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REVIEW ARTICLE

The renin-angiotensin system and angiotensin converting enzyme (ACE) inhibitors

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Summary

Anaesthetists will encounter increasing numbers of patients who are receiving long-term treatment with ACE inhibitors for hypertension, congestive heart failure and prophylactically following myocardial infarction. Our understanding of the physiology and pharmacology of the renin-angiotensin system has dramatically increased in the last decade, and has led to the discovery of endogenous renin-angiotensin systems which may be physiologically more important than the better understood circulating system. There are several reports of adverse interactions between anaesthesia and ACE inhibitors, manifested as hypotension and bradycardia, which may be delayed until the postoperative period. The mechanism behind them is not understood and, as yet, no published studies have attempted to address this issue. It is possible, however, that dehydration associated with the pre-operative fast may play an important role. ACE inhibitors may, in the future, prove to be useful in the subspecialties of cardiac and vascular anaesthesia, where they might be used in an attempt to preserve cardiac function following periods of ischaemia and cardiopulmonary bypass, and to avoid renal damage following aortic cross-clamping. Meanwhile, it would seem prudent to exercise caution when anaesthetising patients taking ACE inhibitors and to be fully prepared to treat the hypotension and bradycardia which may occur.

Key words

Enzymes; angiotensin converting.
Pharmacology; angiotensin converting enzyme inhibitors.

Angiotensin converting enzyme (ACE) inhibitors are now frequently prescribed to patients with systemic hypertension or congestive heart failure. In addition, evidence is accumulating that, following myocardial infarction, survival is improved and there is a reduced incidence of progression to heart failure when they are given long term to patients following myocardial infarction [1,2]. Clearly, increasing numbers of patients who are treated chronically with these drugs will present for anaesthesia. This article reviews the current state of knowledge of the physiology of the renin-angiotensin system, the effect of anaesthesia and surgery on that system, and the clinical effects of anaesthesia in patients taking ACE inhibitors.

Physiology of the renin-angiotensin system

Mechanisms of angiotensin II production

Renin is an aspartyl protease enzyme with 340 amino acid residues. It has a bilobular quaternary structure and one active site between the two lobes. Its substrate is the α-2 globulin, angiotensinogen, which it cleaves between residues 10 and 11 at the amino terminus to produce the decapeptide angiotensin I (Fig. 1).

Angiotensin converting enzyme (ACE) is a large protein with almost 1300 amino acid residues. It has several active sites and is relatively non-specific, cleaving dipeptide units from a variety of diverse substrates, most notable of which are bradykinin and angiotensin I. The enzyme is identical to kininase II, and is responsible both for the breakdown of the potent vasodilator bradykinin and for the generation of the potent vasoconstrictor angiotensin II.

A new picture of the renin-angiotensin system has emerged in recent years from that traditionally found in textbooks, and this has led to an increased understanding of the mechanisms of action of ACE inhibitors [3]. All components of the renin-angiotensin system, including renin and angiotensins, have been identified in cells originating from a wide range of tissues such as brain, heart, adrenal and blood vessel walls. It has been postulated that angiotensin II is produced intracellularly through intracellular ACE, and that it may also be secreted as angio-

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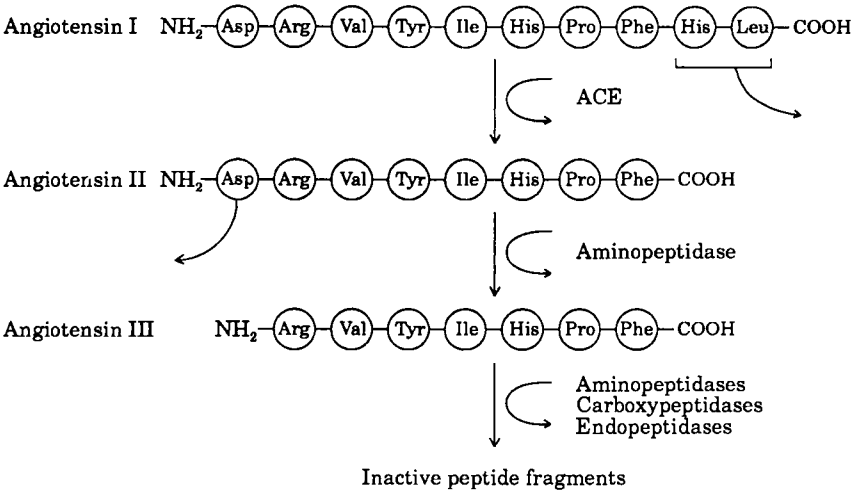

Fig. 1. The generation and degradation of angiotensin II.

tensin I which is converted by surface-bound ACE. It is believed that the angiotensin II produced by these endogenous renin-angiotensin systems has important autocrine and paracrine regulatory functions, and may be implicated in the development of cardiovascular pathology.

