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REVIEW ARTICLE

Rheumatoid arthritis and anaesthesia

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Summary

There has been a great deal of progress in our understanding and management of rheumatoid arthritis in recent years. The peri-operative management of rheumatoid arthritis patients can be challenging and anaesthetists need to be familiar with recent developments and potential risks of this multi system disease.

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Rheumatoid arthritis (RA) is an autoimmune disorder characterised classically as an erosive, symmetrical polyarthropathy most commonly involving the synovium-lined joints of the hands and feet. It is a multisystem disease that may affect the function of other joints and organs in the body. Orthopaedic intervention (e.g. joint replacement and fusion) is common and anaesthetists need to be aware of potential risks in this group of patients.

There has been extensive research into RA over the past 20 years, related to our understanding of the disease, its complications and the introduction of novel treatments. This article aims to provide an overview of these developments and their implications for anaesthesia.

Epidemiology

In the UK, the incidence per 100 000 people per year is 1.5 in men and 3.6 in women. Worldwide prevalence is estimated at approximately 1%, but tends to be higher in the Northern European and North American populations. Peak incidence is in the 7th decade of life.

The aetiology of RA remains unknown, and is thought to be similar to that of other autoimmune diseases i.e. an abnormal immune response to an infectious agent (or a component of that agent) in a genetically susceptible individual. Smoking is a clearly identifiable risk factor [1].

Genetic predisposition is contributed to by HLA DRB1 alleles. The strongest linked alleles all code for a particular amino acid sequence that forms part of the antigen-binding groove. Genome-wide association studies have identified a variety of single nucleotide polymorphisms (SNPs) in a number of genes (*PTPN22*, *CTLA-4*, *TNF-R2*), but so far have been unsuccessful in identifying a clear causative mechanism [2, 3].

Clinical features and diagnostic criteria

Rheumatoid arthritis is a heterogeneous inflammatory arthritis. Typical presentation is with persistent, painful joint swelling with morning stiffness. Generally, the small joints of the wrist and hand are affected in a symmetrical distribution, usually at the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints. The knees and feet are also commonly affected. The synovitis phase is often preceded by a prodrome of fatigue, musculoskeletal symptoms and generalised weakness, that may be present for some weeks or months before joint swelling occurs. Acute flares may be associated with systemic fever and lymphadenopathy.

Characteristically, joint stiffness is worse after prolonged inactivity, and morning stiffness lasting greater than 30 min reliably distinguishes inflammatory from non-inflammatory joint disease. Inflamed joints are

Table 1 American College of Rheumatology/European League Against Rheumatism 2010 diagnostic criteria for rheumatoid arthritis (RA). A score of six or more is required for a diagnosis of RA [4].

Clinical criteria	Score
A Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints	2
4–10 small joints	3
> 10 small joints	5
B Serology	
Negative RF and ACPA	0
Low positive RhF or low positive ACPA	2
High positive RhF or high positive ACPA	3
C Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

RhF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

often warm and swollen with a 'spongy' characteristic on clinical examination, which represents synovial pannus, a metabolically active tissue consisting of inflammatory and synovial cells that interfaces with cartilage and bone causing joint destruction and erosions. Pain is a common symptom and is due to a combination of joint inflammation, erosive destruction of joint surfaces, stiffness, muscle atrophy and weakness. Progressive joint inflammation in the hands leads to classical clinical signs of radial deviation at the wrist, ulnar deviation of the MCP joints and swan-neck (distal interphalangeal joint) or Boutonnière (PIP joint) deformities in the fingers. Similar changes occur in the feet. Subcutaneous nodules may be found, commonly at the elbows.

Diagnosis is clinical, and confirmed with laboratory tests for autoantibodies and raised inflammatory markers. Plain radiography is used to demonstrate periarticular soft tissue swelling, joint space narrowing, erosions and osteopenia, in addition to monitoring disease progression. Ultrasound and magnetic resonance imaging (MRI) may be used to demonstrate earlier disease. The American College of Rheumatology (ACR) diagnostic guidelines from 1987 were updated in 2010 by both the ACR and European League Against Rheumatism (EULAR) [4] (Table 1). The revised criteria aim to identify earlier, less severe disease, and make use of new biomarkers such as anti-cyclic citrullinated peptide antibodies (anti-CCP or ACPA). Those with milder inflammatory arthritis might therefore be recognised earlier, commence disease modifying therapy before the onset of erosive disease, and potentially become eligible for clinical trials.

The distribution of affected joints, course of disease and extra-articular involvement vary widely. Some cases resolve after a single flare, whereas other progress unpredictably into a chronic and disabling disease.

Immunology/pathophysiology

The mechanisms underlying the priming of the immune response, localisation to the synovium and subsequent inflammation remain unknown. Historical disease models considered RA to be a Th-1 (a subgroup of helper T cells) mediated disease. Current understanding of inflammatory arthritis now focuses on RA as consisting of a number of compartments, with key cells and cytokines driving each part. The model can be better appreciated if each component is considered in turn.

