Effects of Calcitonin Gene–Related Peptide on Normal and Atheromatous Vessels and on Resistance Vessels in the Coronary Circulation in Humans

Peter F. Ludman, MA, MRCP; Attilio Maseri, FRCP; Peter Clark, MSc; and Graham J. Davies, MD

Background. Calcitonin gene–related peptide (CGRP) is a potent dilator of normal epicardial coronary vessels in humans, but its effects on myocardial blood flow and atheromatous coronary vessel diameter are unknown.

Methods and Results. Seven patients were entered for study of the effects of CGRP on coronary blood flow and 13 for the comparison of its effects on normal and atheromatous coronary arteries. In the first seven patients, left anterior descending artery (LAD) diameter at an angiographically normal site, coronary sinus oxygen saturation (CSo2S), systemic blood pressure, and heart rate were measured during intracoronary infusion of increasing concentrations of CGRP (up to 200 ng/ml at 2 ml/min) followed by intracoronary adenosine (0.267 μg/ml at 2 ml/min) and finally intracoronary glyceryl trinitrate (GTN) (5 μg/ml at 2 ml/min). CGRP dilated the normal segment of the LAD by 22.6±8% (mean±95% confidence interval), \( p < 0.001 \), with only a small increase in CSo2S from 40.1±2.7% to 47.3±2.7%, \( p < 0.001 \). Adenosine, a potent dilator of myocardial resistance vessels, caused no further increase in LAD diameter but caused a rise in CSo2S from 47.3±2.7% to 76.0±2.7%, \( p < 0.001 \). GTN caused no further increase in LAD diameter. As heart rate–blood pressure product remained unchanged throughout the study, the increase of CSo2S indicated only a small increase in myocardial blood flow after CGRP infusion. In 13 patients with atheromatous coronary artery disease, the effects of intracoronary CGRP at angiographically normal sites, stenoses, angiographically normal sites immediately adjacent to stenoses, and sites of coronary artery wall irregularity were compared after intracoronary infusion of a single dose of CGRP (200 ng/ml at 2 ml/min) followed by intracoronary GTN (5 μg/ml at 2 ml/min). At these four sites, CGRP resulted in dilatation by 17.0±5.6%, 15.3±12.1% (NS), 7.6±5.4% (NS), and 15.9±7.8%, respectively. There was no significant further dilatation after GTN at any of the four sites.

Conclusions. These data indicate that CGRP has little effect in humans at rest on coronary resistance vessels in nonischemic myocardium but causes marked dilatation of normal arteries and variable dilatation of atheromatous epicardial arteries. (Circulation 1991;84:1993–2000)
nisms, we investigated the effect of CGRP on the coronary circulation in humans. The effect of CGRP on myocardial resistance vessels was assessed by measuring its effect on an index of coronary blood flow. In patients with atheromatous coronary disease, we also assessed the effect of CGRP on vessel diameter, both at angiographically normal epicardial coronary segments and at sites of atheroma (both at coronary artery stenoses and sites of wall irregularity).

Methods

Patients

Sixteen patients referred for routine coronary arteriography for the investigation of chest pain were investigated (aged 41–70; mean, 57.6 years; 15 men and one woman). Drug therapy of any form had been discontinued for at least 24 hours before the studies. Seven patients, of whom three had normal coronary arteries, were entered for evaluation of coronary blood flow (Table 1, patients 1–7, protocol A). Thirteen patients, all with atheromatous coronary disease, were entered for study of CGRP on atheromatous coronary arteries; three from protocol A and the rest from protocol B (Table 1, patients 3, 4, 5, and 7–16).

