

Brief Myocardial Ischemia Attenuates Platelet Thrombosis in Remote, Damaged, and Stenotic Carotid Arteries

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Background—Brief antecedent periods of coronary artery occlusion improve subsequent vessel patency in damaged and stenotic coronary arteries via release of adenosine from ischemic/reperfused myocardium and resultant adenosine receptor stimulation. However, the site of receptor stimulation—circulating blood-borne elements (ie, platelets) versus vessel-wall components of the culprit artery—remains unclear. If platelet adenosine receptors are involved, then the benefits of brief coronary occlusion (1) should be manifested systemically and improve patency at a remote site and (2) should be inhibited by an antagonist of adenosine A_2 receptors, whereas, in contrast, (3) brief vascular occlusion not associated with appreciable adenosine release should be ineffective in improving vessel patency.

Methods and Results—In Protocol 1, anesthetized rabbits received 5 minutes of transient coronary occlusion, 5 minutes of transient bilateral carotid occlusion (purported to cause negligible adenosine release from the brain), or no intervention. All rabbits then underwent injury plus stenosis of the left carotid artery, resulting in repeated cyclic variations in carotid blood flow (CFVs). Carotid patency during the initial 2 hours after stenosis (assessed by quantifying the nadir of the CFVs and area of the flow-time profile) was significantly enhanced with antecedent coronary—but not carotid—occlusion versus controls. In Protocol 2, improvement in carotid patency after brief coronary occlusion was corroborated in anesthetized dogs. However, the benefits of brief coronary occlusion were abrogated by the A_2/A_1 antagonist CGS 15943.

Conclusions—Brief antecedent coronary artery occlusion enhanced vessel patency in remote, damaged, and stenotic carotid arteries, largely due to adenosine receptor stimulation on circulating elements. (*Circulation*. 1999;100:843-848.)

Key Words: adenosine ■ platelets ■ thrombosis ■ ischemia ■ cerebrovascular circulation

Recent evidence from our laboratory revealed that the favorable effects of brief “preconditioning” ischemia extend beyond myocyte protection and reduction of infarct size¹; brief antecedent coronary artery occlusion also resulted in better maintenance of subsequent blood flow in damaged and stenotic canine coronary arteries.² Stimulation of adenosine receptors (presumably by adenosine released from the heart during brief ischemia/reflow)^{3–5} was identified as a crucial component of this improved vessel patency.² However, the site of receptor stimulation—ie, adenosine receptors on blood-borne elements (most probably platelets) versus local vessel-wall components (such as vascular smooth muscle of the culprit coronary artery)—was not discerned.

We proposed² that the superior coronary patency seen with brief antecedent coronary occlusion was due to inhibition of platelet aggregation via stimulation of adenosine receptors on circulating platelets.^{6–9} If so, then 3 corollaries should hold true: (1) transient coronary occlusion should provide a systemic benefit and attenuate platelet-mediated thrombosis at a

remote, peripheral site; (2) because A_2 receptors are the subtype present on platelets, administration of an adenosine A_2 receptor antagonist should attenuate this effect; and (3) brief vascular occlusion per se, not associated with substantive adenosine release, should be ineffective in eliciting protection. To test these concepts, we first exploited the fact that in the rabbit, brief carotid artery occlusion causes negligible cerebral ischemia due to the well-developed circle of Willis in this species,^{10–12} and we evaluated the effect of brief antecedent coronary versus carotid artery occlusion on subsequent spontaneous, platelet-mediated thrombosis in damaged and stenotic carotid arteries. We then used the canine model to document, in a second species, the consequences of brief coronary occlusion on the patency of injured and stenotic carotid arteries. Finally, in the canine preparation, we determined whether the benefits of brief coronary artery occlusion on remote, platelet-mediated thrombosis were blocked by administration of the adenosine A_2/A_1 antagonist CGS 15943.

