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## Post Thoracotomy Pain Syndrome

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### 1. Introduction

Post-thoracotomy pain is one of the most severe and long lasting complications after surgery (1-4) which acutely contributes to limit normal respiratory activity impairing the sputum clearance and reducing ventilatory function (5). Along with limb amputation, thoracotomy is the surgical procedure with the highest risk of severe and long lasting acute postoperative pain (6).

Moreover, a chronic post thoracotomy pain syndrome (PTPS) may delay the long term rehabilitation, worsening the quality of life because of the associated neuropathic pain even without recurrences of the primary disease (7). Lung cancer still remains the first cause of death for cancer (8) and prompt pulmonary surgery may be the only effective therapeutic strategy. Consequently, an increasing rate of thoracic surgery will be progressively associated with a higher PTPS incidence in the future.

The syndrome was firstly described in 1944 during the II world war when American surgeons reported persistent intercostal pain in soldiers submitted to thoracotomy (9). Until the end of the nineties, pain treatment was mainly based on intravenous opioids and the incidence of PTPS was about 61% one year after surgery (10).

### 2. Definition and incidence

The International Association for the Study of Pain (IASP) definition of Post Thoracotomy Pain Syndrome is the following: 'Pain that recurs or persists along a thoracotomy scar at least 2 months following surgical procedure' (7).

PTPS incidence between 11 and 80% has been reported in the literature (11-13). This variability is probably related to the setting of retrospective studies, the lack of an homogeneous definition of the severity and duration of the syndrome, the difference in anesthetic and analgesic protocols, the use of different pain evaluation scales and the time of postoperative follow-up. Moreover, the high variability in PTPS incidence may also be explained by the different attitude of patients towards discomfort (14).

### 3. Pain characteristics after thoracic surgery

PTPS is mostly described with the typical characteristics of neuropathic pain, often related to the surgical scar, since 82–90% of pain patients recognize the pain trigger directly to the surgical site (1, 10). Pain is primarily described as aching, tender, with numbness and to a lesser degree burning (1, 15); however, PTPS is sometimes described as tingling and pruritus sensation within the thoracic injured area. Finally, thoracic sensory deficits are referred by

patients in terms of sensory loss and hypoesthesia to cold (16, 17). These neuropathic phenomena are principally located within mammary and sub mammary areas and ipsilateral scapular and interscapular regions.

Comparing to acute postoperative pain, PTPS does not specifically influence the respiratory function but may be able to limit daily activities. In other words, differences between acute and chronic pain are more related to the inability to restore the physiological functions of the organism to homeostatic pre-thoracotomy levels (18). Even if the pain intensity is moderate, normal daily activities might be hampered up to 50 % of cases and sleep disorders could be present in the 25% of patients (10); finally, severe pain could be present in 8% and can persist in more than 40% of cases (15). Unfortunately the social consequences and subsequent analgesic use have only been recorded in a minority of studies with different design (4, 13, 15, 19, 20) so that the actual impact of chronic pain on daily life remains undefined.

#### 4. Pathogenetic features

The mechanisms that lead to PTPS are multiple and the pathogenesis is still unclear. The pathway of the painful experience related to thoracotomy is complex. Inputs from skin, muscles, ribs, and parietal pleura are conducted through intercostal nerves to the dorsal horn. Moreover, the vagus nerve and the autonomic system are involved in the conduction of noxious stimuli from visceral pleura and lung parenchyma; finally, the phrenic nerve is related to noxious stimuli from mediastinum, diaphragm and pericardial pleura (21, 22).

Although the pathogenesis of chronic neuropathic post thoracotomy pain syndrome is complex, the direct damage of intercostal nerves and the consequent effect on pain transmission seems to play a primary role (23). Many important peripheral and central nociceptive adaptations have been described after peripheral nerve injury (23).

Peripherally, ephaptic conduction or "cross-excitation" generated by neurons linked to injured nerves may trigger a distorted pathway of nociceptive stimuli which may be clinically relevant for the ongoing neuropathic pain (23, 24). Moreover, in these neurons the expression of sodium and calcium channels may be altered (23, 25, 26). A collateral sprouting of fibers from sensory axons into denervated areas has been also described in an animal model, but the degree of sprouting was not proportional to the degree of hyperalgesia after nerve section so that the role of this phenomenon seems to be limited (23, 27). Another important role may be played by direct coupling of the sympathetic nerve system and the sensory nervous system in the dorsal root gangliation (28). The trigger signal of this sprouting is still unclear but the release of neurotrophic factors and cytokines following wallerian degeneration is likely to be decisive (29).

