Abstract: Elderly surgical population is growing faster than the rate of population ageing. The risk of postoperative complication is higher in this population, the type of complication and the risk indicators are different from younger patients. There is also a huge heterogeneity in the elderly population. The concept of frailty emerges to explain these specific aspects and to risk stratify older patients. The present work intends to help the anaesthesiologist to take into account the concept of frailty at the preoperative visit. We reviewed, in the light of surgical context, the physiopathology of ageing, the definitions of frailty concept, the current existing strategies for peri-operative optimisation and the different frailty assessment tools. Our conclusions are that preoperative frailty assessment is essential in modern perioperative medicine practice and that the Edmonton Frail Scale stands out from other tools even though it cannot yet be considered as a gold standard.

Keywords: Anesthesiology; frailty; elderly; surgery; perioperative medicine.

Introduction

The risk of perioperative complications is higher in older patients, not only as far as so-called “conventional” complications leading to morbidity and mortality are concerned but also complications specifically resulting in loss of autonomy. As a result, the question is often asked during the preoperative evaluation of such patients as to whether the patient is “too old for surgery?”

There are two factors to be considered in such a question: first, the ageing process is never identical in any two patients and, secondly, the indicators of perioperative risk in an elderly patient are not the same as those in younger patients.

Currently the number of elderly patients undergoing surgery worldwide is increasing steadily, thus making the above question all the more relevant in the current and future practice of perioperative medicine, not only for the quality of the administered care but also for its financial cost-effectiveness.

Over the last twenty years, the concept of “frailty” has been developed to assist in the understanding of the physiological and functional heterogeneity that is found in the elderly population. The aim of this article is to help the anaesthesiologist to take into account the concept of frailty at the preoperative visit, this in order to evaluate more accurately the risk run by elderly patients undergoing elective surgery.

Definitions and Epidemiology

Just as a child is not a miniature adult, so an elderly person is not simply an adult worn out by the passage of time, but instead has a particular physiology that is characteristic of old age. The concept of “frailty” is useful in this context and can be defined using several distinct approaches.
Generally the majority of the medical literature in the field agrees that the physiological features connected with age are based on homeostasis and allostasis processes that are quite different from those in younger adults.

The term homeostasis was originally defined by Walter Bradford Cannon (1) in 1932 as the dynamic equilibrium which maintains life. This concept was a direct extension from Bernard’s “milieu intérieur” concept defined in 1865 (2) as the ability of a system, namely the organism, to maintain its functional equilibrium in the face of external constraints. In 1936 Hans Selye (3) defined allostasis as a “general adaptive reaction” or reaction to stress: “the exposure of an organism to any noxious agent results in the development of a typical syndrome which make up the general adaptive syndrome”.

From such basic principles arise the two principal definitions of “frailty”.

Campbell (4) described frailty in 1997 as “A global phenotype of decreased physiologic reserve introducing vulnerability and limiting a person’s ability to respond to stressors”.

Clegg (5) spoke of frailty as being the most problematic expression of population ageing. “It is a state of vulnerability to poor resolution of homeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime.”

In much the same way as the frivolous comment attributed to Binet on the subject of the intellectual quotient “intelligence is whatever my test measures” meaning that the definition of intelligence is associated with the method measuring it, so the estimates of the prevalence of frailty can vary depending on the method by which it is evaluated.

Two principal models of frailty have been described in the literature:

The phenotype model is based on 5 variables (6) and was developed by Fried in a study of 5,317 patients aged ≥ 65 years over a 7-year follow-up period.

The five variables are: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed and weak grip strength. Thus the model does not take cognitive impairment into account.

The cumulative deficit model is based on 92 separate parameters (7), including symptoms, signs, biological markers, diseases and disability. The more parameters that are present in any individual case, the greater is the level of frailty, as is the risk of death. The cumulative deficit model is seen as a continuous variable.

Depending on the particular study to be considered and the criteria applied, the estimates of the number of people who are considered to be frail in the sub-section of the general population aged more than 85 years of age varies from 25 to 50%.

Fried reported data on the prevalence of frailty and mortality after seven years of follow-up. For the 7% “frail” (3 items or more), mortality was 43%. For the 47% “pre-frail” (1-2 items), mortality was 23% and for the 46% “robust” (0 item), mortality was 12%.

Collard (8) reviewed 21 publications involving a total of 61,500 patients aged > 65 years and reported that the sex ratio was almost 2 female for one male. And the numbers of frail patients increased exponentially with age (4% in the group aged 65-69 years; 7% in the group aged 70-74 years; 9% in the group aged 75-79 years; 16% in the group aged 80-84 and 26% in the group aged more than 85 years).

It is important to note that frailty is cited from the age of 65 years and above, with already nearly one patient in twenty being classed as “frail” in the age range of 65-70 years.

Frailty was considered by Gill (9) as being the most common disorder leading to death. In his paper he highlighted frailty as the most common cause of death in 754 elderly patients with 27.9% as against 21.4% for organ failure, 19.3% for cancer, 13.8% for dementia et 14.9% for other causes.

Aetiologie

Frailty is a multi-systemic challenge that can be characterised at several levels. Over time a combination of genetic and environmental factors modifies cellular functions and can culminate in the expression of particular phenotypes.

At the molecular level, two factors playing central roles in the development of frailty are of particular interest to anaesthesiologists because of their involvement in inflammatory reactions (inflammation is a key point as in response to surgery as in ageing, which gives rise to the so-called “inflam-ageing” concept”) (10). These factors are respectively transient receptor potential vanilloid type 1 (TRPV1), nuclear factor kappa beta (NFκB).

