%; pleural effusion, in 25.5%; consolidation, in 17.0%; enlarged mediastinal lymph nodes, in 14.9%; pulmonary nodules, in 12.8%; and enlarged cardiac silhouette, in 6.4%.

Among the 144 CTA scans that were negative for PTE, 24 were considered completely normal, 21 revealed one abnormality, and 99 revealed multiple findings. The most common findings were atelectasis, in 48.6% of the cases; pulmonary nodules, in 30.6%; pleural effusion, in 29.9%; consolidation, in 21.5%; and emphysema, in 21.5%. Extrathoracic abnormalities were less common (Table 4).

Among the 120 CTA scans that were negative for PTE and revealed abnormal findings, there were 75 that were consistent with an alternative diagnosis that explained the clinical picture of the patient. However, among those cases, there were only 39 (20.4%) in which the same alterations had not been previously

**Table 3.** Chest CT angiography results in 191 patients with suspected pulmonary thromboembolism.

| Finding | Patients |
|---|---|
| Confirmed pulmonary thromboembolism | 47 |
| Type of involvement | |
| Peripheral | 31 |
| Central | 13 |
| Mixed | 3 |
| Location | |
| Right-sided | 22 |
| Bilateral | 20 |
| Left-sided | 5 |
| Unconfirmed pulmonary thromboembolism | 144 |
| Normal results | 24 |
| Abnormal findings | 120 |
| Findings unrelated to the alternative diagnosis | 45 |
| Findings suggestive of an alternative diagnosis* | 75 |
| Findings also present on chest X-ray | 36 |
| Findings on CT angiography only | 39 |

*The findings explain the patient's symptoms.

**Table 4.** Abnormal findings in 144 patients with negative CT angiography results for pulmonary thromboembolism.

| Variable | n | % |
|---|---|---|
| Findings in the chest | | |
| Atelectasis | 70 | 48.6 |
| Pulmonary nodules | 44 | 30.6 |
| Pleural effusion | 43 | 29.9 |
| Consolidation | 31 | 21.5 |
| Emphysema | 31 | 21.5 |
| Enlarged mediastinal lymph nodes | 29 | 20.1 |
| Enlarged cardiac silhouette | 29 | 20.1 |
| Calcified nodules | 22 | 15.3 |
| Ground-glass infiltrate | 12 | 8.3 |
| Micronodules | 9 | 6.3 |
| Pericardial effusion | 9 | 6.3 |
| Interstitial infiltrate | 8 | 5.6 |
| Vertebral or rib fracture | 8 | 5.6 |
| Pleural plaques | 6 | 4.2 |
| Elevated hemidiaphragm | 3 | 2.1 |
| Extrathoracic findings | | |
| Hiatal hernia | 4 | 2.8 |
| Thyroid nodule | 3 | 2.1 |
| Enlarged axillary lymph nodes | 3 | 2.1 |
| Findings suggestive of pancreatitis | 2 | 1.4 |

detected on chest X-rays (Table 3). The major diagnoses made on the basis of CTA, in the absence of chest X-ray abnormalities, are shown in Table 5. Thirty-one patients had pulmonary abnormalities, and 8 had cardiac abnormalities. The most prevalent diagnosis was pneumonia, identified in 20 cases.

## DISCUSSION

Our study assessed 191 consecutive CTAs that were performed for suspected PTE, and the major findings were as follows: 1) the prevalence of PTE was 24.6%; 2) clinical complaints, risk factors, comorbidities, and the proportion of deaths were similar between the groups with positive and negative CTA results for PTE; however, length of hospital stay was longer for the former group; and 3) findings consistent with an alternative diagnosis that explained the patient's symptoms were detected on the CTA scans that were negative for PTE in 39.3% of the cases, although that proportion dropped to 20.4% when only the findings that had not been previously detected on chest X-rays were taken into account.

The prevalence of PTE in our study was comparable to that seen in other studies (19.0-24.3%),[11,20,21,23] but it was higher than that reported by other authors (8.6-9.5%).[16,18,24] Factors such as level of clinical suspicion and compliance with guidelines for the investigation of PTE can affect the prevalence rate of the disease. An objective, systematic evaluation of pretest probability of PTE was described in only 7.3% of the medical records in the present study. In a recent study reviewing 641 chest CTAs, the prevalence of PTE diagnosed by chest CTA was relatively low (9.5%). A careful review conducted by those authors showed that, in 90 cases in their study, the patients had a low probability of having PTE (D-dimers < 500 ng/mL, and Well's score ≤ 4), and there was no formal indication for investigation by CTA. Only two of those patients had PTE.[18] In parallel, a high rate of positive CTA results for PTE might reflect a low clinical suspicion of PTE. Therefore, in addition to assessing the prevalence of PTE, it is important to assess the degree of adherence to the diagnostic algorithm proposed by guidelines for the management of PTE.[8,25] Although the degree of adherence to the institutional protocol for the investigation of PTE was not assessed in our study, our prevalence data are similar to those reported in another study (23.3%).[26]

The symptoms and signs of PTE are well known. Dyspnea, chest pain, and cough were the major symptoms reported by the patients with suspected PTE in our study, with no difference between patients with positive and those with negative CTA results for PTE, suggesting that the symptoms are not specific to PTE. The same symptoms appear as the most common in other studies[9,27]; however, the frequency of pleuritic pain and cough was higher in one such study (76% and 44%, respectively),[27] and the frequency of cough was lower in the other such study (10.8%).[9] In another study, chest pain was the most common symptom (in 41.4%), and dyspnea was observed in only 10% of the patients.[24] The large discrepancy among the findings of various studies might, at least in part, be associated with symptom recording, given that, in retrospective studies, such as the last aforementioned one,[24] the complaints might have been underestimated. The prevalence of hemoptysis in the patients in our study is within the range of prevalence

**Table 5.** Alternative diagnoses made solely on the basis of the chest CT angiography findings.

| Diagnosis | n | % |
|---|---|---|
| Pneumonia | 20 | 51.2 |
| Decompensated heart failure | 8 | 20.5 |
| Pleural effusion due to other causes | 4 | 10.3 |
| Lymphangitic carcinomatosis/progression of cancer | 3 | 7.7 |
| Noncardiogenic pulmonary edema | 2 | 5.1 |
| Connective tissue disease-related lung disease | 1 | 2.6 |
| Atelectasis | 1 | 2.6 |
| Total | 39 | 100.0 |

levels reported in other previous studies of patients with PTE (1.9%-6.0%).[4,9,18,23,27]

A history of cancer, previous hospitalization, and being bedridden were the major risk factors for PTE in our study, having also been reported by other authors.[9] Recent surgery was the seventh most common risk factor in our sample (identified in 13.1%), although this proportion is comparable to those reported in two studies (11.8% and 14.4%)[26,28] but lower than that reported in another study.[18] The lower proportion of postoperative patients in our study might be associated with the source of the cases, given that most patients were referred from the emergency room.

Although risk factors and comorbidities were highly prevalent in our study, there were no significant differences between the groups with positive and negative CTA results for PTE. Likewise, there was no difference in mortality between the two groups. The in-hospital mortality among the patients with positive CTA results for PTE in our study was 12.8%, ranging from 6.4% to 11.4% in other studies.[3-5] However, the patients with positive CTA results for PTE had longer hospital stays than did those with negative CTA results for PTE. Although PTE per se can extend the length of hospital stay, it can also be a marker of the severity of the patient's status, which is associated with hospital stay.

The proportion of normal CTA results in our study was 12.6%; in other studies, that proportion ranged from 12.5% to 29.3%.[18,21,23] In our study, the major abnormal findings on the CTA scans that were negative for PTE were atelectasis, pulmonary nodules, pleural effusion, consolidation, and emphysema. Of note is the significant proportion of nodules and micronodules in our study relative to those reported in other studies,[16,18,20,23,24] which might be related to the high prevalence of granulomatous diseases in Brazil.[29] Such incidental findings, which were not associated with the patient's acute status, often might require further investigation or long-term follow-up.[18,20]

We assessed the clinical relevance of abnormal CTA findings to establishing an alternative diagnosis in the cases with negative CTA results for PTE. Such findings confirmed an alternative diagnosis, which explained the patient's symptoms, in 39.3% of the cases in our study (14.3-33.0% of the cases in other studies).[16,18-21] However, in 20.4% of those cases, the confirmatory findings were identified only on CTAs, i.e., the same alterations had not been previously detected on chest X-rays. To our knowledge, only three studies have taken into account concurrent chest X-ray findings in the analysis of alternative diagnoses. In one study, an alternative diagnosis was established on the basis of CTA findings in 33% of the cases; however, in approximately half of those cases, the same alterations had already been detected on chest X-rays.[16] Another group of authors identified an alternative diagnosis in 14.3% of the patients, chest X-rays having revealed the same findings in 9.8% of the cases.[18] In addition, in another study, CTA revealed findings that supported an alternative diagnosis in 28% of 203 patients, findings being unsuspected prior to CTA in only 8.8% of the cases.[20] Pneumonia was the most common alternative diagnosis in our and other studies,[18,20,21] whereas pleural effusion predominated in two other studies.[16,19]

Some limitations of our study must be taken into account. This was a single-center study, which limits generalizability of results, and data collection was retrospective. Retrospective studies are at risk of selection bias (cases lost to follow-up) and measurement bias (data obtained from medical records). However, the sequential way in which the cases in our study were selected from the records of all CTAs performed in the institution minimized the risk of selection bias. An additional limitation is that patient follow-up was conducted only during hospitalization, providing only data on in-hospital mortality and no data on mid- or long-term survival. In contrast, a positive aspect of the study is that the imaging tests were interpreted by two independent radiologists experienced in interpreting CTAs. In addition, all cases with negative CTA results for PTE were reviewed by two pulmonologists, both from a clinical and radiological standpoint, and a consensus opinion was reached. This allowed increased diagnostic accuracy.

In conclusion, chest CTA was positive for PTE in 24.6% of the cases. Clinical findings and in-hospital mortality did not differ between the groups of patients with and without PTE, but length of hospital stay was longer in the patients with positive CTA results for PTE. Abnormal findings were detected in a large number of CTAs, and such findings were consistent with an alternative diagnosis that explained the clinical picture of the patient in 39.3% of the cases. However, in approximately half of those cases, the same alterations had already been detected on chest X-rays. In summary, our results indicate that chest CTA is useful in cases of suspected PTE, because it can confirm the diagnosis and reveal findings consistent with an alternative diagnosis in a significant number of patients.

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# The Program for the Prevention of Childhood Asthma: a specialized care program for children with wheezing or asthma in Brazil

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## ABSTRACT

**Objective:** To present the *Programa Infantil de Prevenção de Asma* (PIPA, Program for the Prevention of Childhood Asthma) and the characteristics of the patients followed in this program. **Methods:** Implemented in the city of Uruguaiana, Brazil, PIPA has as its target population children and adolescents (< 18 years of age) with asthma or suspected asthma. Patients either enroll in PIPA spontaneously or are referred by pediatricians or primary care physicians. In this retrospective study, we use a standardized protocol to assess PIPA patients. **Results:** By the end of the study period, 646 patients were being followed. Of those, 298 (46.1%) were ≤ 3 years of age. In this group of patients, recurrent wheezing was identified in 60.7%, and the first episode of wheezing occurred in the first six months of life in 86.0%. Severe wheezing was identified in 29.5% and 45.4% in the children ≤ 3 and > 3 years of age, respectively. Physician-diagnosed asthma was reported in 26.5% and 82.2%, respectively. In the sample as a whole, the prevalence of passive smoking was high (> 36%), occurring during pregnancy in > 15%; > 40% of the patients had been born by cesarean section; and 30% had a mother who had had < 8 years of schooling. **Conclusions:** A prevention program for children with asthma is an effective strategy for controlling the disease. Knowledge of local epidemiological and environmental characteristics is essential to reducing the prevalence of the severe forms of asthma, to improving the use of health resources, and to preventing pulmonary changes that could lead to COPD in adulthood.

**Keywords:** Asthma/prevention and control; Asthma/epidemiology; Patient care.

## INTRODUCTION

Asthma is a public health problem worldwide and is one of the most common chronic diseases in childhood. It is highly prevalent, impairs the quality of life of patients and their families, and incurs high costs to the health care system and society.[1]

The current level of asthma control in Latin American countries falls far short of the goals set forth by current international guidelines.[2] Asthma is one of the twenty most common reasons for primary care visits in Brazil, being the third leading cause of hospitalization within the Brazilian Unified Health Care System.[3,4]

The mean prevalence of asthma among children and adolescents in Brazil is estimated to be 20%.[5] In the state of Rio Grande do Sul, Brazil, respiratory diseases are the leading cause of hospitalization in those aged under 19 years, and asthma ranks second among these diseases.[4]

There is as yet no curative treatment for asthma; the primary goal of treatment is disease control. However, despite advances in asthma treatment and in the implementation of guidelines for asthma management, the disease remains poorly controlled.[6]

Possible explanations for this failure include lack of patient access to health care, lack of diagnosis of asthma, inappropriate treatment, and not taking the prescribed medication properly, whether because of lack of understanding or lack of adherence, despite instruction.[7]

Adherence to treatment is one of the most important factors in ensuring treatment success. Many factors, such as knowledge of the disease, cultural standards, socioeconomic factors, lack of perception of asthma symptoms, adverse events, and ability to use inhalers, can influence adherence to treatment and asthma control.[8]

Poor adherence is a serious problem among patients with chronic respiratory disease in developing countries, a problem that is often due to limited access to health care; therefore, in addition to prescription and provision of pharmacological treatment that is appropriate to the level of disease severity, education on self-management is an aspect that must be addressed.[8]

Asthma education for patients so that they know all they need about their disease is not only a right but also an effective strategy of asthma control in the short, medium and long term.[9] Thus, the need to tailor knowledge of asthma education to clinical practice and make it accessible at a public outpatient clinic specializing in

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asthma motivated the development of the *Programa Infantil de Prevenção de Asma* (PIPA, Program for the Prevention of Childhood Asthma) in the city of Uruguaiana, Brazil, in order to decrease the morbidity and mortality of childhood asthma in that city.

The objective of the present study was to present PIPA and the characteristics of the patients followed in this program.

## METHODS

This was a retrospective study of children (< 18 years of age) with asthma or suspected asthma who enrolled in PIPA spontaneously or were referred by pediatricians or primary care physicians. PIPA was established in April of 2012 in the city of Uruguaiana, which has a population of approximately 120,000 inhabitants, in southern Brazil.

After being admitted to PIPA, patients underwent the following treatment protocol: a) a medical visit; b) ancillary tests; c) clinical diagnosis; d) functional diagnosis; e) treatment planning; f) follow-up and monitoring of asthma control; and g) a nursing visit and nursing instruction.

At the medical visit, the parents or legal guardians of the patients completed standardized questionnaires, the use of which depended on patient age and the characteristics of the cross-cultural validation of the questionnaire for use in Brazil. For the youngest patients (those aged up to 3 years, 11 months, and 29 days), we used the International Study of Wheezing in Infants (EISL) written questionnaire,[10] whereas for those aged over 4 years, we used the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire[11] together with the ISAAC phase II questionnaire on risk factors,[11,12] in addition to the Children's Sleep Habits Questionnaire,[13] which began to be used in January of 2014, for those aged between 2 and 12 years. Following the initial interview, patients underwent a detailed physical examination, including assessment of nutritional status (weight and height)), physical examination of the upper airways, cardiopulmonary auscultation, etc.

Ancillary tests included blood workup; quantitative determination of total serum IgE (ImmunoCAP® RAST; Thermo Fisher Scientific Inc., Waltham, MA, USA); determination of 25-hydroxyvitamin D by chemiluminescent microparticle immunoassay; skin prick tests to airborne allergens (*Dermatophagoides pteronyssinus, D. farinae, Blomia tropicalis,* cockroach mix, *Alternaria sp.,* dog dander, and cat dander),[14] and parasitological examination (direct method).[15]

Depending on age and clinical history, patients underwent imaging assessment, which included a chest and/or sinus X-ray.

In this phase, the clinical diagnosis of asthma was made in accordance with the Global Initiative for Asthma (GINA) criteria.[1] For the children aged under 2 years who were referred with suspected asthma, we employed the Asthma Predictive Index (API),[16] and for those aged over 2 years, we employed the modified API, which includes sensitization to airborne allergens as a prognostic factor of disease progression.[17]

The diagnosis of allergic rhinitis was made in accordance with the criteria established by the Third Brazilian Consensus on Rhinitis[18] and by the Allergic Rhinitis and its Impact on Asthma initiative.[19]

The children aged over 6 years who were able to perform the expiratory maneuvers required for functional assessment underwent objective measurements of pulmonary function, whether by spirometry or by determination of maximum peak expiratory flow, with the use of a Spirolab III® spirometer (Medical International Research, Rome, Italy). American Thoracic Society acceptability criteria—values from at least the three best maneuvers were selected—and reproducibility criteria were used.[20] Following the initial spirometric assessment, patients underwent bronchodilator testing with albuterol aerosol (400 μg) administered with a valve spacer, and the spirometric parameters were measured again 15 minutes later.[21]

Maximum peak expiratory flow was determined with a Mini-Wright® Peak Flow Meter (Clement Clarke International, Essex, UK), especially in patient follow-up and monitoring of the response to the treatment regimen.[21]

After completion of the clinical and functional assessment and before establishment of a treatment plan, patients were classified with respect to level of asthma control, as well as to the presence of acute exacerbation, as recommended by GINA.[1]

On that basis, patients received a written treatment plan for maintenance control and possible exacerbations, as recommended by GINA[1] and by the Brazilian Thoracic Association Guidelines for Asthma Management.[3] The medications available through PIPA are as follows: albuterol (metered dose inhaler; 100 μg/puff); and beclomethasone (metered dose inhaler; 250 μg/puff); both of which are distributed free of charge at all "*aqui tem farmácia popular*" facilities of the Brazilian Popular Pharmacy program.[22]

For patients with moderate or severe asthma, montelukast (tablets of 5 and 10 mg) and the combination of albuterol (25 μg/puff) and fluticasone dipropionate (125 μg or 250 μg/puff) metered dose inhaler or dry powder inhaler (Diskus® 50 μg/250 μg) are available free of charge through the Uruguaiana City Hall.

After being admitted to PIPA, patients were followed and reassessed over 1-3 months, as determined by asthma severity and control.[1]

In addition to medical follow-up, patients were followed by nurses who are specialists in asthma care and who are part of the team of professionals involved in PIPA, as recommended by other groups and by international consensus guidelines.[23,24] The responsibilities of these nurses included the following: a) administer quality-of-life questionnaires at the first

nursing visit and 6 months later to assess patient's response to treatment[25]; b) emphasize, to family members, the importance of identifying symptoms of uncontrolled disease early; c) always review the (written) action plan[26] with the following aims—1) recognition of asthma-related symptoms; 2) treatment adjustment based on the medical prescription; and 3) identification of when and where to seek medical attention, for patients with poor disease control with the initial treatment[25]—d) check proper use of inhaled medication at all visits; e) encourage adherence to maintenance treatment and provide instruction regarding the difference between treatment of asthma attacks and maintenance treatment; f) address aspects of environmental control, habits such as smoking, and other triggers; and g) encourage regular visits (every 3 months) even if the patient is asymptomatic.[1]

The study was approved by the Research Ethics Committee of the Uruguaiana Municipal Department of Health, Brazil.

