Renin–angiotensin system inhibitors and angioedema: anesthetic implications

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Purpose of review
Angioedema is a serious complication of renin–angiotensin system inhibitor therapy. The incidence is 0.1–0.7%. It consists of nonpitting edema and involves the face and lips. In severe cases, it extends to pharyngeal and laryngeal structures.

Recent findings
Decreased degradation of bradykinin and its metabolites is thought to be a culprit. When the angiotensin-converting enzyme is inhibited, bradykinin metabolism is dependent on degradation by neutral endopeptidase, dipeptidyl peptidase IV, and aminopeptidase P. When these enzymes are inhibited, as in treatment of diabetes or in transplant recipients, the incidence of angioedema increases significantly. African-Americans, people over 65, women, and those with a history of smoking are especially at risk. A fiberoptic laryngeal examination should be performed in all patients. Patients with rapid progression of symptoms are at risk for airway compromise. Supportive treatment with steroids and antihistamines is not very effective. Recently, icatibant, a bradykinin receptor antagonist, has been used to successfully shorten the resolution of edema.

Summary
Trauma of the airway, especially during difficult intubation, may precipitate severe angioedema. In cases with laryngeal involvement, fiberoptic intubation may be necessary. After the episode of angioedema, lifetime discontinuation of all renin–angiotensin inhibitors may be warranted.

Keywords
airway edema, angioedema, angiotensin-converting enzyme inhibitors, bradykinin, renin–angiotensin system

INTRODUCTION
The renin–angiotensin–aldosterone system (RAAS) is a key player in human physiology. It regulates blood pressure homeostasis, water balance, renal function, and cellular growth. Hyperactivation of RAAS is involved in the development of end-organ damage in a variety of cardiovascular and renal diseases. The beneficial effects of RAAS inhibition extend beyond the antihypertensive effect and include significant cardioprotective and renoprotective effects [1]. The therapies that modulate RAAS have emerged as important armamentarium in the treatment of patients with various cardiovascular and renal disorders. Pharmacological inhibition of RAAS can be obtained via three different mechanisms: inhibition of conversion of angiotensin I (AngI) to active angiotensin II (AngII) via angiotensin I converting enzyme inhibitors (ACEIs); selective inhibition of angiotensin receptor 1 (AT1) via angiotensin receptor blockers (ARBs); and direct inhibition of Angl production via direct renin inhibitors (DRI).

Pharmacological inhibitors of RAAS are among the most commonly prescribed therapeutics in the USA. ACEIs alone were ranked 5th in the total US healthcare market with 168.7 million prescriptions dispensed in 2010 [2]. These medications are usually well tolerated, and the long-term tolerability is similar to other commonly prescribed antihypertensives [3]. The most common adverse effects are headache, dizziness, and fatigue; more serious side-effects include hypotension, hyperkalemia, and renal failure [4]. The overall incidence of

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Angioedema is a life-threatening condition that may develop in patients treated with any medications that inhibit RAAS.

The pathophysiology of angioedema is related to changes in the metabolism of the kallikrein–kinin system.

Management of angioedema includes prompt recognition and triage with mandatory fiberoptic examination of pharyngeal and laryngeal structures as well as intubation for airway protection in severe cases.

Anesthesiologists should be aware that airway trauma, especially during difficult intubation, may trigger angioedema in susceptible patients who are on RAAS inhibitors.

An episode of angioedema may require lifelong discontinuation of all RAAS inhibitors.

Adverse events is about 4–7% [5]. However, in susceptible individuals these medications may induce severe and life-threatening angioedema.

Angioedema consists of subcutaneous or submucosal nonpitting, nonpruritic, painless edema. Angioedema may involve any part of the body; however, the most common sites involve tongue, oropharynx, periorbital, and perioral areas [6–8]. Supraglottic and laryngeal extensions of the edema can quickly progress to airway compromise and may require endotracheal intubation for airway protection [9]. Less commonly, angioedema may involve the gastrointestinal wall (visceral angioedema), which may present as a diagnostic challenge [10,11].

ACEIs are most commonly implicated in angioedema formation and the incidence ranges between 0.1 and 0.68% [12,13]. The incidence of angioedema following ARBs administration is slightly less and occurs in 0.1–0.4% of patients [14,15*]. Incidence of angioedema in patients taking aliskiren is around 0.4% [16,17]. Recent analysis of the adverse events via the US Adverse Event Reporting System revealed that aliskiren has had the highest reporting ratio for angioedema among all RAAS inhibitors, including two deaths [18]. At this time, it is not clear whether aliskiren has a higher risk of life-threatening angioedema compared to other RAAS inhibitors.

