Pragmatic Approach to Small Airways Diagnostics

Pragmatična dijagnostika malih disajnih puteva

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SUMMARY Small airways have an inner diameter of 2 mm or less. They are characterized by lack of cartilage in their wall, sudden increase in total cross-section area, and by an abrupt switch from turbulent to laminar air flow, all of which cause minimal airflow resistance in healthy persons. Conversely, in patients with obstructive lung diseases, small airways are the primary site of airflow limitation. Small airways tests are numerous and they vary considerably in their diagnostic significance, complexity and availability. Currently, none of the existing tests represents the diagnostic "gold standard", and none offer precise cut-off values to distinguish between small airway disease, healthy persons, and individuals with concomitant pathophysiological disorder. Negative results of these tests have significant negative predictive values, i.e. ruling out small airways as the cause of the clinical issue, while positive results of these tests should always be crosschecked to confirm the presence of small airways disorder by other methods. Results of small airways diagnostic tests do not mean much as isolated findings unless they are combined with other diagnostic methods (history, clinical findings, imaging, etc.) to elucidate any specific clinical case. On the other hand, if results are strongly suggestive of the presence of a small airways disease, that can have significant clinical implications, such as application of fine particle aerosols. The suggested diagnostic algorithm is based primarily on tests availability. It should not be implemented uncritically, but rather adapted to the healthcare system at hand.

KEY WORDS: small airways, diagnostic approach

SAŽETAK Mali disajni putevi se definišu kao disajni putevi promera 2 mm ili manjeg. Odlikuju se odsustvom hrskavice u svom zidu, naglim povećanjem ukupnog poprečnog preseka i prelaskom turbulentnog toka vazduha u laminarni, tako da je kod zdravih ljudi u njima minimalan otpor protoku vazduha. Za razliku od toga, u opstruktivnim bolestima pluća mali disajni putevi predstavljaju glavno mesto ograničenja protoka vazduha. Testovi koji se koriste u dijagnostici promena u malim disajnim putevima su brojni i oni značajno variraju u svojoj dijagnostičkoj vrednosti, složenosti i dostupnosti. Trenutno ne postoji test koji predstavlja zlatni standard u dijagnostici bolesti malih disajnih puteva, niti test sa jasnim graničnim vrednostima pomoću kojih bi se mogle razlikovati osobe sa poremećajem funkcije malih disajnih puteva i „zdrave" osobe, odnosno osobe s pridruženim patofiziološkim poremećajima. Negativni rezultati ovih testova mogu sa velikom sigurnošću ukazati na to da mali disajni putevi ne igraju ulogu u datom kliničkom problemu, dok bi pozitivne rezultate pojedinačnih testova trebalo uvek proveriti različitim metodama da bi se potvrdilo prisustvo poremećaja u malim disajnim putevima. Rezultati dijagnostičkih testova za male disajne puteve sami po sebi ne znače mnogo ako se ne kombinuju s drugim metodama i ne uklope u dati klinički problem (anamnestički podaci, klinička slika, vizualizacioni metodi i drugo). S druge strane, ako rezultati ovih testova definitivno ukažu na problem u malim disajnim putevima, to može imati značajne kliničke implikacije, na primer, primenu aerosola sa finim česticama u lečenju. Predloženi algoritam kao osnovni kriterijum uzima dostupnost dijagnostičkih testova. Ovaj algoritam ne treba smatrati definitivnim rešenjem, već ga uvek treba prilagoditi postojećem zdravstvenom sistemu.

KLJUČNE REČI: mali disajni putevi, dijagnostički pristup

For over 50 years small airways have been the focus of respiratory medicine, ever since the paper published by Hogg et al. (1), proving that small airways are the main site of pathophysiological changes in obstructive pulmonary diseases, particularly chronic obstructive pulmonary disease (COPD).

Small airways are defined as those with a diameter of 2 mm or less. They make up airways of seven generations of branching (2). They are characterized with absence of

Više od 50 godina mali disajni putevi su u centru pažnje respiratorne medicine, još od rada Hogga i sar. (1), u kome su pokazali da su upravo oni glavno mesto patofizioloških promena u opstruktivnim bolestima pluća, posebno hroničnoj opstruktivnoj bolesti pluća (HOBP).

Mali disajni putevi se definišu kao disajni putevi promera 2 mm ili manjeg. Oni čine disajne puteve od sedam generacija grananja (2). Odlikuju se odsustvom hrskavice u svom zidu, naglim povećanjem ukupnog poprečnog preseka i

cartilage in the wall, sudden increase in the total cross-section area, and by the switch from turbulent to laminar air flow. The first feature contributes to collapsibility of the airways and eventually their closure towards the end of the expiratory phase (3), while the remaining two result in minimum resistance to airflow in the airways.

In obstructive pulmonary diseases, the small airways are the primary site of airflow resistance. In cases of asthma, inflammation of the small airways and their dysfunction significantly affect severity of the disease and can play an important role in some phenotypes (4). In COPD the small airways are impaired by inflammation manifested as obstructive bronchiolitis associated with parenchymal lesions in the form of emphysema. Small airways in COPD suffer major remodeling during progression of the disease (4).

Although the importance of small airways in pathogenesis and pathophysiological processes in obstructive pulmonary diseases has been recognized for years, there are still no specific functional tests to determine their functionality; precise non-invasive investigations of their morphology has become available only recently.

There are a number of diagnostic tests investigating changes in the small airways, and they can roughly be divided into functional and imaging methods. They vary significantly in their diagnostic value, complexity, accessibility and price, so that their use in routine practice depends on all of the listed parameters, but having the widespread nature of the issue, accessibility remains the key issue (Table 1).

prelaskom turbulentnog toka vazduha u laminarni. Prva karakteristika doprinosi njihovoj kolapsibilnosti i, na kraju, zatvaranju pri kraju ekspirijuma (3), dok ostale dve dovode do minimalnog otpora protoku vazduha u njima.

U opstruktivnim bolestima pluća mali disajni putevi predstavljaju glavno mesto ograničenja protoka vazduha. U astmi inflamacija u malim disajnim putevima i poremećaji njihove funkcije značajno utiču na težinu bolesti, a mogu imaju važnu ulogu u pojedinim fenotipovima bolesti (4). U HOBP-u prisutno je inflamacijsko oštećenje malih disajnih puteva u vidu opstruktivnog bronhiolitisa koje je udruženo sa oštećenjem parenhima u vidu emfizema. Mali disajni putevi u HOBP-u podložni su značajnom remodelovanju tokom progresije bolesti (4).

I pored toga što je značaj malih disajnih puteva u patogenezi i patofiziološkim procesima u opstruktivnim bolestima pluća poznat već dugi niz godina, još ne postoje dijagnostički testovi koji su specifični za njihovu funkciju, dok je precizno neinvazivno ispitivanje njihove morfologije moguće tek u poslednje vreme.

Testovi koji se koriste u dijagnostici promena u malim disajnim putevima su brojni i suštinski se mogu podeliti na testove njihove funkcije i vizualizacione metode. Oni značajno variraju u svojoj dijagnostičkoj vrednosti, složenosti, dostupnosti i ceni, tako da njihova primena u svakodnevnoj praksi zavisi od svih ovih navedenih parametara, ali prvenstveno, s obzirom na rasprostranjenost problema, od dostupnosti (tabela 1.)

TABLE 1. Diagnostics of small airways

TEST	PRECISION	ACCESSIBILITY
Flow measurement • Spirometry	++	+++
Volume measurement • Spirometry • Body plethysmography • Helium dilution	++ ++ +	+++ ++ ++
Airway resistance measurement • Body plethysmography • Impulse oscillometry	+ +++	++ ++
Gas elimination methods • Single-breath nitrogen washout • Multiple-breath nitrogen washout • Capnography	++ +++ +	+ + +
Alveolar nitrogen monoxide fraction in exhaled air	+	+
Imaging methods • Dynamic or static high resolution computerized tomography of the thorax • Magnetic resonance imaging	+++ ++	++ +

The role of pulmonary function tests (except for imaging methods) in diagnostics of disorders on the small airway level will be discussed below.

Spirometry

Spirometry is the most widely used and most accessible pulmonary function test. Changes in the small airways can be detected in expiratory flows and pulmonary volumes.

The flow-volume curve can have a so-called obstructive pattern, characterized with concave shape of the part not depending on exertion, while the values of FEV_1 and FEV_1/FVC ratio can remain within the normal range. Unfortunately, the concave shape of the flow/volume curve is not easily quantifiable (5). It is believed that FEV_1 values below the "normal" range may suggest changes in the small airways even if the FEV_1/FVC ratio remains within the normal range (6).

Most commonly used spirometric parameters for the evaluation of small airways function include forced expiratory flow at 50% FVC (FEF_{50}) and mean expiratory flow between 25% and 75% FVC (FEF_{25-75}). Both parameters are in the expiration part of the flow-volume curve that is not dependent on exertion (7). Most commonly, the small airway disease is functionally defined as FEF_{50} or FEF_{25-75} below the normal range, where the values of FEV_1–FVC and FEV_1 remain within the normal range (7). It is believed that the lower cutoff value of the normal FEF_{25-75} is 60% of the predicted value (8). However, the FEF_{25-75} values significantly depend on FVC, so that this parameter has a diagnostic value for small airways disease only if the FVC value remains within the normal range (9). It is also very difficult to measure the impact of reduced flow through small airways on FEV_1 reduction not only in cases of actual FVC impairment, but in cases of diffuse bronchial obstruction, as well. Further, the use of this parameter in clinical practice is additionally limited by marked physiological variability (10), making it impossible to differentiate between "normal" and "abnormal" findings, by absence of correlation between FEF_{25-75} values and hyperinflation parameters (11) as well as with structural changes in the small airways (12).

FVC is a parameter that marks the moment when most of the small airways have collapsed due to dynamic compression, so that its value can be used for indirect determination of the moment of their closure and level of air trapping (13). Namely, reduction of FVC implies an increase of the residual volume (RV), i.e. increased air trapping due to early closure of small airways. Nevertheless, the predicted value of FVC implies that the total lung capacity (TLC) is in the normal range. In case of TLC increase, such as the case of marked emphysema, reduction of FVC is lower than it should be for the given increase of RV, and in such a case, FVC is a poorer indicator of the air trapping level. It is believed that

U daljem tekstu razmatraće se uloga testova plućne funkcije u dijagnostici poremećaja na nivou malih disajnih puteva, bez posebnog osvrta na vizuelizacione metode.

Spirometrija

Spirometrija je najrasprostranjeniji i najdostupniji test ispitivanja plućne funkcije. Promene u malim disajnim putevima mogu se detektovati promenama u ekspiratornim protocima, kao i promenama u plućnim volumenima.

