The renin-angiotensin system and coronary vasomotion

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Coronary vasomotion, which controls myocardial perfusion, is closely regulated by myocardial metabolic demand and has been assessed by changes of coronary vascular resistance. Only two decades ago evidence of neural and hormonal control overriding the metabolic control of coronary arterioles, which represent the "resistance vessels" was reported (fig 1). Numerous groups reported persistence of a coronary vasodilator reserve or progressive vasoconstriction despite ischaemia.¹⁻¹¹ Studies showed that α adrenergic receptor mediated coronary constriction may restrict metabolic dilatation to avoid wasting blood flow to the heart muscle.¹² Infusion of α receptor stimulating or blocking drugs, and activation of the sympathetic nervous system during β blockade, defined the potential of such influences on coronary blood flow.^{13 14} α Receptor coronary constriction may be one component of the constrictor tone during ischaemia.¹⁴⁻¹⁸ In the meantime, numerous mediators have been identified which may constrict or dilate coronary vessels. Thus receptors are abundant in coronary vas-

culature for various mediators, and the physiological significance of such mediators remains obscure.

Vasomotion of large conductance vessels does not normally contribute to regulation of coronary blood flow. However, in the presence of atherosclerotic lesions, coronary thrombosis, and spasm, large vessels limit myocardial perfusion and induce ischaemia, angina pectoris, and infarction. Abnormal vasomotion of large coronary vessels has been appreciated in the last decades, when coronary angiography became available during acute coronary syndromes. Atherosclerotic vessels seem to respond with vasoconstriction in situations where vasodilatation should be required. The endothelium and mediators released by the endothelium play a critical role in mediating vasomotion in normal and diseased large and small coronary vessels. However, multiple potential mediators confuse our understanding of coronary vasomotion.

Previously, agonists and antagonists of various mediator systems have been used to identify a potential role for coronary vasomotion. Effects of agonists are dose dependent, and it remains unclear from most studies which concentrations of agonists may occur under physiological or pathophysiological conditions. The use of antagonists might increase our understanding, but the specificity of available inhibitors is limited. In addition, the effect of mediators is balanced by other mediators, and blockade of one may activate others. For the coronary circulation, the situation is even more complicated since coronary blood flow is under the influence of aortic pressure, compressive forces of the ventricle, and myocardial metabolic demand. Thus interventions in the coronary circulation with any agonist or antagonist result in complex changes which are difficult to analyse. Response to mediators may be different in various sections of coronary circulation,¹⁹ and diseases which alter vasomotion may affect large and small vessels differently. Finally, acute effects of an agonist or antagonist may be different from chronic effects. Changes of coronary vascular muscle tone are responsible for acute coronary vasomotion, but coronary vasomotion may well be influenced by chronic morphological changes of the coronary vessel wall and perivascular tissue.

Importance of the renin-angiotensin system for instantaneous regulation of coronary vascular tone

Two components of the renin-angiotensin system are now generally recognised: a systemic

Figure 1 Effect of lowering perfusion pressure of a cannulated coronary artery (from right to left) in analogy to progressive coronary stenosis on coronary conductance as determined distal to "coronary stenosis". Solid line represents control situation with an initial autoregulatory increase in coronary conductance (coronary vasodilatation). Further lowering of coronary perfusion pressure to induce myocardial ischaemia (left of broken vertical line), as indicated by lactate production and depression of myocardial function, results in a decrease rather than a further increase in coronary conductance, indicating exhaustion of coronary autoregulation. Intracoronary infusion of adenosine increases coronary conductance, suggesting a vasodilator reserve or a constrictive tone despite myocardial ischaemia. The cyclo-oxygenase inhibitor indomethacin reduces coronary conductance, suggesting a vasodilator tone of cyclo-oxygenase products of arachidonic acid in this model of myocardial ischaemia. (Ertl G. Effect of angiotensin-converting enzyme inhibitors on myocardial perfusion. In: Schultheiss HP, ed. New concepts of viral heart disease. Berlin: Springer Verlag, 1988:454-64.)

