The inflammatory process provoked by ruptured abdominal aortic aneurysm

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Systemic Inflammatory Response Syndrome (SIRS)

Systemic inflammatory response syndrome (SIRS) is the process, which can arise from various causes without infection.[1] The clinical manifestations of SIRS result from the production of the inflammatory mediators as an initial response to harmful stimulus.[2] SIRS can be defined as the detection of one or more of 4 clinical criteria, secondary to pathophysiological changes from the baseline, in the absence of a defined cause for the observed abnormality, such as immunosuppressive induced neutropenia or leucopenia (Table 1).[3] Almost 70% of elective abdominal aortic aneurysm (AAA) repair patients developed SIRS prior or concurrent to organ failure while nearly all ruptured AAA (rAAA) developed the syndrome.[4] While SIRS and organ failure usually recover rapidly in elective AAA repair, following rAAA they can persist, giving rise to multiple organ dysfunction syndrome (MODS).

Multiple organ dysfunction syndrome (MODS)

Multiple Organ Dysfunction Syndrome (MODS) is characterised by organ dysfunction in an ill patient, so much that intervention is required to maintain homeostasis.[3] This definition allows for dynamic changes in organ function and may progress to organ failure and death.[5]

These changes were first described in 1973 after rAAA and is a major cause of death.[6, 7] The bodily systems most responsible for the poor outcome in MODS are respiratory, cardiovascular, renal, hepatic, central nervous system and coagulation.[8, 9] The development of MODS influences postoperative mortality after rAAA repair.[6, 10] Halpern et al reported 23% of the intra-operative mortality of rAAA was secondary to continuous bleeding and irreversible shock.[11] However, their 30-day mortality was 56%, and of these patients 37% died after the first 48 hours. Similarly, in another study of 57 rAAA, there was 32% inhospital mortality, with more than half of these patients dying later than 48 hours post-operatively, where MODS was the cause of death in 90%.[12]

The MOD scores after rAAA repair progressively increase in non-survivors, with significantly worsening renal and hepatic functions.[13] This dysfunction, rather
The free oxygen radical contains unpaired electrons, which render the molecule unstable. This leads to a high affinity for an additional electron to form a pair. These reactive oxygen species are deleterious products that can damage the different organs and systems if produced in overwhelming quantities.

**Oxidative stress and anti-oxidants**

Normally the reactive oxygen species (ROS) are produced in small amounts via aerobic metabolic pathways. In a normal aerobic steady state, there is a fine balance between the pro-oxidant and anti-oxidant. If there is a shift towards a pro-oxidative state, tissue damage by the ROS occurs.

One of the major sources of ROS in ischaemia-reperfusion injury is the xanthine oxidase pathway. During the ischaemic phase there is an rise in electron escape from the respiratory chain and ROS creation because of a deficiency of adenosine phosphate for oxidative phosphorylation. Concurrently, xanthine dehydrogenase is altered to xanthine oxidase by proteolysis and together with the accumulation of hypoxanthine during ischaemia the stage is set for the production of ROS when a surge of oxygen occurs during reperfusion.

The free oxygen radical contains unpaired electrons, which render the molecule unstable. This leads to a high affinity for an additional electron to form a pair. These ROS comprise the hydroxyl radical (•OH), the superoxide anion radical (•O₂⁻), nitric oxide radical (NO•), hydrogen...
peroxide (H\textsubscript{2}O\textsubscript{2}), and single molecule oxygen (\textsuperscript{1}O\textsubscript{2}).\textsuperscript{[23]} These ROS are able to damage cells by targeting cellular molecules such as DNA, lipids, proteins and carbohydrates leading to DNA fragmentation, membrane damage and lipid peroxidation, and consequently to cell death.\textsuperscript{[26, 27]}

Lipid peroxidation is the result of oxygen radical reaction with the fatty acids of cell membranes. It triggers a three-phase reaction. The first or initiation phase results in the production of lipid radicals. This leads to the second phase, which produces lipid hydroperoxide (LOOH) and another lipid radical. The latter enters a chain of repeated reactions, which end in two lipid hydroperoxide radicals that result in non-radical products.\textsuperscript{[28]} Furthermore, the cytotoxic products of lipid peroxidation such as aldehydes can move through the cell membrane to injury other cells.\textsuperscript{[29]} The lipid peroxidation produces damage and subsequently activates the vascular endothelium.\textsuperscript{[30]} This results in increase capillary permeability to protein and consequently tissue oedema and renal albumin excretion.\textsuperscript{[31]}