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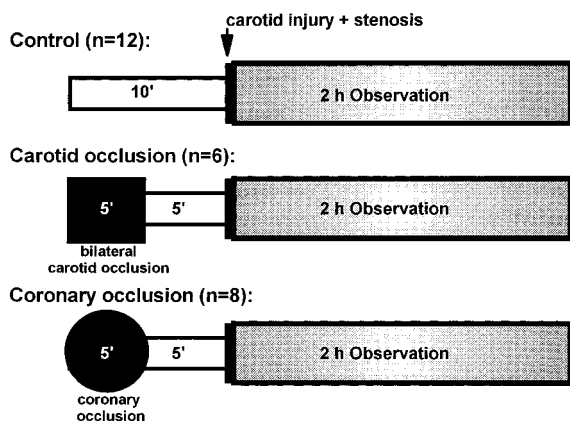
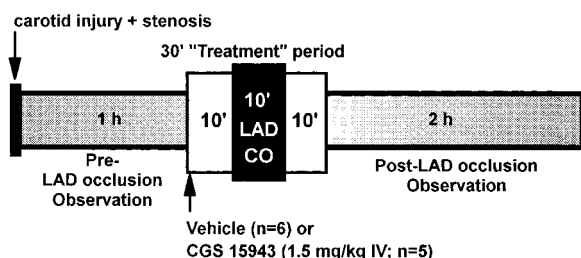
A. Protocol 1: Rabbit Model**B. Protocol 2: Canine Model**

Figure 1. Experimental protocols. CO indicates coronary occlusion.

Methods

These protocols were approved by the Institutional Animal Care and Use Committee of Good Samaritan Hospital and conform with the *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington DC, 1996).

Protocol 1: Rabbit Model**Surgical Preparation**

New Zealand White rabbits (weight 2.2 to 3.2 kg; n=26) were anesthetized with ketamine and xylazine (130 and 30 mg/kg IM) followed by intraperitoneal injections of sodium pentobarbital (≈50 mg/h), intubated, and ventilated with room air. The right femoral artery was cannulated for measurement of heart rate and arterial pressure. Both the left and right common carotid arteries were isolated, and the left carotid was instrumented with a Doppler flow probe. The heart was exposed through a left thoracotomy, and the left circumflex artery (or a large anterolateral branch) was encircled with a snare. Continuous tracings of arterial pressure and mean carotid blood flow were obtained on a chart recorder.

Study Design

After stabilization, each rabbit was assigned to undergo one of the following procedures (Figure 1A): brief coronary occlusion (5 minutes of coronary artery occlusion followed by 5 minutes of reperfusion, accomplished by tightening/releasing the coronary snare; n=8); brief carotid occlusion (5 minutes of bilateral carotid occlusion and 5 minutes of reflow, achieved by applying/removing atraumatic vascular clamps on both carotid arteries and, importantly, purported to cause a negligible deficit in cerebral blood flow^{10–12}; n=6); or a 10-minute control period (n=12).

After the intervention phase, the segment of the left carotid artery located immediately proximal (ie, upstream, toward the heart) to the flow probe was gently compressed with a hemostat to induce endothelial denudation and medial injury, thereby exposing the

highly thrombogenic tunica media and tunica adventitia (confirmed histologically in all rabbits; data not shown). A micromanometer constrictor was then tightened around the site of trauma such that carotid flow was reduced to ≈75% of its baseline value. This, as expected,^{2,13–16} triggered the development of cyclic variations in carotid blood flow (CFVs) caused by repeated spontaneous formation/dislodgement of platelet-rich thrombi at the site of injury plus stenosis. Carotid patency was then monitored without additional intervention for 2 hours after stenosis.

At the end of each experiment, the coronary snare was briefly retightened, and blue pigment was injected into the coronary circulation via the left atrium to confirm the presence of a perfusion defect. All rabbits were killed under deep anesthesia by intracardiac injection of KCl.

Protocol 2: Canine Model**Surgical Preparation**

Mongrel dogs (weight 16 to 23 kg; n=13) were anesthetized with sodium pentobarbital (30 mg/kg IV), intubated, and ventilated with room air. The left jugular vein was cannulated for administration of drugs and fluids, and a long segment of the left carotid artery was isolated and instrumented with a Doppler flow probe. The heart was exposed through a left lateral thoracotomy and suspended in a pericardial cradle. Two adjacent segments of the mid to distal left anterior descending coronary artery (LAD) were then isolated: a second Doppler flow probe was positioned on the distal segment for measurement of LAD flow, whereas the proximal segment served as the site of later LAD occlusion. In addition, a small fluid-filled cannula was positioned in the left ventricular (LV) cavity via the left atrial appendage for continuous monitoring of heart rate and LV pressures. Carotid flow and LV pressures were recorded continuously, whereas coronary flow was monitored before, during, and after LAD occlusion.

