Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis : a narrative review

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Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis.

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Abstract

Perioperative hypersensitivity reactions (POH) constitute a clinical and diagnostic challenge, a consequence of heterogeneous clinical presentations and multiple underlying pathomechanisms. POH do not necessarily involve an allergen-specific immune response with cross-linking of specific IgE (sIgE) antibodies on mast cells and basophils, but can also result from alternative specific and non-specific effector cell activation/degranulation such as complement-derived anaphylatoxins and off-target occupancy of mast cell and/or basophil surface receptors. Moreover, POH and anaphylaxis can occur independent from mast cell and basophil degranulation.

The manifestations of POH primarily affect the cardiovascular, respiratory and integumentary systems. POH presents with reference to a surgical pathology and the effect of surgical and anaesthetic techniques on pre-existing physiological reserve. The majority of cases of appropriately-treated intraoperative anaphylaxis can be considered a compensated cardiovascular anaphylaxis. With increasing severity of anaphylaxis, maldistribution and hypovolaemia lead to reduced venous return and circulatory failure. Treatment with a combination of adrenaline and fluid is critical for successful resuscitation, although the excessive use of adrenaline without adequate volume expansion may be deleterious. The neural control of the airway is important in the pathophysiology of bronchospasm. Anticholinergic drug premedication is beneficial in patients with hyper-reactive airways. Pulmonary oedema may result from a combination of pulmonary capillary hypertension and/or incompetence of the alveolocapillary membrane. Angioedema can be distinguished mechanistically into histaminergic and non-histaminergic, e.g. bradykinin mediated. An understanding of the molecular mechanism and pathophysiology of POH are essential for the immediate management and subsequent investigation of these cases.

1. Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis

1.1 Introduction

According to the revised nomenclature of allergy [1], the term "hypersensitivity" is currently used as an umbrella term to cover all non-expected but reproducible reactions by exposure to a defined substance that is tolerated by normal subjects and go beyond the primary pharmacological activity. Importantly, this definition does not take into account the underlying pathophysiological process and it was proposed to use the terms allergic and non-allergic hypersensitivity to denote an immune or non-immune mechanism, respectively. Similarly, the term "anaphylaxis" should not be reserved for immune, mainly IgE/FcεRI-dependent reactions, but extend to all rapidly developing, life-threatening, generalized or systemic reactions, irrespective the mechanistic endotype. [2] The term "allergic anaphylaxis" is proposed when an immunologic mechanism is demonstrable, all other situations should be referred as non-allergic anaphylaxis. An anaphylactic reaction mediated by cross-linking of allergen-specific IgE bound to the high affinity IgE receptor (FcεRI) on mast cell and basophils may be called IgE-mediated anaphylaxis. The terms "anaphylactoid" and "pseudo-allergic" should be abandoned, especially as novel specific and non-specific hypersensitivity mechanisms have been identified that can explain IgE/FcεRI-independent effector cell degranulation. Nevertheless, many authors still use these obsolete terms which does not benefit harmonization of classification and deepening insights in mechanisms. Here we review the molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis resulting from IgE/FcεRI-dependent and IgE/FcεRI-independent effector cell activation.

1.2 Specific and non-specific mast cell and basophil activation mechanisms

Mast cells and basophils are the key effector cells of POH and anaphylaxis. As illustrated in figure 1, degranulation of these cells can be triggered by various specific and non-specific mechanisms. Classically, degranulation is considered to be a reaction involving activation of the adaptive immune system with production and secretion of allergen-specific IgE (sIgE) antibodies by plasma cells. Subsequent these circulating homocytotropic sIgE antibodies bind to their high-affinity receptor (FcεRI) present in the surface membrane of both effector cells. Encounter of specific allergen that cross-links sIgE/FcεRI-complexes present on the surface membrane of both effector cells induces a complex down-stream signalling cascade that finally culminates in a compounded degranulation with exteriorization of aggregates of secretory granules. The presence of sIgE antibodies is essential but does not suffice for an effective cross-linking of FcεRI complexes resulting in degranulation.

Those requirements are not yet fully elucidated but the number of IgE binding sites on the allergen (epitopes) and the number and duration of cross-links per mast cell or basophil are key elements. [3] In this context it should be kept in mind that unlike proteinaceous allergens, small drug allergens are usually monovalent and require haptenization or other forms of protein binding to be "complete allergens". [4-6]

