Regional Circulatory Adjustments to Moderate and Severe Chronic Anemia in Conscious Dogs at Rest and during Exercise

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With the Technical Assistance of Daniel P. McKown

ABSTRACT

The successive changes in regional blood flows and resistances due to moderate and severe anemia were studied serially in nine conscious dogs after they recovered from implantation of ultrasonic Doppler transducers or electromagnetic flow probes on the left circumflex coronary, the mesenteric, the renal, and the iliac arteries and pressure gauges or catheters in the aorta. Anemia was induced by progressive phlebotomy and volume replacement over a period of 2-4 weeks. In moderate anemia (average hematocrit 22%) heart rate increased from 73 beats/min to 105 beats/min, and mean arterial pressure fell from 98 mm Hg to 94 mm Hg. Flow increased to the coronary bed by 75% and to the iliac bed by 45%, but flow to the mesenteric bed was not significantly affected and renal flow fell by 9%. Coronary and iliac resistances fell by 45% and 32%, respectively, but mesenteric and renal resistances were not significantly affected. In severe anemia (hematocrit 14%) heart rate increased to 129 beats/min, and mean arterial pressure was at control levels; coronary flow increased by 227%, iliac flow by 102%, mesenteric flow by 29%, and renal flow by 20%. Resistance decreased in the coronary bed by 69%, in the iliac bed by 52%, in the mesenteric bed by 23%, and in the renal bed by 19%. Exercise during severe anemia increased heart rate to 224 beats/min, mean arterial pressure to 114 mm Hg, coronary flow by 34%, and iliac flow by 215%; it reduced mesenteric flow by 59% and renal flow by 48%. Thus, blood flow increased and resistance decreased to all beds studied, indicating that in the resting conscious dog compensatory reduction of visceral flow is not a feature of the cardiovascular response to severe anemia at rest, although a redistribution of regional blood flow does occur. However, the added stress of exercise during severe anemia results in substantial reductions in mesenteric and renal blood flows.

KEY WORDS renal flow telemetry isoproterenol coronary flow mesenteric flow exercise limb flow

The primary cardiovascular adjustments to anemia involve an augmentation of cardiac output and oxygen extraction that compensates for the decreased oxygen-carrying capacity of the blood (1). An additional compensatory mechanism involving reduction and redistribution of blood flow from regions which normally extract less oxygen from the blood, e.g., the kidney, to those which have relatively little reserve, e.g., the heart, is also thought to occur (1–9). Thus, renal vascular resistance is thought to increase sufficiently to divert blood flow away from the kidney and thereby provide more blood to the heart and brain.

In the present investigation, to provide a description of the regional circulatory adjustments to moderate and severe anemia, direct
measurements of phasic regional blood flows and arterial blood pressure were made in healthy conscious dogs as anemia was gradually induced over 2–4 weeks by removing blood and replacing volume with the harvested plasma and dextran. Thus, the extent to which the regional vascular beds participate in the response to anemia could be assessed in the same dogs during the gradual transition from the normal to the anemic state.

This study also determined the effects of exercise during severe anemia. It is generally held that the normal peripheral vascular response to severe exercise involves reduction of visceral flows to provide flow to the exercising muscular bed (1, 10, 11). A previous study from our laboratory indicated that in normal dogs running at speeds of greater than 20 mph renal and mesenteric blood flows did not decrease, but that during complete heart block, when the ability to increase cardiac output with severe exercise was limited, marked reductions in visceral flows did occur (12). Thus, it is possible that in the presence of a limited oxygen-carrying capacity of the blood, as occurs during severe anemia, this compensatory mechanism of reduction and diversion of visceral blood flow might be invoked during exercise.

The specific goals of the present investigation were to determine (1) how the regional beds share in the augmentation of cardiac output that occurs during anemia, and thereby how they determine the relative priority for blood flow which is established for the major organ beds, (2) specifically if the compensatory mechanism of reduction and redistribution of visceral flow is used in the circulatory adjustment to anemia at rest, and (3) if this mechanism is invoked in the circulatory adjustment to anemia during exercise.

Methods

Nine mongrel dogs weighing 23–27 kg were studied after recovery from instrumentation and during the entire course of gradually induced anemia. Pentobarbital sodium (30 mg/kg, iv) anesthesia was used for all operations, but all experiments were conducted in conscious unseated dogs. Through a thoracotomy in the fifth intercostal space, miniature Konigsberg P22 pressure gauges were implanted in the thoracic aorta (six dogs), an ultrasonic Doppler transducer was placed around the left circumflex coronary artery (eight dogs), and stimulating electrodes were implanted on the left atrium. Through a midline laparotomy, the spleen was removed (five dogs), ultrasonic Doppler transducers were placed around the cranial mesenteric artery (eight dogs), the left renal artery (eight dogs), and the left iliac artery (eight dogs), and a heparin-filled polyvinyl catheter was placed in the aorta through a lumbar artery (three dogs). In one of these dogs an electromagnetic flow transducer was implanted adjacent to the ultrasonic Doppler transducer on the left renal artery.

In three dogs splenectomy was performed at a subsequent operation after control records of regional flows and arterial blood pressure were made, but in one dog the spleen was not removed. During a subsequent operation, a heparin-filled catheter was implanted in the jugular vein.

Blood flows were measured and telemetered by the ultrasonic Doppler flowmeters. This system, which has been described in detail previously, has a reliable zero reference (13, 14); in the present experiments zero blood flow was determined repeatedly and was confirmed by calibration at the termination of the experiment. The relationship between velocity, as measured by the Doppler transducer, and volume flow is linear as long as the cross-sectional area of the blood vessel within the transducer remains constant. At autopsy, it was observed that the vessels were firmly attached to the flow transducers through a fibrous scar which minimized changes in the cross-sectional area of the vessel within the flow transducers. Furthermore, the linear relationship between velocity and volume flow was confirmed by timed collections of blood flow. This system, which has been demonstrated to provide an accurate measure of volume flow under normal conditions (14), was tested to determine if wide variations in hematocrit affected the accuracy of the flow measurements. Volume flow calibrations were conducted terminally in vivo as hematocrit was varied in decrements to a minimum level of 6%. Over this range the accuracy of the system was negligibly dependent on hematocrit. An additional check on the system was made by conducting one experiment with both the Doppler system and an electromagnetic flow-measuring system (Statham SP2200) simultaneously. In this case zero blood flow was determined using a previously implanted hydraulic occlusion cuff.

Arterial blood pressure was measured with miniature gauges (15) in six dogs. These were calibrated before and after implantation and also in vivo against a calibrated Statham P23Db
strain-gauge manometer. In three dogs arterial blood pressure was measured through the chronically implanted catheter with a Statham P23Db strain-gauge manometer. A Beckman cardiostachometer (9857B), triggered by the instantaneous pressure signal, was used to compute heart rate on a beat-to-beat basis.

The experiments were begun 2-4 weeks after recovery from the operations, when the dogs were vigorous and healthy. While the dogs were lying quietly in the laboratory, control recordings of regional blood flows and arterial blood pressure were made on at least three separate occasions during the week prior to phlebotomy. Recordings of coronary blood flow and arterial blood pressure were also made when the atria were electrically stimulated to a frequency of 130 beats/min. Blood, 20-40 ml/kg, was removed via the jugular catheter, and volume was replaced with a combination of the harvested plasma and dextran. Resting measurements of regional flows, arterial blood pressure, and hematocrit were again made 2-3 days after phlebotomy and subsequent volume replacement. This sequence was repeated until the dogs attained hematocrits of less than 16%. An average of 3 weeks was required to achieve this level of anemia. In this manner the effects of progressively intense anemia on regional flows and pressure were established.

The exercise studies were conducted in five dogs during severe anemia. The apparatus for measurement and telemetry of flow and pressure was carried in a backpack while the dogs ran behind a mobile recording unit in the field at speeds of 4-6 mph. The techniques used here were described in greater detail previously (12). The severely anemic animals were generally lethargic and would run only if a leash was loosely attached to the harness arrangement of the backpack.

To examine the extent to which the coronary bed dilated during anemia, the coronary dynamic response to a known primary and secondary vasodilator, isoproterenol, was determined in five normal dogs and in five dogs with severe anemia. Isoproterenol, 1.0 μg/kg, was administered intravenously in a bolus while the animals were resting in the laboratory.