Kriva protok–volumen može imati tzv. opstruktivni izgled, koji se karakteriše konkavnošću dela krive koji nije zavistan od napora, a da pritom vrednosti FEV_1 i odnosa FEV_1/FVC mogu biti i u normalnom opsegu. Nažalost, nije lako kvantifikovati ovu konkavnost krive protok–volumen (5). Smatra se da vrednosti FEV_1 manje od donje granice „normalnih" vrednosti mogu ukazati na promene u malim disajnim putevima, čak i ako je odnos FEV_1/FVC u normalnom opsegu (6).

Spirometrijski parametri koji se najčešće koriste za procenu funkcije malih disajnim puteva jesu forsirani ekspiratorni protok na 50% FVC (FEF_{50}) i srednji ekspiratorni protok između 25% i 75% FVC (FEF_{25-75}). Oba parametra se nalaze u ekspiratornom delu krive protok–volumen koji nije zavistan od napora (7). Bolest malih disajnih puteva se funkcionalno najčešće definiše kao FEF_{50} ili FEF_{25-75} manji od donje granice normalnih vrednost, pri čemu je odnos FEV_1–FVC i FEV_1 u normalnom opsegu (7). Smatra se da je donja granica normalnih vrednosti FEF_{25-75} 60% od predviđene vrednosti (8). Međutim, vrednosti FEF_{25-75} značajno zavise od vrednosti FVC, tako da ovaj parametar ima dijagnostičku vrednost za bolest malih disajnih puteva samo ako je vrednost FVC u normalnom opsegu (9). Takođe, ne samo kada je prisutno smanjenje FVC već i kada je prisutna difuzna bronhoopstrukcija jako je teško izmeriti uticaj smanjenja protoka kroz male disajne puteve na smanjenje FEV_1. Dalje, korisnost ovog parametra u kliničkoj praksi dodatno je ograničena izraženom fiziološkom varijabilnošću (10), što onemogućava precizno razlikovanje između „normalnih" i „abnormalnih" nalaza, kao i nedostatkom korelacije između vrednosti FEF_{25-75} i parametara hiperinflacije(11) i sa strukturnim promenama u malim disajnim putevima (12).

FVC je parametar koji označava trenutak kada je najveći broj malih disajnih puteva kolabirao zbog dinamičke kompresije, tako da se pomoću njega može indirektno proceniti trenutak njihovog zatvaranja i stepen zarobljavanja vazduha (13). Naime, smanjenje FVC podrazumeva povećanje rezidualnog volumena (RV), odnosno povećano zarobljavanje vazduha zbog prevremenog zatvaranja malih disajnih puteva. Međutim, predviđena vrednost FVC podrazumeva da je totalni plućni kapacitet (TLC) u normalnom opsegu. U slučaju povećanja TLC, kao što je slučaj u izraženom emfizemu, smanjenje FVC je manje nego što bi trebao da

in these cases the difference between the forced and slow vital capacities (FVC-SVC) or the FVC/SVC ratio are better markers of small airway collapsibility that reflect either an obstruction of small airways or the loss of lung parenchyma elasticity (14, 15).

Body plethysmography and helium dilution

Static pulmonary volumes, particularly RV, reflect functional changes in small airways to a certain degree. As it has already been said, RV is the measure of air trapping in the lungs due to early closure of small airways (16). That is why the rise in RV and RV/TLC ratio are considered an early indicator of small airways disease. Unfortunately, RV measurement allows only for volume estimate of early closure of small airways and is not sufficiently sensitive to detect minor changes in conduction and homogeneity of ventilation in the small airways. The difference between RV measured by body plethysmography and the value of the same parameter measured by helium dilution (RV_{pleth}-RV_{dil}) is a somewhat more sensitive parameter for detection of closure of small airways (17). The difference between the inspiratory capacity (IC) measured by spirometry and body plethysmography can be used for the same purpose.

Impulse oscillometry

Impulse oscillometry (IOS) is an important method for the detection of small airways dysfunction, particularly when a spirometry yields results within the normal range (18). Respiratory impedance, the return signal after exposure of the respiratory system to sound waves of different frequencies is composed of resistance, which is the airways resistance, and reactance which is the inertive force of the air column in the conducting airways together with elastic properties of the lung parenchyma. Resistance at frequencies below 10 Hz most probably reflects the function of small conductive airways, while resistance at frequencies over 16 Hz most probably reflects the function of proximal airways. Although the point of transition between the proximal and small conductive airways is not clearly established, clinical and experimental data suggest that distal airway disfunction results in the rise of resistance predominantly at lower frequencies (19). That is why in clinical practice the difference between resistances at frequencies of 5 and 20 Hz (R5 – R20) is most commonly used.

Reactance at the frequency of 5 Hz during the exhaling phase of the measurement is sensitive to airflow limitation caused by the closure of small airways towards or at the end of the exhaling phase, so that it is used in clinical practice for evaluation of small airway function in asthma and COPD (20). The main shortcoming of impulse oscillometry lies in its inability to differentiate uniform changes in the small airways of one pulmonary unit (e.g., basal parts) from bude za dato povećanje RV, pa je u tom slučaju FVC slabiji indikator stepena zarobljavanja vazduha. Smatra se da su, u tom slučaju, razlika između forsiranog i mirnog vitalnog kapaciteta (FVC–SVC) ili odnos FVC–SVC bolji markeri kolapsibilnosti malih disajnih puteva, koji održavaju ili opstrukciju malih disajnih puteva ili gubitak elastičnosti plućnog parenhima (14, 15).