Central mechanisms are also implicated in the development of this syndrome (23). The nerve injury is coupled to a considerable degree of spinal cord reorganization. Large-diameter, low threshold A-beta fibres from mechanoreceptors may wrongly sprout into lamina II, which is normally the termination of high-threshold A-delta and C fibres, leading to an erroneous interpretation of nociceptive stimuli (30). Peripheral nerve injury, similarly to chronic inflammation, is coupled to a persistent state of hyperexcitability of the dorsal horn neurons, a process called "central sensitization" (31, 32). The excitatory amino acid glutamate is known to be the major excitatory neurotransmitter related to noxious stimulation. Many postsynaptic receptors are linked to glutamate release but a strong evidence suggests that N-methyl-D-aspartate (NMDA) receptor subtype is the main

involved in both inflammation and central sensitization (33). The gamma - aminobutyric acid (GABA) pathway represents the major inhibition system in the CNS. The suppression of this pathway with pharmacological inhibitors is associated with a dose-dependent allodynia (34). GABA receptors level is reduced after peripheral nerve axotomy, maybe because of primary degeneration of afferent neuron terminals on which the receptor is localized. The consequent reduction in GABA activity may play an important role in central sensitization (35). A separate pathway of nociceptive modulation in CNS is the purinergic system, including specifically adenosine. Neuropathic patients show a reduction in adenosine concentration in both circulating blood and CSF, suggesting a concurrent effect of adenosine in the modulation of chronic pain (36).

Finally, the reduced ability of opiates in relieving neuropathic pain is widely accepted but the exact extent of this phenomenon is controversial. The dose response function of opiates seems to be unfavorably shifted to the right (23). This clinical evidence may be explained by loss of peripheral opiate effect, loss of spinal opiate receptors and increased activity in physiological opioid antagonism system (23).

## 5. Factors influencing the prevalence of PTPS

### 5.1 Predisposing factors for the development of chronic pain are:

- Female gender (13, 37).
- Age under 60 years (37, 38)
- Genetic factors: genetic control of pain involves several genes such as catechol-Omethyltransferase (COMT), voltage-gated sodium channels, and GTP cyclohydrolase and tetrahydrobiopterin-related genes which are characterized by high level of variability in the population (39, 40).
- Psychological factors: anxiety, depression, malignant disease and social status, may play a determinant role in influencing perception and consequences of chronic pain (13, 41, 42). However the relationship between preoperative psychological factors and PTPS should be investigated with targeted study.
- Preoperative pain and analgesic consumption: the relationship between preoperative pain and analgesic consumption and the development of chronic pain is well established for some kinds of surgery (43, 44). Moreover, assessing the preoperative pain threshold of each patient may be useful to identify risking patients at risk of postoperative pain which may lead to chronification (electrical, heat, cold and pressure tests) (45-49). Unfortunately, the role of pre-surgical pain in PTPS recurrence is still controversial (13, 45, 50, 51).

### 5.2 Perioperative factors are the:

- Type and extent of surgery (intercostal nerve damage, resection of the chest wall, pleurectomy and pneumectomy)
- Intensity and duration of pain during the first postoperative day.

#### 5.2.1 The type and extent of surgery

Many surgical approaches for thoracic cavity are described: median sternotomy, bilateral transverse thoracosternotomy, posterolateral thoractomy, muscle sparing thoracotomy and video-assisted thoracoscopy (VATS) (52).

Intercostal nerves are primarily involved in the rib cage pain transmission. The incision of the skin, soft tissue and muscles triggers an inflammatory response. The retraction of the intercostal space, and sometimes the resection of the ribs themselves, increases the damage to the costovertebral and costotrasversal ligaments with the subsequent involvement of the parietal pleura (53).

The intercostal nerve can be compressed by retractors or damaged during rib resection and closure of chest wall or can be trapped by sutures and healing processes. Nociception from mediastinic and diaphragmatic pleura is transmitted by different nervous pathways (phrenic and vagus nerves). This type of pain is deep and poorly localized. Moreover, this painful sensation triggered by diaphragmatic injury is also referred to the homolateral shoulder pain. Pleural drainage also produces deep pain due to both skin incision and pleural irritation.

In addition to surgical injury, the breathing cycle constantly involves the damaged structures, enhancing the trigger of thoracic pain.

The diagnosis of nerve injury is often associated with allodynia and/ or hyperalgesia plus numbness distributed in the area served by affected nerves.