The data were played back on a direct-writing multichannel oscillograph. Mean arterial blood pressure and mean blood flows were derived from the phasic signals using electronic resistance-capacitance filters with a 2-second time constant. Mean vascular resistances were calculated as the quotient of mean arterial blood pressure and mean blood flow. Late-diastolic coronary resistance was calculated as the quotient of late-diastolic pressure and late-diastolic coronary blood flow.

Results

Heart rate, arterial blood pressure, regional blood flows, and regional resistances were compared in the same dogs at rest before hemorrhage (hematocrit 40 ± 1% se), during moderate anemia (hematocrit 22 ± 1%), and during severe anemia (hematocrit 14 ± 1%). Results before and after splenectomy were not significantly different; accordingly, control values after splenectomy were used.

Moderate Anemia.—Heart rate increased from 73 ± 3 beats/min to 105 ± 5 beats/min, and arterial blood pressure fell slightly, but not significantly, from 98 ± 3 mm Hg to 94 ± 4 mm Hg (Table 1). Mean left circumflex coronary flow increased 75 ± 11% above a control value of 40 ± 3 ml/min, and mean coronary resistance decreased 45 ± 4% from a control value of 2.50 ± 0.19 mm Hg/ml min⁻¹. Late-diastolic flow and resistance followed a similar pattern. Mesenteric flow and resistance were not significantly different from their control values, but renal flow decreased slightly, by 9 ± 4% (P < 0.05), from a control value of 179 ± 11 ml/min and renal resistance increased slightly, but not significantly, from a control value of 0.56 ± 0.04 mm Hg/ml min⁻¹. Iliac blood flow rose 45 ± 11% from a control value of 147 ± 15 ml/min and resistance fell 32 ± 7% from a control value of 0.71 ± 0.07 mm Hg/ml min⁻¹.

Severe Anemia.—Heart rate increased further to 129 ± 5 beats/min, and arterial blood pressure, 96 ± 4 mm Hg, remained almost precisely at the control level (Table 1). Mean left circumflex coronary flow rose to 227 ± 11% of the control value, and resistance fell 69 ± 3% from the control value. These values were significantly different (P < 0.01) from values for both the control state and moderate anemia. Late-diastolic flow and resistance followed a similar pattern. Mesenteric blood flow rose 29 ± 5% above a control value of 314 ± 20 ml/min, and resistance was reduced 23 ± 4% from a control value of 0.32 ± 0.02 mm Hg/ml min⁻¹. These values were significantly different (P < 0.01) from the control values and from those observed during moderate anemia. Renal flow was 20 ± 3%
TABLE 1

Effects of Moderate and Severe Anemia on Regional Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Moderate anemia</th>
<th>Severe anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>40 ± 1</td>
<td>22 ± 1*</td>
<td>14 ± 1*†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 3</td>
<td>105 ± 5*</td>
<td>129 ± 5*†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>98 ± 3</td>
<td>94 ± 4†</td>
<td>96 ± 4†</td>
</tr>
<tr>
<td>Mean coronary flow (ml/min)</td>
<td>40 ± 3</td>
<td>71 ± 3*</td>
<td>131 ± 16†</td>
</tr>
<tr>
<td>Mean coronary resistance (mm Hg/ml min⁻¹)</td>
<td>2.50 ± 0.19</td>
<td>1.36 ± 0.10*</td>
<td>0.78 ± 0.07†</td>
</tr>
<tr>
<td>Late-diastolic coronary flow (ml/min)</td>
<td>47 ± 3</td>
<td>79 ± 5*</td>
<td>153 ± 19†</td>
</tr>
<tr>
<td>Late-diastolic coronary resistance (mm Hg/ml min⁻¹)</td>
<td>1.76 ± 0.16</td>
<td>1.03 ± 0.11*</td>
<td>0.54 ± 0.05†</td>
</tr>
<tr>
<td>Mesenteric flow (ml/min)</td>
<td>314 ± 20</td>
<td>301 ± 19†</td>
<td>402 ± 23†</td>
</tr>
<tr>
<td>Mesenteric resistance (mm Hg/ml min⁻¹)</td>
<td>0.32 ± 0.02</td>
<td>0.33 ± 0.02‡</td>
<td>0.25 ± 0.02‡</td>
</tr>
<tr>
<td>Renal flow (ml/min)</td>
<td>179 ± 11</td>
<td>162 ± 12‡</td>
<td>214 ± 12†</td>
</tr>
<tr>
<td>Renal resistance (mm Hg/ml min⁻¹)</td>
<td>0.56 ± 0.04</td>
<td>0.60 ± 0.05‡</td>
<td>0.46 ± 0.03‡</td>
</tr>
<tr>
<td>Iliac flow (ml/min)</td>
<td>147 ± 15</td>
<td>309 ± 17*</td>
<td>288 ± 18*</td>
</tr>
<tr>
<td>Iliac resistance (mm Hg/ml min⁻¹)</td>
<td>0.71 ± 0.07</td>
<td>0.47 ± 0.06‡</td>
<td>0.35 ± 0.05‡</td>
</tr>
</tbody>
</table>

