REVIEW ARTICLE

Renin Angiotensin System Antagonists and Anesthesia

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Renin angiotensin system (RAS) antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor antagonists are increasingly used to treat cardiovascular and other diseases (1–6). These treatments induce a blockade of the RAS that may affect hemodynamics during anesthesia and surgery. In 1978, Miller et al. (7) reported that the RAS is involved in maintaining normal blood pressure during anesthesia. Although anesthesia is not invariably associated with a deleterious hemodynamic event in RAS-blocked patients (8–10), hemodynamic instability, described as unexpected episodes of hypotension, have been reported (11–13).

Otherwise, stresses such as surgery or hypotension stimulate the generation of angiotensin II, which induces vasoconstriction (14) to maintain blood pressure but reduces blood flow to organs such as the kidneys and bowels. Accordingly, an angiotensin II-induced reduction in blood flow may contribute to acute renal failure (15) and splanchnic ischemia (16), which are obvious factors in postoperative morbidity (17). RAS blockade with ACE inhibitors decreases some consequences of the stress response on the regional circulation (9,18,19), which may then contribute to body protection.

Much of the information regarding the physiology and pathophysiology of the RAS during anesthesia and surgery is based on the effects of ACE inhibitors. Because ACE inhibitors probably act mostly by blocking the RAS, similar effects should be obtained from angiotensin (AT) receptor antagonists. RAS antagonist pharmacology may help us to understand the hemodynamic risk of anesthesia in RAS-blocked patients, to identify predisposing factors, and to determine the potential benefit of RAS antagonists during anesthesia and surgery.

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Physiology of the RAS

Generation of Angiotensin II

The RAS is basically defined as a biochemical cascade (Figure 1) (20). A highly specific proteolytic enzyme, renin, cleaves an ineffective peptide precursor, angiotensinogen, to generate a decapeptide, angiotensin I. Angiotensin I is converted to an octapeptide, angiotensin II, by an nonspecific carboxypeptidase, the ACE. Angiotensin II is considered the effective final product of enzymatic reactions (20–22). The biochemical cascade is self-limited by rapid metabolism of angiotensin II and/or by the negative feedback control of angiotensin II on renin release (20).

The biochemical cascade originates from different organs. The kidney produces renin, the liver produces angiotensinogen, and plasma and vascular endothelium produce angiotensin. However, almost all angiotensin I and angiotensin II (90% and 64%, respectively) is generated within endothelium, rather than in plasma (22–24). The primary determinant of the rate of angiotensin II formation is the plasma level of renin created by the regulated secretion of renal renin (25). The well known areas that regulate renal renin secretion (renal baroreceptors, neurogenic stimulation, or macula densa-mediated RAS activation) have been confirmed at the cellular and subcellular levels (26). All these mechanisms regulate renin expression by Ca^{2+}, adenosine 3′,5′-cyclic monophosphate, and chemiosmotic forces (K^+, Cl^-, and water flux coupled to H^+ movements). Under favorable conditions, prorenin is then processed to renin, which may be secreted by regulative degranulation or divergence translocation (26). The final activity of angiotensin II depends mostly on the level of renin substrate and the availability of ACE. However, alternative pathways for the conversion of angiotensin I to angiotensin II, originating from masocytes and endothelial cells, have been identified (e.g., cathepsin G, chymase, serine proteases, tonin) (Figure 1). They are thought to be involved in modulating local angiotensin II formation in the heart, specifically under ischemic conditions and for structural remodeling (27,28).

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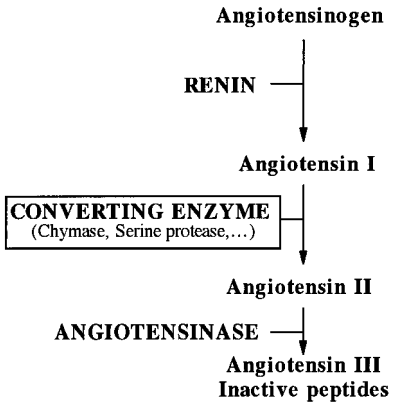

Figure 1. The renin-angiotensin biochemical cascade.

Angiotensin Receptors

Angiotensin II acts on multiple target organs after binding to specific receptors. Angiotensin II binds at least to two specific receptors, angiotensin I receptor subtypes AT1 and AT2, which are polypeptides containing approximately 360 amino acids that span the cell membrane seven times. Despite their similar affinities for angiotensin II, AT1 and AT2 receptors are functionally distinct, with a sequence homology of only 30%. The gene for the AT1 receptor is located on chromosome 3, and the gene for AT2 receptor is on chromosome X. Specific, high-affinity binding of angiotensin is determined by amino acids located on or near the extracellular surface of the membrane-bound receptor, as well as by sequences in the transmembrane domains (4).

The signal-transducing proteins associated with AT receptors is well established for the AT1 receptor. The binding of angiotensin II to the AT1 receptor is coupled to a G protein, which then activates phospholipase C to generate diacylglycerol and inositol trisphosphate. The inositol trisphosphate then releases calcium from intracellular stores. Angiotensin II also increases the entry of calcium into the cell through channels in the cell membrane. Calcium and diacylglycerol activate enzymes, including protein kinase C and calcium-calmodulin kinases, catalyze the phosphorylation of protein, which regulates the cell functions affected by angiotensins. By contrast, little is known about signal transducing by the AT2 receptors, which differs from transduction by AT1 receptors and does not involve phosphoinositides (4).

