

confirm anatomical continuity between the tumor and the renal vein and the vena cava. Treatment of choice is surgery, and outcome in the absence of intervention is poor. In the case reported here, it was difficult to confirm anatomical continuity since the patient had undergone hysterectomy and double adnexectomy 2 years previously. The prognosis of endometrial stromal sarcoma is good, and its evolution and behavior cannot be compared to the considerably more aggressive renal cancer.

In the case of IVC and intracardiac thrombi, surgery is recommended for excision of the tumor thrombosis, with or without IVC resection, in order to prevent sudden death due to pulmonary embolism or the development of congestive heart failure or death due to acute valvular obstruction.⁴ We did not find any published cases of patients treated with anticoagulation only.

To conclude, it is safe to say that although surgery is the treatment of choice for IVC and/or intracardiac tumor thrombosis, for patients with advanced or inoperable disease or those who refuse surgery, chronic anticoagulation may also be a valid treatment option. In our view, there are probably many cases in which tumor thrombosis coexists with non-tumor thrombosis: it is easy to imagine that a lumen occupied by a tumor will favor the development of non-tumor thrombosis. This would explain the almost complete resolution of our case with anticoagulant treatment.

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Francisco Javier Garcipérez de Vargas,^{a,*} Gonzalo Marcos,^a
Sergio Luis Moyano Calvente^b

^a Servicio de Cardiología, Hospital San Pedro de Alcántara, Cáceres, Spain

^b Servicio de Radiología, Hospital San Pedro de Alcántara, Cáceres, Spain

* Corresponding author.

E-mail address: fj.garci@hotmail.com (F.J. Garcipérez de Vargas).

S1455X CFTR Mutation and Upper Airway Colonization With *Pseudomonas aeruginosa*[☆]



Mutación S1455X del CFTR y colonización de vías aéreas altas por *Pseudomonas aeruginosa*

To the Editor:

Cystic fibrosis (CF) is a classic example of an autosomal recessive genetic disorder, and multiple variant forms of this disease have been identified. It is caused by CF transmembrane conductance regulator (CFTR) dysfunction resulting from CFTR gene mutations. Not all CFTR mutations are associated with disease expression. The S1455X mutation is very uncommon (0.22% prevalence in our patient population). Individuals with this mutation have only very mild symptoms, if any. We present the first report of twin brothers, both S1455X mutation-carriers, with *Pseudomonas aeruginosa* colonization of the upper airways.^{1–4}

Patients A and B are 2-year-old monozygotic twin brothers. After birth, patient A was admitted to the neonatal intensive care unit for 7 days due to mild breathing difficulties. Routine neonatal immunoreactive trypsinogen screening results were close to the upper limit of normal (65 mcg/l; normal value <77 mcg/l). When patient A was 7 months old he suffered bronchitis, for which he received inhaled albuterol and fluticasone. At the age of 13 months, he was admitted to a pediatric intensive care unit with lethargy due to severe hyponatremic dehydration and hypochloremic and hypokalemic metabolic alkalosis. At that time a definitive diagnosis of CF was given (chloride sweat levels of 101.6 mEq/l and 105.8 mEq/l; mutations: F508del and S1455X). The patient has pancreatic sufficiency and normal growth (weight: 75th–90th percentile; height: 90th percentile). Serial pharyngeal swab cultures grew *Pseudomonas aeruginosa*.

Following his brother's diagnosis, at the age of 13 months patient B was also diagnosed with CF (chloride sweat levels:

80.7 mEq/l and 81.7 mEq/l, mutations: F508del and S1455X). Similarly, he has pancreatic sufficiency and good growth (weight, 50th percentile; height: 75th percentile). Repeated pharyngeal swab cultures grew *Pseudomonas aeruginosa*.

The case of these two brothers suggests that the S1455X mutation of the CFTR gene in combination with the F508del mutation may be associated with early *Pseudomonas aeruginosa* colonization of the upper airways. This observation has not been previously reported in the literature. In other reported cases of S1455X CFTR mutation, the sweat test was abnormal, but no respiratory disorders were detected.^{1,2} Only one case of a child with mild pulmonary disease due to *Haemophilus influenzae* infection and persistent hyponatremia during a heat wave has been described.³

S1455X is a nonsense mutation causing premature transcriptional termination of CFTR. More specifically, the codon for serine at residue 1455 is replaced by a stop codon, hence the designation S1455X.¹ In the initial description from Mickle et al.,¹ the S1455X mutation was associated with isolated elevated chloride levels in sweat. *In vitro* testing predicted preserved CFTR function in lung and pancreatic cells.¹ Subsequently, Moyer et al.⁴ suggested that the CFTR-S1455 chloride channel defect was caused by mispolarization to the lateral membrane instead of to the apical membrane.

The two cases previously described in the literature as compound heterozygotes for the F508del and S1455X mutations presented a mild phenotype in the sense that S1455X was associated with minor symptoms and a favorable prognosis, even when accompanied by such a severe mutation as F508del.^{2,3} Although our pediatric patients are carriers of this same genotype, they appear to have a more severe clinical presentation than that predicted by other authors, leading us to speculate on the possibility of a predominant F508del mutation. Our cases underline the concept of a variable correlation between the CF genotype and phenotype.

Authorship

Efthimia Kalampouka and Argyri Petrocheilou participated equally in the authorship of this letter.

