Abstract
Bronchoscopy is an invasive and annoying procedure for the patient. During the course of the bronchoscopy, catecholamine release may occur, with tachycardia and hypertension, which, in patients with compromised cardiovascular function can lead to complications and hemodynamic deterioration.

Nowadays, guidelines recommend offer sedation to patients provided there are no contraindications. Sedation improves patient anxiety, tolerance to test, bronchoscopist and patient comfort, cost-effectiveness (particularly in EBUS), and willingness to repeat the test in case of need.

Different drugs have probe its usefulness for bronchoscopy sedation.

Dexmedetomidine is a potent and highly selective $\alpha_2$ adrenoceptor agonist with sedative, analgesic, anxiolytic, sympatholytic and opioid-limiting properties. It offers a conscious sedation, in which the patients seem to be inert but really respond easily when stimulated, which allows them to collaborate if necessary.

Its onset of rapid action and its relatively short duration, make it a suitable agent for performing bronchoscopy sedation because it can be easily titrated. It is noteworthy that dexmedetomidine appears to have minimal respiratory depression, which makes it a safe agent in patients who are breathing spontaneously. In addition, it offers potential benefits in relation to neuroprotection, cardioprotection and kidney-protection.

ABBREVIATIONS
EBUS: Endo-Bronchial Ultrasound; ICU: Intensive Care Unit; FDA: Food and Drug Administration; GPCRs: G Protein-Coupled Receptors

INTRODUCTION
Currently flexible fiberoptic bronchoscopy is a tool commonly used in the study and treatment of patients with respiratory diseases. It is an invasive and annoying procedure for the patient, which can produce dyspnea, nasal or throat irritation (depending on the approach), or cough, that explains the poor tolerance that patients have to this procedure. During the course of the bronchoscopy, catecholamine release may occur, with tachycardia and hypertension, which, in patients with compromised cardiovascular function can lead to complications and hemodynamic deterioration [1,2].

Until a few years ago, and even nowadays, in many endoscopy cabinets worldwide, bronchoscopy is performed without sedation [3,4].

In the early years of bronchoscopy (70’s) there was fear about the risk of complications related to anesthesia. Studies conducted two decades ago have shown that bronchoscopy performed with sedation and without sedation is equally safe [5,6], but patient comfort, tolerance to test and repeatability increase clearly with the use of sedation [7-14].

Twelve percent of bronchoscopies need to be repeated [10]. Without sedation, 6% of bronchoscopies can not be completed [10].

Nowadays, in order to perform a fiberoptic bronchoscopy, the guidelines recommend its implementation under sedation, with the aim of improving comfort, patient cooperation, reducing complications and improving patient satisfaction [15,16]. Sedation improves patient and bronchoscopist satisfaction [16].

There are notable differences in the practice of bronchoscopies in terms of the use of local anesthesia and of sedoanalgesia among the different groups world wide [16].

The degree of sedation used by the different Bronchoscopy Units varies from the absence of sedation to general anesthesia [16]. A 2003 study in the United Kingdom showed that 73% of bronchoscopies were performed with sedoanalgesia [17].

The number of endoscopies has multiplied by 4 in recent years in the United States [18]. So does the use of sedation for these endoscopies, which is already used in more than 90% of
cases [18]. This brings important changes in the management of endoscopy rooms, given the different requirements of bronchoscopy without sedation and with sedation, which will depend on the degree of sedation performed.

**Adrenoreceptor-agonist**

The first α-2 adrenoceptor agonist drug synthesized was clonidine. It was initially used as a nasal decongestant in the early 1960s. Unfortunately, he presented unexpected side effects such as prolonged sedation, severe hypotension and depression of cardiovascular function. Subsequently, it was introduced as an antihypertensive in 1966 and was used as a treatment for withdrawal syndrome, pain management and subarachnoid anesthesia [19].

Dexmedetomidine is a highly selective alpha-agonist, approved in 1999 by the Food and Drug Administration (FDA) for sedation and analgesia in patients admitted to the Intensive Care Unit (ICU). The window of therapeutic uses widened rapidly, and in 2003 the FDA approved its use for sedation in invasive or painful procedures [20].