circulating, and a local renin-angiotensin system. The systemic system controls acute changes of vascular tone and aldosterone release from the adrenals. The local system may control chronic adaptation of the vasculature and perivascular tissue, the growth of smooth muscle cells, cardiac myocytes and fibroblasts, and accumulation of connective tissue. The active moiety of the system controlling coronary vasomotion is angiotensin II. Angiotensin II is liberated by the carboxypeptidase angiotensin converting enzyme (ACE) from the peptide angiotensin I. Angiotensin I is cleaved from the protein angiotensinogen by the proteinase renin. Infusion of angiotensin I to isolated heart preparations results in coronary vasoconstriction, indicated by a dose dependent reduction of coronary blood flow.²⁰⁻²² Angiotensin II exerts a direct coronary vasoconstrictor effect in humans.²³⁻²⁴ This proves the existence of ACE and angiotensin II receptors in the coronary vascular system. The relation of blood flow reduction by angiotensin I to blood flow reduction by angiotensin II may be used to calculate the conversion of angiotensin I to angiotensin II, which has been found to be 10-100% in different models under various conditions.²⁰⁻²² Immunohistology and in vitro hybridisation studies suggest that in the heart ACE is present in the endocardium, epicardial coronary vessels, and in the myocardium.²⁵⁻²⁶ Conversion of angiotensin I to angiotensin II is regulated under pathophysiological conditions.

Effects of inhibitors of the renin-angiotensin system on coronary vessels
ACE inhibitors and angiotensin II receptor antagonists have no effect on coronary blood flow in preparations without activation of the renin-angiotensin system²⁷⁻²⁸ and in patients without heart disease. However, in the latter, the ACE inhibitor teprotide dramatically increased coronary blood flow in three patients with high plasma renin, suggesting a renin dependent coronary effect of teprotide. This effect was also reflected by a good correlation between plasma renin activity and changes of coronary flow after teprotide.²⁹ These data suggest that under normal physiological conditions, angiotensin II does not control coronary blood flow. In contrast, studies which focused on vasomotion of large coronary vessels found vasodilator effects of ACE inhibitors in dogs.³⁰ In anaesthetised dogs, an angiotensin II type 1

(AT₁) receptor antagonist (losartan) induced greater coronary vasodilatation than an ACE inhibitor (enalaprilat), and substantially augmented coronary blood flow.³¹ In rats, sodium depleted dogs, patients pretreated with the diuretic frusemide, and patients with renovascular hypertension which resulted in activation of the renin-angiotensin system, coronary blood flow increased following treatment with converting enzyme inhibitor or angiotensin II receptor antagonist proportionally to pretreatment plasma renin activity.²⁷⁻²⁸⁻³²⁻³³

Pathological conditions

HYPOXIA
Perfusion of the isolated rat heart with hypoxic buffer resulted in an increase in coronary flow and reduced the effect of both angiotensin I and angiotensin II on coronary blood flow.²² However, during hypoxia, the effect of angiotensin I was almost identical to that of angiotensin II, and the conversion calculated by ED50 was approximately 100% (table). Reoxygenation restored the effects of angiotensin I and angiotensin II to control levels, suggesting a reversible rearrangement of the angiotensin II receptor or its second messengers, release of an antagonist to angiotensin II, or upregulation of converting enzyme activity, respectively. In other studies, captopril, enalapril, and ramiprilat increased coronary flow during hypoxia in isolated rat hearts and prevented a fall of coronary flow, which occurred after 15 minutes of hypoxia.³⁴ The ACE inhibitor teprotide increased myocardial blood flow in intact hypoxic dogs,²⁸ suggesting potential control of coronary blood flow by angiotensin II under these conditions.