Apart from causing tissue damage at the site of production, these ROS can lead to injury at remote sites when their production overwhelms the antioxidant protective mechanisms locally. In addition, they can also activate various cascades, such as the arachidonic acid cascade. Activation of this cascade will lead to the generation of thromboxanes, prostaglandins and leukotrienes, either via the cyclooxygenase or lipoxygenase pathways (Figure 1). These mediators, such as thromboxane A\textsubscript{2} and leukotriene B\textsubscript{4} are potent platelet and neutrophil activators, and vasoconstrictors.\textsuperscript{[32]} Thromboxane A\textsubscript{2} acts as a powerful chemoattractant that can encourage neutrophil adhesion to the endothelium.\textsuperscript{[33]} Similarly, leukotriene B\textsubscript{4} results in activation of adhesion

\begin{figure}[h]
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\caption{Arachidonic acid pathway showing the production of the prostaglandins (PG) and leukotrienes (LT).}
\end{figure}
molecules on neutrophils and their interaction with the endothelial cells.\textsuperscript{[34]} However prostacyclin (PGI2) opposes the thromboxane A2 effects. It acts as a vasodilator and has platelets anti-aggregating properties.\textsuperscript{[35]} In normal physiological conditions, there is a balance between thromboxane A2 and PGI2.\textsuperscript{[35, 36]}

Neutrophils

Neutrophil activation and remote tissue sequestration has been implicated in the genesis of SIRS and MODS.\textsuperscript{[21, 37]} Neutrophil-dependent injury is characterised by the adhesion of activated polymorpho-nuclear neutrophils (PMNs) to endothelium and their release of arachidonic acid metabolites, free radicals and proteases such as elastase.\textsuperscript{[38]} These agents have been shown to induce damage to the endothelial cells, resulting in capillary leakage.\textsuperscript{[39]} Neutrophil activation and subsequent interaction with endothelial cells plays an important role in the pathophysiology of the inflammatory response and organ
injury resulting from ischaemia-reperfusion injury. Clinical research has demonstrated that the majority of patients undergoing aortic reconstructive surgery suffer from temporary forms of organ impairment including the lung, intestine and kidney. The common feature is microvascular hyperpermeability.\textsuperscript{40} Experimental data indicates that PMNs adhere to the endothelium as a requirement for cellular modification of the endothelial barrier. The process of cell adherence, activation and migration across cellular barriers involves interplay between expression of endothelial cell leukocyte adhesion molecule, neutrophil activation, and local cytokine activity.\textsuperscript{41} Neutrophil activation is characterised by increased neutrophil cell surface expression of adhesion receptors, such as CD11d and intercellular adhesion molecule-1 (ICAM-1).\textsuperscript{42}

Migration of PMNs across cellular barriers is caused by the united result of chemoattractants and particular cell adhesion molecule interactions. Several groups of chemoattractants have been identified, including leukotriene B\textsubscript{4}, N-formylated peptides, chemokines and some complement components (C3a and C5a). These agents trigger neutrophil migration and cell polarization with redistribution of the adhesion molecules, intra-cellular calcium mobilization and cytosolic granule release.\textsuperscript{43}

Schoenberg \textit{et al} observed that treatment with monoclonal antibody against the leucocyte adhesion glycoprotein complex blocked the endothelial-neutrophil interaction, preventing an increase of myeloperoxidase during the reperfusion phase of the small bowel.\textsuperscript{44} This resulted in a decrease in neutrophil migration and prohibited the development of severe mucosal injury. Although Mbachu \textit{et al} showed that the treatment with monoclonal antibody against cytokine-induced neutrophil activation, in a rAAA model, resulted in attenuation of the increase in intestinal permeability, histological mucosal injury and gut TNF-α level, they did not observe any significant decrease in the intestinal or lung myeloperoxidase activity.\textsuperscript{45}