Locally produced angiotensin II may stimulate specific membrane-bound angiotensin receptors either in the cell where it is produced or in neighbouring cells. Stimulation of these angiotensin II receptors leads to the generation of inositol-1,4,5-triphosphate and diacylglycerol as second messengers, which result in an increase in intracellular Ca^{2+} concentration [4].

A detailed picture of the relative importance of the circulating and endogenous renin-angiotensin systems is still far from clear although there is increasing evidence to suggest that the beneficial effects of ACE inhibitors are largely mediated through inhibition of the local production of angiotensin II [3,5,6].

The role of the renin-angiotensin system in health and disease

Activation of the circulating renin-angiotensin system occurs in response to a variety of different stimuli (Fig. 2) and the resultant angiotensin II exerts a negative feedback effect in attempt to correct any short-term homeostatic derangement. However, long-term endogenous angiotensin II production has been implicated in the development of vascular and ventricular hypertrophy in hypertensive patients, ventricular remodelling after myocardial infarction and the development of intraglomerular hypertension [7].

The renin-angiotensin system does not have an obligatory role in arterial blood pressure maintenance in the normal, sodium replete, well hydrated individual [8–10]. It is primarily the renal-pressure natriuresis mechanism, which comprises a feedback control system between sodium and water excretion and blood pressure, that mainly influences long-term control of blood pressure [11,12]. Sodium and water excretion are adjusted by hydrostatic mechanisms in order to maintain a stable glomerular filling pressure. This, in turn, is subject to influence by various neurohumoral mechanisms affecting sodium and water excretion, including the renin-angiotensin system, antidiuretic hormone (ADH), atrial-natriuretic peptide (ANP) and the sympathetic nervous system [13].

These mechanisms, also, may interact. For example, it is known that the stimulation of β_1 adrenoceptors in the juxtaglomerular apparatus by either endogenous catecholamines or exogenous β receptor agonists stimulates the release of renin, leading to angiotensin II production.

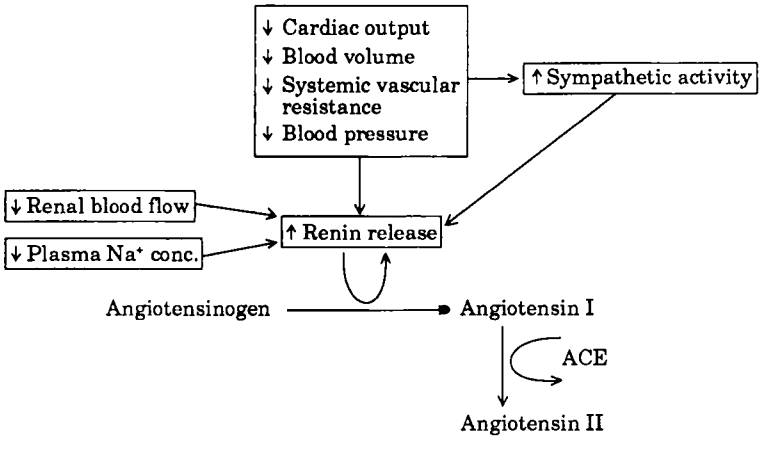

Fig. 2. Factors affecting renin-angiotensin activation.