Many actions of angiotensin II involved in blood pressure control (i.e., vasoconstriction, aldosterone secretion, stimulation of catecholamine release, central pressor and dipsogenic stimulations) are mediated through binding to AT1 receptors (29). Angiotensin II also exerts long-term effects on cellular regulation and growth. Both acute and slower responses are mediated by the signal-transduction events, which are complete in seconds or minutes.

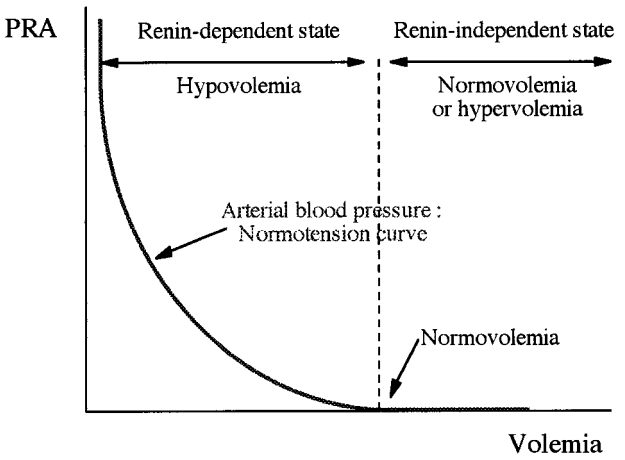

Figure 2. Plasma renin activity (PRA)/effective intravascular volume relationship. In physiologic steady state, normotension is maintained without renin-angiotensin system activity, as assessed by minimal PRA. When intravascular volume is at least maintained, arterial blood pressure is thus renin-independent. Inversely, blood pressure becomes renin-dependent when the intravascular volume decreases.

Role of Angiotensin II

Angiotensin II is involved in short-term regulation of blood pressure and in regulation of intravascular fluid volume and regional circulation. All these aspects are major concerns for anesthesiologists.

Regulation of Systemic Hemodynamics. RAS activation is mainly dependent on body fluid volume, specifically "effective" blood volume, i.e., the blood volume that allows adequate cardiac output (30,31). Blood pressure thus depends on RAS as a function of extracellular fluid volume and intravascular volume (31). Although there is moderate RAS dependence in normal intravascular volume (31,32) and minimal effects with extracellular fluid volume expansion (31,33), the RAS contribution to blood pressure becomes crucial with hypovolemia (31,32) (Figure 2). Inversely, the final purpose of RAS activation is to increase body fluid volume (31–33): angiotensin II is the primary stimulus to aldosterone secretion (31,33), but it also contributes to sodium regulation directly (34) and, indirectly, to fluid volume regulation (35). Any renin-dependent, volume-independent state therefore tends to be converted into a renin-independent, volume-dependent state by the RAS action itself (Figures 2 and 3). For example, an increased blood pressure in experimental renovascular hypertension or coarctation hypertension (32,36) is initially maintained by direct pressor actions of angiotensin II (renin-dependent state) and is thus sensitive to RAS blockade (37). During a later chronic phase, hypertension is due to an increase in intravascular volume that is the result of angiotensin II activity (32,36) but then becomes insensitive to RAS blockade (renin-independent state) (37,38).

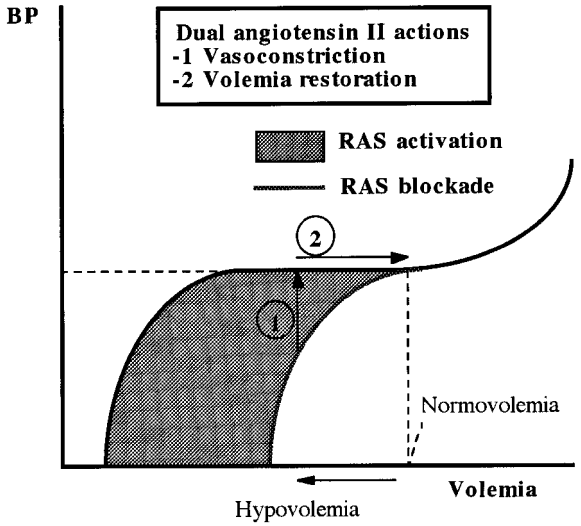

Figure 3. Dual action of angiotensin II. The relationship between arterial blood pressure (BP) and intravascular volume (volemia) is influenced by the renin-angiotensin system (RAS). When (effective) intravascular volume decreases, angiotensin first induces an arterial and venous vasoconstriction that sustains blood pressure (shaded area 1). The intravascular volume then tends to be restored by direct, as well as indirect, angiotensin II actions (aldosterone) (area 2). In the case of RAS blockade, BP tends to be closely related to intravascular volume.

