Intrinsic washout rates of thallium-201 in normal and ischemic myocardium after dipyridamole-induced vasodilation

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ABSTRACT Infusion of dipyridamole has been suggested as an alternative to exercise stress for myocardial perfusion imaging for detection of ischemia, but the mechanism and significance of thallium-201 (201TI) redistribution after administration of dipyridamole are uncertain. If disparate intrinsic cellular efflux rates of 201TI from normal and relatively underperfused myocardium in response to dipyridamole-induced vasodilation were observed, this could explain delayed 201TI redistribution. We investigated the effect of an intravenous infusion of 0.15 mg/kg dipyridamole on the intrinsic myocardial washout rate of 201TI as measured with a gamma-detector probe after intracoronary injection (50 μCi) of the radionuclide in open-chested anesthetized dogs. In six normal dogs the t½ for intrinsic 201TI washout from the myocardium was 89 ± 11 min (SE) at control conditions and became more rapid at 59 ± 10 min (p = .0001) after dipyridamole. This corresponded to a significant increase in microsphere-determined epicardial (0.95 ± 0.11 to 2.23 ± 0.46 ml/min/g; p = .01) and endocardial (0.86 ± 0.10 to 1.53 ± 0.27; p = .029) flows. In 12 dogs with a critical coronary stenosis, the 201TI intrinsic washout rate slowed from 70 ± 5 to 108 ± 6 min (p = .0001) after production of the stenosis and slowed even further to 169 ± 21 min (p = .003) after dipyridamole. Compared to conditions with the stenosis alone, dipyridamole-induced vasodilation caused a fall in mean aortic pressure (91 ± 5 to 74 ± 6 mm Hg; p < .0001), a fall in coronary perfusion pressure (60 ± 4 to 45 ± 3 mm Hg), but an unchanged total coronary flow (53 ± 8 to 52 ± 8 ml/min; p = NS) and stenosis gradient, and hence, stenosis resistance. Although transmural flow was unaltered in the stenotic region after dipyridamole, epicardial flow increased from 1.00 ± 0.18 to 1.27 ± 0.47 ml/min/g and endocardial flow fell from 0.65 ± 0.15 to 0.50 ± 0.22 ml/min/g, resulting in an endocardial/epicardial flow gradient. In the range of transmural flow values between 0.10 and 1.4 ml/min/g, the intrinsic 201TI washout rate became more prolonged as flow decreased. Thus, in the presence of a critical coronary stenosis, the dipyridamole-induced fall in systemic arterial pressure and distal coronary perfusion caused a subnormal endocardial blood flow and ischemia, resulting in a prolonged intrinsic myocardial 201TI efflux rate. The disparate 201TI efflux rates in normal and underperfused myocardium can explain delayed redistribution observed after dipyridamole infusion in the presence of a coronary stenosis.


MYOCARDIAL perfusion imaging has been performed during coronary vasodilation produced by intravenously administered dipyridamole both for detecting coronary artery disease1-12 and for identifying high-risk patients after myocardial infarction.13 This potent coronary vasodilator enhances regional myocardial blood flow in zones supplied by normal coronary arteries but not in myocardium perfused by obstructed vessels, resulting in flow inhomogeneity. Since the initial myocardial distribution of intravenously administered thallium-201 (201TI) is proportional to blood flow,14,15 scintigraphic defects are observed that demonstrate this relative hypoperfusion. We16 and others12,17,18 have demonstrated that under conditions of a coronary stenosis in canine preparations of ischemia or in humans, dipyridamole- or adenosine-induced vasodilation results not only in diminished 201TI uptake but also in subsequently delayed redistribution similar to that observed with exercise scintigraphy. Redistribution defects have also been demonstrated on serial myocardial scintigrams in patients with coronary artery disease receiving dipyridamole before administration of 201TI.1

The mechanism and significance of 201TI redistribution after dipyridamole imaging are uncertain. Total
blood flow in a stenotic vessel is not decreased after intravenous infusion of dipyridamole. Furthermore, myocardial oxygen demand is not increased in response to the drug. The duration of active vasodilation may be more prolonged than that induced by exercise. Dipyridamole as well as adenosine are known to produce a significant endocardial-to-epicardial flow gradient distal to a coronary stenosis. This may produce regions of subendocardial ischemia adjacent to regions of normal or even enhanced epicardial flow.

In an earlier study of serial myocardial needle biopsies specimens from anesthetized dogs with a critical left anterior descending coronary stenosis, we showed that when $^{11}$Tl was injected intravenously after infusion of dipyridamole, net clearance of $^{11}$Tl from the region of stenosis was slower than that from normal myocardium. The difference in net clearance rates resulted in normalization of the initial defect (redistribution). This could be the result of altered delivery of the tracer to the myocardium (blood flow), of altered extraction of the tracer by the myocardium, or of alterations in the intrinsic efflux of $^{11}$Tl from the myocardium. It is not possible to infer the mechanism of redistribution after intravenous injection of the tracer in an intact animal because only the net effect of continuous exchange and recirculation can be observed in such a preparation. The intracellular efflux of $^{11}$Tl can be investigated by using intracoronary rather than intravenous injections of the radionuclide. This method effectively eliminates systemic recirculation of $^{11}$Tl and allows the determination of intrinsic cellular efflux rates. These rates can then be combined with the values of net myocardial clearance to more completely define the mechanism of thallium uptake and washout in the closed system in the presence of systemic recirculation.

Accordingly, the purpose of these experiments was to measure the intrinsic $^{201}$Tl washout rates and alterations in regional blood flow during dipyridamole-induced vasodilation. Disparate efflux rates of $^{201}$Tl in normal and relatively underperfused myocardial regions in response to the drug could explain the delayed $^{201}$Tl redistribution that is seen when the radionuclide is administered intravenously under similar hemodynamic and regional flow conditions.

Methods

Canine preparation. These studies were undertaken in mongrel dogs weighing from 20 to 30 kg. The dogs fasted for 24 hr before surgery and were anesthetized with pentobarbital sodium at a dose of 30 mg/kg iv. After intubation the dogs were ventilated on a Harvard Apparatus respirator at a rate of 13/min with a tidal volume of approximately 500 cc. The respirator frequen-
into epicardial, midwall, and endocardial layers. The resulting 95 specimens were weighed and counted together with the duplicate femoral arterial withdrawals and pure isotope samples for 500 sec in a Packard Gamma Auto Scintillation counter. A multichannel analyzer was used for separation of isotope peaks with the following windows: $^{46}$Sc = 740 to 1300 keV, $^{51}$Nb = 650 to 1818 keV, $^{103}$Ru = 450 to 570 keV.

Myocardial blood flow was calculated with the equation $Q_m = (Cm \times 100 \times Qr)/Cr$, where $Qm$ = myocardial blood flow (ml/min), $Cm$ = tissue counts (counts/min), $Qr$ = withdrawal rate of the arterial samples (ml/min), and $Cr$ = counts in the reference arterial sample. Flow per gram of myocardium was calculated by dividing blood flow by sample weight. Isotope separation and myocardial blood flow values were calculated according to methods previously described.$^{16}$ All myocardial samples were held 2 weeks before counting to permit decay of $^{201}$Ti activity to more appropriate levels. The counts per minutes recorded in each window for myocardial and reference blood samples were corrected for background activity as well as spill activity contributed by the isotopes of higher energy. Standard deviations for the regional myocardial flow values were obtained from the variance computed from counting multiple samples and reflects local inhomogeneity of microsphere deposition or actual flow inhomogeneity. Individual samples typically provided 50,000 counts; therefore, the Poisson statistic was comparatively small and could be considered a minor contribution to the overall sample variance. The individual Poisson error of approximately 0.5% when propagated through the matrix increased to no more than 1% to 2%.

**Measurement of intrinsic $^{201}$TI washout rate.** The intrinsic washout rate of $^{201}$TI was determined after direct intracoronary injection of the radioisotope as previously described.$^{28}$ By this mode of administration there is almost no systemic recirculation of thallium back to the myocardium, thus permitting assessment of the true efflux rate of $^{201}$TI from myocardium into the systemic pool. An external collimated gamma-detector probe was positioned over the heart above the epicardial surface. After intracoronary $^{201}$TI administration, radionuclide counts were recorded and printed every 30 sec by interfacing the gamma probe with a scaler timer and digital recorder. The $^{201}$TI washout rates thus were obtained by a least-squares curve fitting a monoeXponential to obtain the clearance coefficient, $K$, and deriving $t_1/2 = 0.693/K$. Previously, we have shown that the intrinsic washout rates calculated by this method correlate well with the intrinsic washout rate calculated under the same experimental conditions with serial coronary sinus samples used for measuring $^{201}$TI efflux from the myocardium.$^{28}$