The signalling mechanisms that govern mast cell and basophil activation/degranulation and inhibition as well as the exocytic pathways are beyond the scope of this review and have been extensively described elsewhere. [7, 8] However, as elegantly reviewed by Finkelman *et al,* [9] and Reber *et al,* [10] activation/degranulation of these effector cells can also occur independently from allergen-sIgE antibodies. A first putative mechanism of sIgE/FcεRI-independent degranulation includes allergen-specific cross-linking of IgG/FcγR complexes. However, as acknowledged by the authors, evidence for IgG-mediated anaphylaxis is mainly provided by animal models, and, to the best of our knowledge, there have been no unequivocal examples of IgG-mediated POH published yet. Clinical evidence for human IgG-mediated anaphylaxis is currently restricted to a few observations involving the parental administration of significant quantities of (proteinaceous) allergen. For example, potential IgG-dependent anaphylaxis has been described to different chimeric, humanized and even fully human monoclonal antibodies such as infliximab [11-13] and adalimumab, [13] subjects treated with dextrans [14, 15] or aprotinin. [16, 17] However, the pertinence of some of these observations remains uncertain, [17, 18] mainly as in some cases (low) titres of drug-sIgE were demonstrable.

Mast cell and basophil activation can also occur via antibody-independent mechanisms. Complement activation with generation of anaphylatoxins C3a and C5a that bind to their specific G-protein coupled receptors C3aR and C5aR on mast cells and basophils, can occur in reactions to iodinated contrast media, [19] and in reactions to over-sulphated chondroitin sulphate contaminated heparin. [20] Other potential causes for complement-related hypersensitivity reactions, called C activation-related "pseudoallergy" (CARPA). CARPA represents a novel subcategory of acute hypersensitivity reactions which might be preventable by appropriate precautions. However, rarely, it can be severe or even lethal. [21, 22] CARPA mainly involves liposomal and micelle-solubilized drugs. The best-known liposomal drugs are ambisome, a charged non-PEGylated liposome and liposomal doxorubicin sulfate (Doxil®), a PEG-PL-engineered nanomedicine. [23] A well-known micelle-solubilized-drug is paclitaxel (Taxol®).

Mast cell activation can also result from engagement of the Mas-related G-protein coupled receptor MRGPRX2. [24] Since the first description by McNeil et al, [25] evidence has accumulated that off-target occupation of this receptor by various drug classes such as neuromuscular blocking agents (NMBA)

and opioids could constitute an additional mechanism of non-immune IDHR. [26] Alternatively, it is uncertain the opioid receptors to be involved in hypersensitivity to some opiates and semisynthetic opioids. [27]

1.3. Mast cell and basophil degranulation products

Degranulation of mast cells and basophils results in release of mediator that are classically classified in pre-formed (*i.e.* histamine, proteases), newly synthetized lipid mediators (prostaglandin, leukotrienes, PAF) usually generated over minutes, newly synthetized cytokines, chemokines and growth factors usually generated over hours. Because of variability, redundancy and ethical issues in inducing anaphylaxis in humans, it is difficult and challenging to judge the specific effect of each single factor. However, there is evidence that histamine, leukotrienes, PAF are involved in vasodilatation, capillary leak and bronchospasm. Depending of the underlying trigger mast cells and basophils release their mediators in different spatiotemporal manner. For example, sIgE/FcεRI cross-linking results in compound exocytosis, that is, a "delayed" but sustained process with release of large, stable, granules with a high content of inflammatory mediators. On the other hand, MRGPRX2 engagement results in rapid but transient release of unstable granules with low content of inflammatory mediators, a mechanism called kiss and run. [28, 29] The precise mechanisms and the clinical repercussion in the context of POH and drug hypersensitivity in general need to be elucidated. Also, to be further studied is the role, activation processes, and mediators of cells other than mast cells and basophils such as neutrophils, monocyte/macrophages and T cells in POH. It seems that neutrophils are involved mainly in IgG dependent anaphylaxis with PAF as key mediator.

1.4. POH resulting from enzyme interference (mainly inhibition)

As revealed by figure 2, POH can also occur independent from mast cell and basophil activation. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the major causes of IDHR that can mechanistically be classified in two groups. Firstly, most frequently, reactions induced by non-immunological non-specific mechanisms (non-allergic or cross-intolerance reactions) that encompass different clinical phenotypes such as NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD) and NSAID-induced urticaria/angioedema (NIUA). Secondly, the far more rare, reactions resulting from specific immunological mechanisms (allergic or selective reactions (SR)) designated as single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) in whom interclass cross-reactivity is virtually absent. The pathogenesis of the non-immunological NSAID hypersensitivity syndromes (NERD, NECD, NIUA) is related to their pharmacodynamic properties, that is, inhibition the cyclooxygenase (COX)-1 iso-enzyme. Blocking

COX-1 blocks prostaglandin synthesis and increases leukotriene production and can cause NERD, NECD and NIUA. [30]