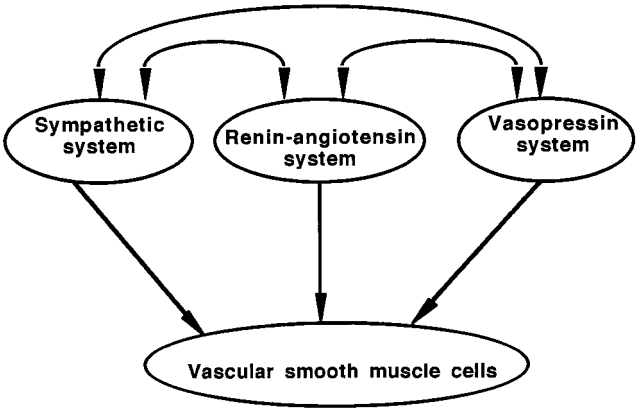

Figure 4. Vasopressor systems in blood pressure regulation. Three different vasopressor systems can be involved in blood pressure regulation to counteract hypotension. Each acts on the same target, i.e., the vascular smooth muscle cell, by inducing an increase in free cytostolic calcium, then a cell contraction. Each system is related to the others and may act as a compensatory mechanism (71).

Fluid volume regulation requires hours to days, but angiotensin II-induced vasoconstriction is quickly activated; therefore, that acute changes in intravascular volume status are initially caused by vasoconstriction. Angiotensin II-induced vasoconstriction is well known for arterioles and contributes to the maintenance of blood pressure by increasing vascular resistance (31–33). As for arterioles, angiotensin II produces constriction of veins either directly (39–41) or by enhancement of the sympathetic nervous system (39), which results in the reduction of vascular capacitance (i.e., decrease in either unstressed vascular volume and/or compliance). Arterial angiotensin-induced vasoconstriction may also improve venous return because cardiac output is redistributed from long time constant compartments to short time constant compartments. An effective intravascular volume therefore may be maintained despite a decrease in absolute blood volume (42,43). Both the arterial and venous actions of angiotensin II improve venous return to the heart, and cardiac output is then preserved (44).

Besides the direct actions of angiotensin II, a cross-over potentiation between angiotensin II and other factors may be involved in blood pressure regulation. Vascular tone results from interactions between vasoactive circulating peptides (angiotensin II, atrial natriuretic peptide, catecholamine) (45) or between angiotensin II and endothelial control of vasomotor tone (46), such as nitric oxide (47). There are also similar interactions with factors involved in angiotensin II-mediated body volume regulation; endothelin may increase angiotensin II-induced aldosterone production (48), and aldosterone may increase angiotensin II receptor number and enhance angiotensin II-stimulated protein synthesis (49).

In summary, during hypovolemia, RAS activation first results in angiotensin II-induced vasoconstriction. Angiotensin II then stimulates fluid volume increase through stimulation of sodium and water reabsorption. When effective intravascular volume is restored, RAS is no longer activated (Figure 3) (30).

Regulation of Regional Circulation. Renal circulation is the most thoroughly investigated regional circulation with regard to the role of the RAS on regulation of regional vascular tone (50–52). Moreover, the kidney was one of the first tissues in which *in situ* formation of angiotensin II was demonstrated (23,53). The intrarenal RAS is involved in the homeostatic regulation of renal bloodflow and glomerular filtration (50), mainly by angiotensin II-induced vasoconstriction of the efferent arteriole of glomerulus (51). Many other tissues are probably affected by the role of RAS in regulating regional circulation, but such a role in local vasoregulation is still debated (54). In addition, the mesenteric circulation is very sensitive to angiotensin II-induced vasoconstriction; therefore, both circulations are adversely altered during RAS activation (16,53,55).

Pharmacology of ACE Inhibitors and AT Receptor Antagonists

Mechanisms of Action and Pharmacokinetics of ACE Inhibitors

ACE is an unspecific carboxypeptidase that is involved in the conversion of angiotensin I to angiotensin II and in the inactivation in central opioids,

encephalins, and bradykinin, a potent vasodilator. Inactivation of angiotensin II formation is the accepted main mechanism of ACE inhibition (1,56).

From the first use of the first orally specific ACE inhibitor, captopril, in humans in 1977 (57), many products with similar basic activity have been developed. Drug specificities have emerged from pharmacological modulations when related to pharmacokinetic profiles (2,58,59). Some are prodrugs that must be converted by esterase activity in the liver to active moieties (e.g., alecepril, benazepril, cilazapril, enalapril, fosinopril), which can delay peak activity. Most have longer terminal half-lives than captopril, which allows one dosage daily but delays recovery of ACE activity after ACE inhibitor withdrawal if the latter is needed before anesthesia and surgery. However, plasma half-life does not necessarily predict duration of action.

Mechanisms of Action and Pharmacokinetics of AT Receptor Antagonists

Losartan is the first orally effective nonpeptide, selective antagonist of the AT1 receptor with a long duration of action. *In vivo* animal studies have confirmed the findings of isolated tissue experiments that losartan specifically and selectively, and without influencing the AT2 receptor-mediated responses to angiotensin, inhibits all the AT1 receptor-mediated actions of angiotensin. A biphasic antihypertensive response is observed in conscious, normotensive rats subjected to the administration of exogenous angiotensin II, as well as in renal hypertensive rats. An acute decrease in arterial blood pressure is followed by a slower reduction the peak effect, which occurs approximately 3 h after injection. These observations suggest the involvement of one or more metabolites in the action of losartan. EXP3174 represents the major metabolite of losartan, with a high potency and a long duration of action; in fact, this metabolite may be responsible for part of the antihypertensive effect of its parent drug, losartan. A dose-dependent increase in plasma renin activity and angiotensin II levels was observed, reflecting inhibition of the negative feedback loop exerted by angiotensin II on renin secretion (6).