Its use is suitable for sedation and analgesia in the surgical and endoscopic field. It has indications such as premedication, adjuvant in general and locorregional anesthesia, as well as sedative and analgesic uses [20].

**Pharmacology of dexmedetomidine**

Alpha-2 adrenergic receptors and 3 subtypes of α 2 receptors (alpha 2A, alpha 2B and alpha 2 C) are known. They are G protein-coupled receptors (GPCRs) and are located on the cell membrane. Adrenaline and, essentially, norepinephrine bind to these receptors and are involved in different physiological functions. Exogenous substances are known to interact with such receptors, such as dexmedetomidine. Stimulation of these receptors produces the pharmacodynamic effects of dexmedetomidine.

Alpha-2a receptor stimulation has been reported to promote analgesia, hypnosis, and sedation. They also produce sympatholysis, inhibition of insulin secretion and have been implicated in the neuroprotective effect of dexmedetomidine. Stimulation of the alpha-2b receptor produces spinal analgesia, inhibits tremor, and produces vasoconstriction. Finally, the alpha-2c receptor has been implicated in the effects of dexmedetomidine at the sensory level and in the mental state, among others [21,22].

The effects of alpha-2 receptor stimulation depend on their location. At the level of the central nervous system inhibit the neuronal discharge producing decrease of the blood pressure and of the heart rate, amnesia and sedation. Other responses include decreased saliva production (especially interesting for bronchoscopy), decreased secretion and digestive tract motility [23].

The sedo-analgesic effects of dexmedetomidine are due to the reduction of noradrenaline release in the brain and spinal cord. Sedation is due to its effects on the pre- and post-synaptic α2 receptors of the locus coeruleus pontine, and analgesia through receptors located at the level of the spinal cord. Dexmedetomidine induces sleep similar to natural sleep, but the patient remains easily aroused and cooperative [20,24-27].

Dexmedetomidine is metabolized at the hepatic level by hydroxylation and glucuronidation in inactive metabolites. There is significant interindividual pharmacokinetic variability, especially in ICU patients, which depends on body size, liver function, cardiac output, albuminemia [20].

The hemodynamic effects of dexmedetomidine (including transient hypertension, bradycardia, hypotension), are due to peripheral vasoconstriction and its sympatholytic properties [20].

Sedation in fiberoptic bronchoscopy and echobronchoscopy.

Sedation improves patient anxiety, tolerance to test, bronchoscopist and patient comfort, cost-effectiveness (particularly in endobronchial ultrasound (EBUS)), and willingness to repeat the test in case of need [7-10,28-38]. It is currently recommended to provide sedation to patients, provided there are no contraindications, and this is especially relevant in prolonged or complex procedures, as well as in patients requiring multiple endoscopies (for example, for patients with carcinoma in situ, intraluminal lesions who require endoscopic treatment, tracheal stenosis, or patients with neoplasias who will require new tissue samples) [15,16].

The complications related to the level of sedation have been evaluated in digestive echoendoscopy and there is no difference when propofol is used for deep sedation compared to opioid-associated midazolam [39].

There are no differences in complications in bronchoscopy with sedation and without sedation [40-44].

**Dexmedetomidine for bronchoscopy**

Dexmedetomidine has sedative, anti-anxiety, amnesic and analgesic properties, and it has been used as a sedative for various procedures [45,46].

It provides a conscious sedation, with easy arousal without depression of the respiratory center. Cardioprotective, renoprotective and neuronal protective effects have been described, fundamentally against ischemic and hypoxic damages [22]. In addition, there are several papers that document the efficacy and safety of dexmedetomidine for flexible bronchoscopy during awake fiberoptic intubation [47,48].

Dexmedetomidine has the advantage of producing sedation, analgesia, sympatholysis, and as a low risk of apnea and respiratory depression [20]. Compared with midazolam, dexmedetomidine causes less oxygen saturation decrease, with the same tolerance [49]. The same is true when comparing propofol associated with remifentanil versus propofol associated with dexmedetomidine: with dexmedetomidine there are fewer episodes of falling oxygen saturation [50].

There is increasing experience with the use of dexmedetomidine for sedation in bronchoscopy [47,34,35,50-52]. Different studies have confirmed the safety of dexmedetomidine for sedation in bronchoscopy and EBUS [3,49,50,52].