## RESULTS

Since the creation of PIPA, 646 patients have been enrolled, all of whom were being followed at this writing. Of those, 46.1% were aged 3 years or younger (Table 1). Most of the patients aged up to 3 years (> 80%) had a history of recurrent wheezing (three or more episodes), which had started early, before 6 months of age. Episodes of severe wheezing were identified in nearly 30% of these patients, more than half of whom had been hospitalized for wheezing. Of all patients aged up to 3 years, 26.5% had physician-diagnosed asthma, 53.0% had been born by cesarean section, and only 29.0% had been exclusively breastfed for at least 6 months (Table 1). Passive exposure to tobacco smoke was reported by 39.5% of the parents/legal guardians of these patients, with exposure occurring during pregnancy in 15.4% of the cases and the smoker being the mother in 18.7% (Table 1). Attending day care was identified in 38.2% of the cases, presence of household mold was identified in 44.6%, and presence of pets in the household was identified in 73.0% (mainly dogs). A maternal education level of less than 8 years was identified in 35.6% of the cases (Table 1).

Among the older patients (those aged over 3 years), it is of note that wheezing in the previous year was reported in 88.7% of the cases, wheezing was severe in 45.4%, and hospitalization for wheezing was required in 8.0% (Table 1). Physician-diagnosed asthma was identified in 82.2% of the cases, and, in most of them, asthma had been classified as uncontrolled. In addition, concomitant rhinoconjunctivitis was reported in 74.4% of

**Table 1.** Patients followed in the *Programa Infantil de Prevenção à Asma* (PIPA, Program for the Prevention of Childhood Asthma) since its establishment, by clinical characteristics and age group – Uruguaiana, Brazil, 2014.[a]

| Characteristic | Follow-up patients | |
|---|---|---|
| | ≤ 3 years (N = 298) | > 3 years (N = 348) |
| Wheezing ever | 298 (100.0) | 336 (96.5) |
| Wheezing in the first year of life | 256 (86.0) | - |
| Recurrent wheezing in the first year of life[b] | 181 (60.7) | - |
| Wheezing in the previous 12 months | - | 308 (88.7) |
| First episode before 6 months of age | 247 (82.8) | - |
| More than 4 attacks of wheezing in the previous year | - | 155 (44.5) |
| Wakes up at night because of wheezing | - | 200 (57.5) |
| Severe wheezing | 88 (29.5) | 158 (45.4) |
| Hospitalization for wheezing/asthma | 50 (16.7) | 28 (8.0) |
| Physician-diagnosed asthma | 79 (26.5) | 286 (82.2) |
| Rhinoconjunctivitis | - | 259 (74.4) |
| Pneumonia | 58 (28.5) | - |
| Hospitalization for pneumonia | 42 (14.0) | 90 (25.8) |
| Exclusive breastfeeding until 6 months of age | 86 (29.0) | 218 (62.6) |
| At least one smoker in the household | 117 (39.5) | 127 (36.4) |
| Maternal smoking | 56 (18.7) | 50 (14.6) |
| Maternal smoking during pregnancy | 46 (15.4) | 61 (17.5) |
| Birth by cesarean section | 158 (53.0) | 141 (40.5) |
| Attended day care in the first year of life | 114 (38.2) | 206 (59.1) |
| Exposure to household mold | 133 (44.6) | 168 (48.2) |
| Exposure to pets | 217 (73.0) | 275 (79.0) |
| Dogs | 190 (64.0) | 163 (47.0) |
| Cats | 71 (23.8) | 21 (6.0) |
| Maternal education level of less than 8 years | 106 (35.6) | 168 (48.4) |

[a]Values expressed as n (%). [b]More than three episodes.

the cases. Exclusive breastfeeding for at least 6 months was reported in 62.6% of the cases; however, passive exposure to tobacco smoke and maternal smoking during pregnancy were reported in 36.4% and 17.5% of the cases, respectively (Table 1). Nearly 60.0% of the patients attended day care in the first year of life, and presence of pets in the household was reported in 79.0% of the cases (most often dogs). A maternal education level of less than 8 years was reported by 48.4% of the respondents (Table 1).

## DISCUSSION

The high prevalence rates of asthma in children (9 to 11 years of age) and recurrent wheezing in infants (12 to 15 months of age) identified in Uruguaiana by the ISAAC[12] and by the International Study of Wheezing in Infants[27] prompted the local managers to establish PIPA.

As can be seen in Table 1, most of the children aged up to 3 years followed in the program experienced symptom onset in the first year of life, and the first episode of wheezing occurred before 6 months of age, as reported by other researchers.[28] In addition, a significant number of children in the two groups studied had severe wheezing.

Recent studies have increasingly shown that COPD has its origins in severe childhood asthma; therefore, identifying these children and the risk factors leading to more severe asthma is of the utmost importance for public health.[29]

Pre- and postnatal exposure to cigarette smoke has been identified as one of the most important risk factors for the development of wheezing in infants and asthma in older children.[30] Among the patients enrolled in PIPA, the prevalence of passive smoking was significant, since, in approximately 40% of the cases, there was at least one smoker in the household, and, in approximately 15%, the smoker was the mother. To this we must add prenatal exposure to tobacco smoke, which was identified in more than 15% of the cases. Knowledge of these factors and of their magnitude is very important, because exposure so early in life can cause epigenetic changes in lung development that may extend to future generations.[31] A recent study also pointed out that exposure to tobacco smoke during pregnancy increases the risk of asthma and wheezing in adolescence, and that pulmonary function changes in these children would be related to potential epigenetic effects of tobacco smoke rather than to immune function changes or atopy.[32]

Another finding worthy of note in this population was the large number of children who had been born by cesarean section, which is identified as a risk factor for developing asthma later in life, especially if associated with a family history of asthma.[33]

Maternal education level, especially in populations in developing countries, has been associated with the development of asthma. A significant proportion of the patients evaluated here had a mother who had had less than 8 years of schooling. Previous studies conducted in Brazil have related a low level of education to an increased risk of asthma or wheezing in children aged under 5 years.[34] This is possibly due to poor understanding of the disease by mothers, unawareness of the possibility of obtaining free controller medications, poor adherence to the asthma action plan, and, in particular, the lack of a bond between mothers and a specific facility where they can feel supported and welcomed if their children experience an acute asthma exacerbation.

For greater success in establishing an asthma program, the following should be taken into consideration: a) get to know the local situation, through a local or regional epidemiological survey, so as to properly adjust the health policies needed for optimal care of the target population; b) build the foundations of the program upon the major consensus guidelines on the different aspects to be addressed in an asthma program[1,3,24,28,35]; c) get different categories of professionals, such as primary care physicians, nurses, physical therapists, social workers, physical education teachers, and community health agents, involved in the program,[36] thus preventing the program from being focused on a single person[9]; d) pharmaceutical care should be seen as a set of tasks performed by the pharmacist and other health professionals, in which medications are the essential material and which involve selecting, scheduling, purchasing, distributing, and dispensing medications, as well as ensuring the quality of the products and services and the follow-up and assessment of their use, with a view to achieving concrete results and improving the quality of life of the population[37]—understanding this concept is of paramount importance, since, often times, medications are distributed regardless of the fulfillment of the necessary criteria for the rational and safe use of these products[38]; e) get the population involved through the use of advisory boards, associations, and the media; f) get managers[9,36] involved and keep them permanently informed about the results of the program; and g) make the asthma program known through the media, television, or new communication tools (such as the Internet), which offer innovations in physician-patient communication and in knowledge and recommendations about the disease.[38] PIPA has a page on Facebook through which it has achieved greater communication and integration with patients and their families, as well as allowing the general public to get acquainted with the activities of the program.

In conclusion, considering that Brazil is a country with many "types of asthma",[39] the establishment of regional asthma programs, based on epidemiological and environmental differences, would facilitate the implementation of appropriately targeted prevention, early diagnosis, and treatment measures, so as to allow proper allocation of financial resources, as occurs in other successful programs in Brazil for adults.[40]

Therefore, there would be appropriate disease follow-up from symptom onset and a consequent reduction in the number of emergency room visits and hospitalizations, especially in patients with undiagnosed, undertreated, or poorly controlled asthma, thus preventing pulmonary changes that could lead to COPD in adulthood.

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# Obstructive sleep apnea related to rapid-eye-movement or non-rapid-eye-movement sleep: comparison of demographic, anthropometric, and polysomnographic features

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Study carried out in the Pulmonology Department, Yuzuncu Yil University School of Medicine, Van, Turkey; and in the Pulmonology Department, Muğla Sıtkı Koçman University School of Medicine, Muğla, Turkey.

## ABSTRACT

**Objective:** To determine whether there are significant differences between rapid-eye-movement (REM)-related obstructive sleep apnea (OSA) and non-REM (NREM)-related OSA, in terms of the demographic, anthropometric, and polysomnographic characteristics of the subjects. **Methods:** This was a retrospective study of 110 patients (75 males) with either REM-related OSA (n = 58) or NREM-related OSA (n = 52). To define REM-related and NREM-related OSA, we used a previously established criterion, based on the apnea-hypopnea index (AHI): AHI-REM/AHI-NREM ratio > 2 and ≤ 2, respectively. **Results:** The mean age of the patients with REM-related OSA was 49.5 ± 11.9 years, whereas that of the patients with NREM-related OSA was 49.2 ± 12.6 years. The overall mean AHI (all sleep stages combined) was significantly higher in the NREM-related OSA group than in the REM-related OSA group (38.6 ± 28.2 vs. 14.8 ± 9.2; $p < 0.05$). The mean AHI in the supine position (s-AHI) was also significantly higher in the NREM-related OSA group than in the REM-related OSA group (49.0 ± 34.3 vs. 18.8 ± 14.9; $p < 0.0001$). In the NREM-related OSA group, the s-AHI was higher among the men. In both groups, oxygen desaturation was more severe among the women. We found that REM-related OSA was more common among the patients with mild-to-moderate OSA, whereas NREM-related OSA was more common among those with severe OSA. **Conclusions:** We found that the severity of NREM-related OSA was associated mainly with s-AHI. Our findings suggest that the s-AHI has a more significant effect on the severity of OSA than does the AHI-REM. When interpreting OSA severity and choosing among treatment modalities, physicians should take into consideration the sleep stage and the sleep posture.

**Keywords:** Sleep, REM; Sleep stages; Sleep apnea, obstructive; Apnea; Sleep apnea syndromes.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder, characterized by recurrent episodes of complete or partial upper airway collapse, accompanied by intermittent hypoxemia and recurrent arousals from sleep. Whereas upper airway collapse can occur during rapid-eye-movement (REM) and non-REM (NREM) sleep, the withdrawal of excitatory noradrenergic and serotonergic inputs to the upper airway motor neurons during REM sleep further reduces the pharyngeal muscle activity and substantially increases the propensity for such collapse.[1] Therefore, in patients with OSA, REM sleep is typically associated with an increased frequency of obstructive events that are often prolonged and are accompanied by severe oxygen desaturation. In some patients, respiratory events occur predominantly during REM sleep.[1-4] A commonly used diagnostic criterion is the ratio between the apnea-hypopnea index (AHI) during REM sleep and the AHI during NREM sleep (the AHI-REM/AHI-NREM ratio), an AHI-REM/AHI-NREM ratio > 2 indicating a predominance of disordered breathing during REM sleep, or REM-related OSA.[5] The reported prevalence of REM-related OSA in clinical studies varies widely, ranging from 10% to 36%.[1-4] That variability is due, in part, to differences in sample characteristics and in the definition of REM-related OSA.[2] It is well known that OSA is more common in the elderly, in males, in individuals with a high BMI, and in individuals who sleep in the supine position.[4,6] However, REM-related OSA is reported to occur more commonly in younger individuals, women, children, and patients with mild or moderate OSA.[2,5,7-9] The main aim of our study was to compare patients with REM-related OSA and patients with NREM-related OSA, in terms of their demographic, anthropometric, and polysomnography characteristics.

## METHODS

This was a retrospective study of 110 patients (58 with REM-related OSA and 52 with NREM-related OSA) who underwent polysomnography in a sleep laboratory operated by the Pulmonology Department of the Yuzuncu Yil University School of Medicine, in the city of Van, Turkey, between January of 2013 and March of 2014. Patients with a sleep efficiency < 40% were excluded,

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as were those with an AHI < 5 events/h, those in whom REM sleep accounted for < 15% of the total sleep time, and those who were under 15 years of age. For all patients, the AHI was calculated for total sleep time, for REM sleep (AHI-REM), and for NREM sleep (AHI-NREM), as well as for sleep in the supine position (s-AHI) and sleep in the lateral position (lateral AHI, right-hip and left-hip). We also collected the following data: age; gender; level of daytime sleepiness; BMI; neck circumference; total sleep time; REM sleep and NREM sleep, as percentages of the total sleep time; the mean oxygen desaturation time; and the minimum $SaO_2$. We then attempted to determine whether any of those parameters differed between the REM-related OSA and NREM-related OSA groups.

### *Polysomnography*

We performed polysomnography using a 16-channel polysomnograph (Embla; Medcare Flaga, Reykjavik, Iceland), with continuous monitoring by a technician. The system consists of four electroencephalography channels, two electrooculography channels, tibial/submental electromyography, and electrocardiography, as well as monitoring of oronasal airflow, thoracic movements, abdominal movements, $SaO_2$, and body position. Polysomnographic recordings were manually interpreted over 30-s intervals in accordance with the guidelines established by the American Academy of Sleep Medicine.[10] Apnea was defined as the complete cessation of airflow for more than 10 s. Hypopnea was defined as a ≥ 30% reduction in respiratory airflow lasting for more than 10 s, accompanied by a ≥ 4% decrease in $SaO_2$. Arousal was defined as a sudden change in the electroencephalography frequency, consisting of alpha and theta activity or waveforms with frequencies > 16 Hz (although not sleep spindles) and a duration of 3-15 s. Respiratory effort-related arousals occur when there is a sequence of breaths that last for at least 10 s, characterized by increased respiratory effort or flattening of the nasal pressure waveform, followed by arousal from sleep, which does not meet the criteria for an apnea or hypopnea event.[11] We determined the average overall AHI, expressed as the number of events per hour of sleep. For each patient, OSA was classified as mild (AHI, 5-15 events/h), moderate (AHI, 16-30 events/h), or severe (AHI, > 30 events/h).

In accordance with a previous report,[5] we identified respiratory disorders predominantly restricted to REM sleep by calculating the AHI-REM/AHI-NREM ratio. Patients with an AHI-REM/AHI-NREM ratio > 2 were categorized as having REM-related OSA, whereas those with an AHI-REM/AHI-NREM ratio ≤ 2 were categorized as having NREM-related OSA.[5] The subjective level of daytime sleepiness was quantified with a self-report questionnaire, the Epworth Sleepiness Scale.[12]

### *Statistical analysis*

The results are expressed as mean ± standard deviation. Student's t-tests were used in order to compare the means of two independent variables such as gender and group (REM-related OSA vs. NREM-related OSA). Age was included in the model as a covariate to remove extraneous influences from the dependent variable, thus decreasing the variance within the group, and to adjust the means of the groups. Chi-square and Fisher's exact tests were used in order to test the independence of categorical variables. Pairwise Pearson correlation tests were carried out in order to estimate the linear relationship between the characteristics. All statistical calculations were performed using the Statistical Analysis System software, version 9.3 (SAS Institute, Cary, NC, USA). Values of $p < 0.05$ were considered statistically significant.

## RESULTS

Of the 110 OSA patients evaluated, 58 met the criteria for REM-related OSA, whereas 52 met the criteria for NREM-related OSA. The mean age of the patients with REM-related OSA was 49.5 ± 11.9 years, compared with 49.2 ± 12.6 years for those with NREM-related OSA (Table 1). There was a predominance of males in our study sample (68%), and the proportion of males was higher in the NREM-related OSA group than in the REM-related OSA group (84.6% vs. 53.4%; Table 1).

There was no statistically significant difference between the REM-related and NREM-related OSA groups in terms of the mean BMI (33.3 ± 5.7 kg/m$^2$ vs. 32.2 ± 5.4 kg/m$^2$; $p = 0.97$). As can be seen in Figure 1, the AHI value correlated positively with the BMI in the REM-related OSA group ($r = 0.343$; $p < 0.01$). In the NREM-related OSA group, the mean BMI was significantly higher in the females than in the males (39.0 ± 4.2 vs. 30.9 ± 4.6; $p < 0.05$). There was no significant difference in AHI between the genders, in either group (Table 2). There was also no statistically significant difference between the two groups in terms of the mean Epworth Sleepiness Scale score (15.4 ± 5.3 vs. 15.6 ± 6.8; $p = 0.94$).

The mean AHI was significantly lower in the REM-related OSA group than in the NREM-related OSA group (14.8 ± 9.2 vs. 38.6 ± 28.2; $p < 0.05$). In the REM-related OSA group, the OSA was classified as mild in 36 (62.1%) of the 58 patients, moderate in 16 (27.6%), and severe in 6 (10.3%), compared with 12 (23.1%), 15 (28.9%), and 25 (48.1%), respectively, for the NREM-related group. In the REM-related OSA group, the AHI correlated positively with age ($r = 0.344$; $p < 0.05$) and with BMI ($r = 0.343$; $p < 0.05$). The AHI also correlated positively with BMI in the NREM-related OSA group, although the difference was not significant.

The supine, right-lateral, and left-lateral AHI values were higher in the NREM-related OSA group than in the REM-related OSA group (Table 1). As can be seen in Figure 2, the AHI correlated positively with s-AHI in the NREM-related OSA group ($r = 0.707$; $p < 0.01$). In NREM-related OSA, the s-AHI was higher among

**Table 1.** Demographic, anthropometric, and polysomnographic features of patients with obstructive sleep apnea.[a]

| Variables | Type of OSA | | p |
|---|---|---|---|
| | REM-related (n = 58) | NREM-related (n = 52) | |
| Age, years | 49.5 ± 11.9 | 49.2 ± 12.6 | > 0.05 |
| Males[b] | 31 (53.4) | 44 (84.6) | < 0.05 |
| BMI, kg/m$^2$ | 33.3 ± 5.7 | 32.2 ± 5.4 | 0.974 |
| Neck circumference, cm | 38.1 ± 3.4 | 39.6 ± 3.3 | 0.589 |
| ESS score | 15.4 ± 5.3 | 15.6 ± 6.8 | 0.943 |
| TST, min | 348.1 ± 63.3 | 344.2 ± 63.8 | 0.931 |
| WASO, % | 89.9 ± 55.2 | 82.8 ± 52.7 | 0.656 |
| Arousals/h | 7.16 ± 11.1 | 7.71 ± 11.7 | 0.756 |
| RERAs | 6.79 ± 5.50 | 8.45 ± 6.29 | 0.343 |
| Oxygen desaturation time,[c] min | 48.5 ± 58.0 | 46.3 ± 44.3 | 0.990 |
| Minimum $SaO_2$, % | 77.0 ± 9.0 | 74.1 ± 16.3 | 0.102 |
| $SaO_2$, % | 89.8 ± 3.7 | 88.3 ± 4.4 | 0.017 |
| AHI, events/h | 14.8 ± 9.23 | 38.6 ± 28.2 | < 0.0001 |
| Supine AHI, events/h | 18.8 ± 14.9 | 49.0 ± 34.3 | < 0.0001 |
| Left-lateral AHI, events/h | 15.8 ± 13.8 | 27.0 ± 32.8 | 0.031 |
| Right-lateral AHI, events/h | 14.0 ± 15.2 | 29.8 ± 32.6 | 0.001 |
| Total apnea events | 9.4 ± 16.8 | 19.2 ± 25.1 | 0.016 |
| Total hypopnea events | 24.8 ± 12.4 | 23.0 ± 17.4 | 0.524 |
| REM sleep, % | 17.4 ± 6.3 | 17.3 ± 16.7 | 0.874 |
| NREM sleep, % | 34.4 ± 19.5 | 42.4 ± 29.0 | 0.851 |
| Comorbid disorders[b] | 13 (22.4) | 12 (23.1) | 0.934 |

OSA: obstructive sleep apnea; REM: rapid-eye-movement (sleep); NREM: non-rapid-eye-movement (sleep); ESS: Epworth Sleepiness Scale; TST: total sleep time; WASO: wake after sleep onset; RERAs: respiratory effort-related arousals; and AHI: apnea/hypopnea index. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Values expressed as n (%). [c]$SaO_2$ < 90%.

men, whereas the right- and left-lateral AHI were both higher among women.