Cell-mediated immunity

The inflammatory infiltrate of the synovial membrane is abundant in CD4+ (helper T) cells, which are thought to orchestrate the cell-mediated responses. CD4+ cells activate B cells via CD28/CD40 cell-surface receptor interactions, and activate macrophages via cell-surface CD69 and by secreting cytokines (interferon (IFN), interleukin (IL)-17). The B cells develop into autoantibody secreting plasma cells, whereas the activated macrophages release cytokines such as tumour necrosis factor (TNF)α and IL-1. These two cytokines attract and recruit neutrophils and macrophages, alter vascular endothelium and influence local cells in the synovium [5].

Synovial changes

Normal synovium consists of macrophage-like and fibroblast-like synoviocytes. These cells form a very thin layer and produce synovial fluid. In RA, the fibroblast-like synoviocytes are directly activated by the CD4+ T cells, TNFα and IL-1, resulting in the phenotype of the cells to alter, multiply and become hyperplastic. The dysfunctional cells secrete matrix-metalloproteinases (MMPs) causing cartilage and bone destruction leading to erosions. Animal models of inflammatory arthritis have shown that if the cell-surface interactions of the fibroblast-like synoviocytes are inhibited (for example by reducing cadherin-11, an

integral protein in osteoblastic cell lines), the inflammatory response in the synovium becomes disorganised and is much reduced [6, 7]. To support this actively replicating tissue, angiogenesis also takes place.

Joint destruction and erosions

As the pannus expands within the affected joint, it interfaces with the cartilage causing progressive cartilage destruction and exposes chondrocytes to the CD4+ T cells, dysfunctional fibroblast-like synoviocytes and TNFα/IL-1. The chondrocytes release MMPs and similar enzymes causing joint damage and exposing osteoclasts and the underlying bone matrix to the same pro-inflammatory mixture. The CD4+ T cells directly activate osteoclasts via cell-surface OPGL (osteoprotegrin ligand) actively causing bone degradation and erosions. Dysfunctional synoviocytes, under the influence of TNFα, produce less tissue protease inhibitors, allowing the damage caused by MMPs and similar enzymes to proceed unchecked [8]. Erosions are the key end point of the rheumatoid inflammatory process that treatments aim to prevent, as they represent irreversible damage and disability.

Cytokines and autoantibodies

A variety of cytokines are involved in driving inflammatory arthritis. However, levels of TNFα and its receptors are persistently elevated in the synovial fluid and serum [9], and this led to it being singled out as a target for the development of monoclonal antibody therapy. Potential cytokine and cellular targets are frequently identified e.g. IL-6, IL-4, spleen tyrosine kinase (Syk), and monoclonal antibodies have been developed to target them [10]. A detailed discussion about the roles of individual cytokines in pathogenesis is beyond the scope of this article.

Rheumatoid factor (RhF), which is immunoglobulin (Ig)M or IgA directed at the Fc component of IgG remains part of the diagnostic criteria. Anti-CCP (ACPA) is a recently recognised autoantibody, which is more specific and appears earlier in the natural history of RA. Citrullination refers to a process of post-translational modification of arginine residues in proteins that may alter peptide presentation by HLA. The role of both these autoantibodies in the immunopathogenicity of joint inflammation remains elusive despite years of study. Both, however, are prognostic indicators, and high levels of either antibody are associated with lower remission rates, more erosive disease and extra-articular involvement. Antibody levels are not monitored during treatment to assess response as the concentration and subtypes of antibody evolve over time as the disease 'matures' (probably due to B-cell class switching). Antibody-negative inflammatory arthritis has different pathological findings on biopsy [11].

Chronic inflammation

The morbidity RA patients suffer due to synovial pathology is further complicated by a sustained systemic inflammatory response, persistently raised circulating antibodies, cytokines and surrogate markers of systemic inflammation (such as C-reactive protein (CRP) and homocysteine). Both these biomarkers are associated with increased long-term cardiovascular risk. If remission is not achieved or acute flares not suppressed promptly, there is a prolonged state of poorly controlled inflammation, that may lead to further organ damage.

Axial skeletal involvement

In addition to the joints of the limbs, the axial skeleton may be involved and present particular difficulties to anaesthetists with respect to airway management and patient positioning. Patients are often asymptomatic, and so a careful and focused history is required to detect subtle signs.

Atlantoaxial subluxation (AAS)

Head and neck manipulation during laryngoscopy and movement during transfer of anaesthetised patients may cause neurological injury to patients with subluxation. Fortunately, the complications of myelopathy, quadriplegia and sudden death, are rare. Clinical symptoms of myelopathy (muscle weakness, altered sensation) can be difficult to distinguish from other co-existing rheumatoid complications such as peripheral neuropathy, joint pain or disuse muscle atrophy. The reported prevalence of AAS detected by plain radiography varies widely (3–44%) [12, 13], and the proportion of patients with symptoms is lower. Detection of subclinical AAS has been improved by MRI assessment of the cervical spine; however, MRI changes have been found to correlate poorly with clinical symptoms and may be no better than conventional radiographs with dynamic views [14–16].

The risk of AAS increases over time, and is greater in patients with higher disease severity scores and in those who are seropositive. Patients who have symptoms suggestive of AAS should be referred to a rheumatologist or spinal surgeon to monitor symptoms and radiographic progression and to consider fixation [17].

Recently, there has been a trend towards less surgery for cervical joint involvement and this may reflect the success of disease modifying therapy, although in symptomatic patients, fixation should be considered before myelopathy occurs.