ISCHAEMIA
In the isolated rat heart, the effect of angiotensin II on coronary vessels was unaffected by ischaemia, while the effect of angiotensin I was enhanced. These data indicate that conversion of angiotensin I was increased to more than 80% in the ischaemic isolated heart from approximately 10% in the control.²² During one hour of perfusion, ACE inhibitors increased coronary flow.³⁵ The angiotensin II receptor blocker saralasin had no effect on coronary blood flow in the ischaemic isolated heart, arguing against a potential role of locally released angiotensin II on coronary vascular tone.²² When angiotensin I was infused into isolated hearts to reduce coronary flow, this flow reduction could be prevented by captopril.³⁶

In dogs with coronary blood flow controlled by a coronary cannula, the vasoconstrictor effect of angiotensin I and angiotensin II was attenuated by a reduction of coronary perfusion pressure, which induced ischaemia.³⁷ However, in other models of myocardial ischaemia, an activation of the renin-angiotensin system has been shown.³⁷⁻⁴² In intact models, increased availability of angiotensin II at the receptor is likely and may be responsible for an attenuated response to exogenous angiotensin II by the coronary vascular sys-

Comparison of angiotensin I/II (ANG I, II) effects in controls, during hypoxia and ischaemia. All the values are expressed as means (SEM)

	ED ₅₀ ANG I (pmol)	ED ₅₀ ANG II (pmol)	ED ₅₀ ANG I/ ED ₅₀ ANG II	Conversion of ANG I (%)†
Control (n = 6)	176.5 (26.8)	16.0 (4.6)*	16.4 (5.6)	10.9 (4.2)
Hypoxia (n = 7)	62.4 (15.6)	57.8 (12.6)	2.0 (0.7) ^b	101.0 (37.4) ^b
Ischaemia (n = 8)	99.8 (27.4)	53.8 (19.9)	2.4 (0.6) ^b	86.0 (27.3) ^b

†Conversion of ANG I (%) = (ED₅₀ANG II / ED₅₀ANG I) × 100.
*P > 0.05 v ED₅₀ANG I; ^bP < 0.05 v control (Tian R, et al, 1991²²).

tem. An effect of inhibitors of the renin-angiotensin system on coronary blood flow can also be shown in these models.

Several studies employing the use of ACE inhibitors have suggested a role for angiotensin II in blood flow regulation during ischaemia. In anaesthetised dogs, plasma renin activity and angiotensin II concentrations were increased above control as early as 30 seconds after coronary occlusion.³⁷ When coronary occlusion was released, characteristic reactive hyperaemia occurred with flow repayment and lactate production.³⁷ When the animals were pretreated with the ACE inhibitor captopril or the angiotensin II receptor antagonist saralasin, coronary flow repayment and lactate production were significantly reduced, supporting a potential role for angiotensin II in blood flow regulation during ischaemia. When coronary occlusion was maintained for 15 to 30 minutes, the increase in plasma renin activity persisted.³⁹⁻⁴¹ Both the ACE inhibitor captopril and the angiotensin II receptor antagonist saralasin significantly increased myocardial blood flow to regions surrounding the ischaemic zone, but not in the centre of ischaemia, and had no effect in sham operated animals without coronary occlusion. In the same model, six hours after coronary occlusion plasma renin activity was still increased, and both the ACE inhibitor and the angiotensin II antagonist increased coronary blood flow over control and reduced systemic vascular resistance and left atrial pressure.⁴² In animals in which nephrectomy was performed three hours before coronary occlusion, captopril had no effect on perfusion of viable myocardium and reduced perfusion of the centre ischaemic zone.³⁹ Unloading of the heart, while improving coronary blood flow, was probably responsible for a reduction of myocardial infarct size in this model. In an isolated heart model of coronary occlusion (for

20 minutes) and reperfusion, pretreatment with the ACE inhibitor ramiprilat or the angiotensin II receptor antagonist losartan resulted in substantial improvement of coronary blood flow in the reperfusion phase.⁴³⁻⁴⁵ In the most recent studies, ACE inhibitors showed some survival benefit in patients with acute myocardial infarction.⁴⁶⁻⁴⁷ In patients with acute myocardial infarction, plasma renin activity and angiotensin II may increase.⁴⁸⁻⁴⁹ The effect of inhibitors of the renin-angiotensin system on coronary circulation of patients with acute infarcts is unknown.