Bergese et al., found that dexmedetomidine and midazolam were associated with better patient cooperation and higher patient satisfaction than midazolam alone [47].
Dexmedetomidine antagonizes sympathetic reflexes triggered by bronchoscopy [47]. In this study the patients were randomized and sedated with rescue dexmedetomidine or midazolam for a level of sedation directed according to the Ramsay scale. Patients treated with dexmedetomidine showed lower blood pressure and heart rate figures compared to placebo-treated patients receiving midazolam. Adverse events and patient recall were similar in both groups [47].

Liao et al., in a prospective study including 226 patients, found that compared with midazolam, dexmedetomidine provided better oxygen saturation, steadier haemodynamics, and was equally well tolerated for conscious sedation in postoperative thoracic surgery patients undergoing bronchoscopy [49].

Ryu et al., in a randomized double-blind trial of 72 subjects, found less oxygen desaturation and oral secretions with dexmedetomidine than with remifentanil, but the recovery time was longer [50].

However, as a single agent, dexmedetomidine may not be sufficient to perform bronchoscopy with sedation, since almost half of the patients require rescue sedation [52]. Lee et al., conducted a pilot trial with dexmedetomidine infusion with a bolus of 0.5mg/kg for 10 minutes followed by an infusion of 0.2 to 0.7mg/kg/h, showing that this doses are unable to reliably provide as a sole agent adequate sedation for bronchoscopy without the need for rescue sedation [52]. For this reason, some bronchoscopist prefer to administer a propofol bolus at the beginning of the endoscopy, just after the loading dose of dexmedetomidine is over [35].

Dexmedetomidine has been used to maintain spontaneous ventilation during rigid bronchoscopy in adults [53] and Children [54,55].

There is a interesting additional benefit when using dexmedetomidine for bronchoscopy, given its ability to reduce cough, both in animals models [55] and human trials [56,57].

Excessive alcohol users, chronic benzodiazepine and opioid users, and polysubstance users are commonly cited as difficult to sedate. There are multiple reports in the literature of the use of dexmedetomidine in alcohol withdrawal syndrome [58], in anticholinergic toxisdrome due to diphendhyramine overdose [59], serotonin syndrome [60], or methamphetamine-overdose [61]. Nevertheless, dexmedetomidine impaired patient-controlled sedation of alcoholic patients during endoscopic retrograd cholangiopancreatography [62], and there is still no data on the usefulness of dexmedetomidine in bronchoscopy sedation in alcoholic patients or drug users patients.

Dose of dexmedetomidine

For sedation in bronchoscopy and EBUS, a loading dose of 1mcg/kg to be passed in 10 minutes, and then an infusion of 0.5 to 1mcg/kg/hour may be used.

Adverse effects of dexmedetomidine

Usually, dexmedetomidine is well tolerated. The adverse effects of dexmedetomidine include initial hypertension, bradycardia, and, above all, arterial hypotension after endoscopy [20]. Dexmedetomidine in bolus is not recommended because it can cause hypotension [63]. Dexmedetomidine may prolong the post-sedation recovery [47,50]. The lack of anti-tussive effect of dexmedetomidine may lead to combine it with other drugs, if necessary (e.g. opioids) [35]. In some patients, the amnesic effect could be insufficient, related to the intensity of stimulation from the airway manipulation, and may be useful to administrate other drugs (e.g. Midazolam) [52].

CONCLUSIONS

Dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sedative, analgesic, anxiolytic, sympatholytic and opioid-limiting properties. It offers a conscious sedation, in which the patients seem to be inert but really respond easily when stimulated, which allows them to collaborate if necessary.

Its onset of rapid action and its relatively short duration, make it a suitable agent for performing bronchoscopy sedation because it can be easily titrated. As has been demonstrated in some studies, short-term sedation is a safe procedure, although hypotension and bradycardia are the most significant side effects. It is note worthy that dexmedetomidine appears to have minimal respiratory depression, which makes it a safe agent in patients who are breathing spontaneously. In addition, it offers potential benefits in relation to neuroprotection, cardioprotection and kidney- protection.

REFERENCES