Cervical spine

Involvement of the sub-axial cervical vertebrae is less common than AAS. Patients may present with neck or occipital pain, radicular symptoms or myelopathy, which are difficult to differentiate from other rheumatoid complications as mentioned above. If there is disease at multiple levels, plain radiography classically demonstrates a 'staircase' appearance. Pannus formation may lead to spinal canal stenosis, which may require MRI imaging for diagnosis and assessment.

Temporomandibular joint involvement

Patients may present with pain or difficulty with eating or mastication. However, it may be asymptomatic but cause significant problems with airway management if not recognised before induction. Assessment of the Mallampati score, mouth opening and mandibular protrusion are therefore essential.

Crico-arytenitis

This may present as hoarseness, stridor, sensation of a foreign body or rarely a mass in the larynx [18].These symptoms may be intermittent, and patients may not volunteer these symptoms or recognise their significance. Occasionally, the larynx is tender to palpation. Both articular surfaces are synovium-lined and may be subject to luxation, erosions and localised swelling. Assessment requires direct inspection by laryngoscopy combined with computed tomography (CT) imaging. Difficulties have been reported following tracheal extubation, and patients require close observation during recovery for signs of airway obstruction secondary to oedema.

The prevalence of both temporomandibular and crico-arytenoid involvement is reported with widely varying frequencies. Recognition therefore requires an accurate history and thorough physical assessment.

Extra-articular involvement

The extra-articular features of rheumatoid disease are summarised in Table 2.

Of particular interest to the anaesthetist are the haematological, pulmonary and cardiac manifestations. It is worth noting, however, that other than anaemia, these extra-articular features remain relatively rare, are often transient and/or usually asymptomatic, and are often only discovered at postmortem examination.

Table 2 Extra-articular manifestations of rheumatoid arthritis.

Cardiovascular	Haematological
Pericarditis	Anaemia
Valvular dysfunction (usually incompetence)	Chronic disease (normocytic)
Vasculitis	Drug toxicity/ myelosuppresion
Conduction abnormalities	Peptic ulceration
Granulomatous myocardial disease	Thrombocytopenia
Restrictive cardiomyopathy (amyloidosis)	Felty's syndrome
	Lymphoma
Respiratory	Hepatic
Pleural effusions	Hepatic fibrosis (drug toxicities)
Pulmonary nodules	Hepatomegaly (amyloid, Felty's)
Pulmonary fibrosis	Hypoalbuminaemia
Restrictive lung disease	
Respiratory myopathy	
Renal	Skin/eyes
Glomerulonephritis	Fragile skin
Tubulointerstitial nephritis	Pyoderma gangrenosum
Amyloidosis	Sicca (Sjogren's)
	(Epi)scleritis
Other	Scleromalacia perforans
(Poly)neuropathy	
Osteoporosis	
Carpal tunnel syndrome	

Cardiovascular manifestations

Perhaps one of the most significant discoveries over the past 20 years has been that the mortality of rheumatoid patients has remained high despite improvements in the standardised mortality ratio of the general population [19]. Epidemiological studies have found that this excess mortality is mostly attributable to cardiovascular disease [20, 21]. Patients with RA do not present with classical symptoms and signs of cardiovascular disease, and so the presence of cardiovascular complications often remains overlooked. Rheumatoid arthritis has been shown to confer independently a similar level of risk for cardiovascular disease as type-2 diabetes mellitus [22]. The reasons for this are uncertain and several mechanisms are thought to contribute.

Chronic inflammation

Essentially, the inflammatory processes and mediators involved in the synovium in RA resemble those

involved in atherosclerosis. Similar cytokines active in RA are implicated in vascular inflammation (TNFα, IL-1, IL-6, MMPs) as are CD4+/CD28− helper T cells and CRP. Atherosclerotic plaque burden in RA patients is not as dramatic as would be anticipated by the excess mortality. It is postulated that plaques in RA patients are more vulnerable to rupture, and post-mortem studies have shown that the plaque disease in RA is histologically distinct from atherosclerotic plaques in control populations [23].

Serum lipid concentrations in RA are similar to those in control populations, with similar levels of circulating low density lipoproteins (LDLs), triglycerides and high density lipoproteins. Persistent inflammation in RA may induce reactive oxidation species-mediated modification of LDL ('oxidative stress') that is atherogenic, whereas immune dysfunction reduces the patient's ability to clear oxidised lipids. Global endothelial dysfunction is exhibited by increased intercellular adhesion molecule (ICAM)-1, E- and L-selectin expression, reduced numbers of endothelial progenitor cells and blockade of endothelial nitric oxide synthase. Raised circulating TNFα and IL-6 could be responsible for all of these effects that cumulatively result in a pro-atherogenic endothelium [24].

Arterial stiffness and carotid intima-media thickness, both of which are subclinical markers of cardiovascular risk, are increased in RA. These surrogate measures of cardiovascular risk directly correlate with raised background levels of CRP and other inflammatory markers [25]. Patients with RA are also in a prothrombotic state, with raised levels of fibrinogen, D-dimer (a fibrin degradation product) and tissue plasminogen activator, thus potentially exacerbating the risks conferred by the unstable atherosclerotic plaques described above [26, 27]. Insulin resistance, which increases the cardiovascular risk, may be due to the disease itself as TNFα inhibits glucose uptake by skeletal muscle, or as a consequence of chronic corticosteroid use.