Telesna pletizmografija i dilucija helijuma

Statički plućni volumeni, posebno RV, u određenoj meri odražavaju funkcionalne promene u malim disajnim putevima. RV je, kao što je već rečeno, mera zarobljavanja vazduha u plućima usled prevremenog zatvaranja malih disajnih puteva (16). Zato se povećanje RV, kao i odnosa RV/TLC smatra ranim indikatorom bolesti malih disajnih puteva. Nažalost, merenje RV omogućava isključivo volumensku procenu prevremenog zatvaranja malih disajnih puteva i nije dovoljno osetljivo da bi detektovalo diskretne promene u provodljivosti i homogenosti ventilacije u malim disajnim putevima. Nešto senzitivniji parametar za detekciju zatvaranja malih disajnih puteva jeste razlika između vrednosti RV izmerenih telesnom pletizmografijom i vrednosti istog parametra izmerenih dilucijom helijuma (RV_{pleth}-RV_{dil}) (17). U iste svrhe može se koristiti i razlika između vrednosti inspiratornog kapaciteta (IC) izmerenih spirometrom i telesnom pletizmografijom.

Impulsna oscilometrija

Impulsna oscilometrija (IOS) predstavlja važan metod za otkrivanje poremećaja funkcije malih disajnih puteva, posebno kada je spirometrija u okviru normalnih vrednosti (18). Respiratorna impedanca, povratni signal nakon izlaganja respiratornog sistema zvučnim talasima različitih frekvenci, sastoji se od rezistance, koja predstavlja otpore disajnih puteva, i reaktanse, koja predstavlja inertnost vazdušnog stuba u disajnim putevima zajedno sa elastičnim svojstvima plućnog parenhima. Smatra se da rezistanca pri frekvencama manjim od 10 Hz najverovatnije odražava funkciju malih sprovodnih disajnih puteva, dok rezistanca pri frekvencama većim od 16 Hz odražava proksimalne disajne puteve. Mada mesto tranzicije između proksimalnih i malih sprovodnih disajnih puteva nije jasno ustanovljeno, klinički i eksperimentalni podaci ukazuju na to da poremećaj funkcije distalnih disajnih puteva dovodi do povećanja otpora pretežno pri manjim frekvencama (19). Zato se u kliničkoj praksi najčešće koristi razlika u rezistancama pri frekvencama pet i 20 Hz (R5–R20).

Reaktansa pri frekvenci od pet Hz tokom ekspiratorne faze merenja je osetljiva na ograničenje protoka vazduha izazvano zatvaranjem malih disajnih puteva pri kraju ekspirijuma ili blizu te tačke, tako da se u kliničkoj praksi koristi za procenu funkcije malih disajnih puteva u astmi i HOBP-u (20).

changes with variable intensity in parallel airways of different width, as well as inability to completely isolate a signal from small airways on the mouth level, where the measurement is taking place. Having all these limitations, it is obvious that IOS is not a fully reliable test for detection of changes in the small airways.

Gas elimination methods

The single breath washout test (SBWT) or multiple breath washout test (MBWT) are practically the only tests used in clinical practice, while capnography (CO_2 elimination measurement) is used quite rarely.

The single breath washout test is based on measurement of exhaled nitrogen concentration after pure oxygen inhalation using the TLC maneuver**,** with exhaled volume on the x-axis and exhaled nitrogen on the y-axis (21). In most people, the rise of nitrogen concentration is registered towards the end of VC, corresponding to phase 4 of the measurement, and marks the beginning of the volume at which small airways at the lung base are closing (closing volume – CV). Increased nitrogen concentration in phase 4 comes from the upper parts of the lungs. In healthy persons, the slope of the curve in phase 3 does not exceed 1.5% (22), while CV is usually expressed as the percentage of VC (CV/VC%) and normally amounts to 25%. The sum of CV and RV is called the closing capacity (CC) and is expressed as the percentage of TLC (CC/TLC%). Since the value of CC/TLC% varies less than CV/VC% and includes RV as the measure of lung inflation, it is considered a better parameter for the evaluation of small airways functionality. SBWT varies a great deal even in healthy persons, due to difficulties in establishing the onset of phase 4 nitrogen elimination, volume variations with closure of airways, variation in the exhaled air volume due to incomplete inhaling or exhaling, and the impact of expiratory flow on phase 4, i.e. inspiratory flow on phase 3 (23).

MBWT is also based on the nitrogen concentration in exhaled air after pure oxygen inhalation, but in this case during repeated slow inhalations. This test, as the previous one, measures inhomogeneity of ventilation in the lungs (21). In case of increased inhomogeneity of ventilation of the lungs, time for nitrogen elimination is prolonged, so that more respirations are needed to wash out nitrogen from the lungs. During this test, phase 3 is calculated for each respiration cycle and divided by the mean exhaled nitrogen concentration (24). Since the airways close at different times during the exhaling phase, gradual increase of phase 3 during the test implies the presence of different nitrogen concentrations in different parts of the lungs, regardless of its same average concentration, i.e. inhomogeneity of ventilation. This method allows for differentiation between two parameters of inhomogeneity of ventilation: acinar

Osnovno ograničenje impulsne oscilometrije je u tome što ne može da razlikuje uniformne promene u malim disajnim putevima jedne plućne jedinice (na primer bazalnih delova) od promena različitog intenziteta u paralelno postavljenim disajnim putevima različitog kalibra, kao i u nemogućnosti da sasvim izoluje signal iz malih disajnih puteva na nivou usta, gde se merenje i odvija. Imajući u vidu ova ograničenja, jasno je da ni IOS nije sasvim pouzdan test za detekciju promena u malim disajnim putevima.

Metodi eliminacije gasova

U kliničkoj praksi koristi se skoro isključivo metod eliminacije azota tokom jednog udaha (engl. *single breath washout test* – SBWT) ili tokom ponavljanih udaha (engl. *multiple breath washout test* – MBWT), dok se kapnografija (merenje eliminacije CO_2) izuzetno retko koristi.

Metod eliminacije azota jednim udahom zasniva se na merenju izdahnute koncentracije azota posle udisanja čistog kiseonika TLC manevrom, pri čemu se na iks osi grafikona registruje volumen izdahnutog vazduha, a na ipsilon osi koncentracija izdahnutog azota (21). Kod većine ljudi pri kraju VC registruje se nagli porast koncentracije azota, koji odgovara fazi IV merenja i označava početak volumena pri kome se zatvaraju mali disajni putevi u bazama pluća (engl. *closing volume* – CV). Povećana koncentracija azota u IV fazi potiče iz gornjih delova pluća. Kod zdravih ljudi nagib krive III faze nije veći od 1,5%(22), dok se CV obično izražava kao procenat od VC (CV/VC%) i normalno iznosi 25%. Zbir CV i RV naziva se kapacitet zatvaranja (engl. *closing capacity* – CC) i izražava se kao procenat od TLC (CC/TLC%). S obzirom na to da CC/TLC% manje varira od CV/VC% i da uključuje RV kao meru inflacije pluća, smatra se boljim parametrom za procenu funkcije malih disajnih puteva. SBWT pokazuje značajno variranje i kod zdravih osoba usled teškoća u određivanju početka IV faze eliminacije azota, varijacija u volumenu pri kome dolazi do zatvaranja disajnih puteva, varijacija u volumenu izdahnutog vazduha zbog nepotpunog udaha ili izdaha i uticaja ekspiratornog protoka na fazu IV, odnosno inspiratornog protoka na fazu III (23).

MBWT se, takođe, zasniva na merenju koncentracije azota u izdahnutom vazduhu posle udisanja čistog kiseonika, ali u ovom slučaju tokom ponavljanih mirnih udaha. Ovaj test, kao i prethodni, meri nehomogenost ventilacije u plućima (21). Kod povećane nehomogenosti ventilacije pluća produžava se vreme potrebno za eliminaciju azota, tako da je potreban veći broj respiracija da bi došlo do ispiranja azota iz pluća. Tokom ovog testa III faza se računa za svaki respiratorni ciklus i podeli se sa srednjom izdahnutom koncentracijom azota (24). S obzirom na to da se disajni putevi tokom ekspirijuma zatvaraju u različito vreme, postepeno povećanje III faze tokom trajanja testa označava da je prisutna različita koncentracija azota u različitim delovima

inhomogeneity (S_{acin}) and conductive inhomogeneity (S_{cond}) (25). S_{acin} represents phase 3 during the first inspiration normalized to ventilation, and this is a parameter specific for inhomogeneity of ventilation on the level of small i.e. acinar airways. In case of normal values of S_{acin}, ventilation on the small airways level is believed to be preserved. On the other hand, abnormal S_{acin} values suggest inhomogeneity of ventilation on the acinar level, i.e. small airways disorder, regardless of the presence or absence of structural changes in the proximal airways. S_{cond} implies a rise in the normalized phase 3 of nitrogen elimination during the test, and this parameter reflects inhomogeneity of ventilation proximal to the acini, i.e. in the conductive airways (24). The main MBWT limitation lies in the fact that in the case of S_{cond} rise, i.e. conductive inhomogeneity, it is impossible to tell whether the disorder is present in the proximal or distal conductive airways.

Volume capnography is based on analysis of carbon dioxide (CO_2) concentration in exhaled air during the expiration phase. Expiratory volume is on the capnogram x-axis, and the CO_2 concentration on the y-axis. A capnogram represents the total amount of CO_2 cleared from the lungs during one expiration, and it is composed of three phases: phase 1 with CO_2 concentration close to zero representing gas from anatomically dead space and proximal parts of conducting airways; phase 2 characterized with abrupt rise of CO_2 concentration representing gas in the alveolae proximal to the centrally positioned airways; phase 3 called the alveolar plateau representing only the alveolar CO_2 concentration. The alveolar plateau (phase 3) is not a straight line but slowly rises towards the end of the expiratory phase, most probably due to continuous diffusion of CO_2 from the pulmonary circulation into the alveolae. Analysis of airway transition from phase 2 to phase 3 is suggested to be able to indicate small airway dysfunction (26), but the impact of CO_2 diffusion on these parameters cannot be ruled out, which substantially impairs the specificity of this method.