Neutrophil elastase has been associated with lung injury and ARDS. This is evidenced by the presence of elevated levels of neutrophil elastase in bronchial alveolar fluids and the reduction in the artificial ventilation period in patients who received neutrophil elastase inhibitor.\textsuperscript{46} Similarly, Fujishima \textit{et al} reported significant increase in plasma levels of neutrophil elastase / α1-antitrypsin complex in patients with ARDS, especially in the presence of SIRS.\textsuperscript{47} In haemorrhagic shock this complex level returned to normal at recovery, while in septic patients its high level persisted and was markedly increased in patients complicated by multiple organ failure. Furthermore, Hoshi \textit{et al} showed that neutrophil elastase inhibitor reduced mortality of critically ill patients with impaired pulmonary function.\textsuperscript{48} An increase in neutrophil elastase / α1-antitrypsin complex has been observed in patients undergoing open abdominal aortic aneurysm repair.\textsuperscript{49, 50} Additionally, Pahl \textit{et al} demonstrated increase in both CD11b and CD18 neutrophil integrins after lower limb ischaemia-reperfusion consequent to abdominal aortic aneurysm surgery.\textsuperscript{51}

**Anti-oxidants**

In normal physiological conditions, the production of ROS is controlled by the body’s antioxidant defence mechanisms. Anti-oxidants are essential to neutralise and prevent the tissue damage that could result from oxygen free radical generation. They interact with free radicals by preventing the latter from reaching their targets and converting them into non-radical products. Anti-oxidants are subdivided into two major sets, namely enzymatic and non-enzymatic (Figure 2).\textsuperscript{52} The three main enzymes capable of scavenging ROS include superoxide dismutase, catalase and glutathione peroxidase. The major non-enzyme defences include antioxidant vitamins (vitamin C, vitamin E and carotenoids), free metals and heme binding proteins.

Various clinical studies have observed an association between low plasma concentrations of anti-oxidants with development of MODS and poor outcome in critically ill patients.\textsuperscript{53, 54} Goode \textit{et al} showed low levels of vitamin E, vitamin A, lycopene & β-carotene in sixteen ICU patients suffering from sepsis compared to healthy subjects.\textsuperscript{53} They also reported higher values of lipid peroxide in patients with three or four organ failure in contrast to those with two or less organ dysfunction. Similarly, Borrelli \textit{et al} observed significantly lower plasma vitamin C concentrations in ICU patients with MODS in comparison to those patients without.\textsuperscript{54} Although similar reductions in antioxidant concentrations following open AAA repair has been reported, others have failed to confirm this.\textsuperscript{55, 56}

In view of these findings, investigators have tried to assess the effect of anti-oxidant supplementation on the outcome of various diseases that may be related to free radical damage. Soong \textit{et al} demonstrated that the use of allopurinol abrogated ischaemia-reperfusion injury following lower limb bypass surgery.\textsuperscript{57} The reduction in free radical induced damage was found to be associated with a reduction in lower limb oedema in the allopurinol group. Wijnen \textit{et al} conducted a prospective randomised study comparing open AAA repair patients receiving multi-antioxidant supplementation, which included vitamin E, vitamin C, allopurinol and N-acetylcysteine, with those on a standard treatment regimen. They showed a significant reduction in creatinine kinase (CK) and lipofuscin, markers of muscle injury and lipid peroxidation respectively within the antioxidant group. A persistently reduced level of white cells in the standard treatment group led the authors to conclude that the administration of
antioxidants minimised the activation and sequestration of these cells.

**Vitamin C**

Vitamin C, a water soluble vitamin, is normally absorbed from the small intestine. Its bioavailability reaches 100% following a small oral dose of 200mg. Its total body half-life is 23 days and is the main antioxidant in the extra-cellular fluid. It reacts with the peroxyl radicals while in the aqueous phase, prior to lipid peroxidation. However, high doses of vitamin C can lead to oxalate nephropathy.

Vitamin C also protects against cell membrane lipid peroxidation by potentiating the activity of tocopherol; it reduces the tocopherol radicals and thus restores the radical scavenger activity of tocopherol. Rumelin et al found a reduction in plasma vitamin C levels by more than 60% during the early post-operative period following major maxillofacial surgery as a result of an increase in distribution volume; this was mainly due to an increase in intracellular uptake by cells such as erythrocytes, where the dehydroascorbate is reduced to ascorbate by glutathione.