In healthy human volunteers, oral losartan given once daily for 8 days inhibited the peak systolic pressure response to angiotensin I in a dose-dependent manner. Even 24 h after a single dose of 40 mg, the response to exogenous bolus injections of angiotensin I was still clearly attenuated. Losartan was well tolerated in normal human volunteers and did not affect basal heart rate or arterial blood pressure (6).

Other nonpeptide AT receptor antagonists are currently marketed (e.g., valsartan, irbesartan, candesartan, eprosartan, telmisartan). All have a long-lasting effect similar to that of losartan. The potential therapeutic interest of this group of drugs is twofold. First, they should not induce the bradykinin-related side effects of ACE inhibitors such as cough, which occurs in 10%–20% of patients receiving ACE inhibitors. Second, because they competitively block AT receptors (AT1), they should suppress angiotensin II effects better than an ACE inhibitor. Indeed, blockade of the converting enzyme favors other metabolic pathways leading to angiotensin II synthesis, especially the chymase pathway. However, the real importance of such converting enzyme-independent angiotensin II synthesis in humans is not well known. In addition, because bradykinin breakdown reduction by ACE inhibitors could also participate in their therapeutic effect, AT receptor antagonists may not provide a similar therapeutic profile. However, during AT1 receptor blockade, all the AT2 receptors remain exposed to the increasing levels of angiotensin II, which could be a source of synergistic effects, as AT2 receptors have the opposite effects of AT1 receptors. Hence, stimulation of AT2 receptors by increasing levels of angiotensin synergically support the effects of AT1 receptor blockade (6). For example, angiotensin II can cause a large significant reduction in arterial blood pressure after losartan-induced AT1 receptor blockade, an effect probably mediated by AT2 receptors (60).

Pharmacology of ACE Inhibitors and AT Receptor Antagonists

Effects on Systemic Hemodynamics. Because angiotensin II is involved in short-term regulation of blood pressure maintenance, the blockade of its effects either by inhibition of angiotensin II production (ACE inhibitor) or by inhibition of the AT receptor-mediated effect (AT receptor antagonists) may interfere with blood pressure regulation.

The effects of ACE inhibitors and AT receptor antagonists depend on the underlying pathophysiologic state and degree of RAS activation. As previously stated, blood pressure is not markedly affected by RAS blockade in patients with a normal sodium balance (5,6,30–32,57,61). However, the vasodilating effect of ACE inhibitors may exceed the complete blockade of angiotensin II formation, as evidenced by decreased blood pressure in normotensive, sodium-replete subjects, i.e., subjects with low plasma renin activity (30). A 10% decrease in arterial blood pressure may occur after a single oral dose of enalapril in normotensive subjects with a normal sodium intake (150 mmol daily) (62). This effect is likely a result of additional hormonal effects of ACE inhibition, such as interferences with degradation of bradykinin or accumulation of prostaglandins (30).

A blood pressure decrease after RAS blockade is basically the result of a decrease in systemic vascular

resistances in both normal or hypertensive subjects (31–33). However, besides arterial vasodilation, RAS blockade interferes with blood pressure regulation by impairing cardiac output adaptation to ventricular loading changes. A striking decrease in cardiac output has been observed during tilting in patients treated with an IV ACE inhibitor (treprotide) (33). The decreased cardiac output is related to inhibition of angiotensin II's effect on the vein, inducing a decrease in venous return (40–42). In addition, the blood pressure decrease was not associated with reflex tachycardia, which may worsen the maintenance of cardiac output; this problem is probably due to a blunting of cardiac baroreflex. However, several studies performed in both animals (63,64) and humans (65–67) have evaluated the heart rate intervals/blood pressure relationships during ACE inhibition. An increased sensitivity of the baroreflex response associated with a resetting, rather than a blunting, of cardiac baroreflex has been demonstrated. Although ACE inhibition holds the balance of autonomic nervous system activity toward an increased parasympathetic tone (65,67,68), the sympathetic response of the baroreflex is intact and capable of appropriate adjustment (66,68). This control works quite well in awake, euvolemic, ACE inhibitor-pretreated subjects, and orthostatic hypotension does not occur (66). Moreover, vasopressin, which may be involved in blood pressure regulation, is also maintained during RAS blockade (66,69,70). Therefore, both the sympathetic system and vasopressin may act as overlapping vasopressor systems to maintain blood pressure during hypovolemia and RAS blockade (71). Nevertheless, despite the complicated control of blood pressure, arterial blood pressure is intravascularly volume-dependent during ACE inhibition (72).

Effects on Regional Circulation. Renal and mesenteric circulations are the regional circulations that may benefit from RAS blockade in renin-dependent states. In experimental studies, both circulations are more sensitive to ACE inhibitor-induced vasodilation than other regional circulations (52,53,55,73,74). Sodium-restricted conscious dogs have impaired renal blood flow and glomerular filtration rate. The administration of an ACE inhibitor at doses that do not affect systemic blood pressure induced a complete recovery of renal function (52). Similarly, losartan induced natriuresis in sodium-depleted subjects (4). Losartan reversed all the angiotensin II-induced renal action, i.e., vasoconstriction, reduced glomerular filtration rate, and increased sodium chloride absorption of the tubules (6). AT1 receptor antagonists dilate efferent glomerular arterioles, as do ACE inhibitors (4). Besides renal circulation, treatment with ACE inhibitors with different chemical structures increased splanchnic circulations in an experimental model of RAS activation (water-deprived Brattleboro rats) (55) or in spontaneously hypertensive rats (73). The potential benefit of such a RAS blockade on splanchnic perfusion has been shown in experimental hemorrhagic shock (75–77). RAS blockade with either AT receptor antagonists (75) or the ACE inhibitors captopril and enalaprilat (76,77) improved postoligemic splanchnic perfusion and significantly reduced the subsequent formation of myocardial depressant factor after hemorrhage in cats (75–77).