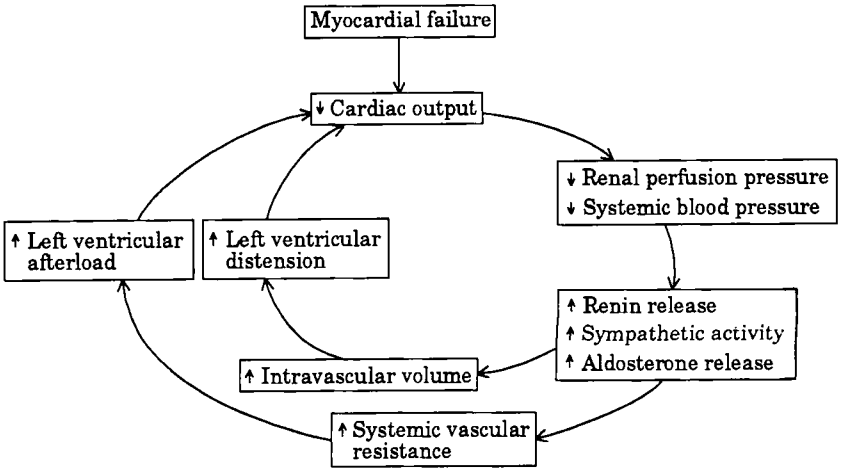

Fig. 3. The vicious loop of congestive heart failure.

Conversely, renin release is inhibited by β adrenoceptor antagonists and also by centrally acting α_2 antagonists. Stress, including that induced by surgery, is known to produce a generalised endocrine and metabolic response which includes activation of the renin-angiotensin system [14, 15]. These mechanisms tend to conserve sodium and water whereas ANP, by mediating peripheral vasodilatation, increases glomerular filtration and sodium and water loss. In addition, ANP inhibits aldosterone and ADH release [16,17]. In the kidney, the actions of angiotensin II lead to an increased prostaglandin secretion, particularly PGE_2 which has a potent vasodilatory action and may counteract the renal vasoconstrictive properties of angiotensin II. Indeed prostaglandins appear to play a vital role in maintaining renal blood flow under stressful conditions. When prostaglandin synthesis is blocked by indomethacin renal blood flow falls sharply due to unopposed angiotensin II-related renal vasoconstriction [18].

In hypertensive patients, plasma renin activity and angiotensin II concentrations are not usually elevated and are normally distributed in both hypertensive patients and the normotensive population [8]. Despite this, ACE inhibitors are effective in the majority of patients with essential hypertension. This may be because activation of the endogenous renin-angiotensin systems described above may have a more important role in this disorder than the circulating renin-angiotensin system. However, the circulating renin-angiotensin system *is* intensely activated in patients with malignant hypertension and reno-vascular hypertension, such as occurs with renal artery stenosis, and ACE inhibition may cause a precipitous fall in blood pressure in such individuals.

The activated renin-angiotensin systems are intimately involved in the development of congestive heart failure. The loss of functioning myocardium leads to the establishment of a compensatory feedback loop which attempts to maintain cardiac output and blood pressure (Fig. 3).

Pharmacology of ACE inhibitors

On the basis of chemical structure, ACE inhibitors can be divided into three distinct groups: the sulphydryl containing agents (only captopril in the United Kingdom), the phosphinic acid derivatives (fosinopril) and the non-sulphydryl containing agents (Table 1). Captopril and fosinopril bind to the zinc ion in the ACE molecule through their sulphydryl and phosphinic acid moieties respectively, whereas other agents bind to the zinc ion through carboxyl residues. Apart from lisinopril and captopril all are prodrugs, which are hydrolysed by gastro-

Table 1. Pharmacokinetic values of some ACE inhibitors.

	Captopril	Enalapril	Lisinopril	Ramipril	Fosinopril	Trandolapril	Cilazapril	Quinapril	Perindopril
Prodrug	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Name of active compound	Captopril	Enalaprilat	Lisinopril	Ramiprilat	Fosinoprilat	Trandolaprilat	Cilazaprilat	Quinaprilat	Perindoprilat
Oral absorption	70%	50–75%	30%	60%	35%	40–60%	45–75%	60%	75%
Effect of food on absorption	Fall in rate and extent	None	None	Minimal	Fall in rate	None	Fall in rate and extent	Fall in rate	Fall in rate and extent
Protein binding	30%	< 50%	None	55–75%	89–98.8%	80%	N/A	97%	< 20%
Tmax; h	0.8–1.0	3	6	1.5–2.5	2.4–4.2	4.0–8.0	1.5–2.0	1.0–2.0	1.0–3.0
Vdss; l	49–53	NA	124	90	9.8–10.6	N/A	20	N/A	9.3
Metabolism of active drug	> 50%	0%	0%	> 80%	< 10%	N/A	None	< 20%	N/A
T1/2 elimination; h	0.5–2.0	5.0–11.0	12.6	10.0–20.0	11.5–12	3.5	1.5	1.0–2.0	1
Excretion	Renal tubular	Renal	Glomerular filtration	Renal	Renal/ Hepatic	Renal	Renal	Renal	Renal