There were no differences between the REM-related and NREM-related OSA groups in terms of the wake after sleep onset and arousal values (Table 1). However, in the NREM-related OSA group, the wake after sleep onset value was significantly lower among the men than among the women (67.7 ± 39.9 vs. 99.2 ± 60.0; p = 0.027; Table 2).

There was no significant difference between the REM-related and NREM-related OSA groups in terms of the mean oxygen desaturation time (48.5 ± 58.0 vs. 46.3 ± 44.3; p = 0.990). However, oxygen desaturation was more severe among the women than among the men, in both groups (Table 2). We also found that, in REM-related OSA, oxygen desaturation correlated positively with age (r = 0.355; p < 0.05) and with BMI (r = 0.287; p < 0.05).

There were no differences between the two groups with regard to comorbidities (Table 1). In the REM-related and NREM-related OSA groups, 13 and 12 patients, respectively, had one or more comorbidities, including COPD (in 5 and 4 patients, respectively), coronary artery disease (in 2 NREM-related OSA group patients), hypertension (in 7 and 2 patients, respectively), and diabetes mellitus (in 4 and 3 patients, respectively). As expected (given the lack of any differences in terms of comorbidities), there were also no differences between the two groups with regard to the medications taken by the patients.

## DISCUSSION

In the present study, severe OSA was more common among the patients with NREM-related OSA than among those with REM-related OSA and was found to be associated mainly with the s-AHI. We also found that the prevalence of REM-related OSA was higher among the female patients, and that the female patients with REM-related OSA were younger and less obese than were those with NREM-related OSA.

During sleep, the most pronounced decrease in muscle tone typically occurs during REM sleep, causing atony, and the loss of tone in the dilator muscles makes it more likely that disordered breathing will occur. Such events, which occur during the night, can be associated with sleeping in the supine position or with REM sleep. Punjabi et al. found that the REM-AHI was higher than the NREM-AHI only in patients with an AHI of < 30 events/h.[13] In another study, similar to the present study, REM-related OSA was found to be more common in patients with moderate OSA than in those with severe OSA.[14] That is in agreement with our findings that the AHI values were lower in the patients with REM-related OSA than in those with NREM-related OSA (the initial phase of REM-related OSA in the literature),[15] and that the prevalence of

**Table 2.** Features of patients with obstructive sleep apnea, by predominant sleep stage and by gender.[a]

| Variables | Type of obstructive sleep apnea | | | | | |
|---|---|---|---|---|---|---|
| | REM-related | | | NREM-related | | |
| | Females | Males | p | Females | Males | p |
| Age, years | 53.5 ± 10.3 | 46.0 ± 12.3 | 0.0166 | 62.3 ± 12.7 | 46.8 ± 11.2 | 0.0009 |
| BMI, kg/m$^2$ | 35.1 ± 5.8 | 31.8 ± 5.3 | 0.0274 | 39.0 ± 4.2 | 30.9 ± 4.6 | < 0.0001 |
| Neck circumference, cm | 36.0 ± 2.7 | 39.9 ± 2.9 | < 0.0001 | 37.2 ± 2.3 | 40.0 ± 3.3 | 0.026 |
| ESS score | 15.4 ± 5.1 | 15.4 ± 5.5 | 0.9752 | 16.8 ± 6.0 | 15.4 ± 6.1 | 0.546 |
| TST, min | 355.6 ± 63.7 | 341.5 ± 63.2 | 0.4103 | 314.8 ± 50.8 | 349.8 ± 65.8 | 0.157 |
| WASO, % | 94,7 ± 63.6 | 89,3 ± 55.0 | 0.840 | 99,2 ± 60.0 | 67,7 ± 39.9 | 0.027 |
| Arousals/h | 7,36 ± 6.35 | 7,14 ± 11.6 | 0.968 | 9,94 ± 11.3 | 5,80 ± 11.3 | 0.210 |
| RERAs | 7,17 ± 5.52 | 6,71 ± 5.59 | 0.858 | 8,88 ± 5.70 | 7,83 ± 7,27 | 0.667 |
| Oxygen desaturation time,[b] min | 61.4 ± 64.7 | 37.4 ± 49.8 | 0.1175 | 59.6 ± 34.6 | 43.9 ± 45.8 | 0.360 |
| Minimum $SaO_2$, % | 74.8 ± 9.8 | 78.8 ± 7.9 | 0.0942 | 69.0 ± 12.7 | 75.0 ± 13.7 | 0.251 |
| $SaO_2$, % | 89.0 ± 4.3 | 90.5 ± 2.9 | 0.1293 | 85.6 ± 5.7 | 88.7 ± 4.0 | 0.068 |
| AHI, events/h | 15.5 ± 9.2 | 14.2 ± 9.3 | 0.5960 | 39.7 ± 39.0 | 38.4 ± 26.3 | 0.908 |
| Supine AHI, events/h | 17.7 ± 13.7 | 19.6 ± 16.2 | 0.6806 | 22.0 ± 24.2 | 53.4 ± 33.9 | 0.023 |
| Right-lateral AHI, events/h | 17.7 ± 18.5 | 11.4 ± 11.9 | 0.1508 | 40.0 ± 50.2 | 27.9 ± 28.9 | 0.374 |
| Total apnea events | 10.7 ± 22.1 | 8.3 ± 10.7 | 0.5952 | 18.0 ± 30.5 | 19.4 ± 24.4 | 0.883 |
| Total hypopnea events | 25.4 ± 12.6 | 24.2 ± 12.5 | 0.7239 | 24.2 ± 9.9 | 22.8 ± 18.5 | 0.844 |
| REM sleep, % | 18.3 ± 7.3 | 16.6 ± 4.7 | 0.2945 | 16.2 ± 7.8 | 17.3 ± 6.6 | 0.637 |
| NREM sleep, % | 81.4 ± 7.6 | 83.0 ± 5.5 | 0.3647 | 83.7 ± 7.8 | 82.6 ± 6.8 | 0.704 |

REM: rapid-eye-movement (sleep); NREM: non-rapid-eye-movement (sleep); ESS: Epworth Sleepiness Scale; TST: total sleep time; WASO: wake after sleep onset; RERAs: respiratory effort-related arousals; and AHI: apnea/hypopnea index. [a]Values expressed as mean ± SD. [b]$SaO_2$ < 90%.

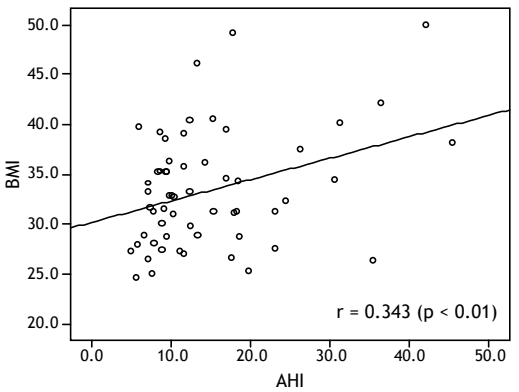


**Figure 1.** Correlation between the apnea-hypopnea index (AHI) and BMI in rapid-eye-movement-related obstructive sleep apnea.

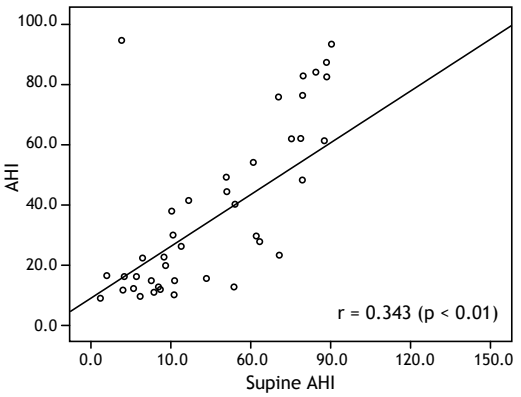


**Figure 2.** Correlation between the overall apnea-hypopnea index (AHI) and supine AHI in non-rapid-eye-movement-related obstructive sleep apnea.

REM-related OSA was higher among the women in our sample.

Various studies have shown that NREM-related OSA is more common among patients with high AHI values (≥ 30 events/h). [15-17] Oksenberg et al.[18] reported that, of their patients with NREM-related OSA, 49.1% had severe OSA, similar to the 48.1% observed in our study. The effects that high NREM-AHI values (due to subnormal REM sleeping times) and sleeping in the supine position had on the overall AHI values were large, because NREM occupies a majority of the sleep time, even under normal conditions.

Despite the negative effects that sleeping in the supine position has on upper airway patency, many people prefer sleeping in that position.[19] In patients with positional OSA, the frequency and severity of respiratory events depend on how long the patient lies in the supine position.[20] During polysomnography, patients with OSA spend 46-51% of their total sleep time on their backs.[21] The supine position has been consistently associated with more severe OSA in adults.[22,23] Sunnergren et al. also reported that the majority of subjects experienced more obstructive events when in the supine position than when in other positions.[24] Sleep posture has different effects on REM sleep than on NREM sleep.[25] Specifically, the effects of sleeping in the supine and lateral positions differ between REM and NREM sleep, as reported by George et al.[6] However, those authors found that the difference in AHI between the two sleep postures was much greater in patients NREM-related OSA. Pevernagie

et al. reported that, among OSA patients, AHI values were higher in the supine position than in the lateral position only during NREM sleep.[25] Cartwright et al.[26] reported that OSA patients tend to sleep in the lateral position more often during REM sleep than during NREM sleep, a difference that we found to be significant in males but not in females. Previous studies have confirmed that women are more prone than are men to show higher AHI values during REM sleep than during NREM sleep, regardless of the sleep posture.[27] In our study, s-AHI values were higher among men, whereas lateral AHI values were higher among women.

Patients with OSA experience fluctuations in oxygen levels during sleep. Sato et al.[28] demonstrated that the drop in $SaO_2$ is particularly dramatic in patients with severe OSA. A number of factors have been reported to affect the severity of oxygen desaturation during an apnea/hypopnea event, such factors including sleep posture,[29] sleep stage,[30] and age,[31] as well as gender and obesity.[32] In addition, comorbidity with COPD has been shown to increase the frequency and severity of oxygen desaturation in OSA.[33] Bednarek et al.[34] compared patients in whom OSA and COPD overlapped (i.e., patients with overlap syndrome) and patients with OSA only, in terms of polysomnographic variables. The authors reported that the patients in the overlap syndrome group had a lower mean oxygen saturation and spent more time in oxygen desaturation than did those in the OSA group.

Muraki et al.[17] found that, in OSA patients, the minimum $SaO_2$ was significantly lower during REM sleep than during NREM sleep, as has been reported elsewhere.[3] In the present study, although there were no differences between our two groups in terms of the minimum $SaO_2$ or oxygen desaturation, the mean $SaO_2$ was lower in the NREM-related OSA group than in the REM-related OSA group. We also found that, in REM-related OSA, oxygen desaturation correlated positively with age and BMI.

The termination of an apnea event is associated with arousal or awakening. Different levels or intensities of arousal can have quite different effects on sleep and breathing.[35] In the present study, some of the effects of REM-related OSA were mitigated by a decrease in the time spent in REM sleep in parallel with increasing AHI-REM. This could be due to an increased number of events during REM sleep, leading to arousals and decreasing the time spent in REM sleep. In our study, there was no difference between the REM-related and NREM-related OSA groups, in terms of the number of arousals.

Punjabi et al.[13] found that the AHI-REM was associated with greater daytime sleepiness, whereas the AHI-NREM was not. However, Haba-Rubio et al., using an objective instrument (the Maintenance of Wakefulness Test), found no difference between patients with REM-related OSA and those with NREM-related OSA, in terms of excessive daytime sleepiness.[5]

Although OSA is a common chronic condition in all adults, its prevalence and severity are higher among men than among women.[29,36] However, a number of studies have shown that REM-related OSA is more common among women.[7-9] We find it interesting that the AHI-REM has been shown to be comparable between men and women.[37] In our study, there was no significant difference between genders in terms of the prevalence of REM-related OSA. However, we found that REM-related OSA was more common than was NREM-related OSA among the women in our sample, whereas NREM-related OSA was more common among the men. In a study conducted by O'Connor et al.,[27] OSA was found to be milder in the women than in the men. The authors reported that the significant respiratory events recorded in the women were associated with REM sleep and therefore concluded that REM-related OSA is more common in women.

Some studies have shown that REM-related OSA is more common among younger patients,[8] whereas others have found no such age-related difference.[5,38] In the present study, there was no significant difference between the REM-related and NREM-related OSA groups, in terms of age. However, in both groups, the women were older than were the men, although the female patients with REM-related OSA were younger than were those with NREM-related OSA, especially in the younger (< 60 year) age group. Koo et al.[7] stated that, in REM-related and NREM-related OSA, the hormonal changes that occur with age in females have a protective effect against the respiratory problems that occur during NREM sleep. Among the women in our sample, REM-related OSA was more common than was NREM-related OSA, as well as being more common in the younger women.

In another study, Koo et al. showed that, with each passing decade of life, the NREM-AHI and REM-AHI increase by 11.2% and 9.0%, respectively, in men, compared with 16.0% and 5.7%, respectively, in women.[8] The authors also showed that each 5-unit increase in BMI results in increases of 13.0% and 17.1% in the NREM-AHI and REM-AHI, respectively, in women, compared with a 24.2% decrease for both in men.[8] In our study, there was no difference between the REM-related and NREM-related OSA groups in terms of the BMI. However, in both groups, the women were significantly heavier than were the men. We also found that, in the REM-related OSA group, the AHI showed a significant positive correlation with age and BMI. The AHI also correlated positively with BMI in the NREM-related OSA group, although the difference was not significant.

The present study has certain limitations. The first is that the study sample was evaluated retrospectively. Second, all of the polysomnography data analyzed for each patient were obtained during a single session of overnight polysomnography, as is customary in the clinical laboratory setting. Data collected over multiple nights of observation would provide important information regarding the impact of the differences in REM sleep and sleep posture, assuming that those

parameters changed from night to night. A decrease in the proportion of REM sleep has been associated with the first night effect, and a total lack of REM sleep can occur in split-night polysomnography studies.[39] Either of those scenarios could lead to an underestimation of AHI in patients with REM-related OSA.

In conclusion, it appears that REM-related OSA is more common among patients with mild-to-moderate OSA, whereas NREM-related OSA is more common among those with severe OSA, the latter being associated mainly with s-AHI. Our findings indicate that s-AHI has a more significant effect on the severity of OSA than does REM-AHI. When determining OSA severity and choosing among treatment modalities, physicians should take into consideration not only sleep stage but also sleep posture.

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# Cervical computed tomography in patients with obstructive sleep apnea: influence of head elevation on the assessment of upper airway volume

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## ABSTRACT

**Objective:** Obstructive sleep apnea syndrome (OSAS) has a high prevalence and carries significant cardiovascular risks. It is important to study new therapeutic approaches to this disease. Positional therapy might be beneficial in reducing the apnea-hypopnea index (AHI). Imaging methods have been employed in order to facilitate the evaluation of the airways of OSAS patients and can be used in order to determine the effectiveness of certain treatments. This study was aimed at determining the influence that upper airway volume, as measured by cervical CT, has in patients diagnosed with OSAS. **Methods:** This was a quantitative, observational, cross-sectional study. We evaluated 10 patients who had been diagnosed with OSAS by polysomnography and on the basis of the clinical evaluation. All of the patients underwent conventional cervical CT in the supine position. Scans were obtained with the head of the patient in two positions (neutral and at a 44° upward inclination), and the upper airway volume was compared between the two. **Results:** The mean age, BMI, and neck circumference were 48.9 ± 14.4 years, 30.5 ± 3.5 kg/m$^2$, and 40.3 ± 3.4 cm, respectively. The mean AHI was 13.7 ± 10.6 events/h (range, 6.0-41.6 events/h). The OSAS was classified as mild, moderate, and severe in 70%, 20%, and 10% of the patients, respectively. The mean upper airway volume was 7.9 cm$^3$ greater when the head was at a 44° upward inclination than when it was in the neutral position, and that difference (17.5 ± 11.0%) was statistically significant ($p = 0.002$). **Conclusions:** Elevating the head appears to result in a significant increase in the caliber of the upper airways in OSAS patients.

**Keywords:** Sleep apnea, obstructive/prevention and control; Sleep apnea, obstructive/therapy; Tomography.

## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is an anatomical and functional disorder in which the chief event is the recurrent narrowing or collapse of the upper airway walls during sleep. Various factors, such as excess neck fat, high BMI, sleeping in the supine position, gravitational effects, craniofacial anomalies, pharyngeal muscle flaccidity, increased tongue volume, and enlarged palatine tonsils, can trigger or worsen the disease.[1]

The definition of OSAS includes recurrent episodes of complete or partial upper airway obstruction (apnea and hypopnea, respectively), with an apnea-hypopnea index (AHI) > 5 events/h, as determined by polysomnography, together with symptoms such as excessive daytime sleepiness. Those respiratory events, in most cases, result in decreased oxyhemoglobin saturation and in arousals (brief awakenings lasting < 15 s, characterized by the intrusion of a faster rhythm in the electroencephalogram).[2]

A recent study showed that the prevalence of OSAS in the population of the city of São Paulo, Brazil, is 32.8%.[3] Given that OSAS results in numerous cardiovascular and metabolic complications, further study on new therapeutic techniques is warranted.[4-6] Imaging methods have been of assistance in airway assessment in OSAS patients and can be used for comparative volumetric analysis before and after intervention.[7,8]

The most well-established treatments for OSAS are the use of continuous positive airway pressure (CPAP) and the use of oral appliances. Surgery, nasal treatment, speech therapy, weight loss, and positional intervention can have clinical benefits.[6] Although there have been studies showing that maintaining a lateral position reduces the AHI, there have been few studies evaluating head elevation as a therapeutic intervention.[9,10] Therefore, a study on postural intervention is warranted in order to evaluate the influence of head elevation in patients previously diagnosed with OSAS on the basis of determination of upper airway volumes by cervical CT.