Study Design

After stabilization, the segment of the left carotid artery proximal to the carotid flow probe was clamped with hemostats to induce endothelial denudation and medial injury (confirmed histologically in all dogs; data not shown). CFVs were initiated by tightening a micromanometer constrictor around the site of injury such that carotid flow was reduced to ≈15% of baseline. Carotid patency was then monitored for 1 hour after injury plus stenosis (Figure 1B).

After 1 hour of observation, 11 animals were randomly assigned to receive an intravenous bolus of CGS 15943 (Sigma RBI; 1.5 mg/kg suspended in 2 mL of polyethylene glycol and 0.1 mL of 1N NaOH, sonicated until clear, and diluted in saline to a final volume of 20 mL; n=5) or vehicle (n=6). CGS 15943 is a potent adenosine A₂/A₁ antagonist with no intrinsic effect on platelet aggregation per se.^{17,18} Ten minutes later, all 11 dogs underwent 10 minutes of LAD occlusion (achieved by placement of atraumatic vascular clamps) and 10 minutes of reperfusion. Carotid patency was then monitored for an additional 2 hours after this 30-minute "treatment" period (Figure 1B). To document the stability of the preparation, the 2 remaining dogs served as time-matched shams, ie, they received vehicle but did not undergo LAD occlusion. At the end of the protocol, all dogs were killed under deep anesthesia by intracardiac injection of KCl.

End Points

Heart rate and arterial/LV pressure were averaged over 5 cardiac cycles. In each protocol, hemodynamics were tabulated at baseline and at multiple time points throughout the experiments.

In protocol 1 (rabbits), mean carotid blood flow was measured at baseline, immediately on relief of brief carotid/coronary occlusion, before stenosis, and immediately after stenosis (before the onset of CFVs). In Protocol 2 (canine model), mean carotid flow was determined at baseline and immediately after carotid injury plus stenosis (before the onset of CFVs).

Mean LAD flow (protocol 2 only) was tabulated at 1 hour after carotid injury plus stenosis (at the onset of the 30-minute treatment

TABLE 1. Protocol 1 (Rabbit Model): Hemodynamics

	Baseline	After Stenosis	End of 2-h Observation
Control			
Heart rate, bpm	175±6	174±5	158±4*
Mean arterial pressure, mm Hg	70±3	72±3	70±3
Carotid occlusion			
Heart rate, bpm	166±7	161±8	141±8*
Mean arterial pressure, mm Hg	71±6	74±6	75±4
Coronary occlusion			
Heart rate, bpm	176±7	185±9	160±7*
Mean arterial pressure, mm Hg	69±4	61±5	65±4

Carotid occlusion indicates brief antecedent bilateral carotid artery occlusion; Coronary occlusion, brief antecedent coronary occlusion.

* $P < 0.05$ vs baseline.

period, immediately before administration of vehicle/CGS 15943, immediately before LAD occlusion, and at 1, 3, and 10 minutes after reflow.

We analyzed CFVs for all observation periods in both protocols by measuring both their frequency and mean nadir.^{2,13–16} In both protocols, a CFV was defined as a slow decrease followed by an abrupt (within ≤ 1 minute) increase in carotid flow, with an amplitude $\geq 20\%$ of the poststenotic flow value.

Carotid patency throughout all observation periods was assessed by measurement of the area of the flow-time profile.² In protocol 1 (rabbits), the area of the flow-time tracing throughout the 2 hours after carotid injury plus stenosis was measured by computerized planimetry and normalized for each animal to the baseline flow $\times 120$ minutes. In protocol 2 (dogs), flow-time area was planimeted: (1) over the first hour of observation (before LAD occlusion) and normalized to baseline flow $\times 60$ minutes and (2) over the final 2 hours of observation (after LAD occlusion) and normalized to baseline flow $\times 120$ minutes.