Alveolar nitrogen-monoxide

Measurement of nitrogen monoxide (NO) in exhaled air is a standard procedure during unchanged air flow in the expiratory phase. However, this method does not allow for differentiation between increased NO production due to changes in the small airways or the alveolae. Analysis of NO concentration in expired air at different expiratory flows allows for determination of alveolar NO concentration (CalvNO) (27). Elevated CalvNO values have been recorded in asthma patients where they show good correlation with FEV_1 values (28), and in COPD patients where it can be used as a potential biomarker of inflammation in distal airways (29). The main limitation of this method is its relatively low accessibility and need for further evaluation in clinical practice.

pluća, bez obzira na njegovu istu prosečnu koncentraciju, odnosno nehomogenost ventilacije. Ovom metodom mogu se definisati dva parametra nehomogenosti ventilacije: acinarna nehomogenost (S_{acin}) i konduktivna nehomogenost (S_{cond}) (25). S_{acin} predstavlja III fazu tokom prvog udaha normalizovanu na ventilaciju, i to je parametar specifičan za nehomogenost ventilacije na nivou malih disajnih puteva, tj. acinusa. Smatra se da je u slučaju normalnih vrednosti S_{acin}, ventilacija na nivou malih disajnih puteva očuvana. S druge strane, poremećaj vrednosti S_{acin} ukazuje na nehomogenost ventilacije na nivou acinusa, odnosno na poremećaj funkcije malih disajnih puteva bez obzira na prisustvo ili odsustvo strukturnih promena u proksimalnim disajnim putevima. S_{cond} je porast normalizovane III faze eliminacije azota tokom trajanja testa i ovaj parametar odražava nehomogenost ventilacije proksimalno od acinusa, tj. u sprovodnim disajnim putevima (24). Osnovno ograničenje MBWT je u tome da u slučaju povećanja S_{cond}, odnosno konduktivne nehomogenosti, ne postoji način da se razlikuje da li je poremećaj prisutan u proksimalnim ili distalnim sprovodnim disajnim putevima.

Volumenska kapnografija je bazirana na analizi koncentracije ugljen-dioksida (CO_2) u izdahnutom vazduhu tokom ekspirijuma. Na iks osi kapnograma nalazi se ekspiratorni volumen, a na ipsilon osi koncentracija CO_2. Kapnogram predstavlja ukupnu količinu CO_2 koja se eliminiše iz pluća tokom jednog izdaha i sastoji se iz tri faze: faza 1 sa koncentracijom CO_2 približnoj nuli koja odražava gas iz anatomskog mrtvog prostora i proksimalnih sprovodnih disajnih puteva; faza 2, koja se karakteriše naglim porastom koncentracije CO_2 i predstavlja gas iz alveola koje su proksimalne u odnosu na centralno postavljene disajne puteve; faza 3, koja se naziva alveolarni plato i sastoji se isključivo iz koncentracije CO_2 iz alveola. Alveolarni plato (faza 3) nije ravna linija, već ima lagani porast prema kraju ekspirijuma, najverovatnije zbog kontinuirane difuzije CO_2 iz plućne cirkulacije u alveole. Smatra se da analiza prelaska faze 2 u fazu 3 i oblika faze 3 može ukazivati na poremećaje funkcije u malim disajnim putevima (26), ali se uticaj difuzije CO_2 na ove parametre ne može isključiti, što znatno smanjuje specifičnost ovog metoda.

Alveolarni azot-monoksid

Merenje azot-monoksida (NO) u izdahnutom vazduhu standardno se radi tokom nepromenljivog ekspiratornog protoka vazduha. Međutim, pomoću ovog metoda ne može da se razlikuje da li je povećana produkcija NO posledica promena u disajnim putevima ili u alveolama. Analizom koncentracije NO u izdahnutom vazduhu pri različitim ekspiratornim protocima moguće je odrediti i alveolarnu koncentraciju NO (CalvNO) (27). Povećane vrednosti CalvNO nađene su kod bolesnika sa astmom, gde su pokazale dobru

Conclusion

There is currently no test with clearly set cutoff values to differentiate between persons with small airways dysfunction and "healthy" persons, i.e. persons with accompanying pathophysiological disorders. No "gold standard" test is available for small airways diagnostics either. Results of all tests discussed above have a better negative predictive value. Negative results of these tests may fairly reliably suggest that small airways do not play a role in the clinical problem at hand. On the other hand, positive results of individual tests should always be verified by different methods to confirm the presence of small airways disorder and rule out the possibility of proximal airways contribution to the clinical issue (24).

The tests currently used in the diagnostics of small airways vary a great deal in their complexity, cost and before all their accessibility. The proposed algorithm (Figure 1) takes accessibility as the main criterion that, in the light of the widespread nature of the problem, is also the main restrictive factor.