In a model with graded reduction and control of coronary blood flow by a coronary cannula in the left anterior descending coronary artery of anaesthetised dogs, pacing to increase heart rates induced myocardial ischaemia, as indicated by a reduction of regional myocardial function and an increase in plasma renin activity.³⁷⁻⁴⁰ Pacing in animals without critical reduction of coronary blood flow did not result in an increase in plasma renin activity.⁴⁰

Saralasin and captopril increased coronary conductance when coronary perfusion pressure was lowered to 36 mm Hg, but had no effect on normal coronary perfusion (fig 2). When pacing was repeated during infusion of an ACE inhibitor or an angiotensin II antagonist, respectively, coronary blood flow and regional myocardial function were preserved.³⁷ In studies where coronary perfusion pressure was not maintained constant, ACE inhibitors tended to reduce coronary flow along with a reduction of loading and arterial pressure.⁵⁰⁻⁵¹ In patients with hypertension and angina, the ACE inhibitor captopril reduced the rate-pressure product and had no effect on coronary vascular resistance.⁵² Changes of coronary flow were proportional to the decrease in rate-pressure product, blood pressure, and myocardial oxygen consumption.⁵² Intravenous captopril tended to increase coronary blood flow and to decrease coronary vascular resistance in patients with stable angina pectoris.⁵³ In patients with dilated cardiomyopathy, the ACE inhibitor enalaprilat increased coronary blood flow when the drug was given directly into the coronary circulation. Intravenous enalaprilat or oral captopril reduced the rate-pressure product in patients with heart failure and coronary arteriovenous oxygen extraction, suggesting a relative increase in coronary blood flow.²⁹⁻⁵⁴⁻⁵⁵ However, ACE inhibition did not generally alleviate symptoms in patients with angina pectoris, suggesting that its potential effect on coronary blood flow and myocardial oxygen consumption did not translate into an antianginal efficacy.⁵⁶

Global coronary blood flow to isolated rat hearts is unaltered in the chronic phase post-myocardial infarction,⁵⁷⁻⁵⁸ and the effect of angiotensin I and angiotensin II is unchanged.⁵⁷ In patients with chronic coronary heart disease and ischaemic response in thallium-201 scintigraphy, plasma renin activity and ACE activity increased during bicycle exercise stress testing.⁵⁹ In these patients, infusion of saralasin or oral cilazapril or captopril resulted in redistribution of thallium-201 or

Figure 2 The effect of saralasin (0.1 µg/kg per min, intracoronary) and captopril (0.25 mg/kg intravenous) on coronary conductance at low coronary perfusion pressure during sinus rhythm and atrial pacing. Both saralasin (SAL) and captopril (CAPT) increased coronary conductance during sinus rhythm and atrial pacing. Atrial pacing reduced coronary conductance at low coronary perfusion pressure (Ertl G, 1987³⁷). *P < 0.01 v sinus rhythm (n = 6).

Figure 3 Coronary flow of untreated and quinapril treated sham and myocardial infarction (MI) hearts during the protocol of control (0–15 min), hypoxia (15–45 min), and reoxygenation (45–75 min) periods.⁵⁸ * $P < 0.05$, sham v MI; $\circ P < 0.05$, sham v sham and quinapril; + $P < 0.05$, MI v MI and quinapril. (Horn M, et al, 1996.⁵⁸)

Tc99mMIBI to the cold spot in the scintigram.^{59–60} Thus, taken together, these results suggest that angiotensin II may control coronary blood flow under certain circumstances and in various models with myocardial ischaemia.

Potential of the renin-angiotensin system for chronic modulation of coronary vasomotion

