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Effect of Hydralazine on Nutritive Flow to Working Canine Gracilis Skeletal Muscle

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The direct smooth muscle vasodilator hydralazine has been used to treat exertional fatigue in patients with chronic heart failure. However, prior studies suggest that arteriolar vasodilators such as hydralazine may actually impair nutritive flow to working skeletal muscle by interfering with the distribution of blood flow within muscle. To investigate this possibility, tension development and metabolism were measured in nine vascularly isolated gracilis muscle preparations perfused at 90 mm Hg and stimulated to contract progressively at rates of 1, 3 and 6/s with each stage lasting 3 minutes. Studies were then repeated after 30 minutes of intraarterial hydralazine (0.02 to 0.12 mg/min).

At rest, hydralazine decreased mean vascular resistance (±SEM) from 15.1 ± 1.4 to 8.6 ± 0.9 × 10^2 units ($p < 0.001$) and increased blood flow from 6.4 ± 0.7 to 11.4 ± 1.2 ml/min ($p < 0.001$), but did not change oxygen consumption ($\dot{V}O_2$) control, 18 ± 1 versus hydralazine, 17 ± 2 μl/min). Hydralazine also decreased vascular resistance and increased flow at a contraction rate of 1/s, but not at 3 and 6/s. Hydralazine had no effect on maximal $\dot{V}O_2$ (control, 254 ± 18 versus hydralazine, 236 ± 19 μl/min), maximal developed tension (control, 353 ± 90 versus hydralazine, 334 ± 74 kg·min) or the response in venous lactate (control, 20.6 ± 2.3 versus hydralazine, 18.1 ± 2.0 mg/dl). Hydralazine also did not change muscle metabolism and function at contraction rates of 1 and 3/s. These data suggest that hydralazine does not adversely affect nutritive flow to working skeletal muscle.

The exercise capacity of patients with chronic heart failure is limited (1–3) partly because of inadequate nutritive flow to working skeletal muscle (2–6). The direct smooth muscle vasodilator, hydralazine, increases limb blood flow at rest (7) and cardiac output during exercise in such patients (8–10). Therefore, this agent has been extensively used to treat patients with heart failure in the hope of improving their skeletal muscle nutritive flow and exercise tolerance (9–12).

It is possible, however, that hydralazine adversely affects nutritive flow. During exercise, local vasodilating factors within working skeletal muscle produce arteriolar vasodilation, permitting greater blood flow to muscle (13,14). Precapillary sphincters also dilate, increasing overall capillary flow and distributing the blood flow to the most metabolically active segments of the muscle (13,14). Administration of the nonspecific vasodilator, hydralazine, may disrupt this normal pattern of flow by redistributing flow away from the most active segments of muscle to less active segments, thereby causing a deficiency of nutritive flow to the most active muscle. In support of this hypothesis, dilation of arterioles in contracting cat gastrocnemius-soleus muscle by histamine, bradykinin and isoproterenol has been noted (15,16) to reduce muscle contractile force, suggesting interference with nutritive flow. The present study was, therefore, undertaken to investigate the effect of hydralazine on skeletal muscle nutritive flow during exercise.

Methods

Experimental preparation. Nine adult mongrel male dogs (≥25 kg) were anesthetized with pentobarbital sodium (30 mg/kg intravenously) and artificially ventilated. Preparation of the gracilis muscle was similar to that described by Flaim et al. (17). In brief, the left gracilis muscle was exposed and vascularly isolated, except for the main gracilis artery and vein. The right femoral artery and veins were cannulated. After intravenous heparinization (300 units/kg), blood from the right femoral artery was pumped to a pres-

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surized perfusion reservoir. The left gracilis artery was then cannulated and connected to the perfