Impact of angiotensin converting enzyme inhibition on post-coronary artery bypass interleukin 6 release

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Background: Angiotensin 1 converting enzyme (ACE) inhibitors reduce morbidity and mortality after coronary artery bypass graft surgery (CABG). This benefit may result from an anti-inflammatory action.

Objective: To examine the effect of ACE inhibition on interleukin 6 (IL-6) concentrations after CABG.

Patients and methods: 161 patients undergoing elective first time CABG were recruited, of whom 41 (25%) were receiving ACE inhibitor treatment; 21 patients with confounding postoperative complications were excluded. After these exclusions there were 33 patients (24%) on ACE inhibitor treatment. Plasma IL-6 was measured preoperatively and again six hours after CABG.

Results: Baseline IL-6 concentrations (geometric mean (SEM)) were non-significantly lower among the patients receiving ACE inhibitors (3.7 (0.1) v 4.3 (0.1) pg/ml, $p = 0.12$). Overall, post-CABG IL-6 concentrations increased significantly (mean rise 177 (12) pg/ml, $p < 0.0005$). This response was blunted among ACE inhibitor treated patients. Median increases in IL-6 concentrations were 117 v 193 pg/ml, for treated v non-treated patients, respectively (Kruskal-Wallis, $p = 0.02$), with peak post-operative IL-6 concentrations lower among the subjects receiving ACE inhibitors than in untreated subjects (142 (19) v 196 (13) pg/ml, $p = 0.02$). The effect of ACE inhibitors remained significant after multivariate analysis ($p = 0.018$).

Conclusions: ACE inhibitor treatment is associated with a reduction in IL-6 response to CABG. The data suggest that this class of drug may have a direct anti-inflammatory effect, which could explain some of its clinical benefit.

Treatment with angiotensin 1 converting enzyme (ACE) inhibitors is associated with substantial reductions in cardiovascular mortality and morbidity among patients with impaired myocardial function.^{1,2} The HOPE (heart outcomes prevention evaluation) study³ has extended our knowledge of the benefits of ACE inhibition in people who are at coronary risk but have normal left ventricular function, with reductions in mortality, myocardial infarction, cardiac arrest, and heart failure. A recent meta-analysis has also confirmed that a substantial reduction in sudden cardiac deaths occurs in patients treated with an ACE inhibitor early after myocardial infarction.⁴ These beneficial effects are inadequately explained by the simple hypotensive and natriuretic effects of systemic inhibition of the renin-angiotensin system.^{3,5} It is now thought likely that an anti-inflammatory action is involved.⁶

Local (myocardial) or systemic inflammatory processes could play key roles in the progression of heart failure,⁷⁻⁹ while local (coronary plaque) or systemic inflammation could mediate atheromatous plaque growth¹⁰ and initiate unstable plaque events.¹¹ It is thought that the pro-inflammatory cytokine interleukin 6 (IL-6) plays a central role in this. Thus IL-6 concentrations are raised in patients with heart failure¹² and indeed may play a causative role in driving heart failure by stimulating cardiomyocyte apoptosis,⁸ while IL-6 induced endothelial activation^{13,14} together with vascular smooth muscle cell proliferation¹⁵ and migration¹⁶ may underlie the atherogenic process.¹⁷

Raised systemic concentrations of IL-6 are thus associated with both the development and the progression of heart failure.^{12,18,19} They are also related to the development of coronary vascular disease,^{20,21} as well as the transition to plaque instability.¹¹ Raised concentrations of IL-6 are also correlated with mortality in elderly people.^{22,23} Atherosclerosis is itself a chronic low grade inflammatory condition characterised by activation of the acute phase response,²⁴ and thus local

plaque IL-6 expression may exert important effects. Both vascular smooth muscle cells and inflammatory cells such as macrophages are key components of the atherosclerotic plaque,^{25,26} in which a high tissue ACE expression increases further upon inflammatory stimulation.²⁷ Concomitant increases in plaque angiotensin II expression²⁸ may drive IL-6 expression. IL-6 is co-localised with ACE within atherosclerotic plaques,^{29,30} suggesting a possible local role of inflammation in the initiation and progression of atherosclerosis.¹⁷ Plaque ACE is thus considered an important therapeutic target in its own right.²⁷ It has thus been postulated that the therapeutic benefits of ACE inhibition may be partly mediated through an anti-inflammatory action, and specifically through reductions in local or systemic IL-6 expression.³¹