### KEY POINTS

- Angioedema is a life-threatening condition that may develop in patients treated with any medications that inhibit RAAS.
- The pathophysiology of angioedema is related to changes in the metabolism of the kallikrein–kinin system.
- Management of angioedema includes prompt recognition and triage with mandatory fiberoptic examination of pharyngeal and laryngeal structures as well as intubation for airway protection in severe cases.
- Anesthesiologists should be aware that airway trauma, especially during difficult intubation, may trigger angioedema in susceptible patients who are on RAAS inhibitors.
- An episode of angioedema may require lifelong discontinuation of all RAAS inhibitors.

### BALANCE BETWEEN THE RENIN–ANGIOTENSIN SYSTEM AND THE KALLIKREIN–KININ SYSTEM

RAAS and kallikrein–kinin system (KKS) interact on several levels in a complex array of crosstalk [19,20]. At some levels they potentiate, and at others they oppose each other; under normal physiologic conditions, they are in equilibrium [20]. Any intervention that affects one system will have a profound effect on the other on multiple levels [21]. ACE is a key enzyme that links these two systems together [20]. Thus, drugs that inhibit RAAS exert their beneficial effect also by potentiating KKS [22–25]. However, the beneficial effect in increasing KKS comes at a certain price. In susceptible individuals, alterations in KKS can lead to severe and sometimes life-threatening angioedema [3*,18,26,27].

Bradykinin is a nonapeptide cleaved from high molecular weight (HMW) kininogen by activated plasma kallikrein assembled with Factor XIIa on endothelial cell membranes. Bradykinin is rapidly metabolized, with a plasma half-life of only 15–17 s. Kallidin (Lys-BK) is a decapeptide generated by enzymatic degradation of low molecular weight (LMW) kininogen by tissue kallikrein. Both Bradykinin and Lys-BK exert their action primarily via B2 receptors [21]. B2 receptors are constitutively and widely expressed on endothelial cells in many tissues. B2 receptor activation leads to release of nitric oxide and prostacyclin (PGI2), and causes vasodilatation, hypotension, and increased vascular permeability [20]. Under normal physiologic conditions, kinins exert their effect in an autocrine and a paracrine manner, with little systemic effects due to a rapid degradation by endothelial-based enzymes. Bradykinin and Lys-BK are rapidly metabolized to inactive products via endothelial cell-based ACE, neutral endopeptidase (NEP), aminopeptidase P (APP), and dipeptidyl peptidase IV (DPP-IV) (Fig. 1). Degradation of Bradykinin and Lys-BK via plasma carboxypeptidase N (CPN) produces active metabolites Des-Arg⁹ Bradykinin and Lys-Des-Arg⁹ Bradykinin, which are potent activators of B1 receptors (Fig. 1). B1 receptors have low intrinsic expression; however, their expression can be induced by tissue trauma, inflammatory cytokines, and endotoxin stimulation. Inducible activation of B1 receptors mediates inflammatory response, exacerbates tissue edema, and may lead to severe vasodilatation, hypotension, and fluid extravasation seen in endotoxic shock.

Inhibition of ACE leads to alterations in the RAAS via decreased production of a potent vasoconstrictor and proliferative agent, AngII, from a precursor, AngI. ACE inhibition also profoundly affects the KKS by decreasing the degradation of Bradykinin and Lys-BK, which leads to their accumulation in the tissues, especially in the heart and in the kidneys. Increase in tissue Bradykinin and Lys-BK is at least partly responsible for the cardioprotective and renoprotective effects of ACEIs. ACEIs may also act as allosteric enhancers of B2 receptors.
The binding of ACEIs to ACE induces a conformational change in ACE which is transmitted to a B2 receptor, resulting in potentiation of its effect. Moreover, ACEIs directly activate B1 receptors in the same range as Des-Arg^9^ Bradykinin and Lys-Des-Arg^9^ Bradykinin by kininase I (carboxypeptidase N). Angiotensin-converting enzyme [ACE] is the main enzyme that metabolizes all kinin peptides into inactive products. In the presence of ACE inhibitors, kinin peptides metabolism is increasingly dependent on other enzymes (APP, NEP, and DPP-IV). When these enzymes are inhibited, as in patients on DPP-IV inhibitors or immunosuppressants, kinin peptides accumulate. Action of kinins via B2 receptors induces hypotension and vasodilatation because of the increased levels of nitric oxide (NO) and prostacyclin PGI2. This effect is thought to be beneficial in patients with hypertension, heart failure and diabetic nephropathy. However, higher levels of kinins may produce exaggerated inflammatory response, tissue edema, fluid extravasation and hypotension via action through B1 receptors. This effect may lead to the development of angioedema.