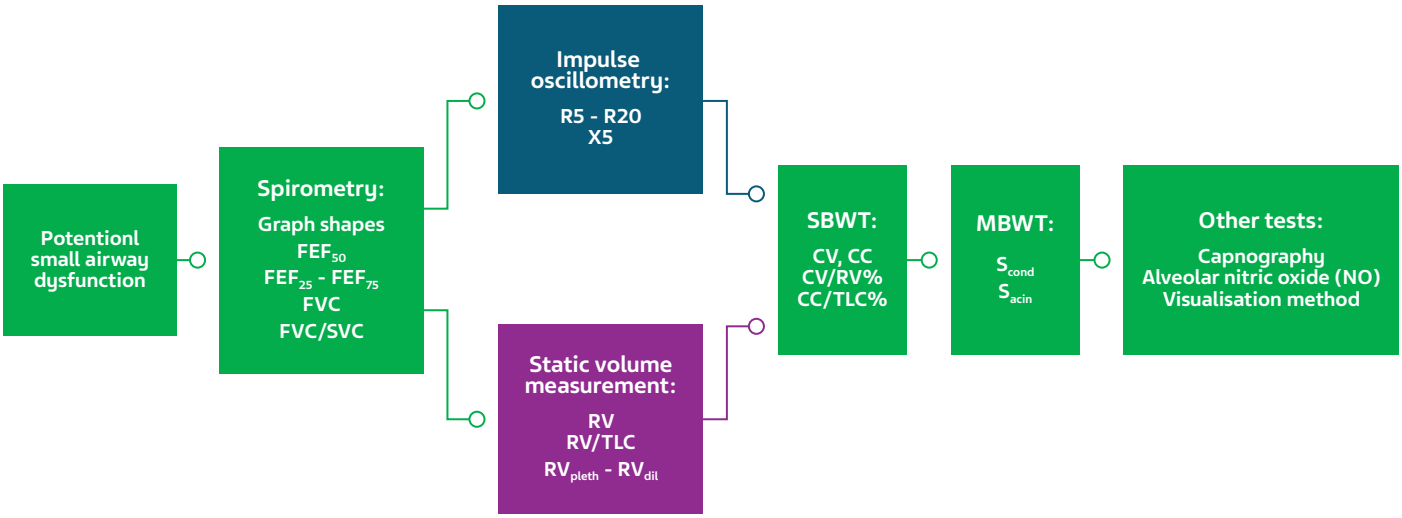
korelaciju sa vrednostima FEV_1 (28), kao i kod bolesnika sa HOBP-om, gde može služiti kao potencijalni biomarker inflamacije u distalnim disajnim putevima (29). Glavna ograničenja ovog metoda su njegova relativna nedostupnost i potreba za daljom evaluacijom u kliničkoj praksi.

Zaključak

Trenutno ne postoji test sa jasnim graničnim vrednostima pomoću kog bi se mogle razlikovati osobe sa poremećajem funkcije malih disajnih puteva i „zdrave" osobe, odnosno osobe sa pridruženim patofiziološkim poremećajima. Takođe, ne postoji test koji predstavlja zlatni standard u dijagnostici malih disajnih puteva. Rezultati svih navedenih testova imaju bolju negativnu prediktivnu vrednost. Negativni rezultati ovih testova mogu sa velikom sigurnošću ukazati na to da mali disajni putevi ne igraju ulogu u datom kliničkom problemu. S druge strane, pozitivne rezultate pojedinačnih testova trebalo bi uvek proveriti različitim metodama da bi se potvrdilo prisustvo poremećaja u malim disajnim putevima i isključila mogućnost da proksimalni disajni putevi doprinose datom kliničkom problemu (24).

Postojeći testovi koji se koriste u dijagnostici malih disajnih puteva znatno variraju po složenosti, ceni, a prvenstveno dostupnosti. Predloženi algoritam (slika 1.) kao osnovni kriterijum uzima upravo dostupnost, koja, s obzirom na rasprostranjenost problema, predstavlja i glavni ograničavajući faktor.

FIGURE 1. Algorithm for small airways diagnostics



This algorithm should not be taken as the final solution, instead it should be adjusted to the current healthcare system (organization of work, financing, level of equipment use, etc.).

Two facts should be highlighted at the end. Results of small airways diagnostic tests should be interpreted taking into account other aspects of any concrete clinical issue as well. Isolated, they do not mean much unless they are combined with other methods (history, clinical presentation, imaging methods and the like). On the other hand, if the results of these tests suggest a small airways disorder, this can have significant implications on, for example, the use of fine particle aerosol in treatment.

Ovaj algoritam ne treba smatrati definitivnim rešenjem, već ga apsolutno treba prilagoditi postojećem zdravstvenom sistemu (organizacija rada, finansiranje, stepen iskorišćenosti opreme i drugo).

Na kraju, treba istaći dve činjenice. Rezultati dijagnostičkih testova za male disajne puteve moraju se uklopiti u dati klinički problem. Sami po sebi oni ne znače mnogo ako se ne kombinuju sa drugim metodama (anamnestički podaci, klinička slika, vizuelizacioni metodi i drugo). S druge strane, ako rezultati ovih testova definitivno ukažu na problem u malim disajnim putevima, to može imati značajne kliničke implikacije, na primer, primenu aerosola sa finim česticama u lečenju.