Protocol A

Diagnostic coronary arteriography was performed with Omnipaque 350 contrast medium using the Judkins technique via the right femoral artery. To measure the oxygen saturation of hemoglobin draining from the myocardial territory of the left anterior descending artery, the coronary sinus was intubated with a 4F fiberoptic catheter (via the left subclavian vein) that was advanced to the origin of the great cardiac vein. The catheter was connected to an oximeter (Hemoreflexometer-Schwarzer IVH, 4 Picker International) to monitor oxygen saturation continuously. With a 7F Judkins catheter engaged in the origin of the left coronary artery, a suitable radiographic projection was selected to obtain clearly defined arteriograms of the left anterior descending artery. From this point, the high-resolution 12.7-cm image intensifier (Optimus M200 Phillips) was not moved. A control infusion of vehicle solution

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Exercise induced</th>
<th>At rest</th>
<th>Exercise ECG result</th>
<th>Angiogram</th>
<th>Site of normal segment analyzed (protocol A)</th>
<th>Site of normal segment analyzed (protocol B)</th>
<th>Site of lesion analyzed</th>
<th>Site of irregularity analyzed</th>
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<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Normal</td>
<td>Mid LAD</td>
<td>Mid LAD</td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>+</td>
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<td>Normal</td>
<td>Mid LAD</td>
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<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>+</td>
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<tr>
<td>4</td>
<td>41</td>
<td>M</td>
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<td>+</td>
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<tr>
<td>5</td>
<td>56</td>
<td>M</td>
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<tr>
<td>6</td>
<td>61</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Normal</td>
<td>Mid LAD</td>
<td>Mid LAD</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>Recent leg fracture</td>
<td>Occ RCA</td>
<td>Mid LAD</td>
<td>Mid LAD</td>
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<tr>
<td>8</td>
<td>70</td>
<td>M</td>
<td>+</td>
<td>+</td>
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<td>Mid LAD</td>
<td>Mid LAD</td>
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<tr>
<td>9</td>
<td>65</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<tr>
<td>10</td>
<td>70</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>RBBB</td>
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<td>Mid LAD</td>
<td>Mid LAD</td>
<td>Mid LAD</td>
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<td>+</td>
<td>–</td>
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<tr>
<td>12</td>
<td>53</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>RBBB</td>
<td>OM 2 patent</td>
<td>OM 1</td>
<td>Mid LAD</td>
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<td></td>
</tr>
<tr>
<td>13</td>
<td>66</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>RBBB</td>
<td>Prox LAD st</td>
<td>Mid LAD</td>
<td>Mid LAD</td>
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<tr>
<td>14</td>
<td>65</td>
<td>M</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Mid LAD st</td>
<td>Mid LAD</td>
<td>Mid LAD</td>
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<tr>
<td>15</td>
<td>57</td>
<td>M</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Mid LAD st</td>
<td>Mid LAD</td>
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<tr>
<td>16</td>
<td>52</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Mid LAD st</td>
<td>Mid LAD</td>
<td>Mid LAD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cx, circumflex artery; dist, distal; ECG, electrocardiogram; F, female; G, graft; IMA, internal mammary artery; LAD, left anterior descending; M, male; mid, middle; N, native vessels; occ, occluded; OM, obtuse marginal artery; PDA, posterior descending artery; prox, proximal; RBBB, right bundle branch block; RCA, right coronary artery; st, stenosis.
(Haemacel-Hoechst, London) was given into the left coronary artery followed by incremental doses of CGRP of 25, 50, 100, and 200 ng/ml, followed by adenosine 0.267 µg/ml (10⁻⁶ M), followed by glyceryl trinitrate (GTN) 5 µg/ml. All infusions were at a rate of 2 ml/min for periods of 5 minutes each. At the end of each infusion period, coronary arteriography was repeated. An interval of 3 minutes was left between the completion of the adenosine infusion and the start of the final infusion of GTN. Three electrocardiographic leads, systemic blood pressure (right iliac artery), and coronary sinus oxygen saturation were monitored continuously throughout the procedure and recorded on analog electromagnetic tape (Store 14DS, Racal Recorders Ltd.).