## METHODS

This was an observational cross-sectional study. The study was approved by the Human Research

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Ethics Committee of the Universidade do Extremo Sul Catarinense, in the city of Criciúma, Brazil (Protocol no. 381.168/2013), and all of the patients gave written informed consent.

Between July and December of 2013, we studied ten consecutive patients (> 18 years of age) who had been diagnosed with OSAS by polysomnography (Alice 5 Diagnostic Sleep System; Phillips Respironics, Murrysville, PA, USA), with an AHI > 5 events/h, accompanied by symptoms (excessive daytime sleepiness, nonrestorative sleep, or fatigue), and were treated at the Criciúma Outpatient Clinic for Pulmonology and Sleep Medicine. The exclusion criteria were presenting with decompensated underlying disease (e.g., decompensated heart failure or uncontrolled asthma), weighing more than 120 kg (which exceeds the CT scanner limit), and measuring more than 64 cm from shoulder to shoulder (a width greater than the internal diameter of the CT scanner). The ten patients analyzed had not previously undergone any treatment for OSAS and were therefore treatment-naive. One patient weighed 125 kg and could not undergo CT. That patient was therefore excluded from the study.

Within one week after enrolling in the study, each patient underwent cervical CT without the use of intravenous contrast. All CT images were acquired on a multislice CT scanner (Brightspeed; GE Healthcare, Milwaukee, WI, USA) in the traditional manner. Subsequently, we positioned a 44° wedge (dimensions: 45.5 cm in its longest side × 43.3 cm × 18.5 cm) on the CT scanner table. Each patient lay, head supported on the wedge, on a line traced on its longest side, and additional cervical CT slices were obtained with a total radiation dose of less than 10 mSv. The 44° head elevation was calculated to allow the wedge to provide maximum head and neck elevation, while still allowing passage through the CT scanner gantry (height, 70 cm). The images were acquired with the patient in the supine position with the skull positioned neutrally in relation to the neck, with and without the use of the wedge. Examples of the patient positioning on the CT scanner table, with and without the 44° head elevation, as well as CT images acquired at those positions, are shown in Figure 1. The CT images acquired with and without the wedge were compared, and the pharyngeal airspace was evaluated, using three-dimensional reconstructions, between the hard palate and the base of the epiglottis in order to determine the amount of volume in $cm^3$. On the workstation, the volume of air within the passage extending from the hard palate to the base of the epiglottis was calculated with a volume rendering program (GE Healthcare, Milwaukee, WI, USA). Linear measurements were not used, because of the possibility of multi-directional variance in airspace shape as a result of the change in the angle of the head, depending on patient biotype. Throughout the CT analysis, the subjects evaluated were awake and remained in a neutral position, avoiding extension or flexion of the neck.

Body weight classification based on BMI (in $kg/m^2$) was as follows: normal weight (18.5-24.9); overweight (25.0-29.9); class I obesity (30.0-34.9); class II obesity (35.0-39.9); and class III obesity (≥ 40.0).

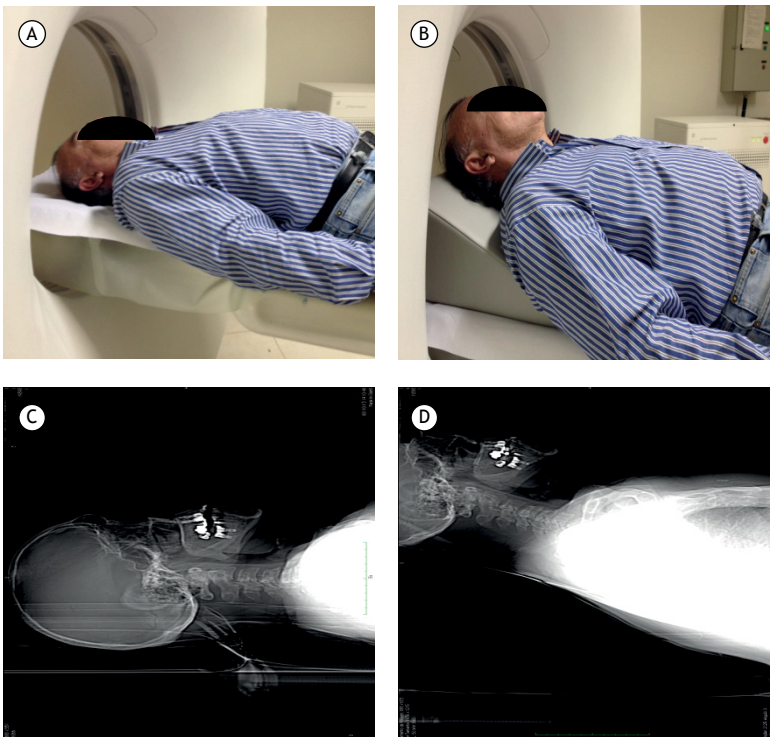


**Figure 1.** Patient without head elevation (neutral position; in A) and with head elevation by a 44° wedge (in B). CT scans obtained with the head in the neutral position (in C) and elevated by 44° (in D).

The criteria used in order to classify OSAS, as well as the parameters used in order to score respiratory events and arousals on polysomnography, were in accordance with those recommended by the American Academy of Sleep Medicine.[11,12]

The study data were tabulated on spreadsheets created using the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). All statistical tests were performed with a significance level of $\alpha = 0.05$ and a confidence interval of 95%.

Numerical variables were expressed as means and standard deviations or as medians and interquartile ranges. Quantitative and qualitative variables were expressed as frequencies and percentages. To analyze upper airway volume with and without head elevation, we used the Shapiro-Wilk test followed by the Student's t-test for paired samples. The variables BMI, neck circumference, and AHI were tested for correlation with the increase in upper airway volume, in percentage and absolute values ($cm^3$), by using the Shapiro-Wilk test followed by Spearman's correlation coefficient.

## RESULTS

The mean age of the patients was 48.90 ± 14.37 years (range, 27-65 years), and six patients (60%) were female. The mean BMI was 30.51 ± 3.52 $kg/m^2$, and the mean neck circumference was 40.35 ± 3.40 cm. With regard to body weight, four participants were classified as being overweight, four as having class I obesity, one as having class II obesity, and one as having normal weight. The mean AHI was 13.7 ± 10.6 events/h (range, 6.0-41.6 events/h). Therefore, the polysomnographic diagnosis (AHI) was mild OSAS in seven patients (70%); moderate OSAS in two (20%); and severe OSAS in one (10%). A descriptive profile of the quantitative variables in the sample is shown in Table 1.

In the CT analysis, the mean upper airway volume was 40.35 ± 16.43 $cm^3$ without head elevation and 48.31 ± 16.21 $cm^3$ with head elevation (Figure 2). The change in mean upper airway volume was 7.9 $cm^3$, with a statistically significant difference ($p = 0.002$) in caliber at a 44° head elevation. The mean percentage increase in upper airway volume, as determined by CT analysis, was 17.49 ± 10.99%. The median (interquartile range) increase in upper airway volume was 5.45 (4.09-11.15) $cm^3$. As an example, we show the case of one of the patients in the study, with an increase of 6.6 $cm^3$ (15.8%) in upper airway volume, as determined by cervical CT (Figure 3).

There was no significant correlation between the increase in upper airway volume and the hypopnea index (tau-b = −0.138; $p = 0.586$). Nor were there significant correlations between the increase in upper airway volume and the variables BMI, neck circumference, or AHI (Table 2). In addition, there were no statistically significant correlations between the various BMI categories and the severity of OSAS.

## DISCUSSION

The present study showed a mean increase of 7.9 $cm^3$ in upper airway volume, as measured by CT, at a 44° head elevation. A study conducted in Taiwan, involving CT evaluation of 16 patients, showed that upper airway volume increased by 6.1 $cm^3$ after maxillomandibular advancement surgery.[8] In the literature, there are conflicting data regarding the percentage change in upper airway caliber after surgery (preoperative and postoperative comparative volumetric analysis).[13-16] For example, one study reported a 26% increase in total volume,[15] whereas another reported a 2% reduction in total volume.[13] In our assessment using CT imaging, upper airway volume was 17.49% greater with head elevation than without. In 18 patients undergoing MRI, Sutherland et al.[17] compared the upper airway

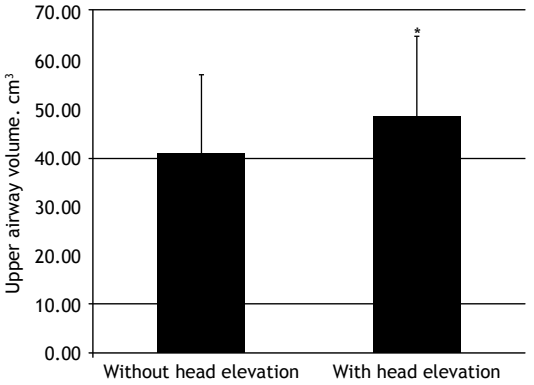


**Figure 2.** Upper airway volume, as measured by cervical CT, before and after the use of a wedge to elevate the head. *p = 0.02.

**Table 1.** Characteristics of the study sample.

| Variable | Mean ± SD or median (IQR) | Minimum | Maximum |
|---|---|---|---|
| Age, years | 48.90 ± 14.37 | 27.00 | 65.00 |
| BMI, $kg/m^2$ | 30.51 ± 3.52 | 24.68 | 35.75 |
| Neck circumference, cm | 40.35 ± 3.40 | 35.50 | 46.00 |
| AHI, events/h | 13.75 ± 10.60 | 6.00 | 41.60 |
| Upper airway volume without head elevation, $cm^3$ | 40.35 ± 16.43 | 14.40 | 75.85 |
| Upper airway volume with head elevation, $cm^3$ | 48.31 ± 16.21 | 18.66 | 79.94 |
| Increase in volume, % | 17.49 ± 10.99 | 5.10 | 36.96 |
| Increase in volume, $cm^3$ | 5.45 (4.09-11.15) | 3.46 | 18.89 |

IQR: interquartile range; and AHI: apnea-hypopnea index.

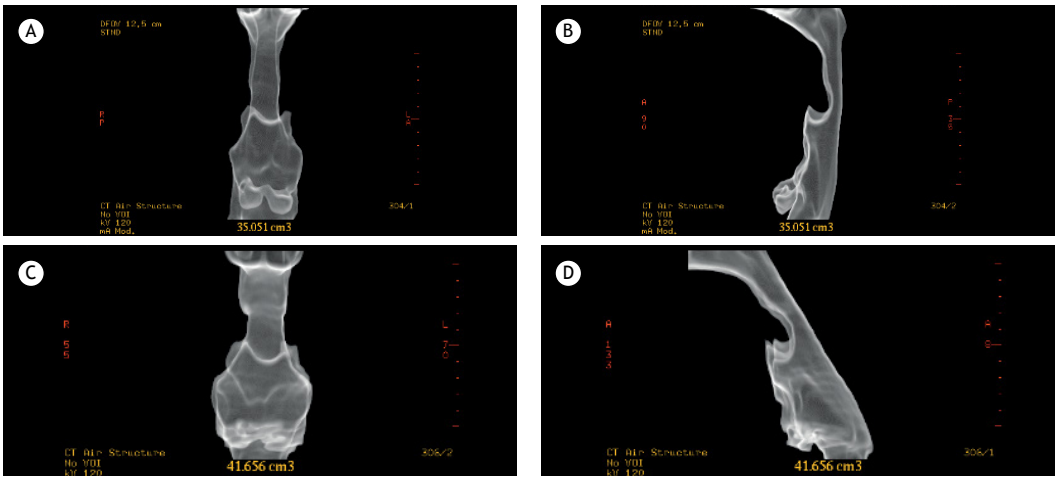


**Figure 3.** Cervical CT for determining upper airway volume—in the neutral position (without head elevation): anterior view (in A) and lateral view (in B); and with the head elevated by 44° with a wedge: anterior view (in C) and lateral view (in D). Volume was measured from the hard palate to the base of the epiglottis.

**Table 2.** Analysis of correlation between numerical variables and the increase in upper airway volume.

| Variable | Increase in volume, $cm^3$ | p | Increase in volume, % | p |
|---|---|---|---|---|
| BMI, $kg/m^2$ | −0.030 | 0.934 | 0.079 | 0.829 |
| Neck circumference, cm | 0.000 | 0.999 | 0.006 | 0.987 |
| AHI, events/h | −0.248 | 0.489 | −0.285 | 0.425 |
| HI, events/h | 0.782 | 0.001 | −0.138 | 0.586 |

AHI: apnea-hypopnea index; and HI: hypopnea index.

structure at baseline (i.e., without an oral appliance), with a mandibular advancement splint, and with a tongue stabilizing device, reporting mean volumes of 13.8 ± 1.0 $cm^3$, 14.3 ± 1.1 $cm^3$, 17.14 ± 1.6 $cm^3$, respectively. Therefore, the volumetric improvement varied only from 0.50 $cm^3$ to 2.84 $cm^3$, depending on the type of appliance employed. In 10 patients undergoing MRI, Schwab et al.[18] showed that the mean airway volume was 11.7 $mm^3$ at baseline (i.e., at 0 $cmH_2O$ of CPAP) and progressively increased to 13.2 $mm^3$, 16.8 $mm^3$, and 20.5 $mm^3$, with CPAP increases of 5 $cmH_2O$, 10 $cmH_2O$, and 15 $cmH_2O$, respectively. However, another study showed a modest increase in upper airway volume, as measured by MRI, with the use of CPAP[19]—upper airway volume was 9.3 mL and 11.8 mL at 0 and 9 $cmH_2O$ of CPAP, respectively, an increase of 2.5 mL ($p < 0.05$).

Elevating the head of the bed is an old postural intervention, widely used to assist in the treatment of subjects with gastroesophageal reflux, that is based on the principle of reducing acid exposure time and changing intra-abdominal pressure.[20,21] This postural intervention yields good results in pH measurements and leads to an improvement in symptoms.[22,23] However, few studies have examined the effect of head or head-and-shoulder elevation on OSAS.[9,10,24,25]

McEvoy et al.[10] studied 13 male patients during the same night and reported a reduction in AHI from 49 ± 5 events/h to 20 ± 7 events/h when patients changed from the supine position to a sitting position at a 60° angle. Skinner et al.[24] studied 14 subjects in the supine position (no elevation), comparing it with head-and-shoulder elevation (with a shoulder-head elevation pillow), and reported a 22% reduction in AHI. Studies have shown that upper airway closing pressure is reduced when the individual is moved from the supine position (no elevation) to an inclined position (30° head elevation),[25] as well as when the individual is moved from the supine position to a sitting position.[26] In a study of 17 patients undergoing polysomnography, Souza et al.[9] evaluated AHIs at baseline (i.e., during standard polysomnography) and after elevating the head of the bed 15 cm, reporting a significant reduction in the mean AHI (20 ± 14 events/h vs. 15 ± 14 events/h; $p = 0.0003$). It has been hypothesized that head elevation contributes to upper airway clearance, prevents rostral fluid shift,[27] and averts tongue collapse,[28] reducing upper airway resistance,[10] changing upper airway critical pressure,[29] affecting gravitational effects,[30] and altering neuromuscular activity.[31]

In our study, the severity of OSAS did not correlate with BMI, which differs from the findings of some epidemiological studies in the literature, such as a study involving 300 patients treated at a sleep clinic in the city of Porto Alegre, Brazil.[32] Nor did neck circumference correlate with OSAS severity. These differences are probably related to the small number of patients in our study.

Although our study is limited by its small sample size, studies that have employed imaging for assessment of upper airway volume after some treatment for OSAS

have evaluated a similar number of patients.[8,9,11,13] Another limitation was that the CT study was not performed with the patient asleep under sedation or anesthesia, but rather with the patient awake, which could have affected muscle tone. Litman et al.[33] showed that propofol-sedated children had higher upper airway volumes in the lateral position than in the supine position; however, the mean increase was 2.7 mL. Other limiting factors of the present study are the lack of a control group, the fact that most of our patients had mild OSAS, and the predominance of females (60%), which is uncharacteristic of OSAS studies, in which males typically predominate. In addition, the fact that we did not take into consideration the anatomical differences between the upper airways of males and those of females constitutes a limiting factor.

We conclude that, in our sample of patients with OSAS, there was an increase in upper airway volume, as measured by cervical CT, at a 44° head elevation. Further studies involving a larger number of patients are needed in order to assess the change in upper airway volume resulting from head elevation and the true clinical benefit of this intervention.

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REVIEW ARTICLE

# Psychological distress related to smoking cessation in patients with acute myocardial infarction

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## ABSTRACT

Among all causes of preventable deaths, smoking is responsible for the greatest number of deaths worldwide and predisposes to fatal, noncommunicable diseases, especially cardiovascular diseases. Lifestyle changes are effective in the treatment of patients with smoking-related diseases and assist in the prevention of premature mortality. Our objective was to investigate the available scientific evidence regarding the psychological distress related to smoking cessation in patients who have had acute myocardial infarction. To that end, we conducted an integrative review of the literature in order to summarize relevant studies on this topic. The selected databases were Scopus, PubMed Central, Institute for Scientific Information Web of Science (Core Collection), ScienceDirect, EMBASE, SciELO, LILACS e PsycINFO. On the basis of the inclusion and exclusion criteria adopted for this study, 14 articles were selected for analysis. Those studies showed that the prevalence of psychological distress is higher among smokers than among nonsmokers, and distress-related symptoms are much more common in smokers with acute myocardial infarction than in those without. Smoking cessation depends on the active participation of the smoker, whose major motivation is the underlying disease. Most studies have shown that there is a need to create treatment subgroups as a means of improving the treatment provided. This review article expands the knowledge regarding smoking cessation and shows the need to invest in future research that investigates subgroups of smokers diagnosed with the major smoking-related comorbidities, such as acute myocardial infarction, in order to develop specific interventions and psychological support strategies.

**Keywords:** Smoking; Stress, psychological; Myocardial infarction; Tobacco use cessation.

## INTRODUCTION

Nicotine is classified as an addictive substance, albeit a licit one. Smoking is a public health problem worldwide, having negative consequences and unfavorable economic implications, as well as being the leading cause of preventable death.[1-3]

Exposure to tobacco smoke is a major risk factor for various conditions that predispose to fatal noncommunicable diseases,[4] especially cardiovascular disease, respiratory disorders, and atherosclerosis, as well as cancer and high blood pressure.[5-8] Worldwide, smoking kills one person every six seconds and accounts for one in ten deaths among adults. It is estimated that up to half of current tobacco users will die from a smoking-related disease.[9]

Studies show that smokers, compared with nonsmokers, have less knowledge of the social, psychological, and physical issues related to smoking, as well as poorer quality of life,[10,11] smokers living, on average, 10 years less than do nonsmokers.[10] In addition, smokers have a two times higher 10-year risk of cardiovascular events, as well as double the relative risk of acute myocardial infarction (AMI) after 60 years of age.[12,13] Smoking cessation is the most effective lifestyle modification in the treatment of patients with coronary artery disease and is an effective way to prevent many diseases, as well as to avoid premature mortality.[2,5,14] Therefore, it is necessary and important to encourage the use of smoking cessation strategies.