Statistics

In protocol 1 (rabbits), the primary end points of the study (ie, the nadir and frequency of the CFVs and percent flow-time area) were compared among all groups by ANOVA. In protocol 2 (dogs), indexes of patency were compared before versus after the 30-minute treatment period (ie, before versus after LAD occlusion) in vehicle- and CGS-treated animals by 2-factor ANOVA (for group and time) with repeated measures. Data from the 2 time-matched shams are reported but were not included in the statistical analyses. In both protocols, hemodynamic parameters, carotid blood flow, and LAD flow (dogs only) were assessed by 2-factor ANOVA with replication. All post hoc comparisons were made by Tukey test. All results are reported as mean \pm SEM, and probability values < 0.05 were considered significant.

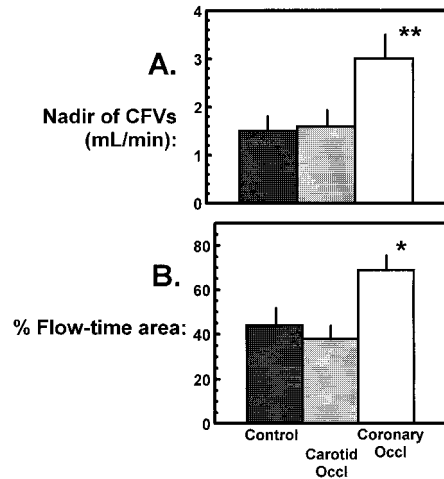


Figure 2. Summary of carotid artery patency throughout the 2 hours after injury plus stenosis for rabbits in control, antecedent carotid occlusion, and antecedent coronary occlusion groups (protocol 1). Results are presented as group means \pm SEM.

* $P = 0.03$, ** $P = 0.01$ vs control by ANOVA. Occl indicates occlusion.

Results

Protocol 1 (Rabbit Model)

Hemodynamics

All groups showed a modest but significant decrease in heart rate at the end of the 2-hour observation period (Table 1). However, there were no differences in heart rate or arterial pressure among the 3 groups at any time during the protocol.

Carotid Flow

Carotid blood flow was comparable among all rabbits at baseline, averaging ≈ 5 to 6 mL/min (Table 2). Immediately on relief of bilateral carotid occlusion, maximal hyperemic carotid flow was increased to 132% of baseline ($P = 0.05$ versus baseline) but did not differ significantly from time-matched measurements obtained in the control and coronary occlusion groups (104% and 113%, respectively). In all groups, carotid flow was significantly reduced to 76% to 78% of baseline ($P < 0.05$) on application of the stenosis.

CFVs and Carotid Patency

All groups exhibited ≈ 4 CFVs during the 2 hours of observation ($P = \text{NS}$). In control rabbits, the nadir of the CFVs was 1.5 ± 0.3 mL/min, and percent flow-time area averaged $44 \pm 8\%$. Similar results were obtained in the cohort that received antecedent carotid occlusion, ie, nadir of the CFVs

TABLE 2. Protocol 1 (Rabbit Model): Carotid Blood Flow

	Baseline	Maximum Flow After Brief Carotid/Coronary Occlusion	Before Stenosis	After Stenosis
Control	5.5±0.3 (100%)	5.8±0.3 (104±4%)	5.5±0.3 (100±2%)	4.2±0.3* (78±2%)
Carotid occlusion	6.6±0.6 (100%)	8.7±1.0* (132±6%)	7.2±0.8 (110±5%)	5.1±0.5* (77±3%)
Coronary occlusion	6.3±0.5 (100%)	7.1±0.6 (113±6%)	6.8±0.7 (106±8%)	4.8±0.4* (76±2%)

Carotid occlusion indicates brief antecedent bilateral carotid artery occlusion; Coronary occlusion, brief antecedent coronary occlusion. Values are mL/min (% of baseline).

* $P < 0.05$ vs baseline.