Tmax, time to peak plasma concentration of active drug after single oral dose; Vdss, steady state volume of distribution; N/A, data not available.

intestinal mucosal and hepatic esterases to the active diacid forms (e.g. enalapril to enalaprilat), as the active metabolites are poorly absorbed after oral administration. Impaired hepatic function can lead to slower de-esterification and hence to a slower onset of clinical action.

All the serum concentration-time curves exhibit polyphasic elimination profiles with a slow terminal phase of up to 120 h representing strong saturable covalent binding to ACE. With the exception of fosinoprilat, all drugs and their active metabolites are heavily dependent on renal function for their elimination. Fosinoprilat can undergo compensatory faecal elimination in the presence of impaired renal function. In the presence of renal impairment, dosages and dosage intervals should be modified.

Clinical effects of ACE inhibitors

Hypertension

ACE inhibitors may be used as first line antihypertensive agents in both the United States and the United Kingdom [19,20]. They are well tolerated, have a good safety profile, and have been shown to improve the quality of life of hypertensive patients [21].

When first introduced, captopril was reserved for the treatment of patients with severe hypertension associated with elevated plasma renin activity who were not adequately controlled with conventional triple therapy. It was confined to this group as it was believed that ACE inhibition would only effectively lower blood pressure in those patients with circulating renin-angiotensin system activation. This was before the existence of endogenous renin-angiotensin systems were postulated and large doses of captopril were used (usually 275 to 375 $mg.day^{-1}$). These large doses were associated with a high incidence of severe side effects which, it were claimed, were related to its sulphydryl moiety [22], and which led to the express avoidance of the $-SH$ group in virtually all subsequently developed ACE inhibitors.

It was soon shown, however, that smaller doses were also effective and avoided the side effects initially reported. Paradoxically, a great deal of interest is currently focused on the potentially beneficial effects of the sulphydryl moiety of captopril due to its ability to scavenge oxygen-derived free radicals [23,24].

The reduction in blood pressure is associated with a sustained fall in systemic vascular resistance of typically 20–30% [25–27]. In addition to dilatation of resistance vessels, ACE inhibitors have also been shown to dilate and improve the compliance and distensibility of large arteries due to the inhibition of production of endogenous angiotensin II, an effect which has been postulated as possibly reducing the long-term risks of hypertension, such as stroke, aneurysm formation and the development of congestive heart failure [3,7,28,29].

Diuretic therapy is associated with renin-angiotensin system activation due to sodium and water loss, and the introduction of ACE inhibitors to hypertensive patients who are already receiving diuretics may lead to a profound fall in blood pressure. Similarly, salt or fluid depletion from any cause may also cause symptomatic hypotension [30]. The anti-hypertensive effect of ACE inhibitors may indeed be augmented by diuretics which should preferably be introduced after ACE inhibitor treatment has been established.

The concomitant administration of indomethacin may be associated with an obtunding of the hypotensive action of ACE inhibitors. This is thought to be due to interference with the ACE inhibitor-induced increase in prostaglandin synthesis, which suggests that prostaglandins may be involved in the antihypertensive effect of ACE inhibitors.

Angiotensin II is known to be a cell growth factor [31–33] and may be implicated in the development of left ventricular hypertrophy in hypertensive patients. This process can be arrested and reversed by converting enzyme inhibition in human hypertensives [28,34]. Moreover, when rats with experimentally induced aortic stenosis were treated with either dihydralazine, nifedipine or the ACE inhibitor ramipril, only the animals treated with the ACE inhibitor failed to develop cardiac hypertrophy [35].