**Experimental protocol.** Six normal dogs served as a control group. A dose of 50 μCi of $^{201}$TI was injected directly into either the left anterior descending or left circumflex coronary artery, after which myocardial $^{201}$TI counts were measured every 30 sec for 15 min with the gamma probe. The first set of radioactive microspheres was also injected into the left atrium as described previously. After baseline pressures were recorded and washout and flow measurements were obtained, a dose of 0.15 (n = 5) or 0.25 (n = 13) mg/kg dipyridamole was infused intravenously over a period of 1 min, after which $^{201}$TI isotopic activity was again recorded for 15 min over the same myocardial region. The second set of microspheres was then injected at 4 min after administration of dipyridamole.

In another 12 dogs receiving 50 μCi of $^{201}$TI via the intracoronary route, a critical coronary stenosis was produced after baseline hemodynamic and $^{201}$TI washout measurements were obtained. For the purpose of these experiments, a critical stenosis was defined as a partial narrowing of the coronary lumen with the hydraulic occluder that nearly or totally ablated the reactive hyperemic response to a transient 10 sec occlusion. $^{201}$TI washout was again measured with the stenosis in place, and radioactive microspheres were injected into the left atrium. After continuous recording of myocardial $^{201}$TI activity for 15 min, 0.15 mg/kg dipyridamole was administered intravenously over 1 min, after which the final hemodynamic measurements were recorded for another 15 min at peak vasodilative effect. The second set of microspheres was injected to assess changes in myocardial blood flow in normal and stenotic regions during dipyridamole-induced vasodilation.

**Data analysis.** In both normal dogs and dogs with a critical coronary stenosis, a t statistic from paired observations was used to test for differences between baseline and postdipyridamole conditions.

**Results**

**Control group.** In the six normal dogs the $t_1/2$ for intrinsic $^{201}$TI washout from the myocardium was 89 ± 11 min (SEM) under control conditions and became significantly more rapid at 59 ± 10 min (p = .0001) after administration of 0.15 mg/kg dipyridamole. Figure 1 shows the serial changes in the $t_1/2$ for intrinsic washout in a representative normal dog receiving dipyridamole after intracoronary injection of 50 μCi of thallium. In this instance the $t_1/2$ was 84 min under basal conditions and shortened to 65 min after coronary vasodilation. In the control group mean heart rate was 145 ± 8 beats/min during basal conditions and was unchanged at 145 ± 7 beats/min after dipyridamole. Mean aortic pressure fell slightly but significant-

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**FIGURE 1.** Serial changes in the intrinsic washout rate in a representative normal dog receiving an intracoronary injection of $^{201}$TI before dipyridamole infusion.
ly from 108 ± 5 to 100 ± 5 mm Hg (p = .006). Distal coronary perfusion pressure also fell slightly from 106 ± 6 to 96 ± 5 mm Hg (p = .006). However, mean coronary flow measured by electromagnetic probe increased from 57 ± 7 to 115 ± 19 ml/min (p = .04).

Figure 2 illustrates changes in mean epicardial and endocardial blood flows in the myocardial region from which 201TI washout values were obtained. As expected, dipyridamole infusion resulted in significant increases in epicardial (0.95 ± 0.11 to 2.23 ± 0.46 ml/min/g; p = .01) and endocardial (0.86 ± 0.10 to 1.53 ± 0.27; p = .029) flows. Transmural flow, which was the average of inner (subendocardial), middle, and outer (subepicardial) sample flow values, rose from 1.04 ± 0.09 to 2.13 ± 0.51 ml/min/g after dipyridamole infusion.

Thus, in normal dogs dipyridamole-induced coronary vasodilation resulted in a more rapid intrinsic myocardial washout rate of 201TI coincident with increases in both epicardial and endocardial blood flow.

