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REVIEW ARTICLE

What Can We Learn from Sarcopenia with Curarisation in the Context of Cancer Surgery? A Review of the Literature

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Abstract: ***Introduction:*** The monitoring of the curarisation is a unique opportunity to investigate the function of the neuromuscular junction (NMJ) during cancer surgery, especially in frailty-induced and age-related sarcopenia.

Method: We conducted a comprehensive literature review in PubMed, without any limit of time related to frailty, sarcopenia, age and response to neuromuscular blockers in the context of cancer surgery.

Results: Several modifications appear with age: changes in cardiac output, a decrease in muscle mass and increase in body fat, the deterioration in renal and hepatic function, the plasma clearance and the volume of distribution in elderly are smaller. These changes can be exacerbated in cancer patients. We also find modifications of the NMJ: dysfunctional mitochondria, modifications in the innervation of muscle fibers and motor units, uncoupling of the excitation-contraction of muscle fibers, inflammation.

Neuromuscular blocking agents (NMBAs) compete with acetylcholine and prevent it from fixing itself on its receptor. Many publications reported guidelines for using NMBAs in the elderly, based on studies comparing old people with young people.

No one screened frailty before, and thus, no studies compared frail elderly and non-frail elderly undergoing cancer surgery.

Conclusion: Despite many studies about curarisation in the specific populations, and many arguments for a potential interest for investigation, no studies investigated specifically the response to NMBAs in regard of the frailty-induced and age-related sarcopenia.

Keywords: Frailty, sarcopenia, neuromuscular junction, neuromuscular blockers, cancer surgery.

1. INTRODUCTION

The world population is ageing. According to the US Census Bureau, the number of Americans over 65 will double between 2010 and 2050. Americans over 65 will account for up to 20% of the population in 2030 [1]. As the same phenomenon is observed in Europe and the number of cancer surgeries in older people is increasing, we will encounter significantly more elderly people in our daily practice in the near future.

Ageing is considered as a progressive deterioration of physiological function, an intrinsic age-related process of loss of viability and increase in vulnerability [2]. The incidence of 30-day complications in ageing frail patients was significantly higher than in younger patients, limiting potentially access to cancer treatment, especially if the surgery in considered at high risk [3].

The most problematic expression of population ageing is the clinical condition of frailty. Screening pre-frail and frail old people appears to be the key for reducing surgical complications.

Frailty and sarcopenia are consequences of this ageing. Frailty is a state of increased vulnerability to poor resolution of homeostasis following stress, which increases the risk of adverse outcomes including falls, delirium and disability [4, 5, 6].

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Coelho *et al*. showed that frailty was associated with short-term (10 months) adverse outcomes [7], and screening is relatively easy in elderly patients [8]. Nevertheless, the relevance is discussed regarding the complexity of the pathophysiology. This includes one specific phenomenon, the sarcopenia.

Sarcopenia is the progressive loss of muscle mass and muscle function in the elderly [9]. Muscle mass can be evaluated by computed tomography (CT) or by magnetic resonance imaging (MRI). Muscle strength can be assessed with handgrip strength (with a dynamometer) or with knee flexion/extension [10].

During anaesthesia, neuromuscular blocking agents (NMBAs) act on the neuromuscular junction (NMJ) and, if age-related modifications in drugs' pharmacology are reported, specific modifications affecting curarisation during cancer surgery may help to understand the pathophysiological process [11].

As no study has yet directly addressed these open questions, the present work will try to answer these by a comprehensive approach of the literature, addressing the frail phenotype, the influence of age, and the use of NMBAs during cancer surgery in these patients.

2. THE FRAIL PHENOTYPE

The frail phenotype is associated with the degeneration of many systems including the nervous system. This is suspected to be the starting point of frailty.

Disorders are observed in neurons with high metabolic demands, such as hippocampal pyramidal neurons. They fail to work

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optimally, due to transport proteins abnormalities, mitochondrial and synaptic dysfunctions [12].

The endocrine system is also involved in the frail phenotype. The production of several hormones such as IGF-1 [13], oestradiol, testosterone, cortisol [14, 15, 16] is modified. Alterations in the immune [17, 18], and muscular systems are observed. These are of two types, one progressive, one stochastic.