Congestive heart failure

The administration of a single dose of captopril (25 to 50 mg) to patients with congestive heart failure typically leads to substantial reductions in right- and left-sided cardiac filling pressures of around 40% [36–38]. These are associated with reductions in systemic and pulmonary vascular resistances of a similar magnitude and an increase in cardiac index and stroke work of around 35%. These acute beneficial changes in haemodynamics are maintained in the long term, and are associated with improvements in clinical symptoms, cardiothoracic ratio, exercise time and New York Heart Association classification of heart failure [36,37,39,40]. They are not associated with a reflex tachycardia. This is thought to be due to their sympatholytic effect and is a feature not commonly shared by other vasodilators.

The Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS) [41] published in 1987 showed a reduction in mortality of 27% in patients with severe heart failure in whom enalapril was added to conventional therapy. Recently, two further studies have demonstrated significant improvements in survival amongst patients treated with either captopril or enalapril who had asymptomatic left ventricular dysfunction [1,2]. Patients in these studies also had a lower incidence of progression to overt heart failure. It has been demonstrated that the degree of activation of the circulating renin-angiotensin system does not correlate with either haemodynamic improvement, clinical response, or survival during long-term treatment with a converting enzyme inhibitor [42]. These beneficial effects of ACE inhibition cannot be explained on the basis of afterload reduction alone and it is thought likely that direct local cardiac actions play an important role [43].

Symptomatic hypotension may also be associated with the introduction of ACE inhibitors to patients whose symptoms of heart failure are not controlled by diuretics and/or digoxin. This problem may be circumvented by discontinuing or reducing the dose of diuretic several days before starting the ACE inhibitor, and by commencing therapy with the lowest possible dose.

The initial CONSENSUS study was followed by a second study aimed at investigating the effect on mortality of the early introduction of enalapril following myocardial infarction [44]. The mean time to treatment with the ACE

inhibitor following infarction was 15 h in these patients. This study had to be stopped before completion following an interim analysis which showed no reduction in mortality and an increase in the incidence of significant hypotension in the treated group. Angiotensin II increases the rate of myocardial protein synthesis, promotes myocyte growth and promotes collagen expansion by fibroblasts [31–33]. In addition, large amounts of ACE are found in myocardial scars shortly after infarction [45]. It is possible that, in the initial hours following infarction, high concentrations of cardiac angiotensin II may actually be beneficial in the healing process.

Renal function

In patients with bilateral or unilateral renal artery stenosis, glomerular filtration is dependent on high intra-renal concentrations of angiotensin II to constrict the efferent glomerular arteriole and to generate adequate filtration pressure. If production of this angiotensin II is prevented by ACE inhibition then the glomerular filtration rate can fall dramatically leading to a rapid deterioration in renal function. This impairment is readily reversible, if noticed, and may be used as a noninvasive diagnostic test for the presence of renal artery stenosis [46,47].

In both healthy volunteers, and patients with congestive heart failure or hypertension, treatment with ACE inhibitors tends to increase renal blood flow despite a reduction in systemic blood pressure. This increase is due to a reduction in renal vascular resistance and is associated with variable changes in glomerular filtration which usually depend on the subject's sodium balance [48, 49].

ACE inhibitors are not normally associated with a significant deterioration in renal function. For example, in the SOLVD study [2] in which over 2000 patients with asymptomatic left ventricular dysfunction took enalapril for an average of more than 3 years, serum creatinine rose by an average of only 3.5 μmol.l^{-1} during the study period. However, functional renal impairment may occur during ACE inhibitor therapy in up to one third of salt-restricted patients with congestive heart failure treated with constant doses of diuretics [50]. This could be predicted, as angiotensin II mediated mechanisms are responsible for the maintenance of renal perfusion pressure during the state of relative dehydration produced by diuretics. It is recommended, therefore, that renal function should be checked in all patients who are to be treated with an ACE inhibitor and that it should be regularly monitored during treatment. Caution should also be exercised when prescribing ACE inhibitors to patients with peripheral vascular disease. This is often a marker of generalised arterial disease which may well affect the renal vessels.

Conversely, there are specific circumstances when ACE inhibition may be beneficial to patients who are at risk of developing renal damage [51]. Proteinuria in patients with intrinsic renal disease of diverse aetiology, including glomerulonephritis, systemic lupus erythematosis and nephrotic syndrome, is significantly reduced by ACE inhibitor therapy [52,53]. ACE inhibitors have also been shown to be effective at reducing microalbuminuria in diabetes mellitus [54], this being an accepted marker for the development of clinical nephropathy [55]. It has been demonstrated that this phenomenon is due to a decrease in filtration fraction by efferent arteriolar dilatation independent of a fall in systemic blood pressure [56]. ACE inhibitors in fact, selectively reduce intraglomerular capillary pressure and glomerular permeability to albumin [55].