Conversely, vitamin C supplementation may be deleterious, promoting iron-induced lipid peroxidation in patients undergoing AAA repair and vascular bypass surgery. Similarly, other investigators reported an increase in oxidative stress after iron and vitamin C supplementation. This paradoxical effect of vitamin C was demonstrated by Seo and Lee, who showed in an ischaemia-reperfusion hepatic model that low dose of vitamin C was beneficial to hepatic secretory and microsomal functions while high dose vitamin C was not.

**Vitamin E (tocopherol)**

Vitamin E is a mixture of α, β, γ, δ-tocopherols and tocotrienols. They present naturally as the R,R,R-stereoisomer. They are lipid soluble and depend on bile for their intestinal absorption. Both α and γ-tocopherols are equally absorbed and transported. They provide their antioxidant protection against lipid peroxidation by reacting with the lipid peroxyl radicals that are generated from the polyunsaturated fatty acids of cell membranes to produce a stable lipid hydroperoxide (LOOH). Furthermore, vitamin E has a similar ability to carotenoids in quenching singlet oxygen ($^1O_2$), which depends on the hydroxyl group in position 6 of the chromane ring.

**Carotenoids**

Carotenoids are a group of over 500 fat-soluble pigments such as β – carotene, α-carotene and Lycopene. β – carotene has a pro-vitamin A activity, while Lycopene is considered to be the most efficient of the carotenoids. Lycopene is the open chain analogue of β – carotene, which does not exert pro-vitamin A activity, although it represents on average one third of the body’s total carotenoid content. The carotenoids are embedded in the lipid bilayer of cell membranes. They act as antioxidants by virtue of their extended systems of conjugated double bonds. They quench singlet oxygen ($^1O_2$) by forming a stabilized carbon centred radical.

**Cytokines**

Cytokines are endogenous glycoproteins and can be divided into four main groups, namely interleukins (IL), colony-stimulating factors, interferons (INF) and tumour necrosis factor (TNF). They are made by immune cells, for example activated monocytes, macrophages and lymphocytes, but in addition by other cell types like endothelial cells, smooth muscle cells, skeletal muscles, adipocyte, enterocytes and fibroblasts. They are classified into pro-inflammatory or anti-inflammatory depending on their function (Table 2).

IL-6, IL-1 and TNF-α are pro-inflammatory cytokines that play crucial roles in the development of inflammatory responses in sepsis, SIRS and MODS. Roumen et al showed that high levels of IL-1, IL-6 and TNF-α in cases of severe blunt trauma, haemorrhagic shock and major vascular surgery were associated with increased risk of ARDS, multi-organ failure and mortality. Meduri et al showed that patients with ARDS who had persistently higher concentrations of IL-6, TNF-α, IL-1 β and IL-8 had a poorer outcome in comparison to patients with less elevation or whose concentrations reduced rapidly.

A number of anti-inflammatory mediators have been identified and include multiple interleukins, transforming growth factor-β, soluble receptors to TNF and IL-1 receptor antagonists. The latter two play a crucial role in downregulating the systemic inflammatory response. However, over production of anti-inflammatory mediators can develop into compensatory anti-inflammatory response syndrome (CARS), which is associated with over immuno-suppression and an increased risk of systemic infection. A combination of SIRS and CARS is called mixed anti-inflammatory response syndrome (MARS).

**IL-6**

IL-6 is made-up of 184 amino acids, with a half-life in serum of less than one hour. IL-6 production is associated with the degree of tissue injury. The elevation in serum IL-6 concentration following surgery precedes and regulates the release of acute phase proteins by the hepatic cells. Furthermore, it stimulates the bone marrow proliferation of precursor polymorph-nuclear neutrophils (PMNs). Although IL-6 is known as a pro-inflammatory cytokine, it has been reported to have additional anti-inflammatory functions by inducing the secretion of IL-1 receptor antagonist and soluble p55 TNF-α receptor (p55
**IL-6 in AAA**

Serum IL-6 concentration is elevated in patients with AAA and may play a role in the aneurysm pathogenesis. Dawson et al showed that IL-6 was not only released by the aneurysm's segment of the abdominal aorta, but that the concentration was also related to the aneurysm surface area.