Firstly, a decrease in muscle strength is noted. Delmonico *et al*. showed that muscle strength is reduced by 3% per year between 70 and 79 years old [19]. Reduction of motor performance is also found in the frail elderly [20]. The frailty-induced changes in skeletal muscle are defined as sarcopenia [21, 22]: Muscle function is assessed using a manual strength test with a dynamometer. Moreover, lean body mass was assessed by CT scan, and the sum of lean mass of the 4 limbs was indexed to body mass index. The limit to establish low lean body mass is < 0.789 for men and < 0.512 for women [23] . These objective criteria are validated as predictive of mobility reduction with a follow up to 3 years [22].

Two types of fibres are found in skeletal muscle:

- Type 1, which have slow twitch, using oxidative ways and resistant to fading. - Type 2, which have fast twitch, using glycolytic ways and with a fast fading.

Sarcopenia leads to a decrease in the size and number of both types of fibers, while type 2 fibers tend to be lost earlier at 70 years old [24]. In parallel, several biochemical and anatomical factors are conjointly involved: Anabolic resistance to protein nutrition [25] , loss of innervation [26], and oxidative damages [27].

Innervation impairments of muscular fibres occur at different steps from the central and peripheral nervous system to the cells of skeletal muscle. They include loss of motor neurons, decreasing the function of the remaining motor neurons and demyelination of neurons in the neuromuscular junction [26, 28, 29]. Considering all these modifications, neuromuscular blockers should act differently in a sarcopenic frail elderly. Moreover, the reliability of neuromuscular monitoring in these circumstances can be questioned.

Why does frailty affect elderly patients differently, sometimes with an apparent stochastic, unpredictable, way? [30, 31]. The complex mechanisms and events leading to frailty are dependent on both environmental and genetic factors [32, 33]. According to Kahn *et al*. even mutations in single genes can markedly affect the ageing process and longevity [34]. However, heritable components seem to account for only about 25% of an individual's life span. The authors report on two types of non-genomic mechanisms that have been identified as playing major roles in ageing and longevity. The first one includes unpredictable variations in events that occur at all levels of biologic organization from molecular to the whole organism. The second one is epigenesis. The epigenetic is defined as "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" [35] . Epigenesis is a lifelong process where the epigenetic state can change as a consequence of some stochastic event or interaction with internal (hormones, growth factors) or external (environmental stressors, diet, oxidative agents) environment. The result is a change in gene expression and in the future form and function of the cell, tissue, or organism. Being exposed to such an environment can affect in different ways the frailty in the elderly people.

3. THE NEUROMUSCULAR JUNCTION IN THE FRAIL ELDERLY

What changes are known to occur in frail, sarcopenic patients? The nerve terminal area and the number of post-synaptic folds are reduced in these patients leading to functional impairment in the post-synaptic response of the NMJ [36]. Moreover, modification in the pre-synaptic plaque occurs with ageing. They include high levels of oxidative damage, decreased number of synaptic vesicles and lower quantities of neurotransmitter released during depolarization [37, 38, 39]. Changes are observed in mitochondria of the NMJ. They are numerically reduced and morphologically modified with disruptions in mitochondrial crests, swelling, and formation of "megamitochondria" due to multiple fusions between adjacent mitochondria [40]. The role of these mitochondria is critical. They produce energy and regulate signal transduction. They are also the primary source of oxygen free radicals generated by the dislocation of electrons travelling across the respiratory chain [41]. With aging, the number of dysfunctional mitochondria increases. These dysfunctional mitochondria are associated with high levels of oxidation and nitrosylation products. Decreased enzymatic activity is noted [42]. Navarro *et al*. hypothesized in their study on Parkinson's disease (PD) that many factors are involved in PD with a constant mitochondrial involvement. They reported that there are two interdependent conditions in PD: brain mitochondrial dysfunction and brain mitochondrial oxidative damage. They observed that the diffusion of mitochondrial hydrogen peroxide and nitric oxide to the cytosol is decreased in the aged brain and may impair mitochondrial biogenesis [42]. The modifications in these dysfunctional mitochondria located in the brain of patients with PD could be correlated with the dysfunctional mitochondria we find in the NMJ of the elderly. Ibebunjo *et al*. showed that in sarcopenic rats with NMJ disruption, the expression of genes implicated in mitochondrial energy metabolism is down-regulated [43]. Because of their high metabolic demand, neurons and muscle fibers can be affected with even minor mitochondrial dysfunction [44, 45].