**PATHOPHYSIOLOGY OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM INHIBITORS-INDUCED ANGIOEDEMA**

In the presence of ACEIs, Bradykinin metabolism is increasingly dependent on NEP, DPP-IV, and APP to produce inactive metabolites. Additionally, ACE inhibition shifts Bradykinin and Lys-BK metabolism toward the production of active metabolites, (AT2) receptors in the presence of AT1 receptor blockade. AT2 receptor activation induces an increase in kinin generation and directly stimulates the B2 receptor (AT2–B2 receptor crosstalk) [31].

DRI aliskiren affects KKS by increasing tissue kallikrein levels, and subsequently Bradykinin formation in the heart by renin-independent mechanism [25].
Des-Arg⁹-Bradykinin and Lys-Des-Arg⁹-Bradykinin, by CPN. These active metabolites are degraded to inactive metabolites primarily by ACE, and in the presence of ACEIs their metabolism is increasingly dependent on the action of APP (Fig. 1). Any further environmental or genetic imbalance in any of the enzymes involved in KKS metabolism may lead to excessive accumulation of Bradykinin and Lys-BK, as well as their active metabolites. Experimental evidence supports this hypothesis and shows significantly higher accumulation of Des-Arg⁹-Bradykinin in patients taking ACEIs who developed angioedema, compared with patients taking ACEI who did not [32]. Des-Arg⁹-Bradykinin and Lys-Des-Arg⁹-Bradykinin activate proinflammatory B1 receptors, resulting in vasodilatation and fluid extravasation leading to edema [33]. In addition, B1 receptor activation on sensory neurons leads to a local accumulation of neuropeptide substance P [34,35]. Release of substance P produces the symptoms of neurogenic inflammation and edema via the NK1 receptors located on endothelial cells and mast cells in the capillaries, further aggravating the edema induced by activation of KKS [35]. Metabolism of substance P is highly dependent on the action of ACE and, in the presence of ACE inhibition, it primarily depends on degradation by NEP and DPP-IV. Therefore, it is not surprising that vaso-peptidase inhibitor omapatrilat (Valnev), which inhibits both ACE and NEP, caused an unacceptably high rate of angioedema (2.16%) as compared to enalapril (0.67%) during the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial [36]. The OCTAVE trial included more than 25,000 patients and led to the rejection of omapatrilat by the Food and Drug Administration (FDA).

DPP-IV is another enzyme that plays a supporting role in the degradation of Bradykinin and substance P. However, DPP-IV has an important role in the inactivation of incretin hormones, such as glucagon-like peptide-1 and glucose-dependent insulino-notropic polypeptide [37]. Diabetic patients have increased DPP-IV activity, which contributes to impaired glucose control and insulin resistance [37]. DPP-IV inhibitors emerged as promising agents in the treatment of diabetes mellitus type 2 (DMT2). In 2006, the first DPP-IV inhibitor sitagliptin (Januvia) was approved by the FDA for the treatment of DMT2 [38], followed by saxagliptin (Onglyza) in 2009. The American College of Endocrinology now places DPP-IV inhibitors in the first line of treatment for DMT2 [39]. However, in 2008, Medwatch, the FDA Safety Information and Adverse Event Reporting Program released a postmarketing experience of serious hypersensitivity reactions, including angioedema in patients treated with sitagliptin [40]. Recent meta-analysis showed that another DPP-IV inhibitor vildagliptin is associated with an increased risk of angioedema, especially when used concomitantly with ACEI (odds ratio 4.57) [7,41]. As HTN and DMT2 occur commonly together, anesthesiologists should be aware of the potential risks of angioedema in patients concomitantly treated with ACEI/ARB/DRIs and DPP-IV inhibitors.