Atypical presentation

Rheumatoid arthritis patients suffer from an increased risk of myocardial infarction (MI), but rarely present with angina. The presentation is usually insidious with 'Silent MI' being almost six times more common in RA patients than non-RA controls. Sudden cardiac death has almost twice the cumulative incidence in RA patients compared with non-RA cohorts [28]. The risks are greater in RhF- and ACPA-positive patients. Coronary vasculitis remains very rare, and is only reported in postmortem studies.

Heart failure is a major cause of death in RA, with twice the risk compared with a control population; it probably contributes most to the excess mortality seen in RA patients [29]. Unlike heart failure in non-RA patients, there is often no history of preceding ischaemic heart disease. Echocardiography and cardiac MRI studies have shown that the ejection fraction is often normal in RA patients with failure, but there is left ventricular hypertrophy and diastolic dysfunction [30–32]. These changes to cardiac structure and function may be due to increased arterial stiffness as opposed to ischaemic heart disease.

Unlike the general population, a lower body mass index in RA patients is associated with higher cardiovascular mortality. This subset of patients probably represents those with a persistently catabolic phenotype ('rheumatoid cachexia') due to sustained and poorly controlled chronic inflammation [33].

Cardiac arrhythmias may also be an important cause of mortality, as tachyarrhythmias are poorly tolerated in patients with diastolic dysfunction. Conduction abnormalities can arise from rheumatoid nodules, amyloidosis or ischaemic disease, and may account for the increased risk of sudden death in RA [28].

Drug toxicity

Corticosteroids cause insulin resistance, hypertension, hypercholesterolaemia and hypertriglyceridaemia. Both COX-2 inhibitors and non-specific non-steroidal anti-inflammatory drugs (NSAIDs) are linked to increased cardiovascular mortality. Links between anti-TNFα therapy and congestive heart failure are contentious, and treatment with biological agents has been shown to reduce the rate of cardiovascular events and improve overall mortality compared with uncontrolled disease [29]. Separating the underlying disease process and its cardiovascular risks from treatment toxicity is difficult to assess in randomised controlled trials.

Overall cardiovascular disease burden and severity in RA tends to be insidious, with no clearly identifiable surrogate clinical signs or biomarkers, which is why the anaesthetist needs to be particularly vigilant. Patients with RA are at higher risk of cardiac complications peri-operatively than the standard population and since traditional history, examination and the electrocardiograph may be normal pre-operatively this risk is difficult to quantify or predict. It is important to recognise, however, that antibody-positive patients and patients with poorly controlled inflammation are more likely to suffer from cardiovascular complications.

Management of rheumatoid arthritis

The primary treatment aims are for symptom relief and to alter the immune response before the onset of erosions (disease modification), thus preventing disability and maintaining joint function. Prevention of flares and chronic inflammation reduces other organ and cardiovascular damage.

Symptom relief

There has been little change in symptom relief over the past decade. The standard treatments of NSAIDs, COX-2 inhibitors and corticosteroids are long established and their toxicities well known. Corticosteroids are primarily used to overcome acute flares whilst the patient becomes established on disease-modifying agents.

Rheumatoid arthritis patients suffer with chronic pain due to immobility, joint destruction, tendon rupture, muscle atrophy and chronic fatigue, in addition to the pain from acute inflammatory flares. Long-acting opioid preparations are often used and may present a challenge to managing postoperative pain.

Disease modification

Disease modifying anti-rheumatic drugs (DMARDs), if effective, reduce flare frequency, prevent erosions and long-term disability. There is a proven mortality benefit over uncontrolled disease. With the introduction of biological agents (biologics), an increasing proportion of patients are now showing signs of disease remission, reflecting the efficacy of these treatments.

Methotrexate

Methotrexate remains the first-line treatment for inflammatory arthritis and, after counselling, newly diagnosed RA patients are commenced promptly on therapy. Methotrexate acts as an anti-metabolite, inhibiting the dihydrofolate reductase enzyme required to produce purines. Gastrointestinal toxicity is a common side effect that can be avoided by subcutaneous administration. Despite concerns regarding its immunosuppressive effects, it remains a safe treatment that is very effective in preventing flares and reducing disease activity and improves both quality of life and mortality rates in RA.

Risks are as with all immunosuppressants and include increased infections, which may become overwhelming if not recognised and treated by temporarily stopping immunosuppressants and starting appropriate antimicrobials. Interstitial lung disease and hepatotoxicity occur infrequently, but are screened for in patients receiving ongoing treatment. Risks are posed by interacting medications that can potentiate methotrexate activity; trimethoprim and other sulphonamide-based medications act as folate poisons and may displace methotrexate from its binding sites on serum proteins. There is a theoretical risk of synergistic action with nitrous oxide and this has been shown experimentally in animal models and in vitro cell lines [34, 35].

Other commonly used DMARDs, their mechanisms of action and common toxicities are described in Table 3. They may be used in combination before commencing biologic treatments. Any of these agents may cause myelosuppression.