Transient Receptor Potential Vanilloid 1

TRPV1 (also known as capsaicin receptor) is a non-selective cation channel activated by
various physico-chemical stimuli of which the most important are temperature (greater than 43°C), acid pH and capsaicin (the active component of chilli peppers) (11).

The functions of TRPV1 are nociception, in response to the above-mentioned stimuli, and the maintenance of body temperature (11, 12).

The receptor is mostly found in the nociceptive neurones of the peripheral nervous system but also in the central nervous system (where it is implicated in pathologies such as anxiety, depression and epilepsy) (13).

TRPV1 can be sensitised by a number of inflammatory mediators and this can lead to hyperalgesia or allodynia (14).

Desensitisation can take place upon prolonged exposure to capsaicin which can explain the paradoxical analgesic effect of capsaicin (11).

It appears that the role of TRPV1 in inflammation is much more than just being sensitised by inflammatory mediators. As Gupta pointed out “TRPV1 plays an anti-inflammatory role in LPS-induced SIRS by, among others, mechanisms limiting the production of TNFα” (15).

It has been shown by Wanner that ageing reverses the role of TRPV-1 channel in systemic inflammation from anti-inflammatory to pro-inflammatory (10).

Nuclear Factor kappa B

The principal function of NFκB, a multi-protein complex, is the activation of several genes involved in immune reactions (for example genes coding for cytokine production). NFκB is a “rapid-acting” primary transcription factor (16).

Its principal activators are Tumor Necrosis Factor (TNF), Interleukine 1 beta (IL-1beta), Toll Like Receptor-4 (TLR-4, sensitive in particular to bacterial lipopolysaccharide, LPS), hypoxia and reactive oxygen species (via activation of Akt/protein kinase).

Its second main function is anti-apoptotic, so playing a role in oncogenesis (17).

Wu et al published in 2015 a meta-analysis in which an association was established between the expression of NFκB and poorer survival in most solid tumors (18).

NFκB has mainly pro-inflammatory effects but it also plays a role in the resolution of inflammatory response, notably by promoting leukocyte apoptosis in certain conditions, so inhibition of this activity extends the length of the inflammatory response and can lead to chronic inflammation (19, 20).

NFκB is a link between innate and acquired immunity via the Toll like receptor by taking part in the intracytoplasmic component of LR4 signalling. In anaesthesia it is interesting to note that certain ligands of TLR especially mimic the structure of an injured cell. So NFκB plays an important role in the inflammatory reaction in surgery and thus in post-operative pain.

What’s more, as mentioned above, another essential ligand of Toll Like Receptors is LPS. So in surgery associated with gram-negative bacteria (GNB) sepsis, for example a GNB peritonitis, the TLR- NFκB axis plays a central role in the subsequent inflammatory reaction (21).

Some anaesthetic drugs interact with TLR and NFκB. For example, ketamine and opioids affect the TLR4-related intracellular signalling pathway. Ketamine and lidocaine affect with TLR4 & TLR4-mRNA expression (22).

The anti-inflammatory properties of ketamine have been well known for several years. In fact it is more a question of an anti-pro-inflammatory effect, which involves an inhibition of NFκB in addition to other mechanisms (23).

In vivo, it has long been known that glial cells exhibit a pro-inflammatory response to opioids. This is one of the phenomena involved in opioid tolerance. Morphine induces up-regulation of microglial and astrocytic activation markers but also up-regulation and release of pro-inflammatory cytokines. Morphine analgesia is enhanced by blocking pro-inflammatory cytokines action but also enhanced with attenuators (e.g., minocycline) and astrocytes inhibitors. There is also evidence that opioids may have toll-like receptor 4 effects (24).

In a recent review on the central role of nitric oxide (NO) in the regulation of cellular oxygen consumption via an inhibitory effect on the mitochondrial respiration/oxidative phosphorylation, Stefano (25) emphasises the interactions between morphine and mitochondrial respiration via functional recruitment of NO action. It is interesting to note that only opiates alkaloid have this property unlike the synthetic opiates fentanyl and methadone. The explanation can be that the mu3, which is an opiate alkaloid selective and opiate peptide insensitive mu receptor subtype, is coupled to constitutive NO production. Even more interesting in the context of this chapter is that constitutive NO production inhibits NFκB in a variety of cells as monocytes. So morphine, but not opioid peptides, modulates NFκB activation and may exert immunosuppressive effects via constitutive NO release.
Stefano also points out a functional link between morphine and inducible NO synthase (iNOS). In septic shock physiopathogenesis, excessive induction of iNOS contributes to vasodilation, myocardial depression and systemic hypotension. Lipopolysaccharides (LPS) and interferon (IFN) stimulate iNOS activity and expression but prior exposure to morphine blocks this stimulation. This morphine ability is explained by its action on constitutive NO production. As a matter of fact, cNOS-coupled NO release is linked to iNOS expression and once cNOS is stimulated, iNOS synthesis cannot be induced. The review also emphasises that cNOS derived NO down regulates cells to become less active and has been shown to be protective in a hypoxic and/or ischemic.

So with these data Stefano speculates in the same publication that with aging an increasing number of mitochondria become dysfunctional and that mitochondrial dysfunctions may be involved in the physiopathogenesis of neurological diseases, given the high oxygen needs of brain structures (e.g., Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, stroke, amyotrophic lateral sclerosis). In the context of a diffuse inflammatory response to surgery, morphine may represent a natural down regulation mechanism of immune, vascular and neural responsiveness. Finally, an insufficient inhibition by endogenous morphine may be involved in chronic inflammatory states (e.g., inflammaging concept).