Differences Between ACE Inhibitors and AT Receptor Antagonists. Many cardiovascular effects are shared by ACE inhibitors and AT receptor antagonists, and this is particularly true with regard to the short-term actions of angiotensin II on blood pressure regulation. However, some aspects of regional circulation and cellular growth (vascular or cardiac cells) may be different between ACE inhibitors and AT receptor antagonists. Most actions of ACE inhibitors on vascular endothelium (NO and prostaglandin production, cellular proliferation, etc.) or on myocardium (hypertrophy) are mediated through potentiation of kinins (78). However, AT1 receptor antagonists blunt angiotensin II's actions on growth of left ventricle and arterial walls (4). More studies are required to provide a clear answer to the questions of the magnitude of these differences and their clinical relevance. Furthermore, these discrepancies may have little impact in the management of the anesthetized patient treated with one of the RAS antagonists.

Treatment with ACE Inhibitors and with Receptor Antagonists

Hypertension

Essential hypertension is usually related to increased vascular resistances. Therefore, the main hemodynamic objective of many antihypertensive treatments is to reduce vasoconstriction (79). ACE inhibition use was initially devoted to obvious high renin pathophysiological states (high plasma renin activity) (80). However, ACE inhibitors are presently considered effective in essential hypertension, regardless of the underlying plasma renin activity, because vascular resistances can be reduced even when previous plasma renin activity was low (1,3). The suppression of endothelial angiotensin production has been advocated for the response of nonrenin hypertension as well as the long-lasting effect with ACE inhibitors (21,81). Similarly, AT1 receptor antagonists decrease blood pressure in hypertensive animals that have high, normal, or low levels of renin (61). In clinical studies in patients with essential hypertension, AT1 receptor antagonists are approximately as effective as ACE inhibitors (4). In a preliminary study of 100 hypertensive patients, the effect of losartan given once daily for 5 days at doses of 50, 100, and 150 mg was compared

with that of enalapril. All three losartan doses induced significant blood pressure reductions compared with the placebo-treated group. On the first day, enalapril was clearly more effective in reducing blood pressure than losartan, but blood pressure levels were not different on the fifth day of treatment, which suggests that long-term AT receptor blockade may be as effective as ACE inhibition in reducing blood pressure in hypertensive patients. There was no difference in the effect of the three losartan doses, which suggests that 50 mg daily may provide close to maximal efficacy (6). Other AT1 receptor antagonists have a clear dose-response relationship (candesartan, irbesartan). The onset of the hypotensive effect of losartan is more gradual than that associated with an ACE inhibitor, probably because of the nonangiotensin II inhibition mechanisms of ACE inhibitors (82,83).

Heart Failure

In congestive heart failure, stroke volume decreases because it is inversely related to changes in outflow resistances (84), and vasodilator therapy improves stroke volume and cardiac output by decreasing afterload (85). Neurohormone (plasma norepinephrine, plasma renin activity, atrial natriuretic peptide) increase correlates with decreased ejection fraction in congestive heart failure (86). Besides sympathetic nervous system involvement and vasopressin secretion, activation of the RAS increases systemic vascular resistances (84) and correlates with the advanced stage of the disease (87). Both ACE inhibitors and AT1 receptor antagonists improve left ventricular function in patients with chronic congestive heart failure (4,61,88–92), but survival rate improvement in severe or mild heart failure is multifactorial and is related to structural protection of the failing heart (93), improvement of heart metabolism (94), and prevention of ventricular arrhythmias (95,96).

These beneficial effects have encouraged the use of ACE inhibitors in the earlier phase of heart disease, before overt heart failure. The administration of enalapril to patients with asymptomatic left ventricular dysfunction reduces morbidity during an average follow-up of 37.4 mo (97). ACE inhibition has also been evaluated in the early phase after acute myocardial infarction. Infarct expansion is attenuated, and left ventricular remodeling is favorably influenced as the result of favorable hemodynamic and neurohumoral responses after ACE inhibition (98–101). Moreover, ACE inhibitors administered within a few days after myocardial infarction to patients with clinical evidence of heart failure, or to asymptomatic patients with ejection fractions $\leq$40%, improved mortality and reduced morbidity (102–104). Although AT receptor antagonists mimic ACE inhibitor effects on cardiovascular hemodynamics, it is not known whether they affect the overall mortality of heart failure (4).

Myocardial Ischemia

Both experimental and clinical reports have revealed that coronary occlusion results in an acute activation of the RAS (105). Angiotensin II may play a role as an independent arrhythmogen in ischemic heart disease (106). Therefore, RAS antagonists provide cardioprotection. In fact, most of the cardioprotective actions of ACE inhibitors are not related to inhibition of angiotensin formation *per se*: antiarrhythmic activity has been demonstrated through free radical scavenging and increased concentration of bradykinin and prostaglandin (107). Improvement of contractile function of the stunned myocardium is consistent with ACE inhibitor-induced potentiation of bradykinin or prostacyclin synthesis (108) or with sulfhydryl-containing ACE inhibitors (105). The clinical relevance of each mechanism is debatable. For example, ACE inhibitors protect the myocardium against pathological structural remodeling created by reactive fibrosis (109) but fail to prevent restenosis after coronary angioplasty (109–111). By contrast, AT1 receptor antagonists are devoid of the nonangiotensin-dependent effects of ACE inhibitors, which may explain why EXP3174 fails to reduce myocardial infarct size (112). Moreover, losartan markedly impaired recovery of myocardial function after ischemia-reperfusion in isolated working rat hearts, a deleterious effect related to angiotensin II's action on AT2 receptors (113).