Myocardial ischaemia and infarction

ACE inhibitors are known to mediate a reduction in left ventricular remodelling and dilatation following myocardial infarction [57–59]. These are the first changes in the development of congestive heart failure and it has recently been suggested that ACE inhibitors should be prescribed to all patients following myocardial infarction [60].

ACE inhibitors dilate coronary arteries but reduce arterial and coronary perfusion pressure, leaving coronary blood flow little changed [61,62]. In patients with heart failure and angina they can lead to an exacerbation of symptoms [63] presumably due to the reduction in coronary perfusion pressure across a fixed stenosis [64,65]. However, ACE inhibitors can preserve cardiac function during various stages of myocardial infarction [66]. In one study [67], after 15 min of coronary occlusion in dogs subendocardial segment shortening did not improve in control animals whereas it returned to 50% of baseline values after 3 h of observation in animals pretreated with the ACE inhibitor, captopril. In this study, captopril also prevented the occurrence of ventricular fibrillation following reperfusion and it was suggested that the improvements seen in function might be partially due to the sulphydryl moiety of captopril, which acts as a scavenger of oxygen-derived free radicals. Captopril was also shown to prevent lactate production after 30 s of coronary occlusion in dogs [67] and has been shown to limit infarct size after 6 h of coronary occlusion [68]. These beneficial changes may be due to pre- and afterload reduction and improved myocardial perfusion due to reduced systemic vascular resistance and left atrial pressure (without inducing reflex tachycardia) and increased coronary collateral blood flow [66,67].

Early after a myocardial infarction, left ventricular diastolic volume increases and is accompanied by an increase in left ventricular filling pressure as the area of infarct expands [69]. This is the first step in the process of ventricular remodelling which, if the infarct is of sufficient size, may lead to progressive dilatation and further deterioration in myocrdial performance resulting ultimately in the development of congestive heart failure [57]. This process has been shown to be attenuated by treatment with an ACE inhibitor [58,59] and may be the mechanism underlying the improved survival of patients with asymptomatic left ventricular dysfunction following myocardial infarction who have been treated with captopril [10].

Cardiac arrhythmias, which are often severe and life-threatening, including ventricular fibrillation, are associated with the reperfusion of previously ischaemic myocardium. This phenomenon is commonly associated with the use of streptokinase and other fibrinolytic agents after myocardial infarction, and frequently occurs after myocardial reperfusion during coronary angioplasty. Oxygen-derived free radicals are believed to play an important role in this process in addition to being responsible for adverse effects on myocardial metabolic and contractile function associated with perfusion [70,71]. It has been suggested that captopril may attenuate reperfusion injury by scavenging free radicals [72]. The ability of this and

Table 2. Possible mechanisms of the beneficial actions of ACE inhibitors in myocardial ischaemia.

Inhibition of production of circulating and endogenous angiotensin II
Increasing local concentrations of bradykinin
Increasing local concentrations of prostaglandins
Reduction in central sympathetic outflow
Reduction of peripheral sympathetic facilitation
Scavenging of oxygen-derived free radicals
Prevention of neutrophil attraction

other ACE inhibitors to scavenge oxygen-derived free radicals has been tested in an *in vitro* study where ACE inhibitors containing the −SH group (such as captopril) were shown to be effective scavengers of the highly damaging non-superoxide free radicals whereas the non-SH containing agents (such as enalaprilat, ramiprilat and perindoprilat) were not [23]. Furthermore, in this study captopril scavenged the other toxic oxygen species, hydrogen peroxide and singlet oxygen, and inhibited microsomal lipid peroxidation, an indicator of cell membrane damage.

ACE inhibitors have many effects at the cellular and subcellular level which could account for their beneficial effects on myocardial function (Table 2). In addition to their effects on angiotensin II production, free-radical scavenging, bradykinin degradation and the sympathetic nervous system, they may directly activate phospholipases and thus induce prostaglandin synthesis, which is believed to have beneficial local effects. They have also been shown to prevent angiotensin II-mediated neutrophil migration, neutrophils being involved in myocardial damage following reperfusion [68].