The acute phase response following coronary artery bypass graft surgery (CABG) is associated with the induction and release of cytokines, including IL-6,³²⁻³⁴ and affords investigators a useful opportunity to study the impact of various factors on the acute phase response. However, to date the impact of ACE inhibitors on post-CABG IL-6 response has not been investigated. We have thus used this model to perform an observational study exploring the hypothesis that ACE inhibition is associated with a reduction in the IL-6 response to acute inflammatory stimuli.

METHODS

Subjects were drawn from the coronary artery surgery inflammation study (CASIS). Briefly, all patients undergoing elective first time CABG at the Middlesex Hospital, London,

Abbreviations: ACE, angiotensin converting enzyme; CABG, coronary artery bypass graft; CASIS, coronary artery surgery inflammation study; HOPE, heart outcomes prevention evaluation study; IL-6, interleukin 6

Table 1 Patient baseline characteristics and operative details

Variable	ACE inhibitor treatment (n=33)	No ACE inhibitor treatment (n=107)	p Value
<i>Baseline characteristics</i>			
Men	27	82	
Women	6	25	
Age (years)	64 (2)	63 (1)	0.73
Body mass index (kg/m ²)	26.5 (0.4)	28.4 (0.7)	0.04
Current smoker	4 (13%)	20 (19%)	0.29
Treated hypertension	18 (55%)	33 (31%)	0.01
Diabetes mellitus	10 (30%)	18 (17%)	0.08
Family history of coronary artery disease	15 (46%)	54 (51%)	0.38
Total cholesterol (mmol/l)	4.8 (0.2)	4.9 (0.1)	0.74
Low density lipoprotein (mmol/l)	2.5 (0.2)	2.6 (0.1)	0.48
High density lipoprotein (mmol/l)	1.4 (0.1)	1.3 (0.1)	0.52
Canadian Cardiovascular Society class	2.6 (0.2)	2.2 (0.1)	0.11
New York Heart Association class	1.8 (0.1)	1.8 (0.1)	0.75
<i>Operative details</i>			
Mean number of grafts	2.8 (0.1)	2.8 (0.1)	0.75
Operation duration (minutes)	190 (8)	195 (3)	0.49
Cardiopulmonary bypass time (minutes)	63 (3)	66 (2)	0.31
Aortic cross clamp time (minutes)	34 (3)	32 (1)	0.58
Length of ventilation (hours)	9.3 (0.9)	10.3 (0.4)	0.24
Length of stay in intensive care unit (days)	2.3 (0.5)	2.3 (0.2)	0.85
Length of postoperative stay (days)	7.0 (1.0)	6.6 (0.4)	0.64

Values are n (%) or mean (SEM).
ACE, angiotensin converting enzyme.

UK, between October 1999 and September 2000 were invited to participate. The study had hospital ethics committee approval, and all patients gave written informed consent.

Subjects undergoing additional surgical procedures (such as valvar surgery or aneurysmectomy) were excluded.

All patients were taking aspirin 75 mg/day, and ceased taking this 10 days before surgery. Other drugs were withheld on the morning of surgery. ACE inhibitor treatment was given as usual the night before surgery. No patient had clinical evidence of active inflammatory or immunomodulatory disease (such as acute coronary syndromes, malignancy, intercurrent infection, renal failure, or autoimmune disease) at recruitment, nor were any receiving anti-inflammatory agents. Similarly, before analysis all data were excluded from those subjects who experienced significant postoperative complications, even if these were only apparent after the six hour sample time point, as IL-6 rises within hours of an inflammatory stimulus. Study exclusion criteria thus included infections requiring antibiotic treatment, prolonged respiratory support, circulatory support, or renal failure requiring haemofiltration.