The difficulty that individuals have in quitting smoking and in maintaining smoking abstinence is multifactorial and complex.[15] Complicating factors such as heart disease appear to increase that difficulty. However, a study carried out in several European countries, in which 48% of the smokers evaluated were successful in quitting smoking, showed that the proportion of individuals in whom smoking cessation interventions were successful was higher among those who had experienced AMI than among those who had no been diagnosed with a smoking-related disease.[16]

Because cardiovascular events, such as AMI, are life-threatening, it is essential that individuals at risk for such events change their behavior and lifestyle. Nonadherence to treatment can inhibit patient recovery and increase the chances that AMI will recur.[17] Current research suggests that smoking cessation strategies targeting smokers in general are not always effective, suggesting that there is a need for strategies focused on specific groups.[18] There is also evidence that the intensive behavioral modification programs designed

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for the general population, involving weekly sessions over a three-month period, will not generate sufficient behavioral changes to prompt individuals at risk for cardiovascular events to adopt a healthy lifestyle,[17] making it necessary to develop new technologies with greater specificity for this type of patient.

Smoking cessation is a dynamic process, considered a great personal challenge that requires considerable effort on the part of smokers.[11] In addition to adapting to a new lifestyle, individuals who quit smoking have to overcome the effects of nicotine withdrawal, which has been linked to cognitive and emotional dysfunction.[19] Some studies have shown that psychological distress is an important factor in the smoking cessation process and should be taken into account in individuals who attempt to quit smoking. The rates of psychological distress are known to be higher among smokers than among nonsmokers.[20] Within this context, the psychological symptoms that are the most common and most widely studied in this group of patients are anxiety and depression.[21,22]

Symptoms of anxiety and depression are often aggravated by the relationship between smoking cessation and the sequelae of AMI, which makes smoking abstinence more difficult and underscores the need to improve the methods employed in helping AMI patients quit smoking. Because the role that psychological stress plays in such patients remains unclear, there is a need for studies investigating psychological distress during smoking cessation, especially among patients with heart disease and AMI in particular. Such studies could increase the effectiveness of smoking control measures targeting this population.

## METHODS

This was an integrative review of the literature regarding psychological distress related to smoking cessation in patients who have had AMI. In this review, we synthesize and analyze the relevant studies published on the subject, summarizing previous research.

In this integrative review, we followed the steps proposed by Ganong[23]: identification of the theme and formulation of the research question; establishment of the purpose of the review; establishment of the inclusion and exclusion criteria for selecting the articles in the sample; definition of the information to be extracted from the selected articles; assessment of the studies included; and presentation and interpretation of the results. Two questions guided this review: "What effects does smoking cessation have in individuals who have suffered AMI?"; and "What role does psychological distress play in the smoking cessation process in such individuals?"

For searches of Latin-American databases, we used the following terms, taken from the MeSH browser and from its Portuguese-language counterpart (the DeCS platform): "tobacco" (*tabaco*), "tobacco use cessation" (*abandono do uso de tabaco*), "myocardial infarction" (*infarto do miocárdio*), and "stress, psychological" (*estresse psicológico*). The descriptors in English and Portuguese were combined by means of the Boolean operators "AND" and "OR". Entry terms (synonyms) listed in the MeSH (and DeCS) records were used for an extended search.

The search for articles was conducted between June and September of 2014. We searched the following databases: Scopus, PubMed Central, Institute for Scientific Information Web of Science, ScienceDirect, EMBASE, SciELO, LILACS, and PsycINFO. Applying the criteria described below, we selected only full studies dealing with the psychological effects of smoking cessation after AMI. We chose to use those databases because they include studies that meet the study inclusion criteria and because we were attempting to encompass all relevant studies that dealt with the theme under study.

In selecting articles, we applied the following inclusion criteria: being an original article; involving human subjects over 18 years of age; having been published in a journal indexed for at least one of the eight databases searched; having its abstract and full text freely available online; having been published between 1990 and 2014; having been published in Portuguese, Spanish, or English; and dealing with smoking cessation, psychological distress, heart disease, and AMI. Our searches were not limited by the gender of the study subjects. We excluded articles that did not deal with the theme under study, as well as those for which the full text was not available in digital form, and those that were not original articles, such as editorials, conference proceedings, working papers, case reports, and review articles.

For the purposes of this review, we developed a specific data collection tool. By using that tool, we were able for collect information in a way that facilitated the description, organization, and interpretation of the results.

## RESULTS

We identified 1,040 articles, 252 of which were duplicates. On the basis of the titles alone, we excluded 564 articles, and 5 of the articles selected were found to be unavailable. The remaining 219 articles were evaluated within the context of the proposed study criteria. On the basis of the abstracts, another 92 articles were excluded, the remaining 127 being read in their entirety. After reading the full texts, we selected 14 articles for analysis (Figure 1).

Given the singularities of access of the eight analyzed databases, the strategies employed to evaluate the articles were adapted in accordance with the previously established inclusion criteria. The 14 articles selected, each published in a different journal, all dealt with issues related to smoking cessation and psychological distress, and some dealt with those issues within the context of a specific population with heart disease, such as AMI.

Of the 14 articles evaluated, 5 (36%) were conducted in the United States; 3 (21%) were conducted in Brazil;

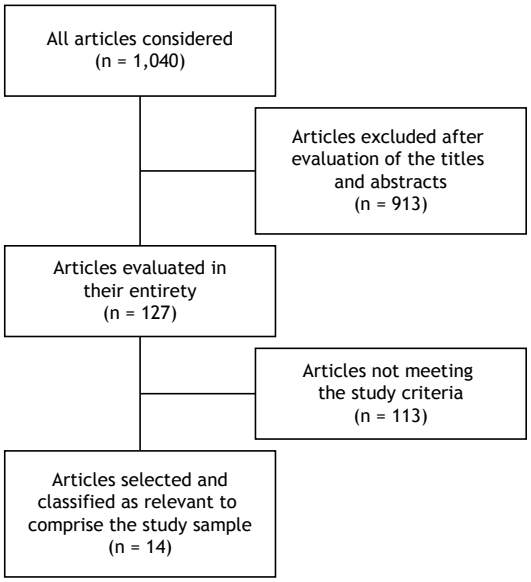


**Figure 1.** Flow chart of the article selection process.

2 (14%) were conducted in Canada; 2 (14%) were conducted in the United Kingdom; 1 (7%) was conducted in the Netherlands; and 1 (7%) was conducted in Italy. Twelve (86%) of the articles were written in English, and 2 (14%) were written in Portuguese.

Most of the articles were published between 2009 and 2013 (mode = 5 in 2009). Outliers were articles published in 1990, 1995, and 2002 (1 each year).

All of the selected studies used a quantitative approach, cross-sectional studies accounting for 42%, compared with 14% each for longitudinal studies and randomized clinical trials. The remaining studies adopted a prospective non-randomized approach (case-control, cohort, retrospective, or double-blind studies).

Seven (50%) of the 14 articles selected presented studies conducted in a hospital setting. Four (28%) were based on nationwide surveys. Among the articles analyzed, the instrument most often employed was the Fagerström Test for Nicotine Dependence (FTND), which was used in order to detect nicotine dependence among smokers in 5 (35%) of the studies.

The results of the studies analyzed suggest that people with high levels of psychological distress are more likely to be smokers, given that psychological distress is approximately two times more common among smokers than among nonsmokers. Psychological distress is also associated with a lower probability of smoking cessation and high levels of nicotine dependence, thus increasing the risk of relapse during the first year of follow-up.[24-26]

Some of the studies evaluated showed that smokers and former smokers have depressive symptoms more often than do nonsmokers, and that smokers who use antidepressants are more likely to suffer from anxiety and insomnia.[27-29] The data also suggest that smoking cessation is associated with reduced anxiety and distress.[29,30]

In one of studies evaluated, the authors observed that depression decreases the likelihood of smoking cessation and increases the susceptibility to relapse during abstinence.[31] In another of the studies, which investigated a sample of patients with coronary artery disease, the authors reported that depressive symptoms and increased use of antidepressants were more common in smokers than in nonsmokers.[28]

In keeping with the objective of this review, some of the studies evaluated showed that AMI is a prevalent heart disease among smokers and that quality of life is poorer among smokers with AMI than among those without.[18,27] Smoking cessation can abruptly expose AMI patients to high levels of psychological stress, and this information is essential for continuous and investigative assessment related to the management of nicotine withdrawal after AMI, given the potential negative impact of psychological stress on physical findings in these patients.[27] The data also indicate that the frequency of a diagnosis of a psychiatric disorder and the level of nicotine dependence are high among AMI patients enrolled in smoking cessation programs. Those factors, combined with the greater stress levels, increase cigarette consumption, which calls for special care, involving cognitive behavioral therapy in order to achieve the best results.[31]

Among the studies analyzed, it can be seen that health problems such as AMI and respiratory problems constitute the main motivation to quit smoking.[31,32] Smoking cessation reduces the risk of death after AMI by half, and health professionals play a major role in the smoking cessation process, especially in the guidance and counseling aspects.[32] There is a need for a differentiated approach to this segment of the population (i.e., smokers who have experienced AMI) and therefore to develop interventions focusing on the motivational aspects, in order to engage such individuals in the smoking cessation process.[33]

Studies show that cigarette consumption and the level of nicotine dependence both correlate directly with the risk of AMI. This risk can be reduced to levels close to that of nonsmokers when abstinence from smoking is maintained for a period of three to four years, regardless of the previous daily cigarette consumption and smoking history (pack-years), again underscoring the importance of smoking cessation.[34,35] Therefore, smoking cessation efforts should be initiated early, especially in individuals who have been diagnosed with a smoking-related disease.[36]

Table 1 summarizes the characteristics of the selected articles. The table shows the specific details of the studies analyzed, including the names of the authors, the year of publication, the country in which the study was conducted, the sample size, and the type of study.

## DISCUSSION

This review highlights the importance of evaluating psychological distress as a way to improve adherence to smoking cessation therapy in patients who have

had AMI, as well as addressing the importance of such evaluations to strengthening the health care system and to developing new lines of scientific research. Therefore, we believe that there is a need for additional studies investigating the issue addressed here, mainly because we determined that there is a lack of such studies, not only in Brazil but also worldwide.

Among the studies evaluated in this review, there was a variety of methodological approaches, and the articles were published in journals covering various areas of health. That reflects the plurality of the theme studied and shows that many different methods can be employed in investigating this type of issue. There was a predominance of articles published in 2009, which clearly shows the importance that this issue had in that year. However, when we compared the studies in terms of the country of origin, we found no predominance of one country over the others. Therefore, the attention given to investigating psychological distress in patients who have had AMI, during the period evaluated, appears to have been evenly distributed worldwide.

In this review, the country that produced the most scientific research on psychological distress during smoking cessation in patients who have had AMI was the United States, which can be explained by advances in heart research in that country. It is likely that researchers in the United States recognized the importance of conducting pathophysiological studies of cognitive aspects, including psychological distress. That type of approach improves the understanding of the subject by encompassing various aspects and enables the development of strategies aimed at specific subgroups. Another country that produced considerable scientific research on this issue was Brazil. However, among the selected articles conducted in Brazil, there were no specific studies involving individuals with AMI—only studies analyzing the smoking cessation process and the associated psychological distress. This indicates the need for further studies of this issue in Brazil. Such studies should analyze important behavioral aspects in comparison with existing studies in the literature in order to improve the planning of interventions aimed at promoting health.

The great majority of the studies evaluated in this review were conducted in a hospital setting, reflecting the central position that this type of institution historically occupies in health care systems worldwide. It should be borne in mind that hospitals also play a prominent role within the context of the issue under study here, mainly in terms of the services provided to smokers and to individuals with cardiovascular disease.

The assessment tool most often used in the studies considered in this review was the FTND. The FTND is an important tool in the evaluation of nicotine addiction because it helps determine the smoking history (in pack-years) and the level of patient motivation for smoking cessation. Higher scores on the FTND indicate greater nicotine dependence, which makes it more difficult for the individual to quit smoking.

Most of the studies evaluated in this review had a cross-sectional design, including a description of the characteristics of the study population. Some demonstrated associations between or among variables, although without showing a causal relationship with the object of study, especially because they failed to identify a temporal relationship between the initial exposure to the risk factor and the subsequent development of disease. Therefore, conclusions related to psychological distress as a consequence of smoking cessation should be drawn with caution.

The main limitation of cross-sectional studies is related to the issue of smoking abstinence in relation to psychological distress. The association between those two factors can be influenced by AMI, making it necessary to investigate the development of psychological distress during the smoking cessation process.

**Table 1.** Articles included in the review.

| Authors | Year | Journal | Country of origin | N | Type of study |
|---|---|---|---|---|---|
| Figueiró et al.[11] | 2013 | Trends Psychiatry Psychother | Brazil | 54 | Cohort |
| Castro et al.[18] | 2010 | J Bras Pneumol | Brazil | 167 | Cross-sectional |
| Lawrence et al.[24] | 2011 | BMC Public Health | USA | 31,428 | Cross-sectional |
| Cosci et al.[25] | 2009 | Addict Behav | Italy | 297 | Double-blind, randomized |
| Hajek et al.[26] | 2010 | Addiction | England | 469 | Randomized clinical trial |
| Pfaff et al.[27] | 2009 | Can J Cardiovasc Nurs | Canada | 57 | Cross-sectional |
| Gravely-Witte et al.[28] | 2009 | J Behav Med | Canada | 1,498 | Prospective, non-randomized |
| Peiper et al.[29] | 2013 | Soc Psychiatry Psychiatr Epidemiol | USA | 133,221 | Cross-sectional |
| Cavazos-Rehg et al.[30] | 2014 | Psychol Med | USA | 4,853 | Longitudinal |
| Aguiar et al.[31] | 2009 | Rev Port Pneumol | Brazil | 567 | Retrospective analysis |
| Greenwood et al.[32] | 1995 | J Epidemiol Community Health | UK | 1,283 | Cross-sectional |
| Sachs-Ericsson et al.[33] | 2009 | Nicotine Tob Res | USA | 4,162 | Cross-sectional |
| Rosenberg et al.[34] | 1990 | N Engl J Med | USA | 3,285 | Case-control |
| Pedersen et al.[36] | 2002 | Neth Heart J | The Netherlands | 28 | Longitudinal |

In other words, the exposure and the outcome of the phenomenon should be studied at different times. Other important factors in the analysis relate to the period of investigation and the duration of psychological distress. To address these key points and to minimize the limitations, we suggest conducting longitudinal studies in which there is an analysis of various time points or periods during the therapeutic process of smoking cessation. Such an approach would provide more accurate evidence of the relationship between the studied factors and the variables of interest.

On the basis of the findings of the studies sampled here, we can conclude that smokers with AMI have greater difficulty in quitting smoking because of their greater propensity to experience psychological distress during the smoking cessation process. Some of the authors showed that quitting smoking rapidly and without preparation by health professionals increases psychological distress, including symptoms related to anxiety and depression, which contributes to the increasing rates of smoking cessation treatment failure in this subgroup of smokers.

In view of the results of the studies sampled here, we can state that smoking cessation treatment failure is linked to the inability of health professionals responsible for treatment to evaluate and guide their patients through the smoking cessation process. In addition, there is the lack of preparation to diagnose psychological distress and to create coping strategies to deal with particular themes, strategies which would ideally be focused on the difficulties encountered by individuals with nicotine dependence and smoking-related diseases, such as AMI. One study showed that the role of the health professional is focused on the importance of developing interventions that are more targeted to specific populations, as well as addressing the differences between men and women.[37]

The literature suggests that, among health professionals, pulmonologists having great potential to promote a reduction of smoking. However, most pulmonologists in Brazil do not consider smoking a medical condition, as evidenced in a survey conducted in Brazil, in which only 35.3% of the pulmonologists surveyed reporting offering the correct smoking cessation regimen—the combination of cognitive behavioral therapy and pharmacological treatment.[38] Another factor that is worrisome is that most of those professionals showed disinterest in the subject, reported not having time to counsel their smoking patients, or did not even know how to combat smoking.[38]

It is very important that health professionals be committed to smoking cessation programs. Training is essential to improve knowledge, particularly in relation to supporting patients during the smoking cessation process.[39] Therefore, developing strategies that fit the profile of each patient is critical to facilitating the search for known predictors of treatment failure, such as psychological distress.[40] All smoking patients should be evaluated in terms of the degree of nicotine dependence and the level of motivation to quit smoking.[41]

Psychological distress should be an important issue in the management of smoking patients, particularly by professionals responsible for smoking cessation programs. According to one of the articles included in this review, psychological distress predisposes the smoker to greater dependence, greater difficulty in quitting smoking, and an increased risk of relapse during treatment or after discharge from the program.[31] Therefore, interventions for smoking control should consider the general characteristics of smokers in order for smoking cessation treatment to be effective.[42] Health professionals should also consider the smoking history of patients enrolled in such programs, in order to improve and individualize practices related to their treatment.[41] With such approaches, clinical evaluations are necessary during smoking cessation therapy, and instruments to analyze the personality and psychological distress of the participants should be employed as a way of developing specific strategies, such as psychological support interventions, for use in subgroups of smokers.[25] The results of this review show that such strategies can increase adherence to treatment and help patients cope with their symptoms, especially during smoking abstinence.

Among the symptoms of psychological distress, depression and anxiety have been the most widely researched. Data in the literature indicate that smoking has a direct bearing on the development of those symptoms, which are also elements responsible for the high relapse rates, making smoking cessation difficult. Our results also show that depression and anxiety are more common in subgroups of smokers, such as those with AMI, underscoring the greater propensity of such smokers to experience psychological distress. That finding could be linked to the clinical picture of the patient with AMI, together with the apprehension factor with respect to fear, because the condition involves the possibility of recurrence and is associated with high mortality. However, one recent study showed that smoking cessation treatment reduces levels of anxiety and depression, as well as increasing motivation and reducing stress. Those changes appear to be more pronounced in patients in whom the treatment was successful.[43] Therefore, in smokers with depression, the intensity of the depressive symptoms should be evaluated before and during the intervention, in order to identify the patients who present a higher risk of relapse.[41]

Nicotine dependence and smoking-related diseases should be taken into consideration in the context of smoking cessation treatment, mainly because most smokers present particular and specific characteristics that require special attention, which makes it important to identify specific subgroups of patients, such as those with AMI. Therefore, a thorough evaluation of the patient seeking treatment is of fundamental importance to optimizing the various treatment strategies, which should take into account psychiatric disorders such as anxiety and depression. This corroborates the findings

of a study demonstrating that those symptoms are factors that hinder patient adherence to treatment.[44]

The type of treatment also has an influence on smoking cessation. One study showed that certain pharmacological therapies, such as nicotine replacement, can increase the occurrence of depressive episodes.[45] In such cases, the drug of choice should be bupropion, because it has been proven to be an effective antidepressant for use in smoking cessation treatment. However, self-administered pharmacological therapy alone has proven insufficient to achieve smoking cessation, making it important to combine it with cognitive behavioral therapy. Cognitive behavioral therapy involves the active participation of the patient. In the case of patients in smoking cessation treatment programs, that means that the patients themselves identify routine risk situations and, together with a health professional, develop coping strategies to deal with these situations.[46] Cognitive behavioral therapy techniques also help smokers modify the pattern of conduct in their cigarette consumption, avoiding situations linked to recidivism. That involves learning how to resist the urge to smoke and adopting strategies to counter the smoking habit.[41]

Most of the articles included in this review highlight the importance of smoking prevention and smoking cessation programs, which should be initiated early in order to reduce the risk of developing major diseases related to smoking, such as AMI, as well as to improve the health of patients already affected by such diseases. One of the selected articles discusses the importance of intersectoral cooperation and the referral/back-referral system as ancillary tools in the attempt to quit smoking.[36] According to the authors of that study, the health system is only effective when the responsibility is shared by all sectors. In other words, nicotine-dependent individuals, with or without smoking-related diseases, should be initially evaluated in the hospital and subsequently referred to group therapy, where they are counseled and monitored by qualified professionals, who tailor the treatment to each specific case.[36] Thus, the health system could increase the effectiveness of smoking control measures, giving more coverage to the population and providing effective, high-quality care.