In patients undergoing elective AAA surgery, IL-6 levels have been found to be significantly elevated 1 hour after clamping of the aorta, peaking between 4 – 48 hours following surgery and then falling back towards baseline afterwards. A continuing elevation of IL-6 is associated with adverse events, with extreme elevations found to indicate infectious complications. The IL-6 response in patients with complications has been observed to precede their clinical signs by 12 – 36 hours. In addition, the rise in IL-6 levels is significantly greater and persisted longer in patients with complications. In addition, Bown et al found that high concentrations of IL-6 following AAA repair were associated with the development of MODS.

The source of IL-6 and other cytokines following AAA surgery is debatable and most likely to be generated due to various insults and by multiple sites. Adembri et al reported that ischemia-reperfusion injury of the lower limb in patients undergoing elective AAA open repair resulted in activation of the IL-6 gene in the quadriceps muscle, with a subsequent increase in plasma IL-6. They also observed that immunoreactivity towards IL-6 was markedly positive in the lower limb endothelial cells during reperfusion, associated with a significant reduction in pulmonary function. They proposed that this remote effect of IL-6 could be because of modulation of pulmonary epithelial and microvascular permeability.

However, others have observed a correlation between the rise in splanchnic IL-6, cross clamping time and apoptosis of the recto-sigmoid junction epithelium in patients who have open AAA repair. Although this may be related to remote intestinal damage following ischaemia-reperfusion injury to the lower limbs, some workers felt that this increase in IL-6 supported the concept that the gut is the major source of IL-6 in aortic surgery. Therefore, either IL-6 is the cause of colonic epithelial apoptosis or the colonic apoptosis resulting from ischaemia-reperfusion injury is the source of the IL-6. Soong et al demonstrated a negative correlation relating the sigmoid colonic pH and IL-6 and between the pH and the APACHE II score. They suggested that ischaemia of the colon during AAA surgery drives IL-6 production. In support of this, Syk et al showed an association between serious post-operative complications, high levels of IL-6 and low pH.

By performing endovascular aneurysm repair (EVAR) instead of open repair, Elmarasy et al found significantly lower concentrations of IL-6. The lower IL-6 concentrations in the EVAR group were associated with preservation of sigmoid colonic pH, leading the authors to suggest that this technique of AAA repair causes less intestinal ischaemia and injury. This finding was supported by Junnarkar et al who demonstrated that the use of EVAR led to less intestinal permeability compared to open repair. Others demonstrated that the elevation in IL-6 concentration was greater amongst patients who had open AAA repair compared to EVAR and that the IL-6 concentration reached its maximum within 24 hours post-operatively. Similarly, Boyle et al reported lower IL-6 concentrations on day one and day two postoperatively in the EVAR group compared to open repair.

IL-6 is elevated in AAA patients compared to controls, as well as ruptured AAA patients compared to those with an intact aneurysm. Indeed the presence of symptoms with an intact aorta provokes a similar rise in inflammatory markers as a rupture, compared to asymptomatic intact aortic patients. However, it is important to note that the imbalance between pro-inflammatory and anti-inflammatory cytokines differentiates AAA patients from controls, as represented by the IL-6 / IL-10 ratio. The elevation of this ratio is also size dependent, with a greater rise in concentration in large AAA relative to small.

Interestingly, while there is a systemic response to symptoms or rupture, there is no associated up-regulation of the inflammatory response at the site of rupture, as demonstrated on aortic wall biopsies. However, the mode of repair may hold the key to modulation of this inflammatory response, with lower cytokine concentrations found after endovascular repair.

**TNF-α and TNF receptors**

TNF-α is a 17kDa polypeptide molecule consisting of 157 amino acids. Its main sources are activated macrophages, T lymphocytes, and natural killer cells (NK). Experimental studies have shown that it is taken up by the kidneys, liver, gastrointestinal tract and skin with a plasma half-life of 6 to 7 minutes. The latter could explain the difficulty and inconsistency in detecting TNF-α in patients following surgical stress and in patients following elective AAA repair.

TNF-α generates its biological effect at the target cells by its high affinity membrane receptors. Two receptor types have been identified, each mediating specific functions; p55TNF-α and p75TNF-α, also known as type 1
and type 2 respectively.[117] The endothelial p75TNF-α receptor (p75TNFr) are crucial for TNF-α induced leukocyte-endothelial cellular interaction by potentiating adhesion molecule expression, which plays a major role in the microvascular hypothesis of MODS.[118] The p75TNFr is mainly confined to immune cells.