There are also changes in the innervation of muscle fibers and motor units. Neuron loss occurs with aging, particularly in the type 2 muscle fiber. This loss is irreversible. Chai *et al*. have shown in mice models that there was no significant difference in the size or number of motor neuron cell bodies at the lumbar level of the spinal cord at 3 and 29 months, respectively young and geriatric mice [26]. However, in the geriatric mice, there was an increase in the percentage of fully denervated NMJ. Consequently, this phenomenon leads to a smaller motor unit and atrophy of the muscles.

What about non-neuronal cells in nervous tissues? Schwann cells play a really important role in synaptic repair following denervation. They produce trophic and growth factors promoting remyelination [46, 47]. It is logical to conclude that impairment in these cells contributes to decreasing capacity to reinnervate denervated fibers, especially in the elderly. The physiology of muscles includes a coupling between excitation and contraction of muscle fibers. According to current views, there is progressive uncoupling of the excitation-contraction in the sarcopenic skeletal muscle [48]. The dihydropyridine receptor (DHPR) - a voltage-dependent calcium channel - functions in skeletal muscle essentially as a voltage sensor, triggering intracellular calcium release for excitation-contraction coupling. Ryanodine receptors (RyR) are located in the sarcoplasmic reticulum membrane and are responsible for the release of calcium from intracellular stores during excitation-contraction coupling in skeletal muscle.

With ageing, uncoupling of the excitation-contraction occurs. It is due to a mismatch between DHPR and RyR. These are more numerous than DHPR. A decreased ratio between the voltage sensor and the calcium release channel leads to reduced calcium release after an action potential, which will have as a consequence a less efficient contraction [49, 50, 51]. Clinically, this muscle strength can be assessed with handgrip strength thanks to a dynamometer.

What can we learn from another dysfunction of the NMJ? Are the modifications, for example, inferred by myasthenia gravis (MG) comparable to those observed in frail elderly cancer/non-cancer subjects? In the MG, muscle weakness is caused by circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the acting potential of the acetylcholine on its receptors at neuromuscular junctions [52]. When neuromuscular blocking agents have to be used, they should be, but

in smaller doses (10% of the ED95) and the patient should be carefully monitored [53]. Many authors have reported successful reversion of rocuronium-induced blockade by sugammadex in patients with MG [54]. Precautions taken to induce and to reverse neuromuscular blockade in patients with MG should be extrapolated to frail sarcopenic elderly.

What about inflammation? As previously mentioned, inflammation is a key player in the ageing process as in cancer. High levels of interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor alpha (TNFalpha) and C-reactive protein (CRP) are found without a clear cause. These lead to chronic low-grade inflammation in aging people, which was qualified as of "inflammaging" by Franceschi *et al*. [55]. This inflammaging accelerates the decline of muscle mass, the strength and the muscle wasting. It could, for example, down regulate the production of Insulin growth factor-1 (IGF-1) which could prevent the age-related decline in the number of DHPR and then prevent changes in the NMJ [48, 56, 57].

In conclusion, there are a lot of modifications affecting the NMJ of the elderly, partially overlapping these one described in cancer, including the mitochondria, the innervation of muscle fibers and motor units, the uncoupling of the excitation-contraction. All these modifications should change the response to curarisation.

4. THE NEUROMUSCULAR BLOCKERS IN THE ELDERLY

NMBAs compete with acetylcholine and prevent it from fixing itself on its receptor. Based on their mechanism of action, NMBAs are classified as either depolarizing (*e.g*. succinylcholine) or non-depolarizing (*e.g*. rocuronium and atracurium [58]).

Matteo *et al*. showed in their study on 40 subjects (20 between 27 and 58 years old and 20 between 70 and 78 years old) that the onset of action of rocuronium in elderly patients is no different than in younger control patients [59]. However, the duration of action of rocuronium (a non-depolarising NMBA) is longer in elderly patients. The authors hypothesized (without measuring it) that the following age-related changes account for these observations. Firstly, the plasma clearance and the volume of distribution in the elderly are smaller. Secondly, the decrease in splanchnic blood flow, liver size and hepatic cell mass found in elderly patients could interfere with the elimination of rocuronium, which happens primarily to be unchanged *via* the bile [11].