Renal Dysfunction

In hypertension and heart failure, ACE inhibition is also associated with a redistribution of regional bloodflow, which especially favors the kidney (55,73,114,115), provided that hypotensive episodes are avoided (116). Improvement in specific alterations of renal function in diabetes, glomerulopathies, or chronic nephropathies associated or not with hypertension (117–119) has also been demonstrated with ACE inhibitors. AT1 receptor antagonists could have a smaller effect than ACE inhibitors because bradykinin may contribute to the protective effect. In fact, there is no difference between the effects of ACE inhibitors and AT1 receptor antagonists on the reduction of proteinuria and filtration fraction in proteinuria unrelated to diabetes (120).

RAS Antagonists and Hemodynamics During Anesthesia and Surgery

Blood Pressure Regulation During Anesthesia

Blood pressure can be sustained by three vasopressor systems: the sympathetic nervous system, the RAS, and

vasopressin. All these systems act by increasing the intracellular free calcium concentration in vascular smooth muscles (Figure 4). Anesthesia interferes with both the sympathetic nervous system and the RAS, but an anesthesia-induced decrease in RAS activation is caused by the anesthesia-induced decrease in sympathetic nervous system. IV anesthetics may attenuate renal sympathetic nerve activity and consequently induce a decrease in renin secretion (121). Similarly, epidural anesthesia suppresses renin release in response to arterial hypotension (122), an effect reversed by a β-adrenergic agonist, epinephrine (123). Differences among anesthetics or anesthetic management are mainly related to their specific effects on the sympathetic nervous system, the worst tolerated occurring with fast and/or extended sympathetic blockade. However, during anesthesia and surgery, blood pressure may become angiotensin-dependent (7,124,125). In fact, the mechanism of RAS activation does not differ from that under awake conditions: decreased "effective" intravascular volume activates RAS (124,126), and blood pressure can therefore be maintained despite intravascular fluid volume changes (124). The anesthesia-induced reduction in sympathetic tone on the vascular capacitance results in a decreased effective intravascular volume, and angiotensin II may counterbalance this effect (127). Accordingly, blood pressure may decrease markedly during general anesthesia when angiotensin II action is impeded by an angiotensin II competitive inhibitor (125). Yet, besides RAS and the sympathetic system, endogenous vasopressin may be involved in blood pressure regulation during anesthesia through binding to receptors involved in vasoconstriction (V1 receptors). During epidural anesthesia and enalaprilat-induced inhibition of the RAS, the plasma vasopressin concentration increases significantly (128). Furthermore, epidural anesthesia induces a very moderate decrease in blood pressure (approximately 10% from baseline), whether each system alone, V1 receptors or the RAS, was blocked. Each individual pressor system may therefore act as a compensatory mechanism whenever other systems are depressed. The RAS contribution to blood pressure support is crucial when the sympathetic nervous system is blocked by epidural or general anesthesia and when endogenous vasopressin is antagonized by a specific V1 receptor antagonist (IND 21862) (128,129). The greatest and most significant decrease in blood pressure occurs with the combination of RAS blockade and a V1 receptor antagonist (128).

RAS Antagonists and Blood Pressure Regulation During Anesthesia

Anesthesia in Patients Without Cardiac Disease. Preoperative ACE inhibition has been used to prevent perioperative hypertension. Some authors report a significant reduction in the pressor response to endotracheal intubation (10,130), but others do not (8,131). Moreover, severe unexpected deleterious hemodynamic events have been described during anesthesia in patients receiving preoperative ACE inhibitors (11,130). In these studies, few ACE-blocked patients (10%–40%) experienced a marked decrease in blood pressure and heart rate (11,130). The induction of anesthesia abruptly reduces the influence of the sympathetic nervous system on the cardiovascular system, especially on venous return, which results in an acute decrease in effective intravascular volume (70). During ACE inhibition, angiotensin II cannot counterbalance this effect, and the induction of anesthesia results in severe hypotension in the case of preoperative hypovolemia. Vasopressin, which is the only vasopressor system available to maintain blood pressure (129), is far less effective on systemic vascular capacity than on arterial resistance (40,132). The intravascular volume dependence of blood pressure in ACE-blocked subjects (72) is amplified during anesthesia. In any case, severe episodes of hypotension have been successfully treated with intravascular fluid administration (11,130). The relative role of inhibition of angiotensin II and bradykinin degradation due to ACE inhibition in the incidence of hypotension is still debatable (133). No data regarding AT1 receptor antagonists and anesthesia in patients without cardiovascular disease have been published; nevertheless, similar effects should be expected with ACE inhibitors and AT1 receptor antagonists because they are mainly related to angiotensin II inhibition.