Angiotensin II stimulates growth of cardiac myocytes, fibroblasts, and vascular smooth muscle cells.⁶¹ Functional and morphological changes of endothelial cells, hypertrophy of smooth muscle cells, and accumulation of perivascular fibrosis may interfere with coronary vasomotion. In fact, coronary flow reserve is impaired in various models of cardiac hypertrophy. Quantitative morphological changes occur in the capillary/muscle relation in human hearts during normal growth, with a reduction of capillary density.⁶² Various types of hypertrophy result in a further reduction of the concentration of capillaries or arterioles.^{62–66} Coronary vasodilator reserve is restricted in models of cardiac hypertrophy, such as rats and dogs with renovascular hypertension,^{64–67} rats with aortic banding^{68–72} or valvular aortic stenosis,⁷³ and in patients with essential arterial hypertension.⁷⁴ Restriction of coronary flow or exhaustion of coronary flow reserve has also been observed in animals and humans with hypertrophy after myocardial infarction^{58–75–77} and in heart failure.^{78–82} In addition, it has been suggested that subendocardial ischaemia perpetuates myocardial failure in patients with non-ischaemic congestive cardiomyopathy.^{79–80–83} It is remarkable in this context that a shift of lactate dehydrogenase enzymes towards the anaerobic lactate metabolism indicates chronic hypoxia in patients with dilated cardiomyopathy⁸⁴ and in models of cardiac failure.^{85–86} Perivascular fibrosis may have

a major impact on restriction of blood flow in chronic hypertrophy and cardiac failure. Prevention of collagen deposition by β aminopropionitrile normalised vasodilator reserve in rats with ascending aortic banding.⁶⁸ In dogs with aortic banding and chronic heart failure due to arteriovenous shunt, increased fibrosis in the endocardial layers was associated with an exhausted endocardial blood flow reserve.⁷⁸ In addition, coronary reserve seems to be determined by medial hypertrophy in rats with aortic banding.⁶⁸

How might the renin-angiotensin system be involved in these processes, and thus chronically alter coronary vasomotion? The AT₁ receptors mediate both vasoconstrictor and hypertrophic responses in smooth muscle cells.⁸⁷ In addition, fibroblasts express AT₁ receptors, which control fibroblast growth.^{88–89} Thus, angiotensin II may control both medial hypertrophy and collagen deposition in the heart.

Inhibitors of the renin-angiotensin system, both at the converting enzyme and at the receptor level, reduce vascular media hypertrophy⁹⁰ and may prevent neointima formation in certain models of coronary injury.^{91–94} The MERCATOR trial, however, failed to show a preventative effect of the ACE inhibitor cilazapril on restenosis after percutaneous transluminal coronary angioplasty.⁹⁵

Inhibitors of the renin-angiotensin-aldosterone system reduce fibrosis in various models of hypertrophy, including hypertension and hypertrophy of surviving myocardium after myocardial infarction.^{96–97} The response to angiotensin I and angiotensin II was unaffected in these hearts.⁵⁷ Chronic treatment with the ACE inhibitor quinapril increased coronary flow in both sham operated and infarcted hearts (fig 3).⁵⁸ It also completely restored the hyperaemic response to hypoxia, which is severely depressed in the heart after myocardial infarction.⁵⁸ However, as stated

Figure 4 Original recording of a protocol using neurotensin ($1.0 \mu\text{g/kg}$ intracoronary [ic]) before and after the angiotensin converting enzyme inhibitor captopril (0.25 mg/kg intracoronary). Left ventricular diastolic pressure (LVDP) and subendocardial segment length (SL) were unchanged by neurotensin, whereas aortic pressure decreased. Coronary perfusion pressure (P_{cor} mean) was held constant by design. After captopril, neurotensin increased coronary blood flow (CBF), whereas only minor changes in CBF were noted before captopril (Bauer B, et al, 1995⁹⁹).

above, the effect of ACE inhibitors is non-specific and does not provide a role for angiotensin II in these processes. Studies using specific AT_1 receptor antagonists are needed to identify a potential role for angiotensin II in the chronic modification of coronary vasomotion.