**Protocol B**

Diagnostic coronary arteriography was performed as above. With a 7F Judkins catheter engaged in the origin of the left coronary artery, a suitable radiographic projection was selected to obtain clearly defined arteriograms of the selected epicardial coronary stenosis, an angiographically normal segment, and, if possible, a segment with vessel wall irregularity. After a baseline arteriogram, CGRP was infused at a dose of 200 ng/ml for 7 minutes followed by GTN 5 µg/ml for 5 minutes. Both infusions were at a rate of 2 ml/min, and arteriography was repeated after each infusion period. Three electrocardiographic leads and systemic blood pressure (right iliac artery) were monitored continuously throughout the procedure.

**Data Analysis**

**Vessel caliber.** It has been shown that the effects of repeated injections of radiographic contrast are transient and do not alter epicardial vessel diameter.⁵ Quantitative analysis of the epicardial vessel diameter was performed with an automated edge contour detection computer analysis system (CAAS, Pie Data Medical). The system was calibrated using the stem of the Judkins coronary catheter, and correction was made for radiographic pincushion distortion.

To assess interobserver and intraobserver variability by using this method of vessel diameter analysis, 24 coronary artery segments were measured by three independent observers. The segments were selected so that there were three groups of eight segments with approximate vessel diameters of 1, 2, and 3 mm, respectively. Differences between observers were examined by analysis of variance using the statistical software package MINITAB.¹⁰ The repeatability of the measurements was quantified by calculating the difference of each vessel measurement from the average of the measurements of that vessel. There were no statistically significant differences between observers 1 to 3 (F=0.29, df=2,69, p=0.75). When the differences of the three observers from their mean were calculated, all except one measurement, or 98.6%, were found to be less than or equal to 0.1 mm in magnitude.

For protocol A, a segment of normal middle left anterior descending artery, well separated from any angiographically abnormal segment of this vessel, was analyzed between branch points from end-dias-tolic frames, and results were presented as percentage changes in mean vessel diameter from control arteriogram. For the second part of the study, only patients with atheromatous coronary disease were selected for analysis. Segments analyzed were those that were clearly seen on the coronary arteriogram, with no overlapping vessels and good contrast opacification at end diastole. Three patients were selected from protocol A (using basal, maximum CGRP dose, and post-GTN arteriograms) and all from protocol B (patients 3–5 and 7–16). Thirteen normal segments, well separated from any angiographically abnormal vessel, were analyzed as above and results presented as percentage changes in mean vessel diameter from control arteriogram. Nine stenotic segments (patients 3, 4, 8–12, 14, and 15) were similarly analyzed but for each stenotic segment, two parameters were measured: 1) the minimum vessel diameter, and 2) the diameter of the angiographically normal vessel immediately adjacent to the stenosis. Results are presented as percentage change in diameter from control arteriogram. Six segments of coronary arteries with wall irregularity but no localized stenosis (patients 5, 10, 11, and 14–16) were also analyzed, and results are presented as percentage change in mean vessel diameter from control arteriogram.

**Index of left anterior descending artery blood flow.** If we make the following assumptions, 1) the great cardiac vein collects the majority of blood draining the left anterior descending coronary artery territory, 2) the predominant determinant of myocardial oxygen consumption is the heart rate–blood pressure product, 3) there was no significant endocardial to epicardial redistribution of blood flow during the study, and 4) CGRP causes no significant change in myocardial contractility in humans, as demonstrated by other workers,¹¹ then we can assume that changes in great cardiac vein saturation reflect changes in myocardial blood flow.

From the indirect Fick principle

\[
\text{Coronary blood flow} = \frac{\text{myocardial oxygen demand (MVO}_2\text{)}}{\text{arteriovenous oxygen content difference (A–V)}\text{O}_2}
\]

**Statistics**

The vessel caliber data were analyzed by analysis of variance using linear models by using a generalized linear interactive models (GLIM) program.* The drugs used (CGRP, adenosine, and GTN), and the segment groupings (normal, stenosis, adjacent to stenosis, and irregular) were specified as within-

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subject factors. Comparisons of means between groups of coronary segment types or between drugs were made by contrasts, and the Bonferroni method was used to adjust for multiple comparisons. The hemodynamic data were analyzed using paired t tests with Bonferroni adjustments on the change from baseline until after maximum CGRP infusion. A probability value of less than 0.05 after adjustment was regarded as significant. The results are presented as mean (or difference between means) ±95% confidence interval both in the text and in the figures.