Surgical procedure

CABG was performed through a midline sternotomy by one of four consultant surgical staff, with subsequent hypothermic cardiopulmonary bypass employing right atrial and ascending aortic cannulation. Myocardial protection was maintained by intermittent cold cross clamp fibrillation, and heparin anticoagulation was reversed postoperatively by protamine sulfate.

A 4.5 ml citrated blood sample was drawn before surgery (with the patient supine and resting) and again six hours after cardiopulmonary bypass. Venous blood was immediately centrifuged (at 3500 *g* for 10 minutes), and the plasma was separated and stored at -20°C until analysis. IL-6 concentrations were measured by enzyme linked immunosorbent assay (R&D Systems, Abingdon, UK) by staff blind to all subject data. Interassay and intra-assay coefficients of variation were 5% and 3%, respectively, and assay sensitivity was < 0.70 pg/ml).

Statistical analysis

All data were analysed using SPSS for Windows version 9 (SPSS Inc, Chicago, Illinois, USA). We analysed raw data when

they were normally distributed. However, the IL-6 values were skewed, so they were normalised by log transformation (the data shown represent geometric means and standard deviations). The effect of ACE inhibitor treatment on IL-6 was assessed by analysis of variance and Student's *t* test for unpaired data. One way analysis of covariance was performed using age, sex, smoking, diabetic status, left ventricular ejection fraction, statin treatment, duration of operation, and cardiopulmonary bypass and aortic cross clamp times as covariates. Following backwards stepwise linear regression modelling, only variables that had a significant effect on IL-6 concentrations were included in the final model. Pearson's correlation coefficient was used to test the relation between IL-6 concentrations and baseline clinical and surgical variables. The study was powered to detect a 10% difference in post-CABG IL-6 with 80% power at *p* < 0.05.

RESULTS

Of 269 elective CABG cases, 172 who fulfilled the inclusion criteria were randomly approached (depending on investigator availability), and of these 161 chose to participate. At enrolment, 41 (25%) were receiving ACE inhibitor treatment: 11 (27%) were on lisinopril, 10 (24%) on ramipril, six (15%) on enalapril, six (15%) on perindopril, four (10%) on captopril, and four (10%) were taking other agents. In all, 111 subjects (67%) were receiving statin treatment. Twenty one patients experienced confounding postoperative complications and were thus excluded, according to protocol. This left a final study group of 140 subjects, including 33 (24%) receiving ACE inhibitors.

Clinical and operative characteristics (table 1) were largely independent of ACE inhibitor treatment, although body mass index was slightly lower. As anticipated, a past medical history of diabetes or hypertension was more common in ACE inhibitor treated patients. Similarly, a higher proportion of subjects receiving ACE inhibitors had a left ventricular ejection fraction below 50% (18/33 *v* 29/107, *p* < 0.01).

The correlation between baseline and post-CABG IL-6 values and the major clinical and surgical variables is shown in table 2. While both baseline and post-CABG IL-6 concentrations were lower in non-diabetic patients, men, and

Table 2 Correlation between IL-6 concentrations and clinical variables

Variable	Preoperative IL-6	Postoperative IL-6
Age	$r=0.05$ ($p=0.57$)	$r=-0.19$ ($p=0.02$)
Body mass index	$r=0.22$ ($p=0.04$)	$r=0.15$ ($p=0.15$)
Ejection fraction	$r=-0.12$ ($p=0.17$)	$r=-0.16$ ($p=0.08$)
Aortic cross clamp time	–	$r=0.08$ ($p=0.41$)
Cardiopulmonary bypass time	–	$r=0.14$ ($p=0.11$)
Total duration of surgery	–	$r=0.23$ ($p=0.01$)

non-smokers, none of these factors was associated with a significant effect on IL-6 concentrations; however, post-CABG IL-6 concentrations were lower in patients receiving statin treatment ($p = 0.029$).