Propofol also has anti-inflammatory properties. The molecular mechanisms responsible for this involves NFκB inhibition (26, 27).

The effect of halogenated ether on NFκB is still a matter of discussion (28, 29). The role of NFκB in ischemic-reperfusion induced cardiac lesions and in peri-operative cardiac protection has been the subject of several studies (30, 31).

As anaesthetists, thus we modulate the TLR4- NFκB intracellular signalling pathway. The consequences of these acute changes are still to be defined.

We can also impact the action of the TLR4- NFκB intracellular signalling pathway to treat pain and some side effects of opioids.

In summary, NFκB is a “master regulator of the inflammatory response”. He can also regulate a great variety of homeostatic responses such as apoptosis, autophagy, and tissue atrophy. Salminen described the ageing process as “an entropic degeneration process driven by NFκB signalling” (32). Sallam and Laher have reviewed the protective role of exercise against aging, and highlighted its antioxidant and anti-inflammatory effect in which the role of NFκB appears once again (33).

**Systemic phenotypes**

**Central nervous system**

With age, neurodegeneration and loss of synapses can be seen, predominantly in the hippocampus (34). It should be recalled that neurodegeneration in the hippocampus has been associated with Alzheimer’s disease (35).

Likewise a preponderance of microglia (immune cells) has been observed and the response of these cells to small stimuli can become excessive and can lead to neuronal death (36-38).

In fact this process is one of the pathophysiological models of delirium, a common post-operative complication in older adults (39). Delirium is associated with poor outcomes including functional decline, longer hospitalisation, institutionalisation, greater costs, and higher mortality (40).

All these studies demonstrate a robust link between frailty, cognitive impairment and dementia and a link can also be established with inflammation.

**Hormones**

The endocrine system plays a central role in the maintenance of homeostasis and in tissue trophicity. The connections between ageing and hormonal metabolism have been the subject of research since the middle of the 20th century (41, 42).

A central regulatory factor in the endocrine system is the hypothalamus-pituitary complex. Throughout the ageing process, the synthesis of several hormones of this complex declines significantly.

The levels of insulin growth factor 1 (IGF-1), an anabolic hormone which acts on neurons as well as skeletal muscles, decrease as a result of a decline in the production of growth hormone by the pituitary (43).

Through a feedback loop, the decline in the gonadal sex steroids results in an increase in the circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) (44).

The circulating levels of dehydroepiandrosterone (DHEA) and of dehydroepiandrosterone sulphate (DHEAS) decline progressively with age due to a drop in their production by the adrenal gland (45).
In contrast, the levels of cortisol, the archetypal catabolic hormone, tend to increase with age (46).

High cortisol release associated with delirium has been reported in elderly patients with hip fracture (10, 47).

It is well known, principally from studies on young patients, that halogenated ethers mildly suppress the cortisol response to surgery while propofol anaesthesia depresses the cortisol response more significantly (48, 49).

Deiner et al. published their results on perioperative stress markers in the elderly (greater than 68 years of age) and confirmed that for these patients a perioperative diminution of cortisol level in the propofol TIVA group in comparison with an increase in the cortisol level in the sevoflurane group (50).

The most effective anaesthetic technique to suppress cortisol response in surgery remains spinal anaesthesia but a meta-analysis carried out in 2010 showed that, for postoperative delirium, there were no statistically significant differences between general anaesthesia and regional or combined anaesthesia (51, 52).

Overall, the various endocrinal consequences of the ageing process produce the effect of loss of muscle mass, anorexia, weight loss and reduced energy expenditure which could lead to, or at least be associated with, frailty (53-55). Again, a link can be established with inflammation and with delirium.

**Immunity and inflammation**

The innate and adaptive branches of the immune system develop in different ways during the aging process.

The innate immunity system tends to maintain its effectiveness or even become hyper-responsive. An increase in the activity of NK cells has been observed as well as increased transcription levels of NFκB and an increase in the levels of pro-inflammatory cytokines (32, 56). Overall this can lead to a low-grade inflammatory state (“inflam-ageing” concept) which is characterised by a hyper-responsiveness to stimuli which persists long after removal of the stimuli (57). It should be remembered that aging has the effect of inverting the role of vanilloid-1 receptor (TRPV1) in the inflammatory process (10).

In contrast to innate immunity, the adaptive immune system undergoes a change during aging which can range from a simple diminution in effectiveness to a complete shutdown (“immunosenescence” concept).

This can be explained by a decrease in the number of naive T lymphocytes, a reduced level of activation (CD 29), a decline in humoral immunity, an increase in memory T lymphocytes and an increase in the process of apoptosis. All this can result in a reduced defence to new antigens, a reduction in the efficiency of vaccines and reactivation of latent viral infections such as CMV, Varicella, Zona, etc... (58).

Thus inflammation plays a central role in ageing and in post-operative complications such as delirium and pain.

**Sarcopenia**

Normal muscle homeostasis is maintained in a delicate balance between new muscle formation, hypertrophy and protein loss. This balance is coordinated by the brain, endocrine and immune systems, and is affected by nutritional factors and physical activity. Ageing shows a progressive loss of skeletal muscle mass, strength and power meaning sarcopenia (5).

**The stakes in perioperative medicine**

**Why Frailty is essential in geriatric surgery?**

The issue of ageing is a major one with implications for both current and the future practice of anaesthesia. Indeed, the number of elderly persons in the world has never been so high and looks set to increase continually throughout the 21st century from an estimated 465 million elderly persons in 2004 through to an estimated 2 billion in 2050 (59, 60).