Adamus *et al*. tried to compare (in a prospective, non interventional, non blinded, clinical study) the pharmacodynamics of rocuronium following a single dose (0.6 mg/kg) in young and older males and females during total intravenous anaesthesia (TIVA) for a scheduled surgery (without other precisions) of 60 to 120 minutes [60]. A total of 158 patients were enrolled (37 young men, 43 young women and 40 old men, 38 old women). This study showed a longer onset time with ageing. Possible explanations include a lower cardiac output, a prolonged circulation time, and a decreased muscle blood flow. They noted that ageing was associated with a prolongation of the clinical duration of curarisation.

The composition of body tissue also changes: lean body weight is lower than in young people and fat tissue content is higher, which could increase clinical duration. Moreover, there is a decrease in the total body water that leads to a smaller central compartment and thus to a higher plasma concentration.

Baykara *et al*. tried to determine (in a prospective, observational, clinical comparison study) the influence of aging on the relationship between post-tetanic count (PTC) and train-of-four (TOF) response during intense neuromuscular blockade caused by 1 mg/kg of rocuronium [61]. A total of 42 patients were enrolled (20 elderly between 65 and 80 years old and 22 young patients between 18 and 40 years old) in a planned surgery of 2 hours. They concluded that the interval between the earliest appearance of a post-tetanic response and the first response to TOF stimulation (T1) was greater in the elderly than in the young. Dubois *et al.* studied the relationships existing between different time course parameters used to describe paralysis onset and offset [62]. They enrolled 60 patients between 40 and 80 years old. The patients were randomized by minimisation in three groups, receiving respectively rocuronium, mivacurium and atracurium. They concluded that after an initial bolus of any NMBA, recovering a TOF ratio of 75% is closely correlated with early recovery parameters which are time between bolus and reappearance of the first response to TOF count (T1) and time between bolus and reappearance T1 to 25% of its initial value. No distinctions were made between young and old people.

All the aforementioned studies compared a group of elderly and a group of young people. A confounding factor could be the fact that the elderly group was considered homogenous. None of these studies screened patients for possible frailty or sarcopenia, which is particularly relevant in cancer surgery.

5. RELEVANCE IN CANCER SURGERY

Cancer is a disease where sarcopenia is clearly an independent risk factor of mortality [63]. This implies the major challenge to try to identify the sarcopenic patient that may benefit from preoperative optimisation, in the hope to improve outcomes. Nevertheless, the molecular mechanisms are only partially identified in cancer-related sarcopenia. These are largely overlapping the mechanisms described above concerning the frailty-induced sarcopenia in elderly patients, as described as a combination of host-specific and tumor-related factors [64]. This overlap has been extensively suggested in animal models, with the identification of key factors like IL-6, or the C-reactive protein levels, which have been shown in return to be correlated with shorter survival in cancer patients [65, 66, 67].

CONCLUSION

We are caring for more older and frail patients during cancer surgery. Frailty has multiple consequences and sarcopenia is maybe one of the most important. Cancer induces sarcopenia in parallel, affecting directly the quality of life. The management of curarisation of these patients can be unpredictable, due to anatomical modifications, to pharmacodynamics and pharmacokinetics changes associated with sarcopenia.

Unfortunately, the opportunity to use the monitoring of neuromuscular blockade as an objective evaluation of sarcopenia, even if seductive, has never supported by strong evidence. The screening, identification and preoperative optimization of frail old people scheduled for cancer surgery remain the most important goals to prevent and decrease the adverse outcomes.

LIST OF ABBREVIATIONS

NMJ	=	Neuromuscular Junction
NMBAs	=	Neuromuscular Blocking Agents
EFS	=	Edmonton Frail Scale
CT	=	Computed Tomography
MRI	=	Magnetic Resonance Imaging
PD	=	Parkinson's Disease
DHPR	=	Dihydropyridine Receptor
Ryr	=	Ryanodine Receptors
MG	=	Myasthenia Gravis
IL-6	=	Interleukin-6
IL-1	=	Interleukin-1
TNF-alpha	=	Tumor Necrosis Factor Alpha
CRP	=	C-reactive Protein
IGF-1	=	Insulin Growth Factor-1

TIVA = Total Intravenous Anaesthesia

PTC = Post-Tetanic Count

TOF = Train-of-Four

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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AUTHORS CONTRIBUTION

GS and MDK initiated the study. GS, AS, MDK participated in the design of the study and the data collection. GS, AS, LVE, OS, MDK and PF participated in the interpretation and helped to draft the manuscript. GS and PF coordinated the study. All authors read and approved the final manuscript.

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