The angiotensin-converting enzyme (ACE) is a key component of the renin-angiotensin system that converts angiotensin I to angiotensin II. It is additionally responsible for the degradation of bradykinin, which is generated from high molecular weight kininogen by kallikrein. Via bradykinin 2 receptors (Bk2R), bradykinin affects vascular permeability and stimulates the release of substance P, which is a peptide that causes vasodilation and fluid extravasation into tissues. Inhibition of ACE and subsequent blockade of bradykinin degradation is thought to be a likely explanation for - sometimes life-threatening – ACE inhibitor (ACEI)-induced angioedema. Angioedema may occur at any time during treatment with ACEIs and may continue weeks after the medication is discontinued. In the context of POH, ACEIs have been assumed to trigger isolated angioedema, that is angioedema without accompanying symptoms, mainly of the oropharynx because of mechanical stress due to (difficult) intubation. [31, 32] To the best of our knowledge there is no information on an impairment of aminopeptidase P and dipeptidyl peptidase IV as risk factor for perioperative angioedema.

1.5. MRGPRX2: a new player in perioperative hypersensitivity/anaphylaxis?

As already exemplified, mast cell and basophil are equipped with various surface receptors, providing them an intrinsic capacity to respond to different stimuli independent from aggregation of IgE/FcεRI complexes by specific allergen. Unfortunately, some of these receptors can also be activated by different drug classes, resulting in detrimental and harmful IDHR. However, for most of these alternative activation mechanisms clinical data are limited, especially in the context of POH (including perioperative anaphylaxis). As a matter of fact, it appears that apart from IgE/FcεRI cross-linking, the main mechanism assumed to be implicated in POH and anaphylaxis probably relates to an off-target occupancy of the MRGPRX2 receptor by drugs such as NMBA (aminosteroids and benzylisoquinolines), [25, 33-36] opiates/opioids [35, 37] and also some antibiotics such as fluoroquinolones [25, 33] and vancomycin. [35, 38] Moreover, by challenging the value of skin testing to discriminate between IgE/FcεRI- and MRGPRX2-dependent mast cell activation, some authors have already proposed to reclassify NMBA as a pharmacological adverse event or “innate hypersensitivity” reaction. [39] However, data were mainly obtained from animal and *in vitro* models and findings are not unanimously. For example, Lansu *et al* could not confirm mast cell degranulation by rocuronium, atracurium, ciprofloxacin and moxifloxacin. [37] Navines-Ferrer *et al* failed to demonstrate human mast cell degranulation in response to rocuronium amongst several other drugs. [35] The explanation for the divergences between mice and human mast cell has probably to be sought in adaptive changes of the MRGPRX2 gene in human evolution [40] making the human receptor less susceptible

for rocuronium than its murine orthologue Mrgprb2. [25, 35] In addition, it seems difficult to us to completely ignore congruent results from complementary basophil activation experiments and drug-specific sIgE assays that point to genuine IgE/FcεRI-dependent reactions to rocuronium [41-43] and atracurium [44, 45] in most of our patients. Collectively, these data indicate that next to IgE/FcεRI-cross-linking, off-target occupation of the MRGPRX2 receptor by NMBA might constitute an alternative pathomechanism for POH. MRGPRX2-dependendent reactions would be clinically indistinguishable from allergic POH resulting from IgE/FcεRI-cross-linking and additional *in vitro* tests are required to resolve between both mechanisms because of uncertainties associated with skin tests. Probably this assumption also applies to immediate opiate hypersensitivity reactions [46] that might require additional *in vitro* testing to discriminate between an IgE/FcεRI- and MRGPRX2-dependent reaction. [47, 48]

2. Pathophysiology of intraoperative anaphylaxis: Clinical implications

2.1. Introduction

The phenotypically indistinguishable POH endotypes interact with the patients' comorbid diseases, surgical pathology, anaesthetic and surgical techniques to create a myriad of presenting syndromes which evolve according to the patients' physiological reserve and the effectiveness of clinician intervention. Most anaesthetic drugs have both a direct depressant effect on the heart and circulation, and an indirect effect via reducing sympathetic activity. If cessation of spontaneous ventilation occurs, the favourable effect of the thoracic pump on venous return is lost. Intermittent positive pressure ventilation (IPPV), usually accompanied with positive end expiratory pressure (PEEP), will result in an increased mean intrathoracic pressure, further reducing the pressure gradient for right atrial filling. Instrumentation of the airway is common, potentially exacerbating bronchospasm and contributing to airway trauma, but also ensuring that airway swelling from angioedema and bronchospasm are not as critical as in the community where they are commonly reported causes of mortality.