What’s more, the total number of surgical procedures to be carried out in elderly patients is increasing at a significantly higher rate than that of the elderly population itself (61, 62).

The incidence of 30-day postoperative complications in the elderly population is significantly higher than with younger patients (63-67) and has consequences not only in terms of morbidity and mortality but also in terms of loss of autonomy and socio-economic losses (68-71).

We are thus faced not only with a population at risk but also one which is growing significantly in purely numerical terms. In addition, in this particular population the risk of postoperative complications cannot be predicted from the chronological age, the ASA classification nor from an exhaustive list of co-morbidities (35, 39). There is also an inability to predict hospital costs using the traditional
preoperative risk stratification models based on baseline co-morbidities and end-organ dysfunction (72-75).

From a purely practical and clinical point of view, Revenig (76) underlined “The need for a standardised, easily reproducible, verified, preoperative risk assessment tool to predict postoperative outcomes. It would greatly aid anesthesiologists and surgeons in preoperative decision-making in the hope of limiting postsurgical complications and improving health outcomes”.

In the elderly population frailty has been shown to be an independent risk factor for postoperative complications and outcomes (77, 78), not just for cardiac surgery but also for non- cardio-thoracic surgery (71-80).

Frailty can also predict length of stay, hospital and post-hospital costs, functional dependence and the need for institutional discharge (68, 69).

It is interesting to note that in their studies, Robinson et al employed a definition of frailty that is easily applicable during the preoperative visit and is based on the addition of 7 items. These are respectively the up-and-go time, the dependence on activities of daily living, the mini-Cog score (cognition assessment test shorter than 3 minutes), albumin level, haematocrit, occurrence of falls in the 6 previous months and the Charlson Index Score (which is a comorbidity score) (81).

The concept of frailty is thus directly pertinent to the fundamental question in perioperative medicine, namely the estimation of the likely risk to the patient so that the appropriate surgical indication (or contraindication) can be determined in order to allow a genuinely informed consent to be obtained and to establish a perioperative and postoperative medical strategy optimally adapted to the needs of the patient. The question of whether surgery is indicated in the elderly person is all the more relevant since there exist alternative procedures considered as minimally invasive, such as Transcatheter Aortic Valve Implantation (TAVI), endovascular abdominal aortic aneurysm repair, prostate radiation therapy, etc, ...

Links between preoperative assessment and outcomes

The other essential question to be posed in perioperative medicine is the determination of whether the likely outcome of a frail patient can be improved by optimisation of the perioperative processes.

The concept of Enhanced Recovery After Surgery (ERAS) was developed to optimise pre-, per- and post-operative strategies. According to Scott, several factors can be considered as key ERAS elements for use in the preparation of patients for surgery. These are risk assessment, optimisation of pre-existing organ function and education.

The following section will deal with the various objectives of pre-operative assessment, firstly from a general point of view and then more specifically in the geriatric context.

According to a recent review published by Partridge (82) “a pre-operative comprehensive geriatric assessment is likely to have a positive impact on postoperative outcomes in older patients undergoing elective surgery but further definitive research is required”.

It is unclear if frailty is an irreversible dynamic process that inevitably evolves to a worsening state, and so is only a prognostic marker, or if improvement can occur, with or without intervention. Lack of a consensus regarding the frailty definition is probably one of the explanations of this incertitude (5, 83-85).

The objective is therefore to improve the postoperative recovery of frail patients without necessarily focussing on the pre-operative improvement of the parameters defining frailty. A standard definition (or measure) of postoperative recovery has not yet been established; Lee recommends measures that functional status and performance should be used (86).

For physio-pathological reasons, the cardio-respiratory capacities of patients have long been the target of studies aimed at the assessment or improvement of a patient’s ability to recover from surgery. Indeed, major surgery leads to a significant systemic inflammatory response and so an increase in oxygen consumption (VO₂). To respond to this, an increase in oxygen delivery (DO₂) is needed and so an increase of cardiac output (CO) and tissue oxygen extraction (ERO₂).

Cardiopulmonary Exercise Testing (CPET) is a non-invasive stress-test which allows the evaluation of an individual’s VO₂ and DO₂ capacity as well as the anaerobic threshold (“AT”, this is the point at which anaerobic metabolism supplements aerobic metabolism with additional CO₂ production).

Several studies have shown a link between poor CPET performance and more specifically lower AT, with accompanying increased postoperative mortality and severe morbidity in major non cardio-thoracic surgery as well as in cardio-thoracic surgery, whether oncologic or not (87-96).
As for AT, as long ago as 1993, a threshold value of 11 ml/kg/min was established as a cut-off point for the prediction of post-operative complications after various surgical procedures in patients older than 60 years of age. Several other studies have confirmed this threshold value in elderly patients (89-98).

The review article published by Levett in 2015 confirmed the association between this threshold value and a statistically significant increase in mortality, in the length of hospital stay and in post-operative costs (92).

So CPET is a valuable tool for studies or for second stage testing but simple clinical scores and screening biomarkers are more useful for screening patients at low cost (92, 95).

An even simpler tool is the 6 minutes walking test (6MWT) which measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. Gillis describes the advantages of the 6MWT as “a measure of recovery include the lack of a ceiling effect and the fact that it is not affected by response shift, unlike self-reported symptoms or health-related quality of life. It does not require specialised equipment and can be administered even in a small place” (99).

Correlations have been established between 6MWT and VO₂/AT values determined by other exercise testing (100).

It is particularly useful to test functional exercise capacity, by which is meant “the ability to undertake physically demanding activities of daily living” (101).