The type of incision is strictly associated to post-thoracotomy pain and damage of intercostal nerves (54). The posterolateral thoracotomy, sparing serratus anterior and trapezius muscles, seems to minimize damaging in intercostal nerves compared to the standard posterolateral thoracotomy. Consequently, this technique is associated with a reduction of pain and improvement mobility of the ipsilateral shoulder in the first seven postoperative days.

However, several studies have questioned these results in terms of both acute and chronic pain after one year. An anterior axillary approach has been proposed to reduce the painful symptoms, but the benefit was not still confirmed by the literature. The technique used for closure of the chest wall may play a role in the intercostal nerve damage.

Nevertheless, all the different surgical approaches described above, may lead either to acute and chronic pain. This finding may be firstly explained by frequent anatomical variants in the intercostal nerves course so that their integrity is not ensured by any surgical choice. Moreover, the surgical retractor, used in all the techniques, may probably play an important role in the damage of the intercostal nerves.

The video-assisted thoracic surgery (VATS) seems to reduce the incidence of PTPS, probably because of multiple small incisions that produce a smaller nerve injury than open thoracotomy. However VATS does not preserve intercostal nerve from damage because the scope may crush nervous fibers against adjacent rib. Moreover the use of retractors to take away the lung section may also damage intercostals nerve (63-27). In conclusion VATS technique does not prevent the PTPS development but seems to reduce the PTPS incidence compared to muscle sparing incision (28)

### **5.2.2 The intensity and duration of pain during the first postoperative day**

Several prospective studies show that the most important predictor for the development of PTPS is the persistent post surgical pain which is strictly related to the severity of acute postoperative pain. Acute postoperative pain, in fact, is related to the amount of intercostal nerves damaged (55, 56). However, some studies found no clear relationship between PTPS and intensity of acute postoperative pain (1, 4, 10). The literature is not exhaustive because no study evaluates overall preoperative, intraoperative and postoperative factors which can influence the incidence of PTPS. Undoubtedly, the strict pain control is mandatory in this kind of surgery.

### **5.3 Postoperative factors**

#### **5.3.1 Social consequences**

The social impact of PTPS as capability to influence daily activities and consequently quality of life were investigated by several studies (4, 10, 13, 15, 20). Commonly the effects of PTPS are registered in the following activities: standing, sitting, getting up, sleep. Even if the pain intensity is moderate, normal daily activities could be hampered up to 50 % of cases and sleep disorders could be present in the 25% of patients (10); finally severe pain could be present in 8% and it's not relieved in more than 40% of cases (50). However, because of lack of right evaluation of this kind of disabilities, the exact impact of PTPS on social field must be better investigated.

#### **5.3.2 Disease relapse – chemo and radio therapy**

Keller et al (57) suggest that relapse of disease can uncontroversibly rise PTPS incidence. However, even if this data is obvious and well comprehensible, much more data are needed to support this evidence. Moreover, since no data are available about the effects of chemo and radio-therapy on PTPS incidence, several studies must be encouraged to understand their role on PTPS incidence.

## **6. Prevention and treatment strategies of PTPS**

### **6.1 Intra and postoperative analgesia**

Postoperative analgesia is commonly based on the use of regional anesthesia and systemic drug infusion. Different regional anesthesia techniques have been used: mostly thoracic epidural anesthesia (TEA) (58, 59), thoracic paravertebral block (PVB) (60), and, secondarily, pleural infusion or intercostal nerves block. The role of intrapleural infusion, intercostal nerve block and local infiltration in reducing PTPS is still unclear because studies evaluating this analgesic technique are confounding and lacking of exhaustive data (45).

TEA and PVB with opioids and local anesthetics mixture are the most used regional techniques. Nowadays, TEA is still considered the gold standard technique even if PVB has recently emerged as valid alternative to TEA (61).

However the role of TEA in reducing PTPS remains controversial and questionable. In any case, multimodal analgesia using different modalities as regional and systemic analgesic techniques is highly recommended (61).

On the contrary, there is no consensus on the drug to use for adjunct intravenous analgesia. Ketamine has been confirmed as a useful agent (62, 63) while COX-2 inhibitors, celecoxib i.e, were recently proposed as a valid alternative (64). Besides, only few studies reported about the efficacy of the S(+) - isomer of Ketamine (65) that has been demonstrated to have twice the anaesthetic and analgesic potency of the racemic ketamine preparation and is judged to induce less psychic emergence reactions, a reduced number of hallucinations (66) and to be followed by a more rapid recovery of vigilance (67, 68) preserving the hypoxic pulmonary vasoconstriction, enhancing oxygenation and decreasing shunt fractions in monopulmonary ventilation (52).