TABLE 3. Protocol 2 (Canine Model): Hemodynamics

	Baseline	End 1-h Pre-LAD CO Observation	After Vehicle or CGS			
			During 30-min Treatment Period			End 2-h Post-LAD CO Observation
			Before CO	1-min Reflow	10-min Reflow	
Vehicle+LAD occlusion						
Heart rate, bpm	154±7	166±10*	168±8*	166±9*	167±6*	168±8*
Peak LV pressure, mm Hg	109±6	131±5*	124±6*	128±6*	133±6*	126±6*
CGS+LAD occlusion						
Heart rate, bpm	157±11	175±12*	167±14	163±18	168±16*	163±12*
Peak LV pressure, mm Hg	112±5	128±10*	121±7	122±11	130±9*	123±8
Vehicle+sham						
Heart rate, bpm	150±5	164±16	157±14	160±11	163±15	163±3
Peak LV pressure, mm Hg	114±6	135±2	122±1	114±6	119±1	123±8

CO indicates coronary occlusion; CGS, CGS 15943.

* $P<0.05$ vs baseline.

averaged 1.6 ± 0.3 mL/min, and percent flow-time area was $38\pm6\%$. In contrast, in rabbits that received brief antecedent coronary occlusion, the nadir of the CFVs was greater (3.0 ± 0.5 mL/min; $P=0.01$; Figure 2A) and percent flow-time area was improved ($69\pm5\%$; $P=0.03$; Figure 2B) versus controls.

Protocol 2 (Dog Model)

Hemodynamics

Both heart rate and peak LV pressure increased modestly but significantly during the protocol, with no differences between vehicle- and CGS-treated cohorts that underwent LAD occlusion (Table 3). A similar temporal profile was observed in time-matched shams.

Carotid Flow

Baseline values of carotid flow averaged 94 ± 13 mL/min in the vehicle control group, 86 ± 4 mL/min in dogs later randomized to receive CGS, and 90 ± 9 mL/min in the shams. Immediately after injury plus stenosis, carotid flow was reduced to 14 ± 2 , 12 ± 1 , and 11 ± 1 mL/min (ie, $\approx 12\%$ to 15% of baseline) in the 3 cohorts, respectively ($P=NS$).

LAD Flow

LAD coronary flow at the onset of the 30-minute treatment period averaged ≈ 16 to 18 mL/min in dogs assigned to

receive vehicle or CGS plus LAD occlusion and was not altered by vehicle or CGS treatment (Table 4). All dogs subjected to coronary occlusion displayed cyanosis and dyskinesia, and all were hyperemic on reperfusion; ie, mean coronary flow at 1 minute after relief of ischemia was $\approx 500\%$ of baseline, with no difference between vehicle- or CGS-treated groups. Time-matched sham animals, as expected, showed no evidence of hyperemia.

CFVs and Carotid Patency

During the initial hour after carotid injury plus stenosis, all groups exhibited ≈ 4 CFVs per 30-minute interval, and all groups were comparable with respect to both the nadir of the CFVs (Figure 3A) and percent flow-time area (Figure 3B). No temporal changes in carotid patency were observed in time-matched shams.

Both the vehicle-treated and CGS plus LAD occlusion groups continued to develop CFVs at a frequency of ≈ 4 per 30-minute interval during the final 2 hours of observation ($P=NS$). However, in dogs that received vehicle plus LAD occlusion, both the nadir of the CFVs (Figure 3A) and area of the flow-time profile (Figure 3B) were significantly increased after the 30-minute treatment period, ie, 8.4 ± 2.4 versus 5.8 ± 2.3 mL/min ($P=0.04$) and $16\pm3\%$ versus $11\pm3\%$ ($P=0.01$) after versus before LAD occlusion, respectively. In contrast, dogs treated with CGS 15943 showed no improve-

TABLE 4. Protocol 2 (Canine Model): LAD Blood Flow (mL/min and % of Baseline)

	End 1-h Pre-LAD CO Observation (Baseline)	After Vehicle or CGS			
		During 30-min Treatment Period			
		Before CO	1-min Reflow	3-min Reflow	10-min Reflow
Vehicle+LAD occlusion	16±1 (100%)	16±1 (101±3%)	75±15* (466±72%)	65±17* (398±84%)	18±3 (113±16%)
CGS+LAD occlusion	18±3 (100%)	18±3 (97±3%)	94±19* (533±71%)	61±16* (333±44%)	18±2 (107±6%)
Vehicle+sham	13±1 (100%)	13±1 (102±2%)	15±2 (113±5%)	15±2 (114±6%)	13±1 (101±2%)

CO indicates coronary occlusion; CGS, CGS 15943. Values are mL/min (% of baseline).