The project was carried out with the approval of the Research Ethics Committee of the Hammersmith Hospital. All patients gave written consent to participation, and patients 1-7 were aware that the insertion of a subclavian cannula was required solely for the purpose of research.

Results

The procedure was well tolerated by all patients. One patient experienced the symptom of flushing toward the end of maximum CGRP dose. There were no other side effects. At the maximum dose of CGRP infusion, some patients showed hemodynamic evidence of the systemic vasodilatation with a small reduction in pulse pressure and a small increase in heart rate. The grouped hemodynamic data from both protocols are presented in Table 2. The only significant change occurred during protocol A, where a fall in systolic blood pressure of 6±4 mm Hg was observed after infusion of the maximum dose of CGRP. In protocol A, vehicle solution was infused at the start of the study, and there was no significant change in vessel diameter, coronary venous oxygen saturation, or hemodynamic parameters after this infusion.

Epicardial Coronary Diameter and Coronary Venous Oxygen Saturation

Protocol A. The effects of intracoronary infusion of incremental doses of CGRP, followed by adenosine, followed by GTN in patients 1-7 are presented in Figure 1. In all seven patients, there was an increase in epicardial vessel diameter at an angiographically normal middle left anterior descending site with CGRP infusion. The mean percentage increase in diameter from control infusion to maximum dose of CGRP (200 ng/ml) was 22.6±8% (mean±95% confidence interval, p<0.001). During this period, the oxygen saturation of blood draining this territory showed a small increase from 40.1±2.7% to 47.3±2.7%, p<0.001. There was no significant change in the product of heart rate and systolic blood pressure (an index of myocardial work) from 9.1±2.8 beats/min/1,000×mm Hg to 10.1±3.0 beats/min/1,000×mm Hg.

Table 2. Summary of Changes in Systemic Blood Pressure and Heart Rate After Infusion of Intracoronary Calcitonin Gene-Related Peptide

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Baseline</th>
<th>After CGRP</th>
<th>Mean change</th>
<th>95% CI for change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol A</td>
<td>Systolic (mm Hg)</td>
<td>131</td>
<td>125</td>
<td>-6</td>
<td>-10 to -2</td>
</tr>
<tr>
<td></td>
<td>Diastolic (mm Hg)</td>
<td>74</td>
<td>74</td>
<td>0</td>
<td>-6 to +7</td>
</tr>
<tr>
<td></td>
<td>Heart rate (beats/min)</td>
<td>69</td>
<td>83</td>
<td>+13</td>
<td>-0.5 to +27</td>
</tr>
<tr>
<td>Protocol B</td>
<td>Systolic (mm Hg)</td>
<td>141</td>
<td>137</td>
<td>-4</td>
<td>-13 to +5</td>
</tr>
<tr>
<td></td>
<td>Diastolic (mm Hg)</td>
<td>66</td>
<td>65</td>
<td>-1</td>
<td>-3 to +2</td>
</tr>
<tr>
<td></td>
<td>Heart rate (beats/min)</td>
<td>70</td>
<td>70</td>
<td>0</td>
<td>-4 to +4</td>
</tr>
</tbody>
</table>

CGRP, calcitonin gene-related peptide; CI, confidence interval.

After infusion of adenosine, all patients responded with a marked rise in coronary sinus oxygen saturation from 47.3±2.7% to 76.0±2.7%, p<0.001, with no significant change in heart rate-systolic pressure product (from 10.1±3.0 beats/min/1,000×mm Hg to 9.8±2.9 beats/min/1,000×mm Hg) and no further significant change in epicardial vessel diameter.