Biological agents (biologics)

Our current understanding of RA implicates TNFα in influencing the behaviour of all the effector cell types involved in the inflammatory cascade in the synovium. There are a variety of other monoclonal antibody treatments with other targets, but it is the anti-TNFα agents that are first-line. Other agents are used for treatment-resistant disease. There is an ever-increasing number of biological agents, and attempting to remember each type may appear daunting to the non-specialist (Table 4).

These drugs are effective treatments in terms of clinical monitoring scores compared with methotrexate, they reduce erosive damage, they reduce disability and they improve quality of life scores. Furthermore, they reduce long-term mortality and may induce remission and even reversal of erosive disease [29]. They have been shown to be even more potent if used in combination with methotrexate [36].

These treatments are expensive (between £8000 and £15 000 per year depending on which agent is used), but health economic analyses in current administration guidelines show biologics to be cost-effective [37–39]. Universal availability of biologics is not economically feasible, and as more sensitive diagnostic algorithms are implemented, RA cases will be diagnosed earlier and ethical dilemmas in whom to initiate biologics are likely to arise.

Biologic agents increase the risk of infections that may be serious. There is a risk of tuberculosis reactivation in patients with prior exposure; this is routinely screened for, as is hepatitis B virus serology. The incidence of surgical site infections is increased in some studies, but this is contested by others and the evidence remains inconclusive. There has been a

Table 3 Disease modifying therapies for rheumatoid arthritis.

Drug	Mechanism of action	Specific potential toxicities
Methotrexate	Antimetabolite, folate poison	Interstitial lung disease Liver toxicity
Hydroxychloroquine	Blocks toll-like receptor on dendritic cells	Ocular toxicity
Ciclosporin	Calcineurin inhibitor, prevents IL-2 action	Hypertension Nephrotoxicity
Leflunomide	Anti-proloferative, inhibits pyrimidine synthesis	Liver toxicity. Extensive hepato-enteric re-circulation
Anakinra	IL-1 receptor antagonist, reduces IL-1 signalling	Pneumonia
Sulfasalazine	Immunomodulation	Stevens-Johnson syndrome
Azathioprine	Anti-proliferative, inhibits purine synthesis	Proportion of population are slow acetylators, and prone to toxicity Pancreatitis
Gold salts	Unknown immunomodulation	Glomerulonephritis

IL, interleukin.

Table 4 Biological agents for the treatment of rheumatoid arthritis.

Anti-TNFα directed (first-line)	
Infliximab	Chimaeric monoclonal anti-TNFα antibody
Adalimumab	Human monoclonal anti-TNFα antibody
Etanercept	TNFα receptor-IgG fusion protein (inactivates membrane-bound and free receptors)
Certolizumab	PEGylated Fab fragment of humanised monoclonal anti-TNFα antibody
Golimumab	Human monoclonal anti-TNFα antibody
Other agents (second-line)	
Abetacept	Anti-CTLA4 monoclonal antibody
Tocilizumab	Anti-IL-6 receptor
Rituximab	Anti-CD20 monoclonal antibody

TNF, tumour necrosis factor; Ig, immunoglobulin; IL, interleukin.

reported increase in the risk of lymphoma and congestive cardiac failure, that appears to be dose-related; however, severe RA itself is also associated with both of these illnesses [40]. Patients in the UK and other European countries on biological treatment are placed on national registers and they have not yet reported any consistent major toxicities.

Given the potency of these immunosuppressants, questions arise over the safety and efficacy of vaccination in these patients. Non-live vaccine use appears to be safe, although response rates in RA patients have been found to be slightly lower than population controls. Current recommendations are to vaccinate before starting biological therapy, especially if receiving combination treatment with methotrexate. Pneumococcal polysaccharide vaccines and influenza vaccine have been shown to induce adequate immune responses in RA patients on biological therapy, and RA patients should be vaccinated annually along with other high-risk groups [41].

Anaesthetic considerations

Pre-operative preparation

A thorough history of the RA including severity and duration of the disease, drug treatments and systemic complications should be taken, and meticulous assessment of the airway should be performed. Screening for the cardiovascular complications described above, especially heart failure, should be carried out. A summary of potential difficulties is summarised in Table 5.

Care should be taken when examining rheumatoid patients who are often in pain and suffer with deformities that restrict simple movements (pronation, shaking hands) and fragile skin. The anaesthetist should note which movements are particularly difficult or painful and anticipate how this may affect positioning when performing procedures peri-operatively (e.g. intravascular access and regional nerve blocks) to minimise injury and discomfort. Involvement of the joints of the wrists and fingers also has implications for the postoperative analgesic plan, as the use of standard patient-controlled analgesia (PCA) may not be a realistic option.

General examination of the patient beyond the cardiovascular and respiratory systems should look for active synovitis in the affected joints. The body mass index should also be noted, as it may indicate rheumatoid cachexia, and poorly controlled disease is

Table 5 Anaesthetic concerns in patients with rheumatoid arthritis.