Anesthesia in Hypertensive Patients. The results obtained after short-term preoperative RAS inhibition (1–2 days) in normotensive or mildly hypertensive subjects (8, 10,130,131) may not occur in chronically treated patients with moderate to severe hypertension. First, chronic administration of ACE inhibitors alters blood pressure regulation differently than short-term treatment: parasympathetic activity is further enhanced after chronic administration of an ACE inhibitor compared with its acute administration (67). Second, in moderate and severe hypertension, chronic ACE inhibition is often administered with other antihypertensive drugs that can also hinder adequate regulation of blood pressure during anesthesia. Moreover, the severity of hypertension correlates directly with the magnitude of potential anesthesia changes (134,135).

For all these reasons, acute sympathetic inhibition induced by the induction of anesthesia and preliminary RAS blockade may cause hypotension. When ACE inhibitors are maintained until the day of surgery, the incidence of hypotension after the induction of anesthesia in hypertensive patients is frequent (75%–100%) (136,137) and mainly related to a decrease in left ventricle preload and cardiac output (137). The risk of hypotension is increased with some associated factors. First, combined antihypertensive drugs or

complete RAS blockade, which mainly depends on the treatment given (dose, time, molecule), increase the impairment of blood pressure control (136,137). Second, severe hypertension with left ventricle diastolic dysfunction amplifies the intravascular volume dependence of blood pressure in ACE-blocked subjects (137). Although the magnitude of the decrease in blood pressure did not correlate with the decrease in plasma converting enzyme activity, the incidence of hypotension after the induction of anesthesia was reduced (<20%) when plasma-converting enzyme activity was restored by withdrawing ACE inhibitors the day before anesthesia (136).

However, episodes of hypotension are brief and easily treated (136,137) by the administration of fluid IV and, possibly, vasopressors. Sympathetic agonists such as phenylephrine and ephedrine are effective in most cases (136,137). Angiotensin II may be an alternative treatment; an IV bolus of 2.5 μg restored arterial blood pressure quickly at the expense of an impairment of left ventricle function and a striking increase in end-systolic wall stress (138). However, angiotensin II is not commercially available, and vasopressin agonists that have potential beneficial effects in a few dramatic hemodynamic situations (139,140) have been proposed for refractory hypotension after anesthesia in patients treated with RAS antagonists. In a recent study, 51 consecutive vascular surgical patients chronically treated with ACE or AT receptor antagonists (for hypertension in 74.5%) received a standardized narcotic-propofol anesthetic (141). Of these 51 patients, 42 (82.4%) experienced at least one episode of hypotension. Ten (19.6%) had a systolic arterial blood pressure (SAP) that did not remain above 100 mm Hg for 1 min despite three bolus doses of ephedrine (18 mg) or phenylephrine (300 μg). In these patients, a bolus dose of 1 mg of terlipressin was injected and repeated twice if necessary. In eight patients, arterial pressure was restored with one injection of terlipressin; in two others, three injections were necessary. One minute after the last injection of terlipressin, SAP increased from 88 ± 3 to 100 ± 4 mm Hg and reached 117 ± 5 mm Hg ($P = 0.001$). Fractional area change and mean velocity of circumferential fiber shortening, as assessed by transesophageal echocardiography, did not change significantly, which suggests no alteration of left ventricular function. No additional injection of vasopressor was required during the perioperative period. In these series, despite ACE inhibitor withdrawal for at least 12 h for captopril and 24 h for the other ACE inhibitors, the incidence of hypotension was >70%, far greater than previously reported (136,141).

Anesthesia in Patients with Congestive Heart Failure. Little is known about anesthesia in patients suffering from heart failure and treated with RAS antagonists. In an experimental model of doxorubicin-induced heart failure in rabbits, a combination of halothane and enalaprilat resulted in improvement of cardiac output and renal blood flow (142), but higher halothane concentrations (1.3 minimum alveolar anesthetic concentration) induced severe circulatory depression (142). Cardiodepressant effects of halothane and ACE inhibitor (143) may be deleterious for severe cardiomyopathy (144). Moreover, doxorubicin alters both diastolic and systolic functions, and enalaprilat was administered IV; therefore, it is difficult to draw any definite conclusion for anesthesia in chronically RAS-blocked patients with pure systolic heart failure. In clinical conditions, besides the improvement of systolic heart function induced by an IV ACE inhibitor (145), Ryckwaert et al. (146) addressed the issue of whether chronic RAS blockade may alter the hemodynamic stability of the induction of anesthesia in patients with heart failure. In that study, the hemodynamic effect of the induction of anesthesia was evaluated in patients with low left ventricular ejection fraction (≤40%) after myocardial infarction. Patients receiving ACE inhibitors until the day of surgery experienced no more hypotension after the induction of anesthesia than those in a control group (146). The incidence of severe hypotension (mean arterial blood pressure <60 mm Hg) was 22% in each group (146). However, chronic preoperative treatment with ACE inhibitors modifies the hemodynamic pattern after the induction of anesthesia. ACE inhibitor-blocked patients have a marked decrease in cardiac index, probably related to a decrease in sympathetic drive (146).