DPP-IV also has an important role in human T-cell biology as a CD26 leukocyte surface antigen [42]. Its DPP-IV enzymatic activity enhances the T-cell response to external stimuli, and the CD26/DPP-IV surface antigen plays an important role in T lymphocyte activation and proliferation [42,43]. As CD26/DPP-IV cellular expression and activity are strongly correlated with transplant rejection [44,45], all immunosuppressant medications inhibit its activity. Indeed, graft survival in transplant recipients is inversely proportional to CD26/DPP-IV activity [45]. However, decreased DPP-IV activity in transplant patients who are concomitantly on ACEI therapy significantly increases their risk of developing angioedema [46]. Incidence of angioedema is increased 24-fold in cardiac transplant recipients and 5-fold in renal transplant recipients who were on concomitant ACEI therapy [46].

To date, there are no data of angioedema in patients who are on triple combination therapy (DPP-IV inhibitors, immunosuppressants, and ACEI/ARB/DR); however, it is very plausible to encounter such patients in the near future because of an ever more complex clinical picture and the advanced medical treatments available today. It is very important to have in mind their increased risk of angioedema, especially during the perioperative period and airway manipulations. Airway trauma, in particular during difficult intubation, may precipitate severe angioedema, and further worsen airway compromise.

**GENETIC FACTORS**

When ACE is inhibited, Des-Arg⁹-Bradykinin inactivation is highly dependent on APP activity (Fig. 1). The APP enzyme exists in two isoforms, the soluble/cytosolic form and the membrane-bound form, encoded by two different genes, XPNPEP1 and XPNPEP2, respectively. *In vivo*, only membrane-bound APP enzyme is involved in Des-Arg⁹-Bradykinin metabolism. Genetic variants of the XPNPEP2 gene have been shown to decrease APP activity [47]. Single-nucleotide polymorphism C-2399A, located in the enhancer region of the XPNPEP2 promoter, is associated with increased risk of ACEI-induced angioedema, especially in African–American men...
Recently, a functional XPNPEP2 promoter haplotype ATG (located in the potent transcriptional enhancer region of the gene) was significantly associated with ACEI-induced angioedema [49**]. The authors suggest that the ATG haplotype may be a useful biomarker for ACEI-induced angioedema risk prediction [49**].

**EPIDEMIOLOGICAL FACTORS**

RAAS inhibitor-induced angioedema is three times more prevalent in patients with African–American ancestry, as compared to Caucasians [3*,50]. African–Americans also tend to have more severe symptoms associated with angioedema and are more likely to require hospitalization and intubation for airway protection. Lower endogenous Bradykinin levels and increased sensitivity to Bradykinin in African–Americans has been proposed [51].

Other risk factors include the female sex, a history of smoking, advanced age (>65), and a history of ACEI-induced cough [3*,50].

The factors of special interest to anesthesiologists are those that may increase the perioperative risk of developing angioedema. Trauma to the upper airway during airway management and intubation may precipitate RAAS inhibitor-induced angioedema, especially if other risk factors are present [9,30].

Risk factors associated with RAAS inhibitor-induced angioedema are summarized in Table 1.

**CLINICAL PRESENTATION AND MANAGEMENT**

Angioedema can be classified according to clinical presentation into three types; mild forms (type 1) are the most common and are limited to face or lip edema, with no or only anterior tongue involvement [52]. Extension to the base of the tongue, floor of the mouth, soft palate or uvula could be classified as moderate (type 2). In severe forms, angioedema extends to supraglottic and laryngeal structures (type 3). Characteristics of the three types of angioedema are summarized in Table 2. As supraglottic edema may not always correlate with tongue edema, flexible fiberoptic laryngeal examination is essential to diagnose more severe forms [9,53**]. In addition, the degree and rapid progression of tissue swelling are sensitive indicators for the necessity of intubation for airway protection [54]. Patients with mild

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**Table 1. Risk factors for the development of RAAS inhibitor-induced angioedema**

<table>
<thead>
<tr>
<th>Genetic factors</th>
<th>Epidemiological factors</th>
<th>Pharmacological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>XPNPEP2 gene polymorphisms [APP enzyme]:</td>
<td>African-Americans</td>
<td>DPP-IV inhibitors (treatment of diabetes mellitus):</td>
</tr>
<tr>
<td>SNP C-2399A</td>
<td>Women</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Promoter haplotype ATG</td>
<td>Age &gt;65</td>
<td>Saxagliptin</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>Vildagliptin</td>
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<tr>
<td>Airway trauma (intubation)</td>
<td></td>
<td>Immunosuppressants</td>
</tr>
</tbody>
</table>

APP, aminopeptidase P; DPP-IV, dipeptidyl peptidase IV; SNP, single-nucleotide polymorphism.