TNF-α has multiple functions, including apoptosis, inflammation and immune mediation.[119, 120] p55TNFr are responsible for TNF-α cytotoxic activity.[121] Although p55TNFr is presented by all cell types, it is observed to be expressed mainly by the immune cells.[122] Hence, the presence of the shed soluble part of the latter receptor could reflect the activity of the immune system and inflammatory process. These TNF-α receptors are released into the circulation as result of proteolytic cleavage from the cell membrane following binding of TNF to the target cells.[123]

As TNF-α is the most powerful stimulator for shedding of the soluble TNF receptors in plasma, the measurement of TNFr could provide information about the presence of systemic TNF-α.[92] These soluble TNFr also act as anti-inflammatory mediators by neutralising the effect of TNF-α. In view of this, p75TNFr fusion protein (etanercept) has been used to inactivate TNF-α and minimise its cardiovascular deleterious effects in patients with cardiac failure and an associated ejection fraction <35%.[124]

TNF-α and TNFr in AAA

Sporadic elevation in the concentration of TNF-α has been observed in patients following AAA repair, with significantly greater levels detected in those who developed ischaemia of the sigmoid colon.[115] This was associated with higher degree of endotoxaemia and led the authors to speculate that the greater systemic inflammatory response was due to an increase in bowel permeability. In support of this, they also found that patients with bowel ischaemia had more organ dysfunction.[157] In addition, Roumen et al showed an association between TNF-α elevation, MODS score and mortality following major trauma and ruptured AAA.[125] They also observed a higher TNF-α in the ruptured AAA group in comparison to the trauma group. A similar elevation in TNF concentration may be observed following revascularisation of ischaemic bowel, which has been found to be a major stimulus for the release of TNF-α from circulating monocytes.[126, 127]

This may explain the two peaks in TNF-α production observed by Cabie et al who observed an initial peak before aortic clamping and a second one following reperfusion in patients who underwent abdominal aortic surgery.[128] They also reported significantly higher concentrations of portal blood TNF-α compared to systemic 22 minutes after reperfusion, further supporting the role of the bowel in the production of pro-inflammatory mediators. However, they did not demonstrate any correlation between endotoxin and TNF-α levels, which again may be due to the difficulty in detecting TNF-α in blood because of its short half-life and sporadic release.[92] Similarly, Gabriel et al were unable to identify any TNF-α in patients after EVAR, which they suggested was due to the considerable variability in TNF-α production between patients.[129] On the other hand, Boyle et al was able to detect low concentrations of plasma TNF-α during and after surgery up to day 5 in patients following both EVAR and open repair of AAA even though the former group had significantly less.[130]

Some workers have therefore, measured TNF-α as an alternative to TNF-α because of the unpredictability in the detection of the latter. Soong et al found significant concentrations of p55TNFr in patients following open AAA repair, which correlated with endotoxaemia and the development of bowel ischaemia.[92] This led them to suggest the bowel as the driver of the host systemic inflammatory response in cohort of patients. Adam et al demonstrated in a prospective study of ruptured AAA patients that the plasma levels of p75TNFr at 6 hours post-aortic clamp release were significantly higher in non-survivors compared to survivors.[131] Similarly, high levels of TNFr have been found to be predictive of mortality in septic and major trauma patients, and also following elective and ruptured AAA repair.[92, 132, 133] However, a lower level of p75TNFr has been reported in patients who developed renal failure requiring haemofiltration after elective AAA repair compared to those who did not develop renal impairment.[131]

Summary

Rupture of AAA is associated with significant morbidity and mortality. Aortic cross-clamping, ligation of the inferior mesenteric artery and hypotension because of blood loss will lead to partial or complete ischaemia of the various organs, especially the intestine and lower limbs. Reperfusion of these organs may exacerbate the injury incurred due to the production of oxygen-derived free radicals. This ischaemia-reperfusion injury has been implicated as the cause of SIRS and MODS following AAA surgery. In addition, the condition in some patients may be worsened by the development of acute abdominal compartment syndrome, which has also been associated with SIRS and MODS. Therefore, even if repair were successful, many patients may still die a few days or weeks later following a protracted course in the intensive care unit as a result of MODS.

Conflicting interests

The authors have declared that no competing interests exist.

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