**Stenosis group.** The changes in the mean 201TI intrinsic washout rate after the production of a coronary stenosis and after dipyridamole infusion in the presence of this stenosis for the 12 dogs in the stenosis group are shown in Figure 3. Before the coronary occluder was inflated, the t1/2 for intrinsic 201TI washout was 70 ± 5 min, not significantly different from the basal 201TI washout in the control group. The washout rate slowed significantly to 108 ± 6 min (p < .0001) after production of the stenosis. After dipyridamole infusion the intrinsic 201TI washout slowed further to 169 ± 21 min (p = .003). Figure 4 shows the changes in the t1/2 of intrinsic 201TI washout in one of the dogs with a critical stenosis receiving dipyridamole after intracoronary 201TI administration. The t1/2 for 201TI

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**FIGURE 2.** Regional myocardial blood flow (ml/min/g) in normal dogs before (control) and after intravenous infusion of dipyridamole (DP).

**FIGURE 3.** Changes in the mean 201TI intrinsic washout rate after the production of a coronary stenosis and after infusion of dipyridamole (DP) in the presence of this stenosis in 12 dogs. 201TI was injected directly into the left anterior descending coronary artery.

**FIGURE 4.** Changes in the t1/2 of intrinsic 201TI washout in a representative dog with a critical stenosis receiving intravenous dipyridamole (DP) after intracoronary administration of 201TI. The t1/2 for 201TI washout is slowed during occlusion compared with the control state and is slowed even further after dipyridamole.
washout was slowed during occlusion (102 min) compared with the preocclusion state (51 min) and was slowed even further after dipyridamole (153 min). This response was contrary to that observed when the drug was given to control animals with totally patent coronary arteries in which the intrinsic ²⁰¹Tl washout became more rapid.

There was no significant change in mean heart rate (beats/min) from control (133 ± 8) to stenotic (135 ± 8) to postdipyridamole (139 ± 6) conditions. As shown in figure 5, no change in mean aortic pressure occurred with production of the stenosis alone, but aortic pressure fell from 91 ± 5 to 74 ± 6 mm Hg after dipyridamole infusion (p < .0001). As also depicted in figure 5, the coronary perfusion pressure significantly decreased from 93 ± 6 to 60 ± 4 mm Hg after the stenosis was established (p < .001) and decreased even further to 45 ± 3 mm Hg after dipyridamole infusion (p < .0001). Total coronary flow measured by electromagnetic probe was 72 ± 9 ml/min at baseline and fell to 53 ± 8 ml/min (p = .008) after placement of the stenosis. After dipyridamole, coronary flow in the stenotic vessel was unchanged at 52 ± 8 ml/min.

Changes in epicardial and endocardial regional blood flow after dipyridamole infusion in the normal region and in the region perfused by the coronary stenosis are summarized in figure 6. Under basal conditions with the coronary stenosis in place, the stenosis alone resulted in a lower baseline endocardial flow in the stenotic region (0.65 ± 0.15 ml/min/g) compared with the normal region (1.22 ± 0.16 ml/min/g; p = .008). In the normal region perfused by the patent coronary vessel, epicardial and endocardial flow significantly increased after dipyridamole (1.08 ± 0.17 to 2.99 ± 0.39 [p < .001] and 1.22 ± 0.16 to 2.51 ± 0.43 [p = .006], respectively) to a degree comparable to that observed in the six control dogs. In contrast, in the stenotic region there was a slight increase in epicardial flow (1.00 ± 0.18 to 1.27 ± 0.47 ml/min/g) but an actual fall in endocardial flow (0.65 ± 0.15 to 0.50 ± 0.22 ml/min/g) after dipyridamole infusion. Although these changes were not statistically significant, there appears to be evidence of an endocardial-to-epicardial “steal” phenomenon in the stenotic region at peak vasodilation. Transmural flow derived from the average flow in the inner, middle, and outer layers was 1.20 ± 0.12 ml/min/g at baseline and decreased to 0.81 ± 0.14 ml/min/g after the stenosis was placed. With dipyridamole infusion transmural flow was unchanged at 0.87 ± 0.34 ml/min/g.

Since coronary flow and the pressure gradient across the stenosis were unchanged after dipyridamole, the stenosis resistance did not change. This is important because it demonstrates that dipyridamole infusion does not cause passive collapse of the stenosis as aortic and distal coronary pressures fall.