Increased cardiovascular risks in those with:
Seropositive disease (RhF, ACPA)
Symptoms of heart failure
Poorly controlled disease
'Rheumatoid cachexia'
Likely pre-existing anaemia; increased requirement for red-cell transfusion
Very fragile skin; extreme care required when handling and positioning
Deformities and fixation of joints can make positioning, especially pronation, difficult
Patients are often in considerable pain; care required during examination and anaesthetic preparations, e.g. 'shaking hands'
Poor peripheral venous access; arterial and central venous access are often difficult
Airway management may be difficult
Glucocorticoid supplementation is required if on long-term steroid therapy
Risk of higher than expected spinal block
Risk of post-extubation oedema due to cricoarytenitis
Postoperative ventilation may be required for those with severe myopathy who are at risk of respiratory failure
Possibility of peri-operative neurological damage

RhF, rheumatic factor; ACPA, anti-cyclic citrullinated peptide antibodies.

associated with an increased long-term cardiovascular risk. Cachexia and poor muscle bulk may also indicate myopathy which may impair respiratory muscle function, and such patients may need to be considered for postoperative mechanical ventilation.

Airway assessment

Adequate airway assessment is essential. Patients with RA requiring cervical spine surgery have a high prevalence of grade-3 or -4 laryngoscopy. The Mallampati score and mandibular protrusion (Table 6) both have a high positive predictive value, but may miss up to half the difficult cases. Plain flexion and extension lateral radiographs, looking for C1/C2 joint space loss, better predicts difficult laryngoscopy in these cases [42].

Symptoms of AAS associated with RA may include neck pain radiating to the occiput and tingling, paraesthesia or numbness of the shoulders and/or arms. It is, however, primarily a radiological diagnosis. Acute subluxation due to neck manipulation can lead to quadriplegia or sudden death due to compression of the spinal cord or vertebral arteries [43]. In the presence of neurological symptoms, patients should be referred to a rheumatologist or spinal surgeon as current opinion favours early fixation. A flexion/extension CT or MRI should be considered, especially if symptoms are associated with severe pain, in the presence of neurological signs or if there is significant abnormality noted on plain X-ray films. However, AAS may be asymptomatic and, even in the presence of suggestive symptoms, it can only be demonstrated by radiological evaluation.

Table 6 Classification of mandibular protrusion.

Class	Maximal lower incisor protrusion
A	Anterior to upper incisors
B	Edge to edge with upper incisors
C	Posterior to edge of upper incisors

The risks of AAS are dependent on the subtype of instability (see Table 7). The most common subtype (anterior AAS) is worsened by C1/C2 flexion, and therefore direct laryngoscopy should be tolerated. In anterior AAS, C1 and the head tend to move as a unit, so that subluxation is worsened by the head moving anteriorly whilst the upper cervical spine is left behind, e.g. putting a pillow behind the head. A useful technique is to keep the upper cervical spine supported whilst the head is not moved anteriorly, e.g. using a doughnut head ring with a large enough hole to accommodate the occiput [44]. This type of head support, which supports the cervical spine without anterior translation of the head, is a logical choice for rheumatoid patients. Posterior or vertical AAS both pose the risk of spinal cord compression during C1/C2 extension, the movement of which occurs during direct laryngoscopy, which should therefore be avoided. They are, however, much less common than anterior AAS, and are very rarely asymptomatic. Subluxation can also occur due to bony erosion and ligament damage at subaxial levels: the 'staircase spine'. Spinal canal stenosis is another possible complication, causing myelopathy due to pannus formation in the spinal canal.

The extent of neck flexion and extension should be assessed and documented, with the aim of avoiding exceeding this range peri-operatively. In practice, however, this is difficult to do accurately as clinical methods are unreliable and anaesthetists are not accustomed to using specialised devices e.g. goniometers. Although neck rotation does not have important implications regarding airway management, excessive rotation may worsen lateral AAS. If present, a history of cervical fixation should be elicited, as cervical fixation devices may cause impaired cervico-cranial extension. It is also worth noting that patients who have had atlantoaxial fixation may have a significantly decreased C1-T1 rotation angle [45].

The Bellhouse technique (angle from the neutral head position to extreme extension, without moving

Table 7 Subclassification of atlantoaxial subluxation.

Type	Incidence	Displacement/abnormality	Radiographic changes
Anterior	80%	C1 moves anteriorly on C2 Destruction of transverse and apical ligaments	> 3 mm gap between odontoid peg and arch of atlas on lateral flexion film
Posterior	< 5%	C1 moves posteriorly on C2 Destruction of odontoid peg	Loss of odontoid peg on lateral flexion film
Vertical	10–20%	Odontoid peg translocates through the foramen magnum Destruction and erosion of lateral masses of C1 and C2	> 4.5 mm migration of odontoid above McGregor line (from hard palate to base of occiput) on lateral film
Lateral/rotatory	5–10%	Lateral or rotational movement of C1 with respect to C2 Degenerative changes at the C1/C2 facet joints	> 2 mm of loss of lateral alignment of C1/C2 via frontal, open-mouth odontoid film
Subaxial (below C2)	Rare	Lateral movement of any vertebra below C2 Facet joint degeneration	> 2 mm loss of lateral alignment on frontal PA films. 'Staircase spine' if at multiple levels

the neck) of assessing the occipito-atlanto-axial (OAA) extension capacity may be unreliable due to compensatory subaxial extension, which may mask underlying pathology of the OAA complex [46]. One study has found the hyo mental distance ratio (difference between hyo mental distance in extended and neutral head positions) to correlate well with OAA capacity [47].