Lee showed that there was an association between lower preoperative values of 6MWT and an increased risk of postoperative complications (102).

It was validated as a measure of post-operative recovery in the colorectal surgical population (103, 104).

In the context of the above concept, what is even more interesting is that 6MWT can discriminate between low and high AT and so could be used instead of CPET. Using linear regression-based techniques, Sinclair obtained a low and a up values for 6MWT (>563m or < 427m) that are predictive for an AT likely to be upper of lower than 11 ml/kg/min. Thus, this test is a method that is particularly useful as a preoperative screening process, reserving more elaborate tests for patients whose 6MWT values lie between these 2 limits (100).

In the specific case of cardiac surgery, several specific predictive scores have been developed and rigorously validated, such as EuroSCORE, EuroSCORE II and STS score (Society of Thoracic Surgeons). Several authors have, however, warned against the weaker predictive value of such scores in patients aged 70 years or older because the scores do not evaluate the ‘biological age’ and frailty status of patients (105).

Simon showed that in the case of cardiac surgery in patients aged 74 years or more, frailty is a predictor of short and midterm mortality independent of age. He recommends the use of CAF (the comprehensive assessment of frailty and FORECAST (Frailty predicts death One year after CArdiac Surgery Test) as additional tools for the evaluation of these elderly patients (106).

Other authors agree with this approach by showing that frailty provides incremental prognostic value above surgical risk scores for predicting mortality or major morbidity in cardiac surgery and that frailty is an independent predictor of in-hospital mortality, institutional discharge and reduced midterm survival (107, 79).

Strategies for peri-operational optimisation

After risk assessment, the second step of ERAS is optimisation of organ function and education. Scott and Carli insisted on the need to involve a multidisciplinary team including anaesthesiologists as well as surgeons, internists, nurses, nutritionists, physiotherapists and psychologists. Of course, they underlined the importance of increasing the patient’s physiological reserves and pharmacological optimisation but they also insisted on the need to educate both patient and caregivers about the process (108).

Because of the demonstrated importance of the functional physical capacity as a predictor of post-operative recovery, initial pre-operative interventions focussed on improvement of physical condition through exercise but the results of this one goal-directed strategy were disappointing.

In 2011, a review of 12 randomised controlled trials (RCT) reported that in patients undergoing cardiac and abdominal surgery, there was a decrease in the length of hospital stay and there were fewer pulmonary complications after preoperative exercise (109).

However in 2013, another systematic review of 8 RCTs failed to demonstrate that physical exercise alone provided physiological improvement and clinical benefit (110).

Moreover, a RCT from Carli comparing moderate versus intense preoperative exercise found that there was actually a deterioration in
functional walking capacity in a third of patients assigned to the intense exercise program. This was associated with very low compliance, implying that this intensity could not be maintained by these patients (111).

Carli and his team continued their work and postulated that preoperative exercise, anxiety-reducing strategies, and protein supplementation may facilitate postoperative recovery.

In 2014, Gillis and Carli published the results of a RCT comparing a strategy of prehabilitation versus rehabilitation in patients undergoing colorectal resection for cancer. For four weeks before surgery, the prehabilitation group received a triple program of moderate-intensity aerobic and resistance exercises, nutritional intervention (diet counselling and protein supplementation) and relaxation exercises. The rehabilitation group received the same program but immediately after surgery. Both groups continued the program for 8 weeks after surgery. At this time it was found that prehabilitated patients were able to walk significantly further in 6 min than the rehabilitation group. It is interesting, but hardly surprising, to note that compliance with the post-operative recovery program was greater in the “prehabilitation” group than in the “rehabilitation” group. There was, however, no difference in clinical outcomes between the prehabilitation and rehabilitation groups (99).

Nevertheless, the authors themselves pointed out that “It is unclear which component of the trimodal intervention contributes most to recovery, or whether the increase in functional walking capacity is an effect of trimodal synergy”.

From the point of view of economics, Lee showed that there were medical cost savings with no increase in morbidity or mortality through use of a multidisciplinary enhanced recovery pathway for oesophagectomy (112).

Dunne showed the value of preoperative assessment by CPET in an ERAS program. He showed that if CPET is used to determine perioperative management, a low AT value does not place patients at significantly higher risk of postoperative complications. Dunne considered that “this suggests CPET-assessed poor fitness should not be used as a barrier to surgical intervention” (90).

HOW ASSESS FRAILTY?

As discussed above, “traditional” preoperative risk assessment is difficult in elderly patients because he is based on existing organic deficiencies (ASA classification) and do not take into account the functional physiological reserve of the patient, nor the patient’s ability to react to a surgical stress where the processes of homeostasis and allostatics have central roles to play in elderly patients.

As shown above, these difficulties provide the rationale for the development of a preoperative evaluation of the degree of frailty in the elderly patient.

In this context, the comprehensive geriatric assessment (CGA) can be considered as the gold standard. The CGA is focussed on elderly individuals with complex problems and on their functional status and quality of life. In the course of time, this concept has evolved in different ways to meet differing needs but some key features can be identified, such as: multidisciplinary assessment; geriatric medicine expertise; identification of medical, physical, cognitive, social, functional and psychological problems; the setting up of a plan of care including appropriate rehabilitation and the monitoring of the application of the plan. The CGA is a complex process and takes some time (30 to 90 minutes for a first “rapid” evaluation) and therefore expensive, so markedly different from a simple score or risk scale (113).

This system has been validated as a sensitive and reliable tool for the detection of the level of frailty and is predictive of death and also the need for institutional care.