* $P<0.01$ vs baseline.

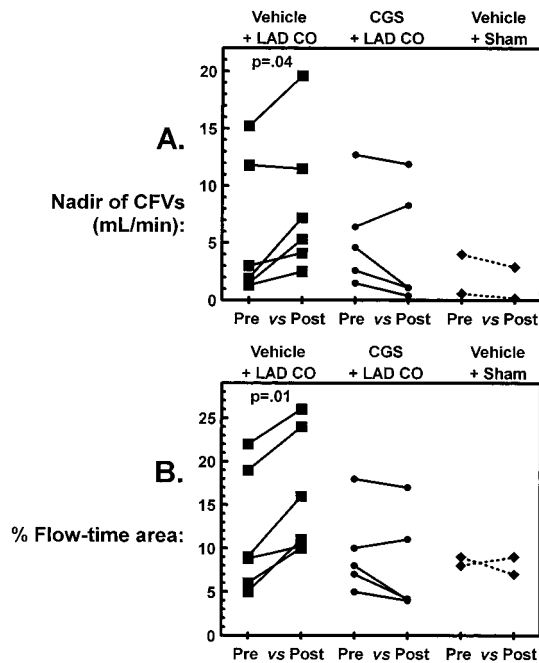


Figure 3. Carotid artery patency assessed before vs after the 30-minute treatment period in dogs that received vehicle or CGS 15943 (CGS) plus LAD occlusion (LAD CO) and in time-matched shams (protocol 2). Each pair of points represents data from 1 animal.

ment in either the nadir of the CFVs (4.6 ± 2.1 versus 5.6 ± 1.8 mL/min) or flow-time area ($8 \pm 2\%$ versus $10 \pm 2\%$) after versus before LAD occlusion.

Discussion

In this study, we make the novel observation that in both rabbit and dog models, brief antecedent coronary artery occlusion enhances subsequent vessel patency in remote, damaged, and stenotic carotid arteries. In contrast, brief antecedent bilateral carotid occlusion in rabbit, known to cause negligible cerebral ischemia and thus minimal release of adenosine, fails to evoke a benefit on subsequent carotid patency. Moreover, administration of the adenosine receptor antagonist CGS 15943 abrogates the improvement in carotid patency seen after coronary artery occlusion in the canine preparation. These latter results implicate release of adenosine from ischemic myocardium and resultant stimulation of adenosine receptors on circulating blood-borne elements (presumably platelets) as an important mediator of the enhanced carotid patency seen after coronary artery occlusion.

Background and Rationale

We previously demonstrated that a brief (10 minute) episode of antecedent coronary artery occlusion elicited a significant and sustained subsequent improvement in blood flow in damaged and stenotic canine coronary arteries. Moreover, we found that the benefits of brief antecedent coronary occlusion were mimicked by brief intracoronary adenosine infusion and blocked by the nonselective adenosine receptor antagonist PD 115,199.² These results suggest that release of adenosine from ischemic/reperfused myocardium and resultant adenosine receptor stimulation contributed significantly to this

enhanced coronary patency.² However, the data did not reveal whether the improved coronary patency seen with antecedent coronary occlusion was specifically due to attenuated platelet aggregation via stimulation of adenosine receptors on circulating platelets^{6–9} or whether local vasodilation or relief of vasospasm via stimulation of adenosine receptors in the media of the culprit coronary artery⁶ also played a role.

It is well recognized that adenosine is generated in ischemic myocardium via the catabolism of ATP and liberated during the initial minutes after reperfusion.^{3–5} This transient release of adenosine, together with its highly labile nature (plasma half-life on the order of seconds to minutes),¹⁹ essentially precludes the sustained transport of adenosine from the heart to a peripheral location, and thus provides the rationale for evaluating the effect of brief coronary artery occlusion on vessel patency in damaged and stenotic carotid arteries. Specifically, if local adenosine receptor stimulation is required to achieve the improvement in flow, then a short-lived release of adenosine from the heart would not be expected to elicit an improvement in arterial patency at a peripheral site. In contrast, if, as we propose,² the improved patency was due to stimulation/binding of adenosine receptors on circulating blood-borne elements exposed to adenosine (ie, platelets traversing the ischemic/reperfused myocardium), then logic would dictate that brief coronary occlusion should effectively attenuate subsequent platelet thrombosis at a site remote from the source of adenosine production. Our current results demonstrating, in both rabbit and dog, a sustained improvement in the patency of damaged and stenotic carotid arteries after brief coronary artery occlusion appear consistent with this hypothesis.