After the final infusion of GTN, the mean coronary sinus oxygen saturation fell back toward the control level, to 51.1±2.7%, and the left anterior descending vessel diameter remained dilated. There was no significant difference in either the coronary sinus saturation or the vessel diameter between maximum CGRP dose and GTN infusion. During the entire infusion period, there was no significant change in heart rate-systolic pressure product.

Effect of CGRP on Angiographically Normal and Atheromatous Segments

The effects of intracoronary infusion of CGRP followed by GTN in patients all with coronary artery disease are presented in Figure 2. Four categories of epicardial vessel region were analyzed: 1) normal segments well separated from any angiographically abnormal segment (patients 3-5 and 7-16), 2) minimum vessel diameter at a stenosis, 3) diameter of angiographically normal vessel immediately adjacent to the stenosis (patients 3, 4, 8-12, 14, and 15), and 4) regions of coronary arterial wall irregularity (patients 5, 10, 11, and 14-16). At all sites, there was no significant difference in degree of dilatation afforded by CGRP compared with additional GTN.

At the normal sites, there was a significant epicardial vessel dilatation of 17.0±5.6% after CGRP and 19.8±5.6% after additional GTN. The mean baseline
stenotic diameter compared with adjacent normal segment was 55.3±9.1%. At epicardial stenoses, the effects of both CGRP and GTN were more variable, infusions resulting in dilatation of minimal vessel diameter by 15.3±12.1% (p=0.015) and 11.0±12.1% (p=0.074), respectively. With the Bonferroni adjustment for eight comparisons, both values fail to reach significance at the 5% level (where probability should be less than 0.0063). Sites adjacent to stenoses that appeared angiographically normal were the least responsive regions analyzed, CGRP resulting in dilatation of 7.6±5.4% (p=0.007, just failing to reach significance at the 5% level) and GTN 8.4±5.4% (p=0.0031, significant). At sites of angiographically demonstrated vessel wall irregularity, there was a significant increase in vessel diameter of 15.9±7.8% after CGRP and 17.5±7.8% after GTN.

There was no significant difference in dilatation afforded by CGRP among each of the four groups of vessel segments measured, and there was no significant additional change in vessel diameter after GTN infusion.

Figures 3 and 4 compare the effects of CGRP alone with the effects of subsequent administration of GTN in individual patients. It can be seen that there is a correlation both at normal and stenotic sites, demonstrating that in individual patients, there is no additional effect after the administration of GTN. Furthermore, there is a correlation between the effects of CGRP at stenoses and at angiographically normal sites, indicating that patients who show
dilatation of normal epicardial vessels in response to CGRP tend to also show dilatation at the site of a stenosis (Figure 5).

Discussion

This study demonstrates that CGRP has little effect in humans at rest on coronary resistance vessels in nonischemic myocardium but causes dilatation of both normal and atheromatous epicardial coronary arteries showing irregularity at angiography, with no further dilatation after additional GTN.

Dilatation of discrete stenoses failed to reach significance in this study, either in response to CGRP or to additional GTN.

Too few patients were studied to allow meaningful randomization of the order in which the agents were administered. CGRP has a relatively long biological half-life of 18 minutes; thus, the observed effects of adenosine and GTN occurred in the presence of circulating CGRP. Nevertheless, the response to adenosine observed in this study was similar to that seen in studies in which adenosine has been used alone; there is therefore no reason to believe that prior administration of CGRP modified the response to adenosine.

Effect of CGRP on Coronary Resistance Vessels

Myocardial work as assessed by heart rate–systolic pressure product remained unchanged throughout the study, and according to the indirect Fick principle, coronary sinus oxygen saturation can therefore be used as an index of myocardial blood flow. The coronary sinus oxygen saturation increased only slightly during CGRP infusion, which contrasts with the large increase observed after adenosine infusion.

Our findings are compatible with a small increase in coronary blood flow in response to CGRP infusion, indicating a small reduction in resistance, and are in line with such measurements in isolated rat hearts in which an increase of about 12% has been observed. However, our results contrast with work by Ezra et al., who measured a 58.8% increase in blood flow in the left anterior descending artery of the anesthetized pig in response to intracoronary infusion of CGRP and so emphasize the interspecies variation in the effects of CGRP on myocardial blood flow.