This integrative review shows that smoking cessation is a dynamic process and requires the active participation of smokers, whose motivation influences the smoking cessation process. Studies show that psychological distress is directly related to nicotine dependence, which increases the difficulty of smoking cessation, as well as increasing the incidence of depression. The success of smoking cessation treatment is linked to adherence to cognitive behavioral therapy and pharmacological therapy, given that health problems, AMI and respiratory problems in particular, constitute the main motivation to quit smoking. However, quitting smoking rapidly and without appropriate preparation increases psychological stress in patients with AMI, making it difficult to maintain smoking abstinence. Treatment failure is linked to the unpreparedness on the part of health professionals responsible for monitoring such patients to diagnose psychological distress, as well as to a lack of specific treatment subgroups created in order to address and deal with particular themes, such as AMI.

This review expands the knowledge on the subject of smoking cessation and psychological distress in AMI patients, showing the need to invest in further research to analyze subgroups of smokers with major smoking-related diseases, in order to develop specific interventions with psychological support. The attention given to the role played by such diseases could be an interesting line of research, in order to improve treatment adherence in specific treatment subgroups and increase smoking cessation rates, which are considered low in comparison with those of the desire to quit smoking. This type of approach would also improve the knowledge of health professionals about dealing with nicotine dependence and thus improve planning, with broader approaches, treatments that are more effective, and a greater number of intervention strategies.

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# Angiosarcoma of the lung

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## ABSTRACT

Angiosarcoma is a rare malignant vascular tumor. Pulmonary involvement is usually attributable to metastasis from other primary sites, primary pulmonary angiosarcoma therefore being quite uncommon. We report a case of angiosarcoma with pulmonary involvement, probably primary to the lung, which had gone untreated for more than two years. We describe this rare neoplasm and its growth, as well as the extensive local invasion and hematogenous metastasis at presentation. We also discuss its poor prognosis.

**Keywords:** Hemangiosarcoma; Lung neoplasms; Sarcoma.

## INTRODUCTION

Angiosarcoma is a malignant endothelial cell tumor of vascular or lymphatic origin and accounts for approximately 2% of all soft tissue sarcomas.[1] The most common primary sites are the skin and the subcutaneous tissue of the head and neck.[2] Pulmonary involvement is almost always metastatic.[3] Primary pulmonary angiosarcoma is extremely rare, only a few cases having been reported.

## CASE REPORT

A 78-year-old female nonsmoker had previously been examined, a CT scan of the chest having shown a left upper lobe pulmonary mass (Figure 1A). At that time, she underwent bronchoscopy with BAL and bronchial biopsy. The BAL fluid and the biopsy sample were both negative for neoplastic tissue. She subsequently dropped out of follow-up. Two years later, she was referred to our hospital with a six-month history of shortness of breath, dry cough, and weight loss. A chest X-ray and a chest CT scan (without contrast) identified a 10 × 7 cm lesion in the left upper lobe without forming cleavage plans with the aorta and the pulmonary artery (Figures 1B and 1C), with a small left pleural effusion and small mediastinal lymph nodes. An $^{18}$F-fluorodeoxyglucose positron emission tomography-CT (FDG PET-CT) scan (Figure 1D) showed increased metabolic activity in many organs, greatest in the mass in the upper left lobe, the maximum standardized uptake value (SUVmax) of which was 22. Metabolic activity was also increased in the mediastinal lymph nodes (SUVmax = 7), as well as in the right and left suprarenal glands (SUVmax = 16 for both); the aortic lumbar lymph nodes (SUVmax = 11); and the right inguinal lymph node (SUVmax = 10). In addition, there was a mesenteric focus, together with subcutaneous tissue nodes and multiple locations in bone.

The bronchoscopic examination revealed a mass occluding the left upper lobe bronchus (Figure 2), and a bronchoscopic biopsy was performed. Before the results of the tissue sample examination had been obtained, she developed right hemiparesis and a new subcutaneous nodule arose. A CT scan showed multiple brain lesions. She was started on corticosteroids. However, she showed no clinical improvement and brain radiotherapy was proposed.

The histological examination of the biopsy specimen showed a soft-tissue neoplasm with a sheet-like or enclosing cleft arrangement of spindle and epithelioid cells with prominent nucleoli, with some multinucleation; mitotic figures were conspicuous, as were extensive necrosis and hemorrhage (Figure 3A). Immunohistochemical staining of the tumor specimen revealed that it was strongly positive for CD31 (Figure 3B), factor VIII-related antigen (Figure 3C), and vimentin; weakly positive for the nuclear transcription factor Fli-1 and cytokeratin AE1/AE3; and negative for CD34, desmin, and smooth muscle actin. Therefore, the histology and immunohistochemistry were both consistent with epithelioid angiosarcoma.

Two weeks after the histologic diagnosis had been made, the patient died. Her death was attributed to the progression of the disease, the brain metastases in particular.

## DISCUSSION

Angiosarcoma in the lung usually represents metastasis from another primary site. Nevertheless, we believe that the case presented here was one of primary pulmonary angiosarcoma. The patient had a two-year evolution of a pulmonary mass that had gone unmonitored and untreated for more than two years. It seems apparent that the previous lesion corresponded to the pulmonary angiosarcoma that evolved and disseminated during that

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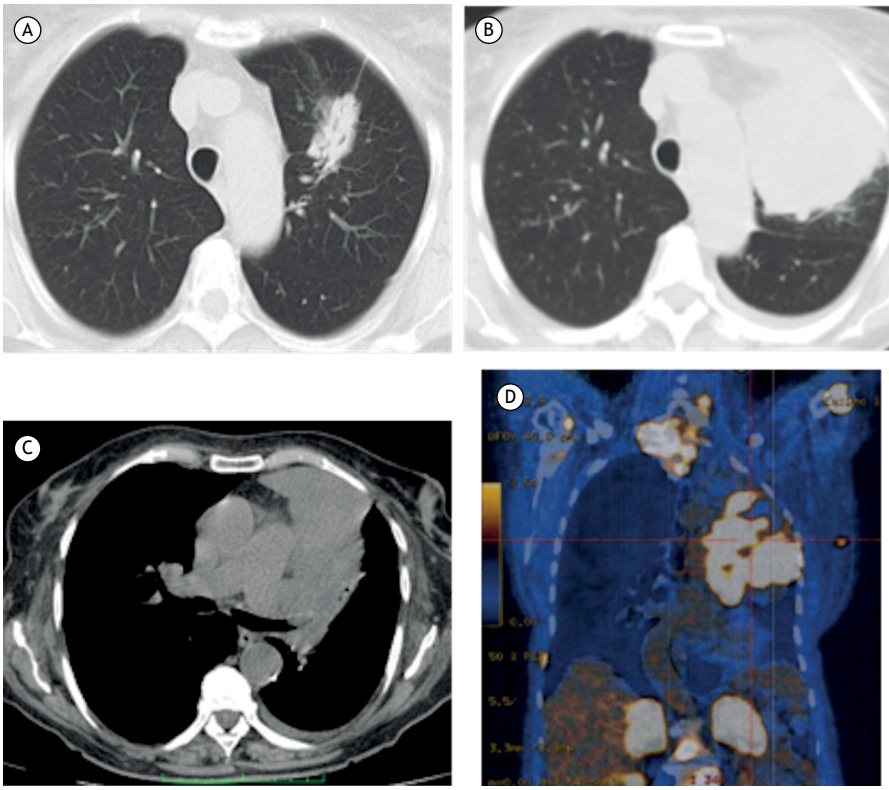


**Figure 1.** Evolution of angiosarcoma in a 78-year-old female nonsmoker: in A, initial CT scan of the chest showing a left upper lobe pulmonary mass; in B and C, CT scans of the chest, obtained two years later, showing a 10 × 7 cm lesion in the left upper lobe, with a small left pleural effusion and small mediastinal lymph nodes; in D, an $^{18}$F-fluorodeoxyglucose positron emission tomography-CT scan showing increased metabolic activity in many organs, greatest in the mass in the upper left lobe.

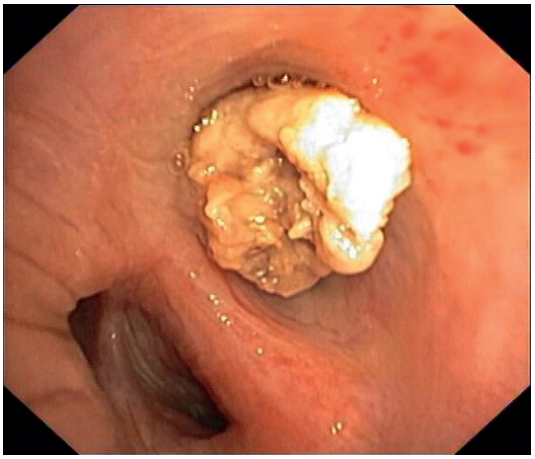

**Figure 2.** Photograph of a mass occluding the left upper lobe bronchus.

time. This case report also documents the behavior of a primary pulmonary angiosarcoma, which is characterized by insidious growth with extensive local invasion and hematogenous metastasis.[4]

Early diagnosis of pulmonary angiosarcoma is not common, because of its rarity and the low index of suspicion. According to data in the literature, the average age of pulmonary angiosarcoma patients is 55.9 years (range, 23.0-82.0 years) and males are more often affected than are female.[5] Patients usually present nonspecific respiratory symptoms that include hemoptysis, cough, dyspnea, chest pain, and weight loss. On CT scans, primary angiosarcoma can be multifocal or can manifest as solitary lesions.[4,6,7] Imaging with PET can be useful in the diagnosis, staging,[8] and follow-up of patients with angiosarcoma.[9] In the case presented here, the FDG PET-CT scan confirmed its usefulness in identifying the regions and systems involved.

Biopsy and immunohistochemical analysis are essential for the diagnosis of angiosarcoma. The histological features can vary within and among cases. Abnormal, pleomorphic, malignant endothelial cells constitute the hallmark of angiosarcoma. Those cells can be rounded, polygonal, or fusiform, with or without an epithelioid appearance. In well-differentiated areas, abnormal endothelial cells form functioning vascular sinusoidal channels that are continuous with normal vascular channels. In patients with progressively more aggressive disease, the architecture becomes more chaotic, with less clearly defined vascular spaces. In poorly differentiated areas, the malignant endothelial cells form continuous monolayers, usually with an epithelioid morphology. An angiosarcoma typically expresses endothelial markers including factor VIII-related antigen, CD34, CD31, and Fli-1. Among those markers, factor VIII-related antigen is

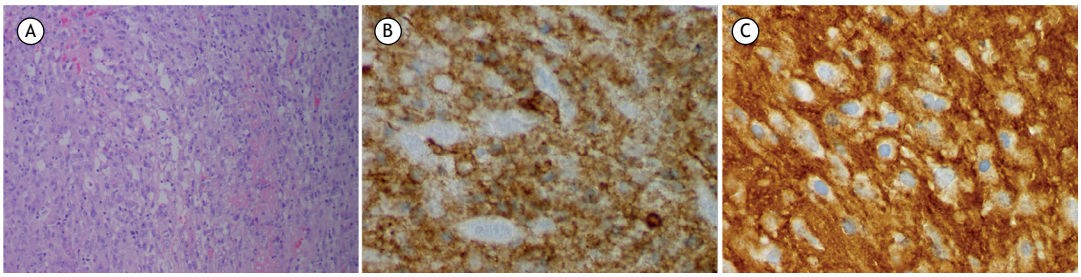


**Figure 3.** Histological examination of the biopsy specimen: in A, extensive necrosis and hemorrhage; in B, immunohistochemical staining for CD31; in C, immunohistochemical staining for factor VIII-related antigen.

the most specific but the least sensitive. Positivity for CD31 is relatively specific and extremely sensitive, being detected in approximately 90% of the cases. In approximately 30% of the cases, angiosarcoma expresses cytokeratin.[10]

Due to the rarity of angiosarcoma, no standardized therapy regimen has been established, especially for primary pulmonary angiosarcoma. Patients with pulmonary angiosarcoma have been treated with radiotherapy,[9,11] surgical resection,[4,9] immunotherapy,[4,6,11] chemotherapy,[4,6,9] or a combination of those.[4,6,9,11] Although none of those treatments have been shown to be effective, there have been reports of effective treatments for the condition,[4,9,11] especially in cases of localized disease. It has been proposed that the most effective treatment is surgery, which should be considered as early as possible for resectable tumors.[5] However, neoplasms are often inoperable at the time of diagnosis. Multimodality therapy, such as the combination of radiotherapy and immunotherapy (recombinant interleukin-2)[11] and that of surgery and chemotherapy,[4] has also proven to be effective. Chemotherapy with gemcitabine and docetaxel has been reported to produce a complete radiographic response.[9]

The prognosis of pulmonary angiosarcoma is poor, mortality within the first few months after clinical presentation, as occurred in the case presented here, approaching 100%.[4-7]

Angiosarcoma is a rare malignant neoplasm, and only a few dozen cases of primary pulmonary angiosarcoma have been reported in the literature. It is a diagnostic challenge for clinicians and pathologists. A high index of suspicion is essential to its early diagnosis and could improve its poor prognosis.

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# Tumor seeding along the needle track after percutaneous lung biopsy

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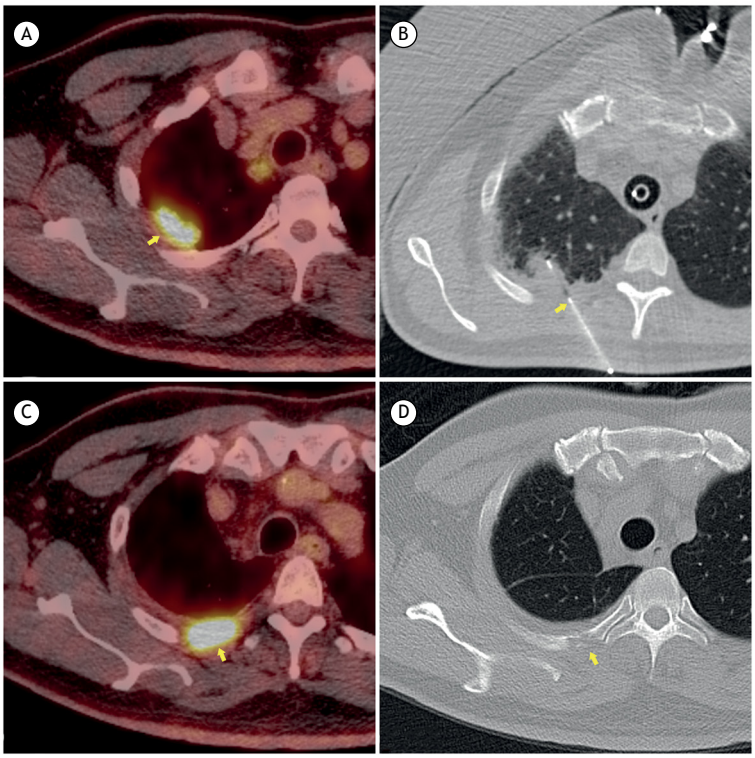


**Figure 1.** Nodule in the right lung apex and percutaneous biopsy of the same: in A, positron emission tomography-CT (PET-CT) scan showing the nodule (arrow); in B, CT scan showing the point of insertion of the coaxial needle (arrow); in C, PET-CT scan after 6 months of follow-up, showing an $^{18}$F-fluorodeoxyglucose-avid soft tissue mass; and in D, CT scan after 6 months of follow-up, showing bone erosion of the right third rib posteriorly (arrow).

A 56-year-old male patient underwent percutaneous biopsy of a nodule in the right lung apex (Figure 1A). The tip of a 19-gauge coaxial needle was positioned in the posterior chest wall (Figure 1B), and six samples of the lesion were obtained with a 20-gauge core needle. The pathological analysis revealed squamous cell carcinoma. Using an anterior approach, we performed right upper lobectomy with tumor-free margins. At 6 months of follow-up, a positron emission tomography-CT scan of the chest showed an $^{18}$F- fluorodeoxyglucose-avid soft tissue mass (Figure 1C) in the T3-4 interspace, along the biopsy tract, as well as bone erosion of the right third rib posteriorly (Figure 1D), suggesting tumor seeding. A subsequent CT scan of the chest, obtained two months later, confirmed local disease progression. We then performed en bloc resection with disease-free pleural margins, and the pathological analysis confirmed that tumor seeding had occurred.

Tumor seeding along the biopsy route is exceedingly rare. Certain factors, such as the use of large-bore cutting needles, increase the risk of such tumor cell dissemination, that risk also being greater when the tumor is an adenocarcinoma.

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# Tracheal lobular capillary hemangioma treated with laser photocoagulation

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## TO THE EDITOR:

Primary tumors of the trachea are rare, with an estimated annual incidence of 2.7 new cases per million population.[1] These tumors are approximately 180 times less common than are lung tumors,[2] accounting for 0.1-0.3% of all tumors.[2,3] Their diagnosis is usually delayed, because the symptoms are initially misinterpreted or patients are misdiagnosed as having asthma.

Lobular capillary hemangioma (LCH), also known as pyogenic granuloma, is a benign vascular tumor most commonly affecting the skin or mucous membranes (oral and nasal). It is extremely rare among all primary tracheal tumors, and there are only few case reports in the literature.[1] Here, we present the case of a rare benign tracheal tumor presenting with recurrent hemoptysis, which was diagnosed by and treated with bronchoscopic techniques.

A 51-year-old female with a 6-month history of recurrent hemoptysis was admitted to the hospital after a significant episode of hemoptysis. She had no other symptoms (i.e., no sputum production, dyspnea, chest pain, weight loss, excessive sweating, or fever). She had a history of papillary thyroid carcinoma, having been submitted to total thyroidectomy and adjuvant therapy with radioactive iodine 16 years prior, with no evidence of relapse to date. Since then, she was on a replacement treatment regimen with levothyroxine sodium. She described herself as a nonsmoker and denied any relevant exposure to tobacco smoke. The physical examination was unremarkable. Routine laboratory tests revealed no abnormalities. A chest X-ray was normal. A chest CT scan with contrast enhancement revealed a newly forming lesion in the left lateral wall of the trachea (Figure 1A), with no other significant changes. Flexible bronchoscopy was performed, confirming the presence of a purple polypoid bleeding lesion in the left lateral wall of the lower third of the trachea, without any additional findings. In order to better control the bleeding, rigid bronchoscopy was performed, with an 8.5 mm bronchoscope (Karl Storz Instruments, Tuttlingen, Germany). The lesion was removed *en bloc* with rigid forceps, resulting in significant hemorrhage, which required local instillation of cold saline and epinephrine (1:10,000); however, bleeding control failed. Hemostasis was then achieved using laser photocoagulation (Multidiode Endolaser 30; INTERmedic Arfran S.A., Barcelona, Spain; Figure 1B). After the procedure, no additional complications resulting from the treatment were noted. The histopathology of the tumor revealed LCH, with no signs of malignancy (Figure 2).