Interaction of the renin-angiotensin system with other mediators controlling coronary vasomotion

The renin-angiotensin system is related to other vasoactive mediators at different levels of the renin-angiotensin cascade. Best known is the pluripotentiality of ACE, a carboxypeptidase which degrades a number of vasoactive peptides. Most studies have focused on the bradykinin degradation, but hydrolysis of the neuropeptides substance P and neurotensin has been shown *in vitro*.⁹⁸ Inhibition of ACE potentiates the effect of neurotensin on coronary circulation in dogs (fig 4).⁹⁹ It has been shown that the ACE inhibitor captopril also reversed the long term "tonic" vasoconstrictor effects of endothelin-1 on coronary circulation in dogs.⁹⁹ ACE inhibitors attenuated the maximum coronary vasoconstrictor response to the highest doses of endothelin-1 in isolated perfused rat heart, but did not shift the dose-response curve of endothelin-1.¹⁰⁰ However, angiotensin II also directly interacts with the sympathetic nervous system.¹⁰¹ Pressure response to sympathetic stimulation and noradrenaline infusion is amplified by angiotensin

II and reduced by ACE inhibition. In isolated rabbit hearts, reduction of coronary blood flow induced by stellate ganglion stimulation was attenuated by ACE inhibition.¹⁰² ACE inhibition attenuates sympathetic coronary vasoconstriction in patients with coronary artery disease,¹⁰² suggesting a potentiating role for angiotensin II on sympathetic influence of coronary circulation. These observations may be of clinical relevance, since inhibitors of the renin-angiotensin system may exert their long term beneficial effects on survival and may reduce the incidence of myocardial infarction or ischaemic complications in part by their interference with the sympathetic nervous system.

The ACE inhibitors captopril and enalaprilat enhanced coronary blood flow in pigs subjected to 30 minutes of left anterior descending coronary artery occlusion followed by one hour of reperfusion. In addition, investigators preserved endothelium dependent microvascular relaxation, tested by adenosine diphosphate (ADP) and the calcium ionophore A23187, during reperfusion.¹⁰⁴

Atrial natriuretic factor (ANF) acts as a vasodilator in most preparations including studies in the human. However, the effect on the coronary circulation depends on the pre-existing ANF plasma concentrations and the activities of the renin-angiotensin system.¹⁰⁵ The ACE inhibitor captopril and the angiotensin II receptor antagonist saralasin, infused directly into the coronary artery of anaesthetised dogs, abolished the vasodilator effect of ANF.¹⁰⁵ In isolated rat hearts, infusion of angiotensin II potentiated the coronary vasodilator effect of ANF, while the ACE inhibitor captopril and the angiotensin II receptor antagonist saralasin abolished the coronary vasodilator effect of ANF (fig 5).¹⁰⁶ Thus the renin-angiotensin system may influence coronary vasomotion by interactions with various other mediator systems, including the sympathetic nervous system, endothelium dependent mechanisms, and ANF. However, we are far from understanding the quantitative importance of these mechanisms or their clinical relevance at this time.

Conclusion

The physiological significance of angiotensin II on coronary vasomotion is unclear. Most studies have shown that in individuals without an activation of the renin-angiotensin system, a vasoconstrictor tone of angiotensin II does not exist on the coronary vascular system. When the renin-angiotensin system is activated by dietary sodium deprivation, diuretics, Goldblatt mechanism, heart failure, or myocardial ischaemia, angiotensin II gains control over coronary blood flow. Beneficial effects of inhibitors of the renin-angiotensin system in numerous models suggest a pathophysiological role of angiotensin II under these conditions. Recent studies showing a preventative effect of ACE inhibitors on acute coronary syndromes may support this hypothesis. Additionally, angiotensin II may influence

Figure 5 Maximum coronary flow increase (CF+) and decrease (CF-) after 40 nmol atrial natriuretic factor (ANF) bolus administration in control group (Co) and groups receiving pretreatment: angiotensin II (ANG II), captopril (Cap), saralasin (Sar), ANP infusion (ANP_i), or ANP bolus (ANP_b). Variations are related to values—after stabilisation for the control group—in the new steady state for groups receiving pharmacological pretreatment. * $P < 0.05$ v control group (Bauer WR, et al, 1994^[10]).

coronary vasomotion by its chronic effects on cardiac and coronary morphology. Coronary arterial medial hypertrophy, intima hyperplasia in coronary lesions, and perivascular fibrosis may influence coronary vasomotion in cardiac hypertrophy, coronary heart disease, and heart failure. The clinical relevance of these observations remains unknown.

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