Values are means ± sis.

*P < 0.01 compared to control.
†P < 0.01 compared to moderate anemia.
‡No significant difference compared to control.
§P < 0.05 compared to control.

above its control value (Fig. 1), and renal resistance fell 19 ± 4% from its control value. These values were significantly different (P < 0.01) from values for both the control state and moderate anemia. Iliac flow had increased further to 102 ± 9% above the control level, and iliac resistance had declined further to 52 ± 4% below the control level. These values were significantly different (P < 0.01) from values for both moderate anemia and the control state.

Effects of Exercise During Severe Anemia.

In five dogs with severe anemia, steady-state exercise (4-6 mph) increased heart rate from 136 ± 9 beats/min to 224 ± 17 beats/min, arterial blood pressure from 96 ± 7 mm Hg to 114 ± 9 mm Hg, mean left circumflex coronary flow by over 34 ± 5% from a control value of 122 ± 8 ml/min, and iliac flow by 215 ± 11% from a control value of 301 ± 24 ml/min (Fig. 2). This level of exercise reduced mesenteric flow 59 ± 5% from a control value of 392 ± 19 ml/min and renal flow 48 ± 5% from a control value of 205 ± 14 ml/min (Fig. 3). Exercise decreased resistance in the coronary bed 17 ± 3% from a control value of 0.78 ± 0.06 mm Hg/ml min⁻¹ and in the iliac bed 72 ± 9% from a control value of 0.32 ± 0.04 mm Hg/ml min⁻¹; it increased resistance in the mesenteric bed 196 ± 17% from a control value of 0.32 ± 0.04 mm Hg/ml min⁻¹ and in the renal bed 129 ± 13% from a control value of 0.46 ± 0.06 mm Hg/ml min⁻¹. All of the changes in regional flow and resistance that occurred during exercise were significantly different from the control values before exercise (P < 0.01).

Effects of Isoproterenol on the Coronary Bed.

To test the extent to which the coronary bed dilated during severe anemia, a relatively large dose of isoproterenol, 1.0 μg/kg, was administered intravenously in a bolus. In five normal dogs it caused a sustained rise in coronary flow (Fig. 4). An early initial vasodilatation occurred, and coronary flow rose 164% above a control value of 38 ml/min, while arterial blood pressure fell by 11 mm Hg. Heart rate increased from 82 beats/min to 156 beats/min, and mean coronary resistance decreased 67%. When mean arterial blood pressure had declined a maximum of 38 mm Hg, mean coronary flow was still 147% above the control value, heart rate was 225 beats/min, and mean coronary resistance had decreased 75%. The maximum
value of coronary flow attained after administration of isoproterenol was less than the value for coronary flow at rest when the dogs had become severely anemic.

In five dogs, with severe anemia the same dose of isoproterenol caused a lesser initial increase in coronary flow: it rose 23% above a control value of 134 ml/min. Arterial blood pressure fell only 9 mm Hg, mean coronary resistance decreased 26%, and heart rate increased from 128 beats/min to 152 beats/min (Fig. 4). When mean arterial blood pressure fell a maximum of 35 mm Hg, coronary flow was essentially at control levels and heart rate attained a maximum value of 204 beats/min. Thus, isoproterenol substantially augmented coronary flow and decreased coronary resistance in normal dogs, but it produced much less additional coronary vasodilatation when the coronary bed was already dilated due to severe anemia.