Tracheal tumors are rare, and there is no clear explanation for that. Some authors suggest that the turbulent flow in the trachea might protect the mucosa, preventing the deposit of inhaled carcinogens.[2]

Tracheal LCH is a benign vascular tumor and is exceedingly rare. Typically, this tumor presents as a painless bleeding mass adhered to mucosal or cutaneous surfaces of the upper respiratory tract, most commonly affecting the lip, nose, oral cavity, or tongue.[4] Histologically, it has a distinctive lobular arrangement of capillaries in an edematous fibroblastic stroma, and the surface is occasionally ulcerated.[1,5]

Although the pathogenesis of LCH is unclear, various factors have been implicated, such as hormonal influence, certain drugs, viral oncogenes, *Bartonella* sp. infection, production of angiogenic factors, and cytogenetic clonal deletion abnormalities,[4,6] There have been no reports that levothyroxine sodium is among the offending drugs. Traumatic lesions have also been implicated, although only in a minority of the cases.[1,4,6] In the case reported here, there was a history of endotracheal intubation 16 years prior, due to the thyroid surgery, and that might have been a contributing risk factor.

Cough and hemoptysis are the most common symptoms of tracheal LCH,[1,5,7] the latter ranging from minor to massive.[8] Our patient presented with a 6-month history of recurrent hemoptysis.

For cutaneous LCH, various effective treatment modalities have been reported, including excision, curettage, electrodessication, chemical cauterization, and laser surgery. Mucosal LCH has been treated with snare cautery, excision biopsy, and plaque radiation. The preferred treatment for LCH of the trachea or bronchus in adults has yet to be established because of the limited number of cases[9]; in general, it depends on the extent or size of the lesion, age of the patient, comorbidities, and other factors contributing to the overall clinical picture.[4] At early detection, LCH is small and can be treated endoscopically with low morbidity.[7] Due to the pathological characteristics of these lesions, bleeding is a common complication during the removal process, and hemostasis is difficult to achieve. Despite this, in most of the reported cases, flexible bronchoscopy produced favorable responses. However, if the risk of bleeding is high, the use of rigid bronchoscopy during the removal process should be considered.[4] In our patient, rigid

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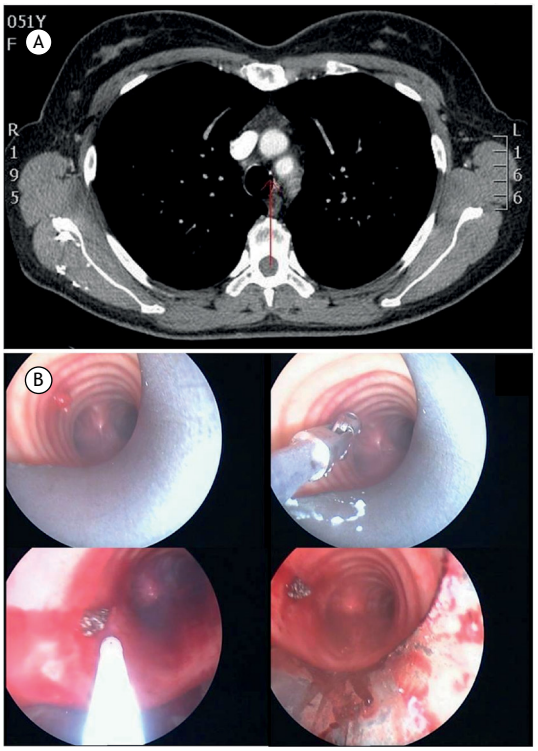


**Figure 1.** In A, a chest CT scan with contrast enhancement showing a small lesion in the left lateral wall of the trachea (red arrow). In B, bronchoscopic images confirming the presence of a purple polypoid lesion in the left lateral wall of the lower third of the trachea; removal of the lesion (with forceps) resulted in significant hemorrhage, which was controlled with laser photocoagulation.

bronchoscopy with laser photocoagulation was the procedure of choice in order to achieve better control of the bleeding. In a previous report, hemorrhage during tracheal LCH removal was successfully treated with laser therapy.[10]

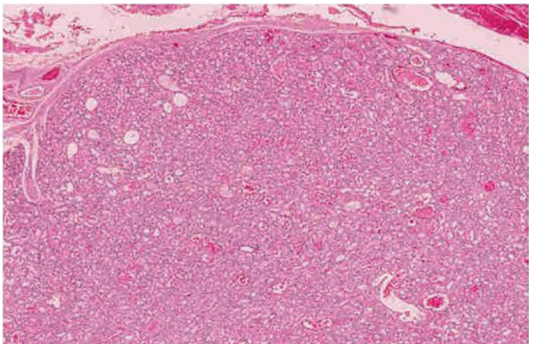

**Figure 2.** Histological examination of the lesion revealed numerous small vessels, some of which were capillaries, arranged in a lobular pattern and separated by a fibrous stroma with accompanying acute inflammatory changes, thus confirming the diagnosis of lobular capillary hemangioma. There were no signs of malignancy (H&E staining; magnification ×100).

The recurrence of skin and mucosal LCH after local therapy is a well-known concern. Although there is no formal recommendation other than clinical re-evaluation, it might be necessary to use bronchoscopy during the follow-up period, because there is a risk of local recurrence.[1]

During the follow-up period, our patient had no recurrence of hemoptysis. At 27 months after the treatment, flexible bronchoscopy showed no signs of relapse. Although exceedingly rare, LCH of the trachea or bronchus should be considered as a cause of recurrent hemoptysis, especially in patients with normal radiological findings.

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# Idiopathic pulmonary fibrosis can be a transient diagnosis

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## TO THE EDITOR:

Usual interstitial pneumonia (UIP) can be accompanied by various clinical conditions, probably the most important of which is idiopathic pulmonary fibrosis (IPF), although the exact incidence and prevalence of IPF, in Brazil or elsewhere, remains unknown.[1-3] The diagnosis of IPF can be established only after the exclusion of other diseases potentially associated with the UIP pattern, such as chronic hypersensitivity pneumonitis, connective tissue diseases, especially rheumatoid arthritis, drug toxicity, and asbestosis.[1,2,4,5] The association between antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis and interstitial lung disease (ILD) has recently been described, including another possible etiology for the UIP pattern. Here, we report the case of a patient with an initial diagnosis of IPF who later developed ANCA-positive vasculitis.

A 62-year-old nonsmoking male patient, a bricklayer, presented with a one-year history of dry cough and slowly progressive dyspnea, classified as grade 2 on the modified Medical Research Council scale. He was being treated with omeprazole, bromopride, and simvastatin for gastroesophageal reflux disease and dyslipidemia. Pulmonary auscultation revealed crackles at both lung bases, and the $SpO_2$ was 97% on room air. The findings of an HRCT scan of the chest (Figure 1) were consistent with a UIP pattern. Pulmonary function tests revealed a mild restrictive pattern (FVC, 78% of predicted/3.6 L; $FEV_1$, 81% of predicted/2.8 L; $FEV_1$/FVC ratio, 0.78; and total lung capacity, 75% of predicted/5.25 L) with normal DLCO (92% of predicted/27.6 mL/min/mmHg). During a six-minute walk test, there was no desaturation (minimum $SpO_2$, 96%), and the six-minute walk distance was 548 m.

The results of laboratory tests were normal, and autoantibody tests were negative, including tests for rheumatoid factor, antinuclear antibodies, anti-Jo-1, anti-Scl-70, and ANCA. The findings of a transthoracic echocardiogram were also normal. A surgical lung biopsy performed at another institution was reviewed and was found to show the UIP histopathological pattern, confirming the diagnosis of IPF. At that time, the patient was still under treatment for gastroesophageal reflux disease.

After one year of clinical stability, the patient was admitted to the hospital with a one-month history of daily fever (38°C) and hematuria, together with swelling and purple lesions in the lower limbs. Laboratory tests revealed anemia (hemoglobin, 9.5 g/dL), elevated C-reactive protein (155 mg/L; reference range, < 5 mg/L) and elevated creatinine (4.5 mg/dL; estimated creatinine clearance, 14 mL/min). Urinalysis showed hematuria, proteinuria, and leukocyturia. There were also a mild reduction in complement C3 (86 mg/dL; reference range, 90-180 mg/dL) and C4 (9.6 mg/dL, reference range, 10-40 mg/dL), as well as positivity for myeloperoxidase-ANCA (1/320), antinuclear antibodies (1/320, with fine-speckled nuclear staining pattern), and rheumatoid factor (97 IU/mL).

A new kidney biopsy was performed, and the analysis of the biopsy sample confirmed the diagnosis of pauci-immune crescentic glomerulonephritis associated with microscopic polyangiitis (MPA), and a skin biopsy of the lower limbs showed leukocytoclastic vasculitis. Methylprednisolone pulse therapy was administered at 1 g/day for three days, after which the patient was started on prednisone at a dose of 1 mg/day that was gradually tapered thereafter. Subsequent treatment with mycophenolate (1.5 g/day) produced gradual clinical improvement. After two years of treatment, the patient continued to have mild dyspnea (modified Medical Research Council scale grade 1), to show normal kidney function, and to test negative for ANCA, and well as to have stable HRCT and pulmonary function test findings.

In patients with ANCA-positive vasculitis, particularly MPA, ILD is an uncommon finding and usually affects older men, with myeloperoxidase-ANCA and a UIP pattern on histopathology. However, the pathophysiology of the association of ILD and ANCA-positive vasculitis has not been fully elucidated.[6]

Recent studies have demonstrated that there is a subset of IPF patients who are ANCA-positive at diagnosis or who convert to ANCA positivity during follow-up and subsequently develop MPA.[6,7] Kagiyama et al.[7] evaluated ANCA positivity and the incidence of MPA in 504 patients with IPF. The authors found that 36 (7%) of the patients were ANCA-positive at diagnosis of IPF. Of the 264 patients who were subsequently tested, 29 (11%) converted to ANCA positivity during the first five years of follow-up. Of the 35 patients who were either ANCA-positive at diagnosis or subsequently converted to ANCA positivity, 9 were diagnosed with MPA.

Two drugs, nintedanib and pirfenidone, both of which slow the decline in lung function, were recently approved for the treatment of IPF.[8,9] However, to date, there is no recommendation regarding the use of those drugs in patients with ILD associated with ANCA-positive vasculitis, in whom it has been suggested that the use of corticosteroids plus cyclophosphamide or rituximab is a

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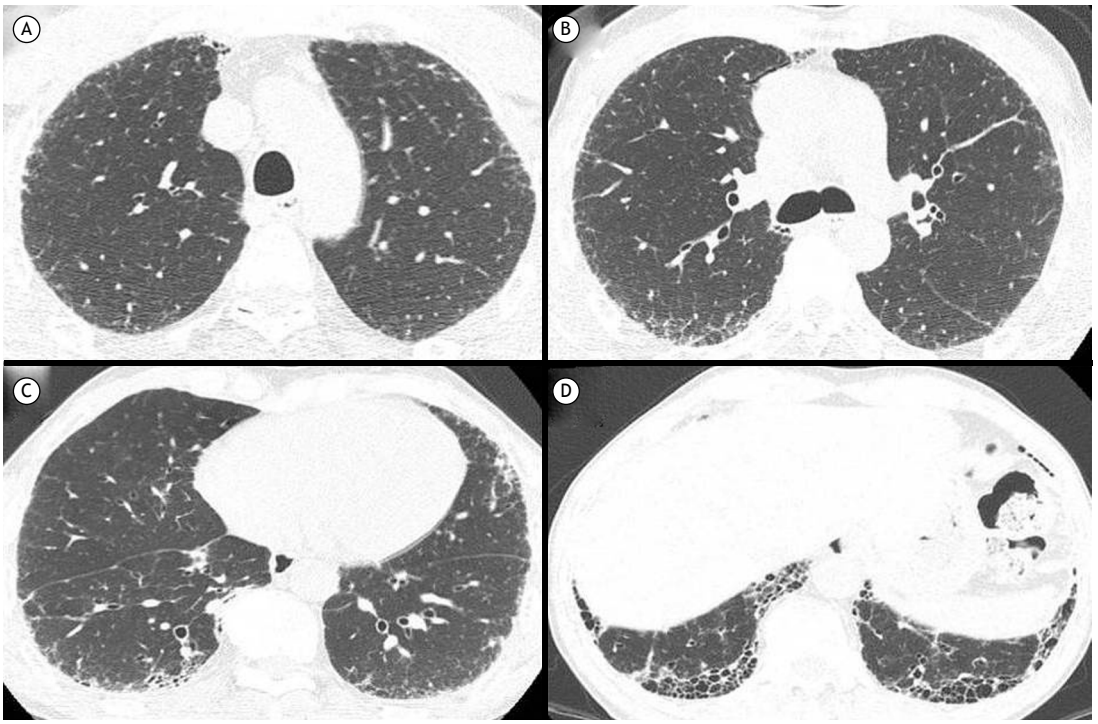


**Figure 1.** Chest HRCT scans showing findings consistent with the pattern of usual interstitial pneumonia: A) discrete subpleural reticular opacities in the upper lobes; B) subpleural reticular opacities and discrete areas of ground-glass abnormalities at the level of the carina; C) peripheral reticular opacities, traction bronchiolectasis, and discrete areas of ground-glass abnormalities predominantly in the lower lobes; and D) peripheral honeycombing and traction bronchiolectasis in the lower lobes.

better approach.[6] The combination of mycophenolate and corticosteroids can also be considered.

The prognosis of patients with ILD associated with ANCA-positive vasculitis has not been fully established. In a study of 49 such patients (82% with MPA), mortality was 34% in the first 60 months after the diagnosis. In a review of 65 patients (85% with a UIP pattern) that were followed for 45 months, 35% showed progression of ILD and the remaining 65% showed stability or improvement,[6] which suggests that the prognosis of ILD associated with ANCA-positive vasculitis is better than is that of IPF.[6]

In conclusion, this report underscores the potential for the occurrence of ILD, including a UIP pattern, in patients with ANCA-positive vasculitis. In that form of vasculitis, interstitial lung involvement can precede systemic manifestations and patients can be initially diagnosed with IPF. We emphasize the importance of an extensive etiological investigation of patients who show a UIP pattern, especially of those in whom the disease has an indolent course. The diagnosis of a secondary cause could facilitate the definition of the best therapeutic strategy and the determination of the prognosis in such patients.

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# Crazy-paving pattern

Bruno Hochhegger[1,2], Roberto Schumacher Neto[1], Edson Marchiori[3,4]

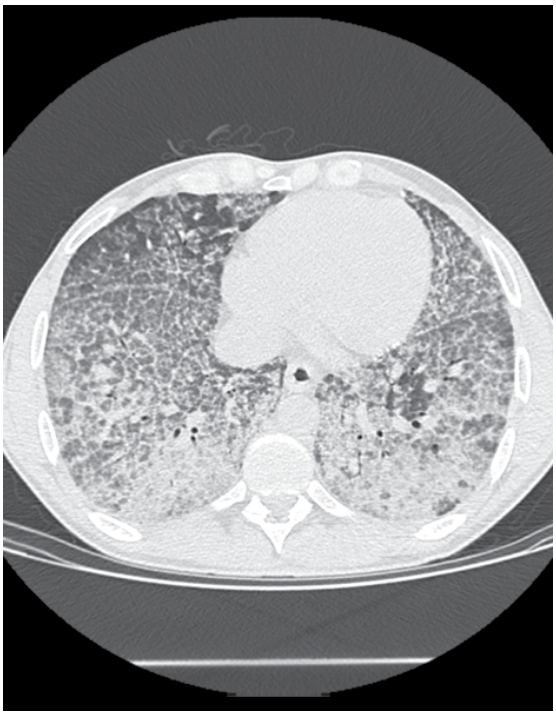

**Figure 1.** Axial CT scan showing extensive areas of ground-glass attenuation and diffuse interlobular septal thickening in both lungs in a patient with pulmonary alveolar proteinosis.

A previously healthy 41-year-old male farmer presented with a seven-month history of progressive dyspnea requiring home oxygen supplementation. He was a smoker (with a smoking history of 45 pack-years). Physical examination revealed mild respiratory distress, bilateral crackles at the lung bases, and an $SpO_2$ of 81% on room air. The patient had no anemia, and his leukocyte count was normal, as were other laboratory test results. An HRCT scan showed extensive areas of ground-glass attenuation, as well as interlobular and intralobular septal thickening, together with areas of consolidation, particularly in the basal and posterior segments (Figure 1).

The aforementioned HRCT findings constitute the crazy-paving pattern, which is characterized by diffuse ground-glass opacities in the lung parenchyma, together with interlobular and intralobular septal thickening.

The crazy-paving pattern is primarily seen in acute and chronic diseases. A specific etiologic diagnosis is generally made by analyzing the temporal evolution of the condition and the clinical and radiological findings.

A crazy-paving pattern associated with chronic progression is primarily due to interstitial pneumonia, which is usually associated with reticular opacities, traction bronchiectasis/bronchiolectasis, and architectural distortion, with or without honeycombing; adenocarcinoma with a lepidic growth pattern, which exhibits slowly progressive growth and is usually accompanied by weight loss, anorexia, and mild cough, being asymptomatic in some cases; lipoid pneumonia, which is often associated with disorders that facilitate chronic aspiration, including esophageal motility disorders and swallowing disorders associated with the use of mineral oil, CT scans showing a crazy-paving pattern predominantly in the posterior and lower lung segments, together with consolidation and fat attenuation; and alveolar proteinosis, which is a rare disease that is characterized by impaired surfactant clearance, resulting in alveolar filling with protein- and lipid-rich material and eliciting an interstitial inflammatory response, which is strongly associated with smoking and, on CT scans, appears as a diffuse but predominantly central crazy-paving pattern associated with chronic progression and, in some cases, well-defined lobular areas of normal lung parenchyma.

In the case reported here (a previously healthy patient with a significant smoking history and a crazy-paving pattern associated with chronic progression), initial working diagnoses included neoplasm and alveolar proteinosis, the latter being confirmed by lung biopsy.

## RECOMMENDED READING

1. Rossi SE, Erasmus JJ, Volpacchio M, Volpacchio M, Franquet T, Castiglioni T, McAdams HP. "Crazy-paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics. 2003;23(6):1509-19. http://dx.doi.org/10.1148/rg.236035101

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# What is survival analysis, and when should I use it?

Juliana Carvalho Ferreira[1,2], Cecilia Maria Patino[2,3]

## INTRODUCTION

Researchers used a national registry of lung cancer patients in the United States to identify the impact of tumor size and histological type on patient survival. They included 7,965 patients treated between 1988 and 2000. As can be seen in Figure 1, they found that survival times were shorter among the patients with larger tumors (> 5 cm) than among those with smaller tumors (< 1 cm).

The misconception that mortality and survival are interchangeable comes from the lay use of the terms. However, in biostatistics, survival is a concept derived from a specific analytical procedure, whereas mortality is a dichotomous outcome variable usually compared between or across two or more groups at a specific time point (for example, at five years). Survival, in turn, deals with a time-to-event variable: it measures the time between the beginning of observation until the occurrence of an event.