However as pointed out above the CGA is expensive and time-consuming and is more suitable for clinical studies or as a reference against which a simpler test can be validated or in the case of initiating long-term geriatric care. In any case the CGA is not appropriate for a rapid clinical screening test during a pre-operative visit.

Several scores and standardised questionnaires have therefore been set up.

In their 2012 review, Bouillon et al. described 27 relevant publications dealing with the measurement of frailty. These publications can be classified in three categories: self-reported items only (11/27); directly measured components only (5/27) or both (11/27). According to Bouillon et al.’s review of the literature, the most frequently used scores were the Fried’s Frailty Scale (69%), Mitnitski’s Frailty Index (12%) et the Edmonton Frail Scale (4%). There is, however, a bias in these statistics since the analysis penalises the most recently introduced scores as well as the fact that the publications originating from the authors’ close circle of influence were not excluded (114).
Based on the recommendations in the Standards for Educational and Psychological Testing, Bouillon et al considered that it was vital that information be available on the basic principles of the development of the test such as reliability and validity. Only seven of the papers in the review actually provided such information. These were: the CSHA Clinical Frailty Scale; the Edmonton Frailty Scale; the Groningen Frailty Indicator; the Subjective Frailty Score; the Tilburg Frailty Indicator; Klein’s Frailty Index and the Clinical Global Impression of Change in Physical Frailty.

In preoperative anaesthetic consultations, what is needed is a rapid test that can be carried out easily by non-geriatricians and which addresses potentially reversible factors (with a view to preoperative optimisation of the state of the health of the patient). According to Partridge (82) the ideal tool for preoperative evaluation of frailty must enable risk stratification (and therefore be validated surgically) and must address potentially reversible factors (with a view to preoperative optimisation of the state of the health of the patient). We would add that such an ideal test should also be able to be carried out easily by non-geriatricians and must have ideally shown its validity in defining frailty with respect to the Gold Standard in the field, namely the Comprehensive Geriatric Assessment (CGA).

The seven scores mentioned above will now be analysed using these criteria:

The CSHA Clinical Frailty Scale is a subjective opinion (a ranking on a scale of 1 to 7) that the clinician attributes to the patient after a structured and relatively detailed geriatric anamnesis has been established. The CSHA Frailty Scale has not been validated in the perioperative context. Being totally subjective, it does not enable the objective targeting of factors that should be optimised. The actual time needed to carry out the test has not been specifically described but it is established only after a detailed geriatric consultation (it was in this context that the scale was validated) and therefore is not suitable for a preoperative screening program (7).

Gerdhem’s Subjective Frailty Score involves making a general assessment of health and appearance within 15 sec from first sight of the patient and the recording of this in an arbitrary scale. It therefore suffers from the same drawbacks as the CSHA-CFS apart from the fact that it is extremely rapid to establish (114).

Klein’s Frailty Index is totally based on four objective performance characteristics, namely: a timed 10-ft walk (score=1 if in the highest quartile, stratified by sex); handgrip strength (score=1 if in the lowest quartile, stratified by sex); peak expiratory flow rate (score=1 if in the lowest quartile, stratified by sex) and the ability to stand from a sitting position without using the arms in one try (score=1 if unable). The index has only been validated with respect to visual acuity and contrast sensitivity and only evaluates the physical capacity aspects of frailty. The time needed to actually measure the index has not been described but seems on the face of it to be suitable for a preoperative visit (115).

The Clinical Global Impression of Change in Physical Frailty is a mixed score used to evaluate changes in physical frailty. It includes 38 items from several areas e.g. mobility, balance, strength, endurance, nutrition, and neuromotor performance, medical complexity, healthcare utilisation, appearance, self-perceived health, activities of daily living, emotional status, and social status. It deals well with the various aspects of frailty but has been designed to detect and monitor changes and has been validated in this context by a panel of experts and clinicians n panel with respect to Web-based cases. The score is not intended for non-geriatricians. It takes geriatricians 10 minutes to establish the score (116).

The Groningen Frailty Indicator (GFI) is a one-dimensional scale validated in home dwelling and institutionalised elderly people and based on an overall sum score of 15 self-reported items. A person is considered as frail if the GFI score is 4 points or higher, without reference to specific geriatric problems such as sensorimotor, cognition, mobility or psychosocial dysfunction. Tegels showed a significant relationship between mortality from gastric cancer surgery and GFI while Pol showed the utility of GFI in the preoperative detection of those vascular surgery patients at high risk of postoperative delirium. It is simple and relatively rapid, thus making it suitable for use in a preoperative visit. However it has not been designed to differentiate the multiple dimensions of frailty although a publication by Bielderman suggests that a multidimensional assessment of frailty with the GFI is possible. It has not been validated with respect to CGA (117-120).

The Tilburg Frailty Indicator is a self-reporting questionnaire of 25 items with responses provided from three areas: physical, psychological and social. One of the advantages of the indicator is that it doesn’t include questions on disability. It appears quite appropriate for use in preoperative consultations but it has not been validated, neither with respect to CGA nor in a perioperative situation (121-124).
Similar results were found in other animal models (128).

Although it remains to be demonstrated formally, these nutritional interventions appear to exert their beneficial effects on endothelial function via activation of cell homeostasis/stress resistance pathways that inhibit inflammation and oxidative stress (136-138).

**Pharmaceutical drugs**

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, calcium channel blockers, statins, thiazolidinediones, and beta blockers generally improve endothelial function in older patients with cardiometabolic diseases or cardiovascular risk factors (128).