There are no published evidence-based guidelines or general consensus on the need to obtain cervical spine X-rays before surgery in asymptomatic patients. The arguments for and against the routine use of this investigation are listed in Table 8.

Temporomandibular joint involvement can make direct laryngoscopy very difficult. This can be assessed pre-operatively using the Mallampati score, mouth opening and mandibular protrusion.

As discussed above, cricoarytenoid arthritis is variable in frequency, intermittent and often unrecognised. Patients have both joint and soft tissue swelling, so that the overall effect is of stenosis. Symptoms may include hoarseness, stridor, a sense of pharyngeal fullness when speaking and swallowing or dyspnoea. Secondary infection of the upper respiratory tract may worsen any swelling/stenosis and tracheostomy may be required [51, 52]. A pre-operative nasendoscopy is advisable if there is any suspicion of involvement, and consideration given to:

1 Using a facemask or supraglottic airway device.
2 Using the smallest internal diameter tracheal tube possible.
3 Avoiding trauma at intubation.

Table 8 Competing arguments for pre-operative cervical radiographs in rheumatoid arthritis.

Arguments for	Arguments against
Asymptomatic subluxation is common [12]	Decline in the incidence and severity of cervical instability and associated neurological involvement in recent years [50]
Flexion/extension radiographs good predictors of difficult direct laryngoscopy [42]	No difference in anaesthetic management of patients with or without cervical instability. No reported neurological complications [49]
No standard 'safe' head position – the 'protrusion position' may reduce atlanto-dental interval in anterior AAS, but may worsen posterior subluxation [44]	Seventy-seven rheumatoid patients underwent 132 operations. A third of the pre-operative cervical spine X-rays were inadequate or of limited diagnostic value [48]
Proven instability on radiographs alters anaesthetic management by reducing neck manipulation [44]	Serial cervical radiographs over the past 2 years in 14 patients with craniocervical instability showed no progression [49]
Incidence of AAS progresses over time, rising fourfold after the third decade. Serial X-rays may show disease progression regardless of findings on previous films [48]	May delay surgery, expose patients to unnecessary radiation and not alter management

AAS, atlantoaxial subluxation.

4 Considering the use of an airway exchange catheter at extubation.
5 Extubating in a suitable environment and at the appropriate time (obstruction often develops some time after extubation).
6 In severe cases, a pre-operative tracheostomy may be required.

Other considerations and investigations

Anaemia is common and may be due both to anaemia of chronic disease (normocytic, normochromic) and from treatment toxicity (gastrointestinal haemorrhage, myelosuppression). Patients with RA are therefore more likely to require perioperative blood transfusion.

An electrocardiogram should be performed to check for left ventricular hypertrophy and conduction disturbances. An echocardiogram with a reported normal ejection fraction may be falsely reassuring. Requests to perform this study should ask specifically for evidence of diastolic dysfunction, left ventricular hypertrophy and valvular abnormalities. Diastolic dysfunction may be suggested by the echocardiographic analysis of the E:A ratio which relates to the relative proportion of ventricular filling during early diastole (E) or following atrial contraction (A) measured at the level of the left ventricular inflow or mitral valve annulus. In diastolic dysfunction, there may be an increase in the atrial component (high A peak, reversed ratio) or rapid fall in the E peak. In addition, there may be an enlarged left atrium (in the absence of atrial fibrillation or mitral valve disease), and inspection of the ventricular myocardium in early diastole should be performed to assess its recoil as measured by tissue doppler.

There should be a low threshold for ordering respiratory investigations (e.g. chest radiographs, arterial blood gases and lung function tests with flow volume loops) due to the possibility of pulmonary involvement (fibrosis, nodules, effusions) or respiratory myopathy.

Most studies have suggested that methotrexate can be continued in the peri-operative period without impaired wound healing or a substantially raised risk of peri-operative infection. Furthermore, good disease control in the peri-operative period is beneficial. Unfortunately, there is lack of data regarding the use of other immunosuppressants; however, knowledge of available therapy and its possible side effects should be weighed against the risk of flare-up for each patient [53].

Peri-operative discontinuation of biological therapy for elective surgery remains controversial. A study in 2006 showed that the peri-operative use of anti-TNF agents was associated with a high incidence of postoperative infections [54]. However, a more recent study suggested that their use does not cause specific adverse effects and may improve recovery from postoperative anaemia [55]. An immunisation history for pneumococcal and influenza vaccines should be recorded for patients on biological or combination therapy.

Intra-operative management

Choice of anaesthetic technique will depend on the patient's general condition, type of surgery, patient preference and anaesthetic skill. Regional anaesthesia, general anaesthesia or a combination of the two may be employed.

Regional anaesthesia, if feasible, should always be considered, as it minimises neck movement and avoids airway manipulation. It also provides good postoperative pain relief and reduces polypharmacy. Regional blocks, however, may be technically difficult due to severe lumbar and thoracic spine arthritis and loss of anatomical landmarks from contractures or deformities. Furthermore, if surgery is prolonged, positioning of the patient may be uncomfortable and the operation may outlast the duration of anaesthesia.

For patients undergoing spinal anaesthesia, a higher than normal block should be anticipated. In a recent study, subarachnoid injection of plain bupivacaine in rheumatoid patients resulted in the mean spread of sensory block 1.5 segments higher than in patients without the disease [56].