Discussion

The present study determined the relative participation of four major regional circulations in the response to the hypoxic stress
induced by moderate and severe anemia. The greatest percent increase in blood flow and the greatest reduction in resistance was observed in the coronary bed. This augmentation of flow occurred during both diastole and systole while the phasic wave form changed in character, since systolic flow during anemia no longer approached zero (Figs. 3, 4). The increases in coronary flow and the decreases in resistance were proportional to the severity of anemia, an observation also noted by others (16–19). Thus, the coronary bed, which can increase oxygen extraction only slightly during anemia (17), adjusts to the hypoxic stress by reducing resistance and increasing blood flow. Since coronary flow is known to vary directly with heart rate (20, 21) and since heart rate increased significantly during anemia, the relative contribution of tachycardia to the augmentation of coronary blood flow was measured by electrically stimulating the atria in the dogs prior to anemia to approximately the cardiac frequency attained during severe anemia, 130 beats/min. This rise in heart rate increased mean coronary flow 19 ± 3% and decreased mean coronary resistance 16 ± 3%. The increase in coronary flow with simple tachycardia was approximately 10% of the total increase observed during severe anemia, and the decrease in resistance was approximately 20% of the total reduction observed during severe anemia.
Comparison of the response to isoproterenol, 1 µg/kg, on phasic and mean arterial pressure, phasic and mean left circumflex coronary blood flow, and heart rate in the control state (left) and after severe anemia had been induced (right).

The coronary vascular response to severe anemia at rest can be compared to the response of the normal coronary bed to severe exercise (22) or to a large dose of isoproterenol (Fig. 4). The responses of the coronary bed to exercise (Fig. 3) and to administration of isoproterenol (Fig. 4) during severe anemia were characteristic of an already dilated bed in that the increases in flow and the decreases in resistance caused by these challenges were blunted. However it is remarkable that resistance still declined 17% during exercise and 26% after administration of isoproterenol. These findings suggest that anemia may not have produced maximal coronary dilatation, or it is also possible that anemia opened collateral channels in the coronary bed and that the capacity of the coronary bed to vasodilate may have been augmented.

The circulation to the limb, i.e., the iliac bed, in the present study showed the second largest response to anemia. With increasingly severe anemia, the increase in iliac blood flow and the reduction in iliac resistance increased progressively. Results from previous studies on the response of the limb circulation have been conflicting. Several studies have reported that limb flow decreases during moderate anemia (6, 23), some have reported little change (1, 9, 24) or no change during moderate anemia and increases during severe anemia (25), but still others have reported only increases (26-30). The apparent discrepancy between our findings and some of those reported previously can be reconciled on two bases. First, in the present study iliac blood flow was measured directly, whereas the previous studies used indirect techniques to measure limb flow (1, 6, 9, 23-30). Second, some of the previous studies measured only the response of the hand (23). It is conceivable that flow to the muscle increases but that flow to the bone and skin decreases during anemia; thus, total limb flow could increase even in the face of a reduction in flow to the hand. Indeed, Abramson et al. (26) found an increase in flow to the forearm and a reduction in flow to the hand in man, and Hatcher et al. (27) observed an increase in flow to the calf and a decrease in flow to the paw in the dog.