The relationship between transmural myocardial blood flow and the t½ for the intrinsic washout rate of thallium is plotted in figure 7. The points shown on the

![FIGURE 6. Regional myocardial blood flow values (ml/min/g) after dipyridamole (DP) in the normal region and in the region perfused by the coronary stenosis. The basal state represents the conditions with the stenosis in place before dipyridamole infusion.](http://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.106.181838)
FIGURE 7. Relationship between transmural myocardial blood flow and the t½ for the intrinsic washout rate of 201Tl. The points shown on this graph were obtained from 201Tl washout and microsphere flow values under all conditions of the experimental protocols. Data from normal and stenotic dogs have been pooled.

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Transmural Blood Flow (ml/min/g)

Discussion

In these experiments the effect of dipyridamole was to increase myocardial capillary blood flow to approximately 2 to 2½ times its baseline value in normal regions supplied by a patent coronary artery. When a critical stenosis was in place on a coronary artery, the infusion of dipyridamole produced no significant change in the total flow as measured by the electromagnetic flowmeter through the partially occluded coronary artery. The mean aortic pressure and consequently the pressure proximal to the stenosis fell from an average of 91 to an average of 74 mm Hg after dipyridamole infusion. The mean pressure distal to the occlusion fell from 60 to 45 mm. Thus the pressure gradient across the stenosis was approximately 30 mm Hg and remained nearly the same after dipyridamole infusion. This pressure gradient across the stenosis in combination with the lowered systemic arterial pressure induced by dipyridamole resulted in a very significant reduction of arterial pressure distal to the stenosis. In the region distal to the stenosis, epicardial blood flow increased slightly but the endocardial blood flow dropped.

The flow pattern observed was that of an epicardial “steal” phenomenon after administration of the vasodilator. This could be the result of inactivating vasconstriction, which otherwise would have maintained a uniform myocardial flow distribution. Alternatively, this transmural flow gradient could be the result of the sharply decreased perfusion pressure in the supplying coronary artery. It would appear that below 40 mm Hg there is simply insufficient pressure in the coronary artery to maintain adequate capillary blood flow to the endocardium. This concept is supported by the plot in figure 7. This figure shows the endocardial blood flow as a function of coronary arterial pressure derived from all of the individual samples taken in these experiments except for those representing increased flow after dipyridamole infusion in myocardium in normal control dogs without a coronary stenosis. This graph illustrates loss of endocardial perfusion at coronary pressures below about 30 mm Hg, suggesting partial or complete endocardial capillary closure at this pressure.
The intrinsic thallium washout rate was measured by external counting of the intact myocardium and would have to be considered a transmural sample. When there is a gradient of flow between the epicardium and endocardium, the washout rate determined from the probe data will represent the integration of this continuum and the washout coefficient must be considered a lumped constant. The washout rate obtained from these samples as a function of transmural capillary blood flow is illustrated in figure 7. For above-normal blood flow values of approximately 1.4 ml/min/g, the intrinsic efflux half-time is nearly constant and hence independent of blood flow. This would appear to be a regime in which thallium efflux is rate-limited by its diffusion across the cell membrane and thus becomes flow independent.

At subnormal myocardial blood flow levels the intrinsic efflux half-time becomes sharply prolonged. This could be the result of diminished active transport by ischemic myocardial cells. It could also be the result of slower clearing of the interstitial space and cellular reuptake when capillary blood flow is diminished. The prolonged intrinsic efflux may also be the result of partial capillary closure where thallium already extracted is “trapped” and will have a lengthened diffusion path to reach the blood compartment.

Although all three of the above mechanisms for delayed thallium efflux when blood flow is reduced may be simultaneously at work, the latter mechanism involving partial capillary closure is consistent with the observation that the endocardium may be near or at the level of capillary closure at the level of coronary pressures measured distal to the critical stenosis after the administration of dipyridamole (figure 8). We have demonstrated an almost equivalent phenomenon in a previous series of experiments by measuring the intrinsic myocardial thallium efflux rate after production of graded stenoses in the absence of dipyridamole. It was shown that the intrinsic thallium efflux approaches an almost asymptotic rise when the pressure in the coronary supply artery falls to about 30 mm Hg. This, combined with the present data showing that endocardial blood flow drops essentially to zero at about the same pressure, suggests a stop-flow phenomenon that appears at the same coronary arterial pressure regardless of whether the pressure decrease was caused by graded stenosis or by the infusion of dipyridamole.