If a general anaesthetic is indicated and considered appropriate, there are several options for managing the airway depending on the patient and the type and duration of surgery.

Laryngeal mask airways (LMAs) and other supraglottic airway devices have the advantages of requiring minimal neck manipulation for insertion and causing relatively little trauma and subsequent laryngeal oedema compared with a tracheal tube. They may, however, be difficult to insert in patients with fixed flexion deformities of the neck, in which case a reinforced LMA may be more appropriate.

Tracheal intubation may be indicated depending on the patient's size, aspiration risk and the type and length of surgery. There are several reasons why a difficult intubation may be encountered and should be anticipated, as discussed above.

If tracheal intubation is indicated, neck manipulation should be minimised, ideally with manual, in-line stabilisation, even if there is no overt cervical spine

instability. To date, there are no case reports of spinal cord injury secondary to direct laryngoscopy, nor is there any evidence of outcome difference with a particular technique. Furthermore, intubation is inevitably followed by a variety of other hazards to cervical stability, thus confounding the risks of laryngoscopy alone in patients who suffer subsequent neurological deterioration. However, lack of evidence does not mean that the phenomenon does not exist [57].

The intubating LMA could be used to aid intubation with minimal neck manipulation. However, the risk of failure and associated trauma to the airway limit its widespread use.

Fibreoptic intubation is considered the appropriate and safer option in rheumatoid patients with an anticipated difficult airway or known cervical spine instability. It generally carries less risk of major difficulties than tracheal intubation using direct laryngoscopy in this subgroup of patients [58]. Awake fibreoptic intubation under sedation should be considered in patients with known cervical spine subluxation, which allows for assessment of neurological symptoms indicating spinal compression. Expertise is required for this technique, and it is unlikely to be appropriate under emergency conditions, or if excessive blood or secretions are in the airway.

A surgical tracheostomy under local anaesthesia may be indicated in emergency situations and in patients who have symptoms of upper airway obstruction.

Intra-operatively, patients with RA present problems with positioning due to joint deformities and fragile skin due to steroid therapy. Pressure points should be meticulously padded, the neck adequately supported and skin handled with care. Excessive manipulation of stiff and fixed joints should be avoided.

It is worth noting that the prolonged, relative spinal malposition inherent in the use of general anaesthesia, in a patient with possible spinal stenosis, may have a profound deleterious effect. In the American Society of Anesthesiologists Closed Claims Analysis, most cervical cord injuries occurred in the absence of traumatic injury, instability and airway difficulties. Cervical spine procedures and operations performed in the sitting position were identified as being particularly high-risk [59].

'Awake' cervical positioning is a potential solution for such procedures, but it cannot be predicted whether a position will still be tolerable some hours later. Attention to the maintenance of spinal cord perfusion may be important and hypotension should be avoided. Spinal cord monitoring techniques (sensory and motor evoked potentials) may be of use in assessing cord perfusion and preventing prolonged hypotension, but they have not been shown to improve outcome [57].

In patients receiving general anaesthesia, special attention should be considered in patients receiving methotrexate due to the potential interaction with nitrous oxide. The potential for folate depletion has only been demonstrated experimentally, but these studies suggest nitrous oxide should be avoided [32, 33].

The use of immunosuppressive treatments put patients with RA at an increased risk of infections. Strict aseptic technique should be adopted for intravascular access and regional blocks. Appropriate antibiotic prophylaxis should be given before starting surgery.

Patients taking more than 10 mg prednisolone per day should be given appropriate peri-operative steroid cover. Patients should continue their regular prednisolone and receive hydrocortisone intra-operatively to cover the stress response to surgery. Depending on the type of procedure, hydrocortisone may need to be continued into the postoperative period [60].

Postoperative management

Careful observation of the airway and breathing are required in the immediate postoperative period. Pre-existing glottic stenosis due to bilateral ankylosis of the cricoarytenoid joints (see above) may be asymptomatic pre-operatively, but with the additional oedema caused by tracheal intubation, complete airway obstruction may occur following extubation. There are multiple case reports highlighting this complication, which may arise several hours postoperatively, necessitate reintubation or in some cases a tracheostomy, and may be fatal [12, 61–63].

Appropriate thromboprophylaxis should be prescribed, as patients with RA tend to have a slower recovery and return to mobilisation. Patients with RA, in general, are considered to be in a hypercoagulable state. Such patients receiving corticosteroids showed a hypercoagulable state compared with patients suffering from osteoarthritis in the peri-operative period following total knee arthroplasty [64].

Patients with RA may be at higher risk of peptic ulceration, especially if they are on a combination of steroids and NSAIDs, and appropriate prophylaxis should be considered.

Standard physiotherapy and breathing exercises should be instituted as early as possible due to the increased infection risk. Importantly, if signs of a

postoperative infection develop, DMARDs should be suspended temporarily.

Pain should be adequately controlled to avoid delayed mobilisation, venous thromboembolism and chest infections. Opioid analgesia can be used in carefully monitored doses to reduce the incidence of side effects. Patients may find it difficult or impossible to use a PCA due to joint deformity and muscle weakness. In these cases, nurse-controlled analgesia or modified devices are possible alternatives.

Competing interests

No external funding or competing interests declared.

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