[☆] Please cite this article as: Kalampouka E, Petrocheilou A, Kaditis AG, Doudounakis SE. Mutación S1455X del CFTR y colonización de vías aéreas altas por *Pseudomonas aeruginosa*. *Arch Bronconeumol*. 2014;50:499–500.

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Efthimia Kalampouka,^a Argyri Petrocheilou,^{a,*}
Athanasios G. Kaditis,^b Stavros-Eleftherios Doudounakis^a

^a Cystic fibrosis Center, Agia Sophia Children's Hospital, Atenas, Greece

^b First Department of Pediatrics, University of Athens Medical School, Agia Sophia Children's Hospital, Atenas, Greece

* Corresponding author.

E-mail address: apetroch@gmail.com (A. Petrocheilou).

Effect of Drug-Targeting Nebulization on Lung Delivery[☆]



Efecto de la nebulización dirigida de fármacos en la administración pulmonar

To the Editor:

It has been difficult to develop more effective nebulizers for the improved delivery of drugs directly to the lungs. Adaptive nebulizers were designed for the administration of drugs at a specific time during inspiration, depending on the intended target (drug-targeting nebulization). Controlled inhalation nebulizers, such as AKITA[®], have recently become another addition to adaptive aerosol delivery systems.¹ The aim of our study was to measure the inhaled dose and pulmonary bioavailability obtained from drug-targeting nebulization, compared to conventional continuous nebulization.

We used the AKITA[®] delivery device (Activaero; Germany) that provides individualized, controlled flow and inhalation volumes in several puffs. Aerosolized drug delivery was either continuous or targeted (Fig. 1) during each 4-s controlled inhalation. The number of inhalations was 43 or 86, respectively.

The inhaled dose of a solution of amikacin (125 mg/ml) was measured *in vitro* using a residual gravimetric method.² Five healthy non-smoking male volunteers (mean age 27.8 ± 4.7 years) were selected, and approval was obtained from the ethics committee.

Subjects were randomized to receive a solution of salbutamol (GlaxoSmithKline, Belgium) (625 mg/ml) *via* continuous or targeted nebulization.

Subjects swallowed 100 ml of activated charcoal before and after nebulization (Carbomix, Norit, Netherlands). Urine samples were obtained before nebulization and 30 min after (Cu-30), and then from each spontaneous micturition and 240 min (Cu-240) after the start of nebulization. The volume of each micturition was measured.

Salbutamol levels in urine were measured in triplicate by HPLC.³ The amount of salbutamol excreted in urine (Cu) was calculated by multiplying the concentration by the volume of each sample. Pulmonary bioavailability was compared using the Cu-30 sample.

Mean anthropometric and spirometric values were as follows: height 177.6 ± 8.8 cm and weight 80.0 ± 19.6 kg, FVC 103.7% ± 16.8% of the predicted value and FEV1 100.3% ± 14.5% of the predicted value.

[☆] Please cite this article as: Reyhler G, Aubriot AS, Masquelier J, Muccioli GG, Liistro G. Efecto de la nebulización dirigida de fármacos en la administración pulmonar. *Arch Bronconeumol.* 2014;50:500–501.

The inhaled dose was not significantly different (15.8% versus 16.5%, respectively, $p=0.975$) but the amount of drug delivered with the continuous nebulization method was twice that of the targeted method ($p<0.001$).

The excreted amounts of salbutamol are summarized in Table 1. Cu-30 was similar for both delivery systems ($p=0.947$). The accumulated amount of salbutamol excreted in urine was significantly higher with the targeted nebulization system ($p<0.05$).

Pulmonary bioavailability of nebulized salbutamol is a reproducible measurement for predicting drug deposition in the lung⁴ and for determining the amount of drug that is provided to the body *via* the pulmonary route and rapidly excreted in the urine. Concentrations may be overestimated in healthy individuals,⁵ but this does not affect the comparison of the delivery methods. Our results

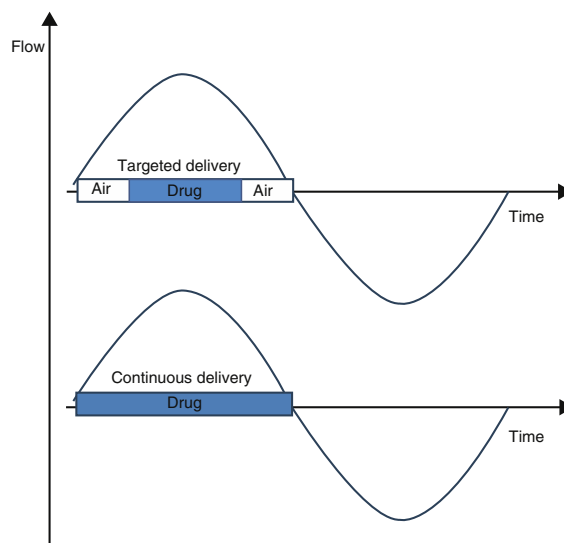


Fig. 1. Nebulization delivery modes during one inspiratory cycle.

Table 1

Excreted Salbutamol (mcg) Retrieved After Nebulization With the Continuous or Discontinuous Delivery System in 5 Healthy Individuals.

	Continuous	Discontinuous
Cu-30	36.69 ± 31.56	35.56 ± 28.39
Cu-60	30.59 ± 15.63	51.72 ± 37.24
Cu-240	51.08 ± 25.87	84.89 ± 36.47
Accumulative amount	118.36 ± 47.77	172.18 ± 46.82 [*]

Results expressed as mean ± standard deviation.

^{*} $p<0.05$.