There have been many animal models of anaphylaxis studied but the findings are not necessarily applicable to man because of the dramatically different effects of anaphylaxis between species. Knowledge gained from the collective experience of managing human anaphylaxis in the operating theatre environment has been critical in understanding the physiological effects, set out below, that are responsible for changing an often benign process into a lethal one. Most cases of anaphylaxis respond rapidly to treatment and are not associated with longstanding sequelae. Some cases are unresponsive to treatment, shock supervenes, cardiopulmonary resuscitation is required that can be unsuccessful in as many as 1-9% of cases. [49-51]

2.2. Compensated cardiovascular anaphylaxis

Hypotension is the most common presenting feature of perioperative anaphylaxis, and is frequently associated with tachycardia. [52] Nonetheless, in the majority of cases of appropriately treated intraoperative anaphylaxis, the cardiac output is maintained or increased. [55] Hypotension is a consequence of reduced cardiac preload and afterload, rather than myocardial dysfunction, although there is a quinary of causes of cardiovascular anaphylactic shock (see figure 3), and myocardial dysfunction can complicate any cause of hypoperfusion. Two reports of grade III, human intraoperative anaphylaxis - in which invasive monitoring had been incidentally applied - indicated that hypotension was initially associated with a reduction in systemic vascular resistance and pulmonary capillary wedge pressure. Left ventricular stroke volume was maintained or increased as a consequence of large compensatory increases in ejection fraction, although both the end-diastolic and end-systolic volumes were severely decreased. With compensatory tachycardia, cardiac output was maintained or increased. Endogenous epinephrine and norepinephrine blood levels became elevated 5.5 and 3.5 times respectively from baseline, counteracting to some extent the cardiovascular depressant effects of histamine. [53, 54]

2.3. Chronotropicity

Tachycardia is more common than bradycardia during intraoperative anaphylaxis, a consequence of the direct myocardial effects of histamine on cardiac H2-receptors, endogenous catecholamine effects on cardiac β-receptors, and reflex sympathetic activation. [55] However, in the less common cases of anaphylaxis complicated by cardiac arrest bradycardia was more common. [52] A postulated explanation is a precipitous reduction in venous return causing a vasodepressor response – the Bezold-Jarisch reflex. The afferent limb of the reflex involves cardiac mechanoreceptors in response to cardiac underfilling, and paradoxical arterial baroreceptor discharge in response to severe hypotension (‘collapse firing’). [56] The more frequent observation of bradycardia in severe anaphylaxis therefore suggests that in these cases a lack of venous return may be a key feature.

2.4. Shock

In increasingly severe or prolonged anaphylaxis, the ability to maintain cardiac output and blood pressure will be compromised by an unpredictable combination of distributive, hypovolemic, obstructive or, less commonly, cardiogenic aetiologies of shock. In animal models, regional blood flows are altered and the abolition of cerebral autoregulation results in pressure-dependent flow. [57] Clinical features to suggest inadequate perfusion include a reduction in end-tidal carbon dioxide partial pressure, poor peripheral perfusion resulting in failure of oximetry readings, or a delay in the appearance of skin manifestations of anaphylaxis. In ventilated patients suffering intraoperative anaphylactic shock to

neuromuscular blocking agents, end-tidal CO_2 tensions were reduced in 57% of grade III cases. [58]

2.5. Maldistribution and hypovolemia

The reduction in venous return and preload is secondary to fluid loss and redistribution of blood within vascular compartments. Extravasation of fluid from systemic capillaries is enhanced by both an increase in blood flow, due to vasodilatation, and disruption of the endothelial barrier by histamine and platelet activating factor. [59] The magnitude of fluid loss has been estimated by observing the degree of hemoconcentration, a decrease in blood volume of 30-37% in unresuscitated anaphylaxis. [60]

Reduced preload can only be compensated for by reducing the left ventricular end-systolic volume until a mechanical limit is reached, thus volume replacement is essential and in the severest cases resuscitation is impossible if replacement inadequate. Venous return is determined by the gradient between the mean systemic filling pressure - itself determined by the stressed volume in the venous compartment - [61] and right atrial pressure. Raised intrathoracic pressure and the reduction in stressed volume combine to severely compromise the pressure gradient that drives return of blood to the heart. The primacy of circulatory failure, rather than myocardial dysfunction, has been demonstrated by a case of human anaphylaxis during cardiopulmonary bypass. [62] Gelofusine® anaphylaxis was immediately associated with a reduction in return of venous blood from the patient to the circuit reservoir, requiring the addition of 73% of the patients estimated blood volume by weight (51 mL kg^{-1} of fluid) in the subsequent 15 minutes to maintain extracorporeal flow. The contribution of reduced venous return due to venous maldistribution in this case was similar to that of fluid extravasation, although the site of this maldistribution has not been clearly elucidated in man. In dog and rat models of anaphylaxis, sequestration of blood in the venous compartments of organs drained by the portal system is associated with acute increases in portal venous pressures. [63-65] Regardless, severe circulatory failure may occur despite the presence in this case of a functional (extracorporeal) pump, and is consistent with the majority of patients suffering grade IV anaphylactic shock who do not have pre-existing myocardial co-morbidities.