We further reasoned that if adenosine plays an important role, then no benefit should be seen in response to local brief vascular occlusion not accompanied by appreciable adenosine release. To test this corollary, we used the rabbit model to evaluate the effects of brief antecedent bilateral carotid artery occlusion on later carotid patency. Although there is no question that as in heart, profound cerebral ischemia results in ATP catabolism and adenosine production,¹⁰ it is equally well established that the rabbit possesses a highly redundant blood supply to the brain such that shunting of blood via the circle of Willis can compensate for even prolonged periods of bilateral carotid artery obstruction.^{10–12,20,21} In fact, occlusion of multiple cerebral arteries,²² sometimes combined with systemic hypotension,¹⁰ is needed to induce a significant perfusion deficit. Our measurements of carotid blood flow in the rabbit corroborate this concept: maximum hyperemia immediately after brief bilateral carotid occlusion was only $\approx 130\%$ of baseline (Table 2), in marked contrast to the ≈ 5 -fold increase in coronary flow seen on reperfusion of acutely ischemic myocardium (Table 4), thereby implying that cerebral adenosine release was indeed negligible in rabbits that underwent antecedent carotid occlusion. Our results obtained in protocol 1 with bilateral carotid occlusion reveal that arterial occlusion per se does not ensure a favorable influence on the subsequent patency of that same artery after injury plus stenosis. Rather, arterial occlusion resulting in ischemia appears to be required.

Data obtained in protocol 1 implied, but failed to establish, that adenosine (and subsequent binding to adenosine receptors) is the metabolite primarily responsible for the sustained benefit of coronary artery occlusion on "remote" vessel patency. Thus, as a final test of our hypothesis, we reasoned that administration of an adenosine receptor antagonist should attenuate the improved carotid patency seen after coronary artery occlusion. Indeed, in protocol 2, we found that brief coronary occlusion was ineffective in triggering an improvement in carotid patency in dogs that had received CGS 15943, an A₂/A₁ antagonist devoid of intrinsic platelet effects.^{17,18} Platelet adhesion and aggregation is a complex process,²³ and we cannot exclude the possibility that other metabolites liberated from ischemic myocardium (including NO, prostaglandins, and bradykinin), acting alone or in concert with adenosine, might also play a role. In this regard, it is interesting to note that synthesis of NO, which is also a potent inhibitor of platelet aggregation,^{23–26} may be initiated as a secondary consequence of adenosine A₂ receptor stimulation.²⁷ However, our observation that CGS 15943 abolished the benefits of brief coronary occlusion suggest that the improved vessel patency manifest "at a distance" is due in large part to adenosine.

Limitations and Unanswered Questions

We acknowledge that despite the implicit involvement of adenosine, we did not measure adenosine concentrations in heart or blood; rather, we rely on previous studies by our group and others unequivocally documenting massive release of adenosine from rabbit and dog hearts in response to brief coronary occlusion/reperfusion.^{3–5} Second, although we infer from our data that the benefits of brief coronary occlusion on carotid patency are in all likelihood due to binding to and stimulation of adenosine A₂ receptors on circulating platelets, it must be recognized that CGS 15943, despite its high affinity for the A₂ receptor,¹⁷ is not subtype specific. Direct documentation of increased activity of platelet A₂ receptors in response to brief coronary occlusion will be required to definitively resolve this issue. Finally, although carotid blood flow was significantly enhanced, brief coronary artery occlusion clearly did not prevent subsequent platelet-mediated thrombosis at the peripheral site. It is, however, noteworthy that even under the severe conditions required to elicit CFVs in the large, muscular, and high-flow carotid arteries of the dog (ie, medial injury plus tightening of the stenosis to reduce carotid flow to ≈15% of baseline), brief coronary occlusion nonetheless elicited a significant improvement in carotid patency.

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