## WHY USE SURVIVAL ANALYSIS?

Survival analysis is important when the time between exposure and event is of clinical interest. In our example, five-year survival among patients with tumors < 1 cm was 85%, compared with 52% among those with tumors > 5 cm. Of the patients in that latter group (the high-risk group), approximately half were dead in five years. However, knowing that survival after two years was 70% is also clinically relevant. For highly lethal diseases, like metastatic cancer, a subgroup submitted to a new treatment might have a survival advantage in the first three years but similar mortality after five years. Comparing mortality at the end of the period does not distinguish between longer and shorter survival times.

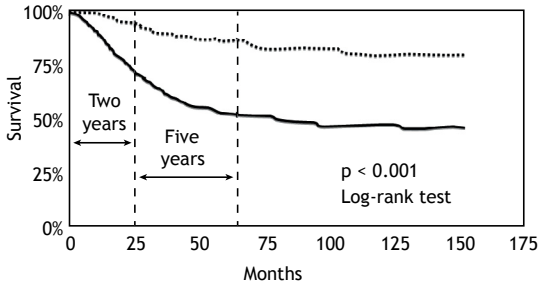


**Figure 1.** Survival for participants with larger tumors (> 5 cm, solid line) and for those with smaller tumors (< 1 cm, dotted line). Adapted from Ost et al. (Recommended reading).

Calculating survival is also useful for methodological reasons; for example, when study participants are lost to follow-up. When the study ends, investigators might not know if a given participant is dead or alive, but they know that he or she was alive at least until their last visit. In addition, some participants might be followed for less than five years because they enter the study at a later date. When the study ends, they might have not experienced the event because their follow-up was interrupted. In Figure 1, it can be seen that survival continues to decrease from two to five years. In survival analysis, data related to participants who did not experience the event by the end of the study or were lost to follow-up are censored: they contribute to the analysis up to the last point at which the investigators knew that the participants were still alive.

Survival analysis uses conditional probability; that is, the probability of surviving up to time *t*, given that a subject was alive at the beginning of a specified time interval. The Kaplan-Meier method is used in order to estimate survival probability at several time intervals and to graphically illustrate survival over time. The log-rank test is a nonparametric test used in comparing survival curves between two or more groups.

## SOME INTERESTING FACTS ABOUT SURVIVAL

In survival analysis, censored data are not the same as missing data. Participants whose data are censored are not excluded and contribute time at risk to the analysis up to the last interval during which they were alive. Therefore, imputation methods are not needed.

Censoring due to loss to follow-up is only acceptable for a small percentage of cases and when the prognosis of participants lost to follow-up is assumed to be the same as those remaining in the study.

The outcome of survival analysis does not have to be time-to-death; it can be other time-to-event outcomes, such as time-to-pregnancy after fertility treatment and time-to-ventilator weaning.

## RECOMMENDED READING

1. Ost D, Goldberg J, Rolnitzky L, Rom WN. Survival after surgery in stage IA and IB non-small cell lung cancer. Am J Respir Crit Care Med. 2008;177(5):516-23. http://dx.doi.org/10.1164/rccm.200706-815OC
2. Glantz SA. How to analyse survival data. In: Glantz SA. Primer in Biostatistics. 7th ed. New York: McGraw-Hill Medical; 2011. p.229-44.

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**Manuscript:** How many patients with idiopathic pulmonary fibrosis are there in Brazil?

**Publication:** J Bras Pneumol. 2015;41(6):560-1.

**DOI:** http://dx.doi.org/10.1590/S1806-37562015000000165

On page 561 of the original publication, right column, first paragraph, lines two to nine, where it is written

"From Table 1, we might assume that the annual incidence of IPF cases is between 6,841 and 9,997 cases/100,000 population, whereas its prevalence ranges between 13,945 and 18,305 cases/100,000 population. Because IPF is quite rare in young people, if we limit the analysis only to the ≥ 55-year age bracket, the projected prevalence might be between 9,986 and 16,109 cases/100,000 population."

it should read

"From Table 1, we might assume that the annual incidence of IPF is between 6,841 and 9,997 cases (3.5-5.1/100,000 population), whereas its prevalence ranges between 13,945 and 18,305 cases (7.1-9.4/100,000 population). Because IPF is quite rare in young people, if we limit the analysis only to the ≥ 55-year age bracket, the projected prevalence might be between 9,986 and 16,109 cases (5.1-8.3/100,000 population)."



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**Manuscript:** Cost analysis of nucleic acid amplification for diagnosing pulmonary tuberculosis, within the context of the Brazilian Unified Health Care System

**Publication:** J Bras Pneumol. 2015;41(6):536-8.

**DOI:** http://dx.doi.org/10.1590/S1806-37562015000004524

On page 536 of the original publication, where it is written

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it should read

Márcia Pinto, Aline Piovezan Entringer, Ricardo Steffen, Anete Trajman.



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J Bras Pneumol. 2016;42(1):80-80
http://dx.doi.org/10.1590/S1806-37562016000000095errata



**Manuscript:** Bronchiectasis caused by common variable immunodeficiency

**Publication:** J Bras Pneumol. 2015;41(5):482-3.

**DOI:** http://dx.doi.org/10.1590/S1806-37132015000000095

On page 482 of the original publication, where it is written

Paulo Henrique do Amor Divino, José Henrique de Carvalho Basilio, Renato Moraes Alves Fabbri, Igor Polônio Bastos, Wilma Carvalho Neves Forte,

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Whenever the authors mention any substance or uncommon piece of equipment they must include the catalogue model/number, name of manufacturer, city and country of origin. For example:

"... ergometric treadmill (model ESD-01; FUNBEC, São Paulo, Brazil) ..."

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"... guinea pig liver tTg (T5398; Sigma, St. Louis, MO, USA) ..."

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**Abstract:** The abstract should present the information in such a way that the reader can easily understand without referring to the main text. Abstracts should not exceed 250 words. Abstracts should be structured as follows: Objective, Methods, Results and Conclusion. Abstracts for review articles and case reports may be unstructured.

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National Library of Medicine Medical Subject Headings (MeSH), available at: http://www.nlm.nih.gov/mesh/MBrowser.html.

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**Letters to the Editor:** Letters to the Editor should be succinct original contributions, not exceeding 800 words and containing a maximum of 6 references. Comments and suggestions related to previously published materials or to any medical theme of interest will be considered for publication.

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**Tables and Figures:** All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, TIFF or JPG files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which staining and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available at: http://www.abnt.org.br.

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**Examples: Journal Articles**

1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

**Abstracts**

2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

**Chapter in a Book**

3. Queluz T, Andres G. Goodpasture's syndrome. In: Roitt IM, Delves PJ, editors. Encyclopedia of Immunology. 1st ed. London: Academic Press; 1992. p. 621-3.

**Official Publications**

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

**Theses**

5. Martinez TY. Impacto da dispnéia e parâmetros funcionais respiratórios em medidas de qualidade de vida relacionada a saúde de pacientes com fibrose pulmonar idiopática [thesis]. São Paulo: Universidade Federal de São Paulo; 1998.

**Electronic publications**

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

**Homepages/URLs**

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

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In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.

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## NACIONAIS

**XVII Curso Nacional de Atualização em Pneumologia**
Data: 21 a 23 de abril de 2016
Local: São Paulo/SP
Informações: eventos@sbpt.org.br
Fone: 0800 61 6218

**VII Curso Nacional de Ventilação Mecânica**
**IV Curso Nacional de Sono**
Data: 18 a 20 de agosto de 2016
Local: São Paulo/SP
Informações: eventos@sbpt.org.br
Fone: 0800 61 6218

**Curso de Imersão em Pneumologia**
Data: 17 a 18 de junho de 2016
Local: SERHS Natal Grand Hotel – Natal/RN
Informações: eventos@sbpt.org.br
Fone: 0800 61 6218

## INTERNACIONAIS

**ATS 2016**
Data: 13 a 18 de maio de 2016
Local: San Francisco/CA-USA
Informações: www.thoracic.org

**SEPAR 2016**
Data: 10 a 13 de junho de 2016
Local: Granada/Espanha
Informações: www.separ.es

**ALAT 2016**
Data: 06 a 09 de julho de 2016
Local: Centro de Convenções Casa Piedra, Santiago/Chile
Informações: https://www.congresosalat.org/

**ERS 2016**
Data: 03 a 07 de setembro de 2016
Local: Londres, Reino Unido
Informações: www.ersnet.org

# 7 PESSOAS MORREM DE ASMA POR DIA, NO BRASIL.[2]


# Clenil® HFA

## dipropionato de beclometasona

O tratamento da asma ao alcance de todos[1]

- Reduz os sintomas e controla a inflamação[3]
- Pode ser usado em combinação com broncodilatadores de curta ação, conforme o GINA preconiza[4]

**COMODIDADE POSOLÓGICA:**[5]

**ADULTOS:**

**200 mcg - 1 dose, 2-4 X ao dia**

250 mcg - 2 doses, 2-4 X ao dia

250 mcg Jet® - 2 doses, 2-4 X ao dia

**CRIANÇAS:**

50 mcg - 2 doses, 2-4 X ao dia

NOVIDADE


AQUI TEM FARMÁCIA POPULAR

**Custo Zero para seu paciente**[1]

**Referências Bibliográficas: 1-** Ministério da Saúde. Gabinete do Ministro. Portaria nº 1.146, de 1 de junho de 2012. Altera e acresce dispositivos à Portaria nº 971/GM/MS, de 17 de maio de 2012, para ampliar a cobertura da gratuidade no âmbito do Programa Farmácia Popular do Brasil. DOU, Brasília, DF, 4 de junho de 2012,. P72-73. **2-** http://portaldasaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/noticias-anteriores-agencia-saude/2740. **3-** Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o manejo da asma - 2012. J. Bras Pneumo. 2012; 38 (supl. 1) S1-S46. **4-** Global Strategy for asthma management and prevention. GINA 2014. **5-** Bula do medicamento Clenil® HFA.

**Clenil® HFA** dipropionato de beclometasona. **USO ADULTO E PEDIÁTRICO** (somente a apresentação de 50 mcg). **COMPOSIÇÃO, FORMA FARMACÊUTICA E APRESENTAÇÕES:** Solução pressurizada para inalação (aerossol). Clenil® HFA Spray 50, 200 e 250 mcg: aerossol com 200 doses. Clenil® HFA Jet® 250 mcg: aerossol com 200 doses. **INDICAÇÕES:** tratamento e prevenção da asma brônquica e bronquite, bem como nos processos inflamatórios das vias aéreas superiores. **CONTRAINDICAÇÕES:** hipersensibilidade individual aos derivados corticosteroides, hipersensibilidade ao álcool ou a qualquer outro constituinte desta formulação, tuberculose pulmonar, herpes simples ou crises asmáticas. **CUIDADOS E ADVERTÊNCIAS:** como todo corticoide inalatório, Clenil® HFA deve ser utilizado com cautela em pacientes com tuberculose ativa ou latente e infecção fúngica, bacteriana ou viral das vias aéreas. Também utilizar com cautela em pacientes portadores de anormalidades pulmonares como bronquiecstasia e pneumoconiose, uma vez que as mesmas estão relacionadas com maior susceptibilidade à infecções fúngicas. **Uso em idosos, crianças e outros grupos de risco:** como qualquer outro medicamento recomenda-se atenção especial na administração em pacientes idosos. O tratamento de pacientes com anomalias pulmonares como bronquiectasia e pneumoconiose, com a possibilidade de infecções fúngicas, deve ser restrito. **Administração durante a gravidez ou aleitamento:** em mulheres grávidas, o medicamento deve ser utilizado no caso de efetiva necessidade e sob supervisão médica. O uso do dipropionato de beclometasona em mães amamentando requer que os benefícios da terapêutica sejam levados em consideração frente aos riscos para mãe e lactente. **Interações medicamentosas:** os pacientes devem ser avisados que o medicamento contém pequena porcentagem de álcool e glicerol. Em doses normais, não há risco para os pacientes. Há um potencial teórico de interação particularmente em pacientes sensíveis a álcool utilizando dissulfiram ou metronidazol. **Reações adversas/Efeitos colaterais:** candidíase na boca e garganta, rouquidão e irritação na garganta, rash cutâneo, urticária, prurido, eritema, efeitos colaterais sistêmicos (supressão da adrenal, retardo no crescimento de crianças e adolescentes, diminuição da densidade mineral óssea, catarata, glaucoma), edema de olhos, faces, lábios e garganta, broncoespasmo paradoxal, chiado, dispneia, tosse, hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão, agressividade, mudanças comportamentais (predominantemente em crianças), dor de cabeça, náusea. **POSOLOGIA: Clenil® HFA 50 mcg: Crianças:** a dose usual inicial é de 100 mcg a 400 mcg, de 12 em 12 horas. Dependendo da severidade da condição asmática, a dose diária pode ser fracionada de 8 em 8 horas ou ainda de 6 em 6 horas. **Adultos (incluindo os idosos):** A dose inicial usual é de 200 mcg a 800 mcg, (4 jatos) de 12 em 12 horas. A dose total diária pode ser dividida em tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Clenil® HFA 200 mcg: Crianças:** NÃO DEVE SER UTILIZADO POR CRIANÇAS. **Adultos (incluindo os idosos):** A dose inicial do produto é de 200 mcg (um jato), de 12 em 12 horas. De acordo com a necessidade do paciente, pode-se prescrever doses mais altas (até 4 jatos por dia). A dose total diária deve ser dividida em tomadas de 12 em 12 horas, tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Clenil® HFA 250 mcg: Crianças:** NÃO DEVE SER UTILIZADO POR CRIANÇAS. **Adultos (incluindo os idosos):** A dose inicial do produto é de 2 jatos (500 mcg), de 12 em 12 horas. Dependendo da severidade da doença, doses mais altas (até 8 jatos por dia) podem ser divididas em tomadas de 12 em 12 horas ou tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Pacientes com insuficiência renal ou hepática:** Nenhum ajuste de dose é necessário. **VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** Reg. M.S.: 1.0058.0111. SAC: 0800-114 525. www.chiesi.com.br

**INTERAÇÕES MEDICAMENTOSAS:** Há um potencial teórico de interação particularmente em pacientes sensíveis a álcool utilizando dissulfiram ou metronidazol. **CONTRAINDICAÇÕES:** hipersensibilidade individual aos derivados corticosteroides, hipersensibilidade ao álcool ou a qualquer outro constituinte desta formulação, tuberculose pulmonar, herpes simples ou crises asmáticas.

Material destinado exclusivamente à classe médica

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Chiesi
People and ideas for innovation in healthcare

Fevereiro/2016

# UMA NOVA ESPERANÇA NO TRATAMENTO DA FIBROSE PULMONAR IDIOPÁTICA[1]

**Aprovado pela ANVISA OFEV® (Nintedanibe) para o tratamento de pacientes com FPI**

**OFEV® retarda a progressão da doença através da redução do declínio anual da CVF em aproximadamente 50%, em diversos perfis de pacientes incluindo:[2]**

— Com doença inicial (CVF >90% do predito)
— Sem faveolamento em TCAR
— Com enfisema concomitante

Adaptado de Richeldi et al, 2014.

**INPULSIS®-1**


**INPULSIS®-2**


**Além disso, OFEV® demonstrou reduzir em 68% o risco de exacerbações adjudicadas.***

**OFEV® (Esilato de nintedanibe) -** uso adulto. **Apresentação:** cápsulas de 100 mg e 150 mg - embalagens com 60 cápsulas moles. Indicação: tratamento e retardo da progressão da fibrose pulmonar idiopática. **Contraindicações:** em casos de hipersensibilidade conhecida ao nintedanibe, amendoim, soja, ou a qualquer excipiente do produto e durante a gravidez. **Reações adversas:** diarreia, náuseas e vômitos, dor abdominal, diminuição do apetite, perda de peso e aumento das enzimas hepáticas. **Precauções:** diarreia deve ser tratada com hidratação adequada e medicamentos antidiarreicos (como loperamida) e pode exigir a redução da dose ou interrupção do tratamento; se vômitos persistirem mesmo com tratamento de suporte adequado (incluindo terapia antiemética), pode ser necessário reduzir ou interromper o tratamento. Valores de transaminases hepáticas e bilirrubina séricas devem ser investigados antes do início do tratamento, periodicamente ou quando clinicamente indicado. Não deve ser usado em pacientes com insuficiência hepática moderada e grave. Tratar pacientes com maior risco cardiovascular, incluindo doença arterial coronária conhecida, requer cuidados. A interrupção do tratamento deve ser considerada em pacientes com sinais ou sintomas de isquemia miocárdica aguda. Pacientes com risco conhecido para sangramento somente devem ser tratados se o benefício superar o risco. Não deve ser usado em gestantes, pois pode causar dano fetal (categoria D), ou lactantes. Recomenda-se o uso de métodos contraceptivos adequados (preservativos) durante pelo menos até 3 meses após a última dose. Não há indicação do uso em crianças e adolescentes. **Interações:** O uso dos seguintes medicamentos podem aumentar ou reduzir o efeito do tratamento com nintedanibe: cetoconazol, eritromicina, rifampicina, carbamazepina, fenitoína e erva-de-são-joão. **Posologia:** 150 mg por via oral de 12 em 12hs junto com água e alimentos. Ajustes de dose: além do tratamento sintomático, o manejo dos efeitos colaterais de pode incluir a redução da dose (para 100 mg duas vezes ao dia) ou a interrupção temporária. Havendo esquecimento da dose, não tomar uma dose adicional. Não se deve exceder a dose diária máxima recomendada de 300 mg. NECESSIDADE DE REFRIGERAÇÃO (conservar entre 2° C e 8° C) e na embalagem original para proteger da umidade. Bula aprovada pela ANVISA em 26/10/2015. **OFEV® É UM MEDICAMENTO, SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. VENDA SOB PRESCRIÇÃO MÉDICA. MS 1.0367.0173.** Boehringer Ingelheim do Brasil Química e Farmacêutica Ltda. Rod. Regis Bittencourt (BR116), km 286. Itapecerica da Serra – SP. CNPJ /MF nº 60.831.658/0021-10, Indústria Brasileira. SAC 0800-7016633. Se persistirem os sintomas, o médico deverá ser consultado.

Referências: 1. Gary M. Hunninghake, A New Hope for Idiopathic Pulmonary Fibrosis. N Engl J Med 2014; 370:2142-2143 2. Richeldi L et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. N Engl J Med 2014;370:2071-82.

**CONTRAINDICAÇÃO:** EM CASOS DE HIPERSENSIBILIDADE CONHECIDA AO NINTEDANIBE, AMENDOIM OU SOJA. **INTERAÇÃO MEDICAMENTOSA:** CETOCONAZOL OU ERITROMICINA PODEM AUMENTAR A EXPOSIÇÃO AO NINTEDANIBE.

FPI: Fibrose Pulmonar Idiopática
CVF: Capacidade Vital Forçada
TCAR: Tomografia Computadorizada de Alta Resolução
*Exacerbações adjudicadas: exacerbações agudas relatadas pelos investigadores e que foram confirmadas por um comitê de adjudicação cego em uma análise de sensibilidade pré-especificada.

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