Differences in response of large and small vessels within one vascular bed have been reported in animal experiments and in humans for both mediators of
dilatation (acetylcholine)\textsuperscript{16} and constriction (neuropeptide Y).\textsuperscript{17}

CRGP appears to have differing effects on other vascular beds in humans. Studies on the human mesenteric vessels in vitro suggest there is a greater vasodilator effect on arterioles than the larger arteries,\textsuperscript{18} and in vivo studies in humans have demonstrated a rise in forearm blood flow in response to CRGP infusion of 174±24\% in one study\textsuperscript{19} and 177±75\% in another,\textsuperscript{12} implying a greater effect on resistance than conducting vessels, though the diameter of the larger forearm vessels was not measured.

Evidence supports both an endothelial dependent and independent mechanism of action for CRGP, with differences between species and, within species, between vessels of differing caliber. Endothelium-dependent mechanisms have been demonstrated in vitro in rat aorta and mesenteric artery preparations\textsuperscript{6,20} and in human radial, coronary, gastric, and cerebral arteries.\textsuperscript{18} Endothelium-independent mechanisms have been demonstrated in bovine circumflex artery,\textsuperscript{21} cat middle cerebral and pial artery, human pial and rabbit pial arteries,\textsuperscript{22} and pig coronary arteries.\textsuperscript{23} In isolated bovine aortic endothelial cells, CRGP has been shown not to be coupled with endothelium-derived relaxing factor (EDRF) release.\textsuperscript{24}

Stimulation of EDRF production by the intracoronary administration of acetylcholine leads to a large increase in coronary flow,\textsuperscript{16} suggesting that either CRGP does not operate via an endothelium-dependent mechanism in human coronary artery or that appropriate receptors are mainly concentrated on the endothelium of epicardial vessels rather than arterioles, which would be supported by recent autoradiographic mapping studies of CRGP receptors by Coupe and coworkers.\textsuperscript{25}

\textbf{Effect of CRGP on Angiographically Normal and Atheromatous Segments}

Dilatation of epicardial vessel irregularity but not discrete stenoses occurred when CRGP was administered with no further change after additional GTN. It is known that endothelium lining the epicardial coronary lumen at the site of atheroma is functionally abnormal or is anatomically deficient,\textsuperscript{26} and the response to CRGP at irregular segments may therefore be explained in several ways: 1) dilatation may be due to direct action on the vascular smooth muscle, 2) it could be dependent on EDRF released from functionally intact endothelium of the vasa vasorum, though we have shown CRGP to have relatively little effect on other small vessels within the myocardium, or 3) the endothelium lining irregular segments, though abnormal, may still be sufficiently functionally intact to respond to CRGP. To support this suggestion, recent observations\textsuperscript{27} with substance P (which causes endothelium-dependent vasodilatation in most species\textsuperscript{28}) have shown that similar vasodilatation occurs at both angiographically normal and angiographically irregular coronary segments.

\textbf{Conclusions}

The pharmacological effect of intracoronary CRGP infusion is similar to that of glyceryl trinitrate,\textsuperscript{29} with a vasodilator action predominant in the larger conducting vessels both at angiographically normal and irregular sites and with little effect on resistance vessels. CRGP may therefore play a role in improving myocardial blood flow in ischemic heart disease.

The potential use of CRGP in the treatment of angina is worthy of further consideration as in vivo studies of forearm blood flow\textsuperscript{12} suggest that tachyphylaxis does not occur.

\textbf{Acknowledgments}

We thank Mr. Andrew Porter, Miss Bonita Chetham, Mr. David Dawson, and all the nursing staff of the Collier Building, Royal Postgraduate Medical School, for their assistance with this project.

\textbf{References}


KEY WORDS: resistance vessels, vasoactive peptide, neuropeptide, endothelium, vasodilatation, coronary blood flow
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P F Ludman, A Maseri, P Clark and G J Davies

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