Some data also indicate a possible interest in using these medications for primary prevention in the elderly (138, 140).

NSAID, aspirin and some salicylates can improve endothelial function in older animal models via antioxidant effects (141-143).

Mitochondria are a major source and target of vascular oxidative stress when dysregulated. This mitochondrial dysregulation is associated with primary ageing and so it is particularly studied (144).

Gioscia-Ryan showed that a mitochondria-targeted antioxidant ameliorates vascular endothelial dysfunction in old mice. She also showed that these improvements are associated with the normalisation of mitochondria-derived oxidative stress and markers of arterial mitochondrial health. This also confirms the fact that mitochondria-derived oxidative stress is an important mechanism underlying the development of age-related vascular endothelial dysfunction and so may be a promising therapeutic target (144).

N-Acetyl-L-Cysteine is well known for being a powerful antioxidant (145). It also enhances lymphocyte and phagocyte membrane function (146) and has anti-cancer activity (147).

Furthermore, Oh and al. demonstrated an increased lifespan on Caenorhabditis elegans (worms) by N-Acetyl-L-Cysteine via an increased resistance to oxidative, UV and heat stresses (148).

Nutraceutical compounds, vitamins and adaptogens

Evidence of the antioxidant and anti-inflammatory properties of polyphenolic phytochemicals are broadly accepted. Furthermore, recent studies...
suggest that polyphenolic phytochemicals that share structural similarities to curcumin have antidepressant properties that may be linked to their effects on serotonergic neurotransmission, hypothalamic–pituitary–adrenal axis activity and forms of plasticity that include hippocampal neurogenesis (149).

Several of antioxidant compounds derived from natural products (nutraceuticals) have demonstrated neuroprotective activity in either in vitro models of neuronal cell death or in vivo models of neurodegeneration (150).

Many of these natural antioxidants are not only active scavengers of free radicals but also modulators of pro-survival or pro-apoptotic signaling pathways. Here are some of these molecules (150).

Among the flavonoid polyphenols, we found Epigallocatechin 3-Gallate (from green tea) and Quercétine (from apple and capers). In the non-flavonoid polyphenols family is Resveratrol (natural compound of red wine) and Curcumine (from Curcuma longa). Rosemary belongs to group of phenolic acids and diterpenes. At least, the organosulfur compounds with Alllicin (from garlic) and L-sulforaphane from broccoli and other cruciferous vegetables.

Vitamins C, E and D, lipoic acid, Tempol (a superoxide dismutase mimetic), omega 3 & 6 fatty acids and also folate are endothelial function protectors but the evidences of this effect depend of studied populations and experimental protocols (doses, duration, molecules association). They also act as antioxidant and anti-inflammatory (128).

Adaptogenes (as Ginseng, Echinacea, Rhodiola, etc…) are also studied intensively in anti-ageing medicine context, especially for their antioxidant and anti-inflammatory properties (and even neuroprotective, according to some studies) (151-153).

**Hormonal therapies**

Bao published in 2014 a review of endocrine therapy in ageing context. Among those, hormone replacement therapy is still the most used today (the most common 4 are growing hormone, androgens, oestrogens and progesterone). Endocrine therapy, especially hormone replacement therapy, generally demonstrated be able to improve some ageing symptoms but at the price of a lot of side effects, including an increased risk of cancer (154). The future anti-ageing endocrine therapies will probably interact directly on critical genes of the endocrine regulatory networks (154, 155).

**Melatonin**

Melatonin, well known as circadian rhythm regulator, has pleiotropic properties which are summarised in Vaiserman’s review (128).

Melatonin show direct free radical scavenging and indirect antioxidant effects. It has anti-inflammatory and immunoregulating properties and also is an oncostatic agent.

Ageing and some ageing-related pathologies are linked to the loss of melatonin secretion and to the decline of circadian amplitude of the melatonin rhythm (128, 156).

On Drosophila Melanogaster modeld, Izmaylov and Bonilla showed an increase of lifespan effect of melatonin but Teran showed not only an increase in maximum lifespan but also a decrease in mean lifespan (157-159).

On Mus musculus model, Anisimov and Rodriguez showed an increase in lifespan effect of melatonin (160-162).

**Preconditioning**

Cardiac ischemic preconditioning represents the most powerful endogenous protective mechanism against ischemia (163).

This phenomenon is an adaptive mechanism in response to brief episodes of myocardial ischemia and it is able to reduce the cellular damage subsequent to a more prolonged ischemic injury (164).

Several studies demonstrate that ischaemic preconditioning is reduced with aging in both experimental and clinical (164).

This lost of effectiveness with ageing is due to alterations in gene/protein expression, signal transduction cascades, and mitochondrial function (165, 166). Anaesthetics induced preconditioning also decrease with advancing age (164).

In his review, Abete highlighted that a lot of pharmacological stimuli failed to induce an ischemic preconditioning in the ageing heart excepting nicorandil, a mitochondrial potassium channel activator.

On the other hand, some lifestyle interventions such as exercise training and caloric restriction separately, and more powerfully taken together, are able to completely preserve and/or restore the age-related reduction of ischaemic preconditioning in both animal and human studies (164).

Zhu demonstrated that a 4 weeks 4-Hydroxy-TEMPO treatment restores isoflurane preconditioning in the senescent rat heart (167). This effect is
associated a significant improvement of mitophagic response (168).

**Perioperative issues**

We need more studies of the postoperative outcome effect of these different preoperative interventions. For this, we also need to determine a few objective tests to evaluate the patients and check their actual health status, and also to evaluate the effect of the type of therapy they receive. It will also be important to consider the duration of the therapy in order to reach the maximal beneficial effect before surgery.