Four further supporting observations implicating maldistribution and hypovolemia in severe anaphylactic shock include upright posture and lack of volume resuscitation in fatal cases, and the efficacy of reversal of neuromuscular blockade and external chest compressions in resurrecting severe cases. Pumphrey reported a pattern of sudden death after a change to the upright posture in 4 patients suffering out-of-hospital anaphylactic shock, with at least 10 out of 38 patients who died in a series of community anaphylactic shock cases being resuscitated while positioned in an upright posture. [66] This ‘fatal’ posture was also noted in a high proportion of anaphylaxis fatalities in Australia. [67]

Intraoperative echocardiography in severe or nonresponsive anaphylactic shock almost universally demonstrates a hyperdynamic left and right ventricle with low end-diastolic and extremely low (negligible) end-systolic volumes. In these circumstances, the primary correctable defect is lack of venous return to the heart. In a European series of three fatal cases of NMBA anaphylaxis, volume expansion was absent or inadequate. [68]

There is a dichotomy between continuing reports of beneficial use and a lack of plausible mechanism for sugammadex in rocuronium-induced IgE-mediated anaphylactic shock. *In vivo* and *in vitro* experimental evidence indicates that sugammadex does not influence the extent or duration of the immunological response to rocuronium in patients with immediate hypersensitivity to rocuronium. [68, 69] It is equally effective in ameliorating severe anaphylactic shock induced by IgE-mediated POH triggered by either rocuronium or cephazolin, suggesting that the most likely mechanism is non-immunological. [70] The onset of exercise has been demonstrated to result in an immediate increase in the mean circulatory filling pressure as a consequence of the effect of muscle contraction on venous capacitance in exercising muscle and the abdomen. The volume shift has been estimated to be of the order of 500-1100mL (8-16mL kg^{-1}), and a similar autotransfusion during anaphylaxis could explain observed clinical improvements. [71] Reversal of neuromuscular blockade by sugammadex in anaphylaxis, regardless of the trigger, would be expected to similarly increase muscular tone and cause a sudden reduction in venous capacitance.

The resumption of spontaneous (negative-pressure) ventilation may also ameliorate anaphylactic shock. Obstruction to venous return as a consequence of raised intrathoracic pressures from positive pressure ventilation, with or without bronchospasm, will further impair cardiac filling in the setting of hypovolemia and increased venous compliance. Vena caval compression may occur, and any increase in intrathoracic pressure will increase right atrial pressure. Administration of sugammadex and conversion from positive- to negative-pressure respiration may widen the gradient for flow between mean systemic filling pressure and right atrial pressure. A similar principle has been used to explain the return of a spontaneous circulation in cases of circulatory arrest during dynamic hyperinflation of the lungs after cessation of resuscitative efforts (‘Lazarus phenomenon’).

Distinct from this previous example, the neurological-deficit-free survival from pulseless electrical activity (PEA) during POH is unexpectedly high. [72] Diastolic (organ-perfusing) pressure during external chest compressions must therefore be higher than would be expected of a pure vasoplegic state. If PEA results from the inability of the passively-filled heart to maintain a cardiac output, external chest compressions might result in an effective arterial pressure by overcoming the impediment to venous return to the right ventricle by creating a negative intrathoracic pressure (suction) during the

decompressive phase of external chest compressions (thoracic pump mechanism). There will also be increased left ventricular filling as a consequence of reduced pulmonary vascular capacitance during the compressive phase. [73]

The discussion above relates to impaired biventricular filling. There are multiple mediators that have either vasodilatory or constrictive effects on the pulmonary circulations and may cause impairment only of left ventricular filling. In dogs and mice, acute pulmonary hypertension and right heart failure has been observed, with a reductions in left ventricular preload. [74, 75] This has not been observed in man except after IgE-independent anaphylaxis such as a type III, immune-complex reaction to protamine.

2.6. Myocardial depression

Intraoperative anaphylaxis occurs most commonly in patients who do not have a reduced myocardial reserve, as are the majority of patients in which cardiac arrest is a complication. [72] However there will be some patients with pre-existing cardiac disease in whom hypotension and increased myocardial work (from tachycardia) result in secondary cardiac dysfunction because of inadequate myocardial perfusion. Myocardial ischemia during anaphylaxis has been reported secondary to a number of different etiologies. These have been collectively described as Kounis syndrome [76] that include three variants, coronary vasospasm with normal coronary vasculature, plaque erosion or rupture leading to myocardial infarction and stent thrombosis. These syndromes are not commonly seen during anesthesia.