The renal circulatory adjustments to anemia are even less well established. Although some studies have noted no change or a slight increase in renal blood flow during anemia (30-33), it is generally held that the renal bed...
responds to anemia with marked vasoconstriction to provide additional blood flow for the heart and brain (1-9). This response of diversion of renal flow has teleological attractiveness since there is normally a wide arteriovenous O₂ difference across this bed, which could thus tolerate a reduction in arterial oxygen content without necessarily impairing oxygen delivery. However, in this study we observed that during moderate anemia renal blood flow was only slightly reduced and during severe anemia (hematocrit < 15%) renal flow had actually increased 20% above the control level and renal resistance had fallen. The mesenteric bed, which also normally has a wide arteriovenous O₂ difference, responded in a similar fashion; the increases in blood flow and the reduction in resistance in that bed during anemia were slightly greater than those in the renal bed. It must be noted that since the blood viscosity decreases during anemia (34, 35) at the same arterial blood pressure a variation in blood flow might not reflect a change in vasomotor tone despite a change in calculated resistance. Studies on the effects of hematocrit on blood viscosity in the canine hind limb (34, 35) indicate that a reduction in hematocrit from 40% to 14%, as occurred in the present study, could decrease blood viscosity 20-25%. Thus, viscosity changes alone could not account for the decreases in resistance observed in the coronary and iliac beds, but they might be entirely responsible for the 20-25% increases in flow and reductions in calculated resistance observed in the mesenteric and renal beds during severe anemia. However, regardless of whether the increase in blood flow to the visceral beds is due to reduction in vasomotor tone or in viscosity, it can be concluded that in the conscious dog a compensatory reduction of renal and mesenteric flows is not a feature of the cardiovascular adjustment to severe anemia at rest.

There are several possible explanations of the apparent discrepancy between our findings and those reported by others (1-9). The technique which was used in most of these studies (1-5, 7, 8), i.e., para-aminohippurate (PAH) clearance, is insensitive to renal arterial inflow which is shunted around the peritubular capillary network. Since intrarenal shunting occurs during anemia, the PAH-clearance technique underestimates renal plasma flow (36-40), and discrepancies between renal blood flow measured directly and that measured with the PAH technique have been demonstrated in anemic animals (36-39). The discrepancy is probably not species dependent, since renal cortical shunting during anemia has been described in man as well (40).

The degree of anemia appears to be important in evaluating the response to anemia. In the present study a slight reduction of renal blood flow occurred during moderate anemia (average hematocrit 22%) but was not observed as anemia became more intense. Some of the studies describing renal vasoconstriction and reduction of flow were conducted only during moderate anemia (2, 6, 9). Thus, diversion of a small quantity of flow from the renal bed appears to occur during moderate anemia, and this compensatory shunting could be exaggerated by the inaccuracies inherent in the PAH-clearance technique during anemia. However, in the present study renal blood flow returned to the control value and actually increased above this value as the level of anemia became more intense.

Also in this study the experimental animals were normal and healthy other than being anemic, whereas in some previous studies some of the human subjects with anemia had diseases which might have affected renal blood flow, e.g., chronic renal disease and disseminated carcinoma (3, 5). There is evidence to support the hypothesis that associated renal disease might affect the renal vascular response to anemia; studies in patients with sickle cell anemia have shown that in the child with this disease renal blood flow is greater than normal (33), but in the adolescent and young adult the trend reverses and renal flow decreases to levels substantially below control (41). Thus, the general physical condition of the patient and particularly the
status of the kidney may alter the normal renal hemodynamic response to anemia. Although severe anemia did not reduce mesenteric and renal blood flows, exercise in the presence of severe anemia caused marked and sustained reductions in these flows (Figs. 2, 3). The response to severe exercise in normal dogs does not involve sustained reductions in visceral blood flows (12), but when normal compensatory adjustments to exercise are limited reduction of renal and mesenteric blood flows occurs. The mechanism of diversion of visceral flow during exercise can be invoked when the normal increase in heart rate is limited as in complete heart block (12), when the normal increase in stroke volume is limited as in congestive heart failure (unpublished observation), or when the oxygen-carrying capacity of the blood is limited as in the present study.

Thus, the regional beds adjusted to the hypoxic stress of anemia in the following manner. During moderate anemia blood flow to the limbs increased but not to as great an extent as coronary blood flow, mesenteric flow remained essentially constant, and renal flow decreased only slightly. During severe anemia blood flow increased and resistance decreased in all beds studied. The largest increases in flow and decreases in resistance occurred in the coronary bed and the second largest in the limb circulation. Mesenteric and renal flows were also significantly elevated above their control levels indicating that, although redistribution of blood flow occurred, compensatory reduction of mesenteric and renal flows was not one of the cardiovascular adjustments to severe anemia at rest. However, when the stress of exercise was added to the hypoxic stress induced by severe anemia, the compensatory mechanism of reduction and diversion of visceral flows was invoked.

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References


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