Only few trials have demonstrated the effect of iv ketamine as an adjunct to TEA. Suzuki et al (69) demonstrated the efficacy of 0,05 mg Kg<sup>-1</sup> h<sup>-1</sup> racemic ketamine combined with TEA with ropivacaine and morphine on acute pain control until 3 months postoperatively but not at 6 months follow-up. Dualé et al (63) confirmed that racemic ketamine (1mg kg<sup>-1</sup>h<sup>-1</sup> during surgery and 1 mg kg<sup>-1</sup>h<sup>-1</sup> in the first 24 hours) was effective in the immediate postoperative

pain but failed to prevent a reduction of chronic PTPS at 6 weeks and 4 months after surgery.

S-(+)-isomer of Ketamine has been demonstrated to be more effective than the racemic mixture with a lower incidence of side effects. Argiriadou et al (65) recently proposed the use of the S(+)-isomer of Ketamine in conjunction with thoracic paravertebral ropivacaine providing better early postoperative pain relief than ropivacaine alone or in adjunction with parecoxib.

In the last years a great interest has been elicited by the use of the preemptive analgesia and the administration of Ketamine during and after surgery to prevent and lessen the processes involved in the development of neuropathic pain (70) even if some contrasting results have been published on the use of Ketamine for postoperative pain control (71).

Patients treated with TEA in pre-emptive modality with opioids and local anesthetics showed a lower incidence of chronic PTPS if compared to patients who received only intravenous opioids (72). Moreover, the exclusive intravenous administration of opioids may induce hyperalgesia and tolerance to opioids themselves, both processes NMDA receptors activation mediated (73).

NMDA receptors antagonists may prevent the acute tolerance to opioids and, among them, ketamine at a blood concentration of 30-120 ng ml<sup>-1</sup> is able to strengthen the nociceptives effects of opioids without altering sedation indexes (74).

The preoperative administration of 0.1 mg/Kg epidural ketamine reduced the area affected by hyperalgesia and allodynia around the surgical wound in the first 30 days after incision; the same dosage given intramuscularly did not produce the same effects (75). The limitations to these observations are that the neuropathic lesion and pain could appear after a period longer than expected (76).

The administration of NMDA receptors inhibition is hampered by the need of a prolonged administration which could be more efficient via an oral route administration (77).

## 7. Conclusions

Many progresses have been done in the identification and the pathophysiological understanding of PTPS even if we are far from a well defined understanding of this syndrome. From the clinical point of view the priority resides on the continuous collaboration among anesthetists, surgeons, pharmacists and nurses to guarantee to any patient the best approach and the most correct pharmacological therapy.

Multimodal analgesia using different modalities as regional and systemic analgesic techniques is highly recommended (61).

In our opinion, pain unit in the management of patients undergoing thoracotomy is likely to warrant intensive and aggressive pain control with multimodal strategy in order to assure high level of comfort in the perioperative period and consequently reduce the incidence of PTPS.

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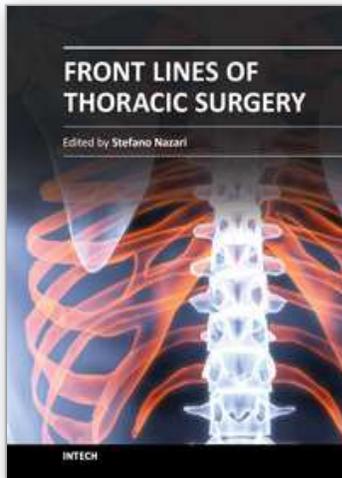
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Front Lines of Thoracic Surgery collects up-to-date contributions on some of the most debated topics in today's clinical practice of cardiac, aortic, and general thoracic surgery, and anesthesia as viewed by authors personally involved in their evolution. The strong and genuine enthusiasm of the authors was clearly perceptible in all their contributions and I'm sure that will further stimulate the reader to understand their messages. Moreover, the strict adhesion of the authors' original observations and findings to the evidence base proves that facts are the best guarantee of scientific value. This is not a standard textbook where the whole discipline is organically presented, but authors' contributions are simply listed in their pertaining subclasses of Thoracic Surgery. I'm sure that this original and very promising editorial format which has and free availability at its core further increases this book's value and it will be of interest to healthcare professionals and scientists dedicated to this field.

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