The main effect of dipyridamole may have been the reduction of mean arterial (aortic) pressure in the presence of a critical stenosis. In this setting the pressure gradient across the stenosis before dipyridamole was significant but perfusion pressure distal to the stenosis was still adequate to maintain near-normal transmural blood flow. After dipyridamole the aortic pressure fell only moderately but further reduced the coronary pressure distal to the stenosis to a level at which frank endocardial ischemia was inevitable. This suggests that the role of systemic arterial pressure alterations is critical in the evaluation of coronary artery disease with dipyridamole.

Our observations are consistent with those of Goldhaber et al., who found, using an isolated perfused Langendorff rat heart preparation, that as coronary blood flow is reduced, the myocardial release rate of 201Tl decreases. In their study, when flow was reduced from 12 to 3 ml/min, the t½ for 201Tl washout was prolonged by a factor of two. Bergmann et al. also showed a prolonged t½ of 201Tl washout with a decrease in coronary perfusion in an isolated perfused heart preparation when the myocardium was initially loaded with 201Tl.

Finally, the observation of reduced 201Tl efflux in regions of reduced perfusion is an important mechanism in understanding 201Tl redistribution. When thallium is introduced intravenously, the myocardial region with low blood flow will extract proportionately less thallium. After the initial extraction the defect area tends to lose thallium more slowly in comparison with a normally perfused area, so that the defect will tend to normalize after sufficient time has lapsed. The net loss rate of thallium from myocardium is a balance between the influx from systemic recirculation and the intrinsic efflux that we measured in these experiments. Thallium redistribution can be understood in terms of

![FIGURE 8. Endocardial blood flow vs coronary arterial pressure.](http://circ.ahajournals.org/content/pdf/8.png)
increased influx in those situations where myocardial blood flow was transiently reduced and then restored to normal.\textsuperscript{32,33} This is seen when \textsuperscript{201}TI is administered during occlusion of a coronary artery, after which reperfusion is established during a transient episode of coronary vasospasm or after thrombolysis. However, redistribution has also been observed with long-term reduction of coronary blood flow,\textsuperscript{34,35} which can be understood only in terms of diminished \textsuperscript{201}TI efflux in chronically ischemic myocardium. We have shown a similar decrease in myocardial efflux during the time when abnormal myocardial (endocardial) perfusion is being sustained by dipyridamole infusion. Thus some redistribution during vasodilator stress may therefore be anticipated even when the myocardial flow abnormality is being sustained by the action of dipyridamole and endocardial flow is not immediately restored to normal. The redistribution kinetics with dipyridamole appear to be similar to the kinetics in preparations of chronic ischemia induced by high-grade stenoses\textsuperscript{36} and to preparations of transient ischemia such as exercise stress under circumstances in which dipyridamole is administered before thallium and the vasodilation is subsequently nullified by the administration of amino-phylline.\textsuperscript{36}

The vasodilatory effects of dipyridamole diminish over time after injection. As subendocardial flow in the stenotic region gradually increases with a rise in coronary perfusion pressure, an increase in \textsuperscript{201}TI delivery to this previously ischemic layer will occur via recirculation of the radionuclide and will contribute to delayed redistribution even if aminophylline is not administered.

There are several clinical implications of this study. Leppo et al.\textsuperscript{13} recently reported that presence of \textsuperscript{201}TI redistribution on a predischarge \textsuperscript{201}TI dipyridamole scintigram is a sensitive predictor of future cardiac events. Leppo et al.\textsuperscript{8} also reported that myocardial segments showing initial defects with subsequent redistribution after dipyridamole usually demonstrate preserved resting wall motion, and persistent defects are usually associated with akinetic myocardial segments, similar to what has been observed with exercise \textsuperscript{201}TI scintigraphy.

We are grateful to New England Nuclear Corp. for providing the thallium-201 and radioactive microspheres used in these experiments and to Ms. Beth Howk for her superb secretarial assistance in preparing this manuscript.

References
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G A Beller, H H Holzgrefe and D D Watson

Circulation. 1985;71:378-386
doi: 10.1161/01.CIR.71.2.378

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/71/2/378

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