REFERENCES

1. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 1968;278(25):1355–60. DOI: 10.1056/NEJM196806202782501. –1360.
2. Ding M, Chen Y, Guan WJ at al. Measuring Airway Remodeling in Patients With Different COPD Staging Using Endobronchial Optical Coherence Tomography. Chest 2016;150(6):1281–90. DOI: 10.1016/j.chest.2016.07.033.
3. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 1967;22(1):95–108. DOI: 10.1152/jappl.1967.22.1.95. PMID: 6017658.
4. Braido F, Scichilone N, Lavorini F at al; Interasma Executive Board; WAO Board of Directors; ARIA; GA²LEN. Manifesto on small airway involvement and management in asthma and chronic obstructive pulmonary disease: an Interasma (Global Asthma Association - GAA) and World Allergy Organization (WAO) document endorsed by Allergic Rhinitis and its Impact on Asthma (ARIA) and Global Allergy and Asthma European Network (GA2LEN). Asthma Res Pract 2016;2:12. DOI: 10.1186/s40733-016-0027-5.
5. Lee J, Lee CT, Lee JH at al; KOLD Study Group. Graphic analysis of flow-volume curves: a pilot study. BMC Pulm Med 2016;16:18. DOI: 10.1186/s12890-016-0182-8. Erratum in: BMC Pulm Med 2016;16(1):115.
6. Stănescu D, Veriter C. A normal FEV1/VC ratio does not exclude airway obstruction. Respiration 2004;71(4):348–52. DOI: 10.1159/000079638.
7. Pellegrino R, Viegi G, Brusasco V at al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948–68. DOI: 10.1183/09031936.05.00035205.
8. Burgel PR. The role of small airways in obstructive airway diseases. Eur Respir Rev 2011;20(119):23–33. DOI: 10.1183/09059180.00010410. Erratum in: Eur Respir Rev 2011;20(120):123. Dosage error in article text. Erratum in: Eur Respir Rev 2011;20(120):124.
9. Hansen JE, Sun XG, Wasserman K. Discriminating measures and normal values for expiratory obstruction. Chest. 2006;129(2):369–377. DOI: 10.1378/chest.129.2.369.
10. Sorkness RL, Bleecker ER, Busse WW et al; National Heart, Lung, and Blood Institute Severe Asthma Research Program. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. J Appl Physiol (1985) 2008;104(2):394–403. DOI: 10.1152/japplphysiol.00329.2007.
11. Knudson RJ, Lebowitz MD. Maximal mid-expiratory flow (FEF25-75%): normal limits and assessment of sensitivity. Am Rev Respir Dis 1978;117(3):609–10. DOI: 10.1164/arrd.1978.117.3.609.
12. Newball HH. The unreliability of the maximal midexpiratory flow as an index of acute airway changes. Chest 1975;67(3):311–4. DOI: 10.1378/chest.67.3.311.
13. Chapman DG, Berend N, King GG, Salome CM. Increased airway closure is a determinant of airway hyperresponsiveness. Eur

Respir J 2008;32(6):1563–9. DOI: 10.1183/09031936.00114007.
14. Cohen J, Postma DS, Vink-Klooster K et al. FVC to slow inspiratory vital capacity ratio: a potential marker for small airways obstruction. Chest 2007;132(4):1198–203. DOI: 10.1378/chest.06-2763.
15. Wenzel SE, Schwartz LB, Langmack EL et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 1999;160(3):1001–8. DOI: 10.1164/ajrccm.160.3.9812110. .
16. Contoli M, Bousquet J, Fabbri LM et al. The small airways and distal lung compartment in asthma and COPD: a time for reappraisal. Allergy 2010;65(2):141–51. DOI: 10.1111/j.1398-9995.2009.02242.x.
17. Tantucci C, Guerini M, Boni E, Corda L, Pini L. Tidal airway closure during bronchoconstriction in asthma: usefulness of lung volume measurements. J Asthma 2011;48(1):33–40. DOI: 10.3109/02770903.2010.528499.
18. Oppenheimer BW, Goldring RM, Berger KI. Distal airway function assessed by oscillometry at varying respiratory rate: comparison with dynamic compliance. COPD 2009;6(3):162–70. DOI: 10.1080/15412550902918410.
19. Goldman MD, Saadeh C, Ross D. Clinical applications of forced oscillation to assess peripheral airway function. Respir Physiol Neurobiol 2005;148(1-2):179–94. DOI: 10.1016/j.resp.2005.05.026. PMID: 15990365.
20. Kanda S, Fujimoto K, Komatsu Y, Yasuo M, Hanaoka M, Kubo K. Evaluation of respiratory impedance in asthma and COPD by an impulse oscillation system. Intern Med 2010;49(1):23–30. DOI: 10.2169/internalmedicine.49.2191.
21. Robinson PD, Latzin P, Verbanck S et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J 2013;41(3):507–22. DOI: 10.1183/09031936.00069712. Erratum in: Eur Respir J 2013;42(5):1432.
22. Becklake MR, Leclerc M, Strobach H, Swift J. The N2 closing volume test in population studies: sources of variation and reproducibility. Am Rev Respir Dis 1975;111(2):141–7. DOI: 10.1164/arrd.1975.111.2.141. PMID: 1111402.
23. McFadden ER Jr, holmes B, Kiker R. Variability of closing volume measurements in normal man. Am Rev Respir Dis 1975;111(2):135–40. DOI: 10.1164/arrd.1975.111.2.135.
24. Verbanck S. Physiological measurement of the small airways. Respiration. 2012;84(3):177–88. DOI: 10.1159/000341742.
25. Wenzel SE, Schwartz LB, Langmack EL et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 1999;160(3):1001–8. DOI: 10.1164/ajrccm.160.3.9812110. PMID: 10471631.
26. Veronez L, Moreira MM, Soares ST et al. Volumetric capnography for the evaluation of pulmonary disease in adult patients with cystic fibrosis and noncystic fibrosis bronchiectasis. Lung 2010;188(3):263–8. DOI: 10.1007/s00408-009-9213-z.
27. Mahut B, Louis B, Zerah-Lancner F, Delclaux C. Validity criteria and comparison of analytical methods of flow-independent exhaled NO parameters. Respir Physiol Neurobiol 2006;153(2):148–56. DOI: 10.1016/j.resp.2005.10.005.
28. Mahut B, Delacourt C, Zerah-Lancner F, De Blic J, Harf A, Delclaux C. Increase in alveolar nitric oxide in the presence of symptoms in childhood asthma. Chest 2004;125(3):1012–8. DOI: 10.1378/chest.125.3.1012.
29. Brindicci C, Ito K, Resta O, Pride NB, Barnes PJ, Kharitonov SA. Exhaled nitric oxide from lung periphery is increased in COPD. Eur Respir J 2005;26(1):52–9. DOI: 10.1183/09031936.04.00125304.

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