Among these potential tests, IL-6 serum levels, endothelium function markers or tests and heart rate variability will be discussed in this chapter.

**IL-6**

Inflammatory markers such as IL-6 increase with age and are robustly associated with incident disease, disability and mortality (including cardiovascular disease, diabetes and cancer) (169, 170).

IL-6 appeared to be the principal “not at risk” marker for mortality and frequency of hospitalisation and could reflect the extent of comorbidities/disability and so the risk of decreasing health. For Adriaensen, “a single measurement of low IL-6 serum levels should become the first choice to guide clinical practice in the oldest old and could summarise the short-term risk of death and hospitalisation” (171).

In cardiac surgery with cardio-pulmonary bypass context, IL-6 levels rose throughout the period of myocardial ischemia and reperfusion in young and old patients but was greater (threefold higher) in the age group >70 than patients who are aged <70. In the same study, the myocardium does not appear to be the principal source of the IL-6 production and/or release, as the levels of IL-6 were similar in the coronary sinus and the ascending aorta (172).

Sander correlated increased IL-6 levels during cardiac surgery in all age patients with an increased risk of infection (173).

In fact, interleukin 6 is a predictor of postoperative systemic inflammatory response syndrome, and is able to do it before the onset of clinical symptoms. Postoperative systemic inflammatory response syndrome and sepsis are associated with high morbidity and mortality rates. Early detection of postoperative systemic inflammatory response syndrome improves the outcome (174).

Peak IL-6 concentration is associated with the magnitude of the operative injury and operative procedure. This peak occurs 12–24 hours postoperative and circulating IL-6 concentrations have been reported to be reduced dramatically by 48–72 hours in patients with no postoperative complications (170).

According Watt, these markers may also help to assess which components of Enhanced Recovery after Surgery are likely to improve patient outcome (170).

**Endothelial function**

Large studies demonstrated that the age-associated phenotype of arteries involves, among other changes, the development of a dysfunctional arterial endothelium. This dysfunctional endothelial phenotype is common to humans and non-human primates as well as rodents (175).

A major sign of vascular endothelial dysfunction is impaired endothelial dependent dilation, which is predictive of future cardiovascular disease (175).

Increased age is the strongest independent correlate of endothelial dependent dilation and oxidative stress and inflammation are the major mechanisms of endothelial dysfunction with advancing age (175).

Reciprocally, recent studies indicate that endothelial cells can be an important contributor to chronic inflammation and to the development of age-related diseases (176).

The gold-standard evaluation of impaired endothelial dependent dilatation remains the direct measurement of this dilation during coronary angiography. However, various indirect approaches can be found in general practice (e.g. the measurement of brachial artery diameter via non-invasive ultrasound imaging in response to flow-mediated reactive hyperaemia). These measurements of peripheral arterial vasoreactivity are concordant with coronary artery endothelial-dependent and checked in controlled comparative studies (177).

Circulating plasma biomarkers can reflect pathogenic events occurring within developing lesions per se (e.g. IL-1, IL-6, soluble VCAM, sE-selectin) as well as CRP or high-sensitivity CRP (177).

It suggests that there should be an intrinsic link connecting vascular ageing, ageing of the whole organism, and ageing-related diseases (178).
Heart rhythm variability

Reduced heart rhythm variability has long been known to be a good predictor of cardiovascular morbidity and mortality (179, 180).

Heart rate variability decreased with ageing, independent of pathological conditions or medication use. This fact suggests that cardiac autonomic modulation diminishes due to normative aging (181).

In his review, Nicolini found several studies which demonstrate that reduced linear and nonlinear measures of heart rhythm variability or abnormal heart rate turbulence are associated with mortality in the general elderly population (180).

Not in a perioperative context, Mahinrad found a link between lower 10-second heart rate variability and worse performance in reaction time and processing speed, independent of medications, cardiovascular risk factors, and comorbidities. This kind of fast and simple clinical test is potentially very interesting in the context of a preoperative evaluation among the frailty patient (182).

**Conclusion**

Elderly people have a (patho) physiology which is unique to this class of patients, particularly as far as the reaction to stress situations such as surgical operation is concerned.

In anaesthesia as perioperative and preventive medicine, it is essential to stratify risk in order to enable practitioners to balance the advantages and benefits of invasive procedures, to choose a non-invasive procedure if necessary, to enable the patient to give true informed consent and to implement perioperative strategies for the patients at highest risk.

To attain these objectives, the evaluation of the frailty of the elderly patient is vital given that such patients have an increased level of complications whose risk cannot be predicted through use of the same methodology and tools as those used with younger adults, not to mention hospitalisation and post-hospitalisation costs. This represents both a current and future challenge given the growing number of elderly patients in the general population, and even more so in the population requiring surgery. “Not too old for surgery but too frail”.

It has recently been shown that a strategy of pre-operative optimisation could slightly improve patients’ post-operative recovery. These strategies are useful but do not yet prove to really change the post-surgical outcome. Nevertheless, and although this has not yet been evaluated in a purely geriatric context, this kind of strategy still seems promising for use with frail patients. Studies also indicate that savings could be made in healthcare costs.

From a practical point of view, there are a number of tools available which can be used to detect and measure frailty. In the preoperative situation, the Edmonton Frail Scale stands out from other such tools even though it cannot be considered as a gold standard given the current state of evidence.

Given that most studies on frailty have shown the advantages described above and have been carried out in patients aged 65 years and over, it seems logical to recommend that frailty should be determined routinely at pre-operative visits for patients of this age.

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