The renin-angiotensin system during anaesthesia and surgery

In the well hydrated, sodium replete subject, anaesthesia *per se* is not a significant stimulus to the circulating renin-angiotensin system [73,74]. However, a relative fluid deficit during surgery is closely associated with a rise in plasma renin activity indicating renin-angiotensin system activation [15]. This finding is consistent with the evidence that the circulating renin-angiotensin system is intimately involved in the maintenance of fluid and sodium balance. Little change has been found in plasma renin activity during induction and maintenance of anaesthesia with a variety of agents [75], although the degree of activation was found to be dependent on sodium balance and blood volume status.

Surgery, however, is a potent stimulus of renin-angiotensin activation, plasma renin activity increasing threefold from baseline values irrespective of blood loss [15,73]. In the presence of sodium depletion or dehydration both the baseline plasma renin activity and increases from baseline associated with surgery are increased [15,75]. There are three potential stimuli to renin-angiotensin system activation in the surgical environment which are of particular interest to the anaesthetist: controlled hypotension, cardiopulmonary bypass and aortic cross-clamping. Controlled hypotension with sodium nitroprusside is associated with a doubling of plasma catecholamine concentrations and plasma renin activity [76], which may represent a physiological attempt to maintain blood pressure in the presence of the potent vasodilator. The dosage of sodium nitroprusside used in this study was directly proportional to the plasma renin activity response.

Cardiopulmonary bypass is a potent stimulus of renin-angiotensin activation and has been implicated in the development of postoperative hypertension. The rise in plasma renin activity seen intra-operatively persists for many hours into the postoperative period [77–79] and may not be associated with a rise in plasma catecholamine concentrations [77]. In one early study comparing renin-angiotensin system activation in patients undergoing closed mitral valvotomy or open-heart procedures using cardiopulmonary bypass [80], plasma renin activity and plasma angiotensin II concentrations rose substantially only in those patients who underwent cardiopulmonary bypass, and the rise began only after bypass commenced. Plasma angiotensin II concentrations decreased in all but one patient after operation. In this individual the plasma angiotensin II concentration continued to increase and was associated with peripheral vasoconstriction and acute renal failure. He died 48 h postoperatively from low cardiac output syndrome associated with subendocardial necrosis. It is not clear whether the progressive increase in angiotensin II concentrations represented cause or effect.

Aortic cross-clamping in the absence of cardiopulmonary bypass is also associated with renin-angiotensin system activation and an increase in plasma angiotensin II concentrations. This occurs regardless of whether or not distal aortic perfusion is maintained by mechanical means and persists for several hours after unclamping [81,82]. This activation is associated with a fall in renal blood flow which can be up to 38% during infra-renal cross-clamping [83].

ACE inhibitors in surgery and anaesthesia

There have been several reports of adverse reactions in ACE inhibitor treated patients undergoing anaesthesia. Most involve hypotension and/or bradycardia. Russell and Jones [84] describe a case of hypotension in a hypertensive woman receiving treatment with enalapril, who became profoundly hypotensive in the recovery room following general anaesthesia with thiopentone, nitrous oxide and enflurane. This was successfully treated by intravenous fluid infusion. The authors suggest that an accumulation of bradykinin may have been responsible. McConachie and Healy [85] report several instances of severe and persistent hypotension in ACE inhibitor treated hypertensive patients undergoing anaesthesia using drugs and techniques, which unfortunately they did not describe.

Several studies have examined the possibility that ACE inhibitors might obtund the pressor response to laryngoscopy. Yates and Hunter [86] studied the effects on perioperative cardiovascular stability of a single tablet of enalapril 5 mg or placebo in 22 patients anaesthetised with thiopentone, nitrous oxide and halothane. They found that the enalapril treated patients had a significantly blunted pressor response to tracheal intubation and skin incision, but there were no differences in heart rates between the two groups.

Murphy and colleagues gave four different doses of intravenous enalaprilat and placebo to 24 and six patients respectively 17 min before induction of anaesthesia for procedures requiring tracheal intubation [87]. The drugs used in all patients were thiopentone, suxamethonium,

nitrous oxide, atracurium and enflurane. They were unable to show reduced pressor response to laryngoscopy with their regimen, although all their treated patients had reduced mean arterial blood pressure immediately before induction. One patient who received enalaprilat became profoundly hypotensive after induction of anaesthesia, but her blood pressure returned to an acceptable value after tracheal intubation; the patient remained normotensive and problem free throughout the rest of the procedure.