The effect of ACE inhibitor treatment on IL-6 concentrations is shown in fig 1. A trend towards lower preoperative IL-6 concentrations among patients receiving ACE inhibitors (mean (SD), 3.7 (0.1) v 4.3 (0.1) pg/ml, $p = 0.12$) became less strong after multivariate analysis. Among the group as a whole, surgery was associated with a significant increase in IL-6 concentrations (mean rise, 177 (12) pg/ml, $p < 0.0005$ by paired t test). However, this response was significantly blunted among ACE inhibitor treated patients: median increases in IL-6 concentrations were 117 pg/ml in treated patients and 193 pg/ml in non-treated patients (Kruskal–Wallis, $p = 0.02$), with peak postoperative IL-6 concentrations lower among the 33 patients receiving ACE inhibitors than in the 107 untreated subjects (142 (19) v 196 (13) pg/ml, $p = 0.02$). The effect of ACE inhibitor treatment on post-CABG IL-6 concentrations remained significant after multivariate analysis (analysis of covariance, $p = 0.018$).

DISCUSSION

While the anti-inflammatory role of ACE inhibitors has been reported previously *in vitro*,^{35,36} this study suggests for the first time that ACE inhibitor treatment is also associated with a reduction in IL-6 response to coronary artery bypass surgery. Although observational in nature and not derived from a randomised double blind control study, these data have important therapeutic implications in at least three fields.

Firstly, the pronounced inflammatory response to CABG is implicated in the pathogenesis of subsequent hyperdynamic circulatory instability, delayed myocardial recovery, and organ dysfunction.^{33,37} More specifically, prolonged increases of circulating IL-6 are also associated with increased morbidity and mortality after cardiac operations.³⁸ It has already been shown that ACE inhibition may improve outcome in patients undergoing CABG,³⁹ although a mechanistic explanation for this observation remains elusive. Our data would support the suggestion that inherent anti-inflammatory properties of ACE inhibitor drugs may be responsible.³⁵ However, as the study was designed only to include subjects with an uncomplicated postoperative course, it is unsurprising that there was no significant difference in the length of hospital stay between those patients who did or did not receive an ACE inhibitor.

Secondly, there is evidence of cross signalling between the renin–angiotensin system and IL-6, so the former may contribute to the pathogenesis of atherosclerosis. Angiotensin II stimulates IL-6 production by smooth muscle cells, an effect that can be inhibited by captopril and ramiprilat.³⁶ Steady state mRNA for IL-6 can also be augmented after stimulation with angiotensin II, suggesting regulation of angiotensin induced IL-6 release at the pretranslational level.³⁶ Moreover, angiotensin II can also activate the pro-inflammatory transcription factor nuclear factor κ B, which is necessary for transcription of most cytokine genes, including IL-6.⁴⁰ Thus it is likely that

Figure 1 Effect of ACE inhibitor treatment on post-coronary artery bypass graft IL-6.

angiotensin can elicit an inflammatory response in human vascular smooth muscle cells by stimulating cytokine production and the activation of nuclear factor κ B.³⁶ Our data would support an anti-inflammatory role for ACE inhibition in reducing vascular event rates in those at risk.³

Finally, the dramatic benefit of ACE inhibition in patients with heart failure remains to be explained, although our data once again support a potential anti-inflammatory role in mediating those effects.⁴¹

It remains possible, of course, that it is not the ACE inhibition on its own that is associated with a reduced IL-6 response, but the condition that led to such treatment in the first place. However, we think that unlikely.⁴² If anything, the inflammatory response to surgery might be expected to be greater among patients with pre-existing cardiac dysfunction or diabetes.⁴³ In any event, with the increasing indications for ACE inhibitor treatment (hypertension, diabetes,⁴⁴ coronary artery disease,³ and cardiac dysfunction^{1,2}), there are ethical concerns about performing a randomised controlled trial of ACE inhibition in patients selected for coronary surgery.⁴⁴

Clearly further studies are required, both *in vitro*, to investigate the effect of ACE inhibitor on IL-6 production using preparations of cells implicated in IL-6 synthesis (such as macrophages, fibroblasts, and endothelial cells), and *in vivo*, to explore the effect of ACE inhibition on the IL-6 response to other types and grades of inflammatory stimulus—for example, following acute coronary syndromes or coronary intervention. Any such studies need to be both randomised and double blind in design. Nonetheless, these data are supportive of an *in vivo* anti-inflammatory effect of ACE inhibition in humans.

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