Takatsubo's cardiomyopathy is a rare condition characterized by reversible left ventricular dysfunction due to regional wall motion abnormalities predominantly affecting the apex of the heart. Because of its association with emotional stress, it may alternatively be called 'broken heart syndrome'. There is a complex interaction between the brain and the cardiovascular system that, if dysfunctional through neurological injury, such as subarachnoid hemorrhage or emotional processing can lead to both circulating and myocardial catecholamines reaching damaging levels. [77] Although ST-segment elevation and/or T-wave inversion may occur with normal or marginally elevated troponin levels, coronary angiography usually demonstrates normal coronary vasculature. Takatsubo's cardiomyopathy associated with anaphylaxis is more commonly reported in non-anaesthetized patients presenting to emergency departments from the community. Anesthesia will obtund the effects of the heart-brain axis and thus Takatsubo's cardiomyopathy is uncommon with anaphylaxis in the anaesthetized patient, but may be a cause in this setting by over-aggressive treatment with adrenaline. The most plausible hypothesis to explain Takatsubo cardio-depression is that is it caused by the action of adrenaline on β2-adrenoreceptors that are more prevalent in the apex of the heart. [78] Noradrenaline, having less β2 activity, does not cause the same contractile effects in animal models.

2.7. Left ventricular outflow obstruction causing obstructive shock.

Excessive use of adrenaline in association with inadequate volume replacement can result in a hyperdynamic, underfilled heart that results in dynamic left ventricular outflow obstruction with systolic anterior motion of the mitral valve and severe mitral regurgitation. [79] This condition is most commonly seen with anatomical abnormalities of the outflow tract of the left ventricle such as hypertrophic obstructive cardiomyopathy but in association with anaphylaxis, they can occur with normal cardiac anatomy. It is exacerbated by positive pressure ventilation, inadequate fluid resuscitation and positive inotropes. Continued use of adrenaline in this situation is likely to worsen the condition and may be fatal, in which case it is salutary to recognize that at postmortem there would be no evidence of the cause of death.

It can therefore be seen that the cardiovascular manifestations of anaphylaxis are not stereotypical and the individual response depends on the reserve of each component of the cardiovascular system. This, in turn, is influenced by the surgical procedure being performed, the stage of the procedure, surgical pathology, anaesthetic techniques, and clinician interventions. Finally, patient comorbid diseases and pharmaceutical treatments (beta-blockers, antihypertensives or antihistamines) may exacerbate or ameliorate the presentation.

3. Pathophysiology of bronchospasm

Many patients presenting for surgery have a predisposition to developing bronchospasm. Some of these will not admit to, or ignore, asthma symptoms. Asthma medication is often mistakenly omitted particularly before emergency surgery. Neither sedative nor anticholinergic medications are now fashionable as premedication before surgery. Anxiety, irritant volatile anaesthetics, airway instrumentation and many histamine-releasing drugs will cause bronchospasm in these patients. POH is not the most common cause of perioperative bronchospasm. When it does occur, allergic POH results in bronchospasm triggered by the actions of degranulation products - including histamine and platelet activating factor – and may have some mediators in common with non-allergic POH (e.g. Cysteinyl leucotrienes). It is likely that the severity of bronchospasm when anaphylaxis is triggered is determined by the underlying state of the airway and the presence, or not, of anticholinergic medication. In a recent report of a series of patients with intraoperative anaphylaxis, the incidence of bronchospasm in at-risk patients was not increased, but the severity of reactions when they did occur were more severe. [80]

3.1. Neural control of the healthy airway.

In normal lung, efferent parasympathetic nervous control via the vagus nerve is the predominant determinant of airway tone. In disease states such as asthma the role of the nervous system has

consistently been understated. [81] There is no sympathetic nerve supply to bronchiolar smooth muscle but β-adrenergic receptors are widely expressed explaining the effectiveness of β2-agonist drugs as bronchodilators. Vagal preganglionic fibres enter the lung and terminate in ganglia within the bronchioles. The airways of healthy humans are tonically constricted, maintained by efferent vagal activity acting via postganglionic fibres that release acetylcholine, the ligand for muscarinic receptors (M_3) on bronchiolar smooth muscle fibres (see figure 4). This excitatory effect is balanced by a negative feedback loop via M_2 receptors on the postganglionic nerve. [82] Afferent sensory neurons respond to chemical stimulation as well as to bioactive molecules released during inflammation. Their cell bodies are in vagal and cervical dorsal root ganglia via which signals are transmitted to the brainstem and spinal cord. [83]

3.2. Neural control of the diseased airway.

Studies of the airway in asthma demonstrate that there are both sensory afferent and motor efferent vagal neural responses which are altered by the disease process. Acetylcholine, as well as histamine, are potent vasodilators of the tracheobronchial circulation, causing submucosal swelling and contributing to the changes in airway resistance compounding that mediated by airway smooth muscle. [84] Mice sensitised to ovalbumin develop a marked immune reaction in the lung with leucocyte infiltration and airway hyperreactivity. Ablation of a subset of sensory neurones will completely abolish the hyperresponsiveness but have no effect on the inflammatory component. Indeed, in man, bronchial thermoplasty is successful in moderating severe asthma, in part, by interrupting central and local reflexes responsible for activating bronchospasm. [85] In asthma, inflammatory mediators sensitise vagal sensory neurones resulting in an exaggerated response to bronchoconstricting stimuli, common during anaesthesia. [86]

Efferent neurones also contribute to the exaggerated response to airway stimulation. In asthma the blockade of M_2 receptors by major basic protein from eosinophils that invade the bronchioles as part of the inflammatory process is one example. Viral neuraminidase has a similar effect and is recognised as a cause of airway hyperreactivity, particularly in children after respiratory tract infections. Gallamine, a muscle relaxant of historical interest, is a selective antagonist at the M_2 receptor that blocked autoinhibition, causing bronchospasm on vagal stimulation. [82] More recently rapacuronium, a rapidly acting muscle relaxant, was developed speculatively to replace suxamethonium. After a number of deaths from bronchospasm in children, thought to have been allergic in origin, the drug was withdrawn. It was only proven later that the bronchospasm was due to rapacuronium having antagonist effects at the M_2 receptor and an indirect agonist effect at the M_3 receptor. [87] Administration of an anticholinergic drug such as atropine causes dilatation of the airways by blocking M_3 receptors. Since the advent of

general anaesthesia atropine has been universally used as a premedication, until relatively recently, because of its beneficial effects in blocking undesirable cholinergic effects such as excessive salivation, bradyarrhythmia's and reflex bronchoconstriction in response to non-antigenic stimuli.

The UK lifetime prevalence of patient-reported symptoms of asthma is 29.5% and 15.6% for patient-reported clinician-diagnosed asthma. It is estimated that 1.2 million people (2% of the population) have chronic obstructive pulmonary disease (COPD). [88] If one includes smoking it is clear that a large percentage of people presenting for surgery have hyperreactive airways and are at risk of developing bronchospasm. Many of those with COPD will be treated with selective short or long-acting anticholinergic drugs such as ipratropium bromide and tiotropium bromide respectively. Some asthmatics will also have had benefit from these drugs.

Studies in guinea pigs, that develop anaphylaxis characterised by lethal bronchospasm on exposure to an antigen to which they are sensitised, are completely protected if pre-treated with atropine. Similarly, asthmatics exposed to antigen aerosols of grass pollen or house dust mite will develop bronchospasm but are protected if pre-treated with atropine but not if it is administered after the allergen exposure. [89]

4. Pulmonary oedema

Pulmonary oedema is a rare, but described, complication of anaphylaxis. Pulmonary capillary hypertension and/or incompetence of the alveolocapillary membrane will result in egress of fluid from the pulmonary circulation and cause alveolar oedema if it exceeds the capacity of pulmonary lymphatic drainage. In Ovalbumin-sensitised rats, anaphylaxis is associated with an almost immediate decrease in pulmonary compliance due to massive tracheal, bronchial and intrapulmonary microvascular leakage, causing bronchospasm. [90] In described human cases, pulmonary artery and pulmonary capillary wedge pressures are reduced, although it is possible that pulmonary arteriolar dilatation and/or pulmonary venous constriction could still result in raised pulmonary capillary hydrostatic pressures. In some instances of anaphylaxis, fulminant pulmonary oedema with a high fluid protein content (>70% fluid/serum protein concentration) has been described, and this membrane oedema may occur with normal or low pulmonary capillary hydrostatic pressures, and in the presence of high mean positive airway pressures (with positive-pressure invasive ventilation). Severe membrane oedema has been associated with the subsequent development of hypovolaemia and hypoxaemia.

5. Angioedema

Angioedema may be subclassified into cases with and without urticaria. [91] Urticaria is a manifestation of anaphylaxis in the skin, with red, raised and itchy lesions as a consequence of vasodilatation, increased blood flow and increased capillary permeability. Urticaria occurs in the superficial dermis, while

angioedema is the same pathophysiological process occurring in the deeper tissues. Angioedema is defined as non-pitting, non-gravity-dependent, transient swelling of the skin or mucous membranes (as distinguished from edema which is pitting and gravity dependent). Angioedema can be distinguished mechanistically into histaminergic (including anaphylactic) and non-histaminergic (complement or bradykinin-mediated). Bradykinin-mediated angioedema [92] often involves the upper airways, and will not respond to antihistamines, corticosteroids or adrenaline.

A feared complication of intraoperative anaphylaxis is angioedema and potential airway obstruction. Intraoperative presentations of anaphylaxis less commonly involve the respiratory system, with only 20% of fatal cases involving the respiratory system. [67] Respiratory presentations are more common in drug allergies in other hospital settings or in the community, and particularly with food allergies.

Although generalised oedema is common after IgE-mediated anaphylaxis, tongue and laryngeal swelling is more common after non-allergic reactions. [93] This is particularly the case when airway instrumentation is a precipitant for localized tissue bradykinin activation. The syndrome of airway swelling in this situation can be prolonged (>48 hours), and will not respond to usual therapies for anaphylaxis-induced angioedema. In a series of 72 patients intubated and admitted to intensive care after idiopathic angioedema, the mean duration before extubation was 93.5 hours. [94] Contrastingly, in a series of 205 patients with grade II-IV intraoperative (post-induction) anaphylaxis, only 97 patients were admitted to intensive care intubated (47%) and only 21 remained intubated 24 hours after admission to ICU (10%). No patient with grade II anaphylaxis was still intubated after 24 hours. [72] The incidence of angioedema was not sought in this study, however only 10 remained intubated 48 hours after admission (4.9%), and at least 4 of these had complications unrelated to airway swelling to account for prolonged intubation (Takatsubo's cardiomyopathy, ventilator-associated pneumonia or hypoxic encephalopathy). Therefore, the incidence of airway swelling requiring ventilation for more than 48 hours after intraoperative anaphylaxis is likely to be less than 3%.

ACE-inhibitor induced angioedema is more likely to affect the larynx than allergic angioedema or hereditary angioedema resulting from C1-inhibitor function deficiency. [95] The anaesthetist should be vigilant for cases of IgE-independent anaphylaxis, particular in patients on ACE-inhibitors which may progress to life-threatening airway swelling.

6. Summary

The current definition of POH includes allergic and non-allergic phenomena, and the non-allergic phenomena may involve both mast cell/basophil-dependent and independent syndromes such as COX1 inhibition and generation of bradykinin. These distinct underlying pathomechanisms result in heterogenous clinical presentations which, as is the case for hypersensitivity reactions in the

community, are modified by the patients comorbid conditions. POH is further complicated by the intersection of these derangements with the surgical pathology and the effects of surgical and anaesthetic techniques, creating both a diagnostic challenge and newly-recognised treatment paradoxes. The suspicion of POH may be raised because of an unexpected diversion from the normal physiological or pharmacological response to the anaesthetic drugs used. Manifestations such as hypotension, mild increases of airway resistance and even transitory patchy erythema are not uncommonly caused by anaesthetic drugs but it is the magnitude, duration, combination of signs and response to treatment that suggest POH. The most severe result of POH is anaphylaxis that in most cases rapidly responds to recommended treatment with adrenaline and fluids. Occasionally protracted resuscitation is required and it is in this setting that a good understanding of the pathophysiology is critical in managing a severe multisystem disorder that is not stereotypical. Cardiovascular effects of POH may be mediated by a variable effect on various aspects of the circulation and heart, while the respiratory manifestations have to be distinguished from more common causes of bronchospasm under anaesthesia, or pathophysiologies of angioedema that would not be expected to respond to the usual therapies for anaphylaxis. The pathophysiology of POH is a topic with incomplete knowledge and further investigation has the potential to improve patient outcomes.

Legends of figures

Figure 1: Mast cell and/or basophil activation can occur via non-specific and specific pathways. Non-specific activation mainly involves occupation of complement receptors C3aR and C5aR by the anaphylatoxins C3a and C5a that are generated through activation of the complement system. Another way of non-specific mast cell activation implies occupation of the Mas-related G protein coupled receptor MRGPRX. Note that MRGPRX2 is not constitutively expressed by basophils. Specific activation of basophils requires activation of B lymphocytes of the adaptive immune system with production of allergen-specific antibodies.

Figure 2: possible pathomechanisms for clinical picture suggestive of perioperative hypersensitivity reactions. [96]

Figure 3: A Quinary of Causes of Cardiovascular anaphylactic shock. Severe anaphylactic shock may result from any or all of the five mechanisms indicated. Abbreviations: CVV (central vascular volume), CO (cardiac output), left ventricular outflow obstruction (LVOTO)/SAM (left ventricular outflow tract obstruction and systolic anterior motion of the mitral valve leaflets). "Copyright, P Sadleir, R Clarke, P Platt: reproduced with permission."

Figure 4: Irritant receptor – vagal reflex. Neuromuscular junction acetylcholine stimulates postsynaptic bronchial smooth muscle (bronchoconstriction) via M_3 receptors, an action limited by its effect on inhibitory, presynaptic M_2 receptors, which impede the exocytosis of further acetylcholine. "Copyright, P Sadleir, R Clarke, P Platt: reproduced with permission."

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