RAS Antagonists and Systemic Hemodynamics During Surgery

During cardiac surgery, ACE inhibitors are administered to prevent hypertension. Hypertension after either noxious stimulation, such as sternotomy (147), or coronary artery bypass graft surgery (8) is not specifically mediated by RAS activation. However, the IV ACE inhibitor enalaprilat may reduce hypertension during cardiac surgery (148). Nevertheless, RAS may be activated during cardiopulmonary bypass (CPB), as assessed by either increased plasma renin activity (9,149,150) or high plasma angiotensin II concentrations (151). RAS inhibition with an ACE inhibitor is not associated with deleterious systemic hemodynamic events during coronary artery bypass grafting or valvular surgery (9,133), but chronic preoperative treatment may contribute to increased vasoconstrictor drug (phenylephrine, dopamine, or norepinephrine) requirements after moderate hypothermic CPB (152). In one study, however, vasoconstrictors were required only for the first 4 h in the intensive care unit, and patient outcome was not significantly affected (152). Nevertheless, cases of very low systemic vascular resistance after hypothermic CPB in patients chronically

treated with ACE inhibitor have been reported (153). In these cases, anesthesia and CPB before cooling were uneventful, but severe hypotension occurred during hypothermia and lasted after rewarming. Separation from CPB was only possible with an angiotensin II infusion; α-adrenergic agonists were ineffective (153). This attenuated adrenergic responsiveness after the institution of hypothermic CPB in patients chronically treated with ACE inhibitors has been confirmed (133). By contrast, the IV administration of an ACE inhibitor may blunt the increase of the vasoactive substances (epinephrine, norepinephrine, endothelin), which are normally observed in cardiac surgery, with a potential benefit for microcirculation (148).

RAS Antagonists and Organ Functions During Surgery

Renal Function

Some surgical techniques are likely to provoke renal hemodynamic impairment. Therefore, does the stimulated RAS during CPB exert a deleterious effect in such circumstances? CPB is a model of decreased renal perfusion (9) and is associated with a stimulation of the RAS (151). An ACE inhibitor, captopril, given just before surgery impedes the reduction in effective renal plasma flow and glomerular filtration rate during CPB, although systemic hemodynamics are not significantly altered (9).

Similarly, RAS activation can be produced by thoracic aortic cross-clamping (18). Joob et al. (18) studied the effect of RAS blockade with enalapril on systemic and regional circulations using microspheres before, during, and after thoracic clamping in a canine model. In the control group, aortic clamping induced an increase in plasma renin activity and a decrease in renal and liver bloodflows; both persisted after declamping. The ACE-blocked group experienced identical decreases in plasma flows during clamping, but clamp release resulted in full recovery in renal and liver plasma flows.

Decreased renal bloodflow and increased plasma renin activity during infrarenal aortic cross-clamping (154,155) suggests that RAS is involved in the renal hemodynamic impairment associated with infrarenal aortic surgery (156). However, treatment with enalapril in patients scheduled for aortic reconstructive surgery failed to improve effective renal plasma flow and glomerular filtration rate during aortic cross-clamping (157,158). Thus, the RAS is not such an important determinant of the renal vasoconstriction associated with infrarenal aortic cross-clamping (157). Although renal hemodynamics were not improved during clamping in ACE-blocked patients, hemodynamic changes were less marked during surgery, and renal hemodynamics were well preserved before and after clamping in the ACE-blocked patients compared with control subjects (157,158).

The most beneficial effects of ACE inhibitors have been observed in controlled prospective studies in which little or no deleterious effect on systemic hemodynamics was observed with an ACE inhibitor. However, renal circulation can be impaired in patients with a blocked RAS if renal perfusion is inadequate due to either renal artery stenosis (3) or inadequate control of intravascular volume during surgery (159).

Other Organ Function

Based on experimental reports, RAS antagonists may provide myocardial protection against ischemia. In one study, patients scheduled to undergo coronary artery bypass graft surgery and treated with enalaprilat given after anesthesia and before CPB experienced less myocardium ischemia as assessed by lower plasma concentrations of CKMB, troponin T, and glycogen phosphorylase BB than control patients (160).

Although several experimental studies provide evidence of improvement of splanchnic circulation with RAS antagonists, the clinical relevance is still unknown. The preoperative administration of captopril produced no beneficial effect on gut mucosal perfusion in infants undergoing hypothermic nonpulsatile CPB. However, the captopril dose in that study was small, and no control of the level of plasma ACE activity was described (161).

Conclusion

Besides the long-term regulation of extracellular fluid volume, the RAS plays an important physiologic role in maintaining venous return and blood pressure during acute hemodynamic stresses. RAS antagonists (ACE inhibitors and AT antagonists) may therefore alter venous return and cardiac output regulation during anesthesia and surgery. These effects may be regarded as a drawback of RAS antagonists when other factors interfere with cardiovascular homeostasis; deleterious hemodynamic events may therefore occur when effective intravascular volume is decreased. One solution is to temporarily withdraw preoperative treatment when predisposing factors (e.g., severe hypertension, risk of hypovolemia, left ventricle diastolic dysfunction) accumulate. However, this would allow recovery of RAS control of blood pressure at the expense of some regional circulations. An alternative solution should be not stopping RAS antagonists preoperatively, provided that intravascular volume is maintained during surgery. Some regional circulations may then benefit from RAS blockade (kidney, heart). Nevertheless, whether withdrawing the RAS antagonist or not, hypotension may occur after the

induction of anesthesia in hypertensive patients. Blood pressure can then be restored in most cases (>75%) by administering sympathetic agonists (phenylephrine, ephedrine). In patients with hypotension resistant to sympathetic agonists, a vasopressin agonist (terlipressin) may be effective.

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