McCarthy and coworkers studied the pressor response to tracheal intubation in 40 patients following sublingual captopril or placebo [88]. They found that treatment was successful at preventing excessive increases in arterial blood pressure during laryngoscopy after the administration of thiopentone, vecuronium, nitrous oxide and isoflurane, although they reported several instances of hypotension in the treated group, one occurring in the recovery period. They also had two instances of bradycardia, one in the treated and one in the placebo group.

The use of ACE inhibitors for controlled hypotension during surgery has been investigated. Jensen and colleagues studied cerebral blood flow during general anaesthesia with thiopentone, tubocurarine, nitrous oxide and enflurane in 29 healthy patients undergoing minor surgery after pre-treatment with either placebo, metoprolol, or captopril [89]. They found that the captopril treated group had significantly lower cerebral blood flows than either of the other groups in association with a lower mean arterial pressure. In another study, Woodside and colleagues [90] assessed the effect of pre-treatment with captopril on sodium nitroprusside requirements during hypotensive anaesthesia (thiopentone, morphine, pancuronium) for spinal fusion in 12 otherwise fit adolescents with idiopathic scoliosis. They found that sodium nitroprusside requirements were significantly reduced in those patients given captopril and that there were no significant differences in cardiac outputs between the two groups.

Other investigators have studied the ability of ACE inhibitors to control intra- or postoperative hypertension. Kataja and coworkers treated the hypertension associated with aortic cross-clamping during abdominal aortic surgery with either isoflurane or intravenous captopril [91]. They found that both agents reduced systemic blood pressure but that cardiac index was preserved only in those receiving captopril. These workers did not, however, find captopril to be an effective antihypertensive agent in the post-operative period. The effectiveness of captopril in controlling arterial blood pressure after aortic cross-clamping is probably due to the previously described surge in renin-angiotensin system activation. After release of the cross-clamp concentrations fall rapidly which may account for the apparent lack of effect following clamp release.

Colson's group [92] has investigated, in 19 patients, the effect on postoperative hypertension of pre-operative renin-angiotensin system blockade with captopril 400 mg or placebo given for 2 days before coronary artery surgery. Arterial blood pressure decreased slightly in the captopril group following induction and before cardiopulmonary bypass. There was no difference between the blood pressures of the two groups during bypass or after operation. The treatment failed to prevent postopertive hypertension although the numbers involved were small. These workers also showed [93] that the same pre-operative treatment regimen prevented the reduction in effective renal plasma flow, and creatinine clearance which occurred in the placebo group during cardiopulmonary bypass for coronary artery surgery, and that the urinary excretion of sodium was greater in the captopril-treated patients. During operative closure the treated patients also had a higher mean creatinine clearance than the placebo-treated groups although the difference was not statistically significant. The group called for further studies to look at the effect of ACE inhibitors on the renal function of patients at high risk of developing renal dysfunction.

In another study Colson and colleagues measured the cardiovascular changes associated with the induction of anaesthesia for coronary artery or vascular surgery in hypertensive patients chronically treated with either ACE inhibitors ($n = 8$) or other antihypertensive regimens ($n = 8$) using a standard technique comprising flunitrazepam, fentanyl and pancuronium [94]. The ACE inhibitor treated patients were all receiving a second hypotensive agent and had a higher pulmonary capillary wedge pressure (PCWP) at baseline than the control group. Mean arterial pressure, cardiac index and pulmonary capillary wedge pressure fell in both groups, but the fall in MAP and cardiac index were greater in the ACE inhibitor-treated group. Because of the lack of comparability between the two groups, however, it is difficult to interpret the significance of these findings.

It is difficult to make firm recommendations concerning which anaesthetic drugs to use or avoid in patients taking ACE inhibitors as there are few controlled studies and most evidence is anecdotal. The main problems involve hypotension and bradycardia. The advisability or otherwise of spinal or epidural anaesthesia in these patients is also unclear as is the choice of vasopressor. The ideal vasopressor would be angiotensin II and it is currently undergoing clinical evaluation.

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