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**Table 2. Clinical presentation and management of RAAS inhibitors-induced angioedema**

<table>
<thead>
<tr>
<th>Type of angioedema</th>
<th>Clinical presentation</th>
<th>Management</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (Type 1)</td>
<td>Face, lip, and anterior tongue edema</td>
<td>Observation in emergency room or on regular ward</td>
<td>Corticosteroids and antihistamines</td>
</tr>
<tr>
<td>Moderate (Type 2)</td>
<td>Edema extension to base of the tongue, floor of the mouth, soft palate, and uvula</td>
<td>ICU admission</td>
<td>Add s.c. or racemic epinephrine if stridor is present</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FFP</td>
</tr>
<tr>
<td>Severe (Type 3)</td>
<td>Edema involving supraglottic and laryngeal structures</td>
<td>ICU admission</td>
<td>As in type 1 and type 2</td>
</tr>
<tr>
<td></td>
<td>Drooling, odynophagia, hoarseness, or dyspnea</td>
<td></td>
<td>Fiberoptic endotracheal intubation in airway compromise or rapid progression of symptoms</td>
</tr>
</tbody>
</table>

FFP, fresh frozen plasma; s.c., subcutaneous.
forms may be observed in the emergency department or hospitalized on the regular floor. Patients with moderate and severe angioedema should be observed in the intensive care unit. Patients with rapid progression symptoms (drooling, odynophagia, hoarseness, and dyspnea) are at a high risk of airway compromise and the airway should be secured with elective fiberoptic intubation. Contrary to the previous reports, patients with RAAS inhibitor-induced angioedema do not have a higher incidence of intubations, compared to other types of angioedema [55]. However, if RAAS-inhibitor-induced angioedema occurs after airway management during the perioperative period, intubation is almost always required.

Angioedema is self-limiting and usually resolves within a few days after discontinuation of the drug. Standard treatment with corticosteroids and antihistamines is not very successful; however, it is still widely used as a supportive measure [53,54]. Epinephrine injection or nebulized racemic epinephrine may be used in cases with stridor. Fresh-frozen plasma has also been used to replete the enzymes in more severe cases [57,58]. More recently, icatibant (Firazyr), a B2 receptor blocker approved in the USA in 2011 for the treatment of hereditary angioedema [59], has been successfully used in the treatment of ACEI-induced angioedema [60]. In one case series, icatibant significantly shortened the resolution of edema in all patients, and none of the patients required intubation for airway protection [60]. Even though initial experiences with icatibant are very promising, the efficacy and safety of its use in RAAS inhibitor-induced angioedema need to be established in large randomized clinical trials.

CONCLUSION

Taken together, both environmental factors and genetic predispositions play important and likely synergistic roles in angioedema formation in susceptible individuals. Prompt recognition and timely intervention, including lifetime discontinuation of RAAS inhibitors, is of paramount importance. It is also important to keep in mind the high recurrence rate with any of the drugs that act via the RAAS/KKS pathway. As more data are emerging regarding pathophysiological mechanisms, future research should focus on new therapies targeting inhibition of specific molecules and receptors involved in the mechanism of the disease. One of the new therapies may include NK-1 receptor antagonists, which may inhibit substance P-mediated effects in angioedema formation [62]. Development of new therapeutics that inhibit the B1 receptor may also prove beneficial. Pharmacogenomic tests may allow for screening of patients who are at risk. In conclusion, there are exciting new avenues of research that may help in the prevention, diagnosis, and treatment of this potentially life-threatening condition.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 395).


A detailed review of pathophysiology, epidemiologic data, and clinical presentation of ACEI-induced angioedema.


This study evaluated the incidence of angioedema recurrence after the discontinuation of ACEIs. It revealed that patients are still at risk of developing angioedema several months after they discontinued ACEIs.

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East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2007 [cited 12 October 2011].


East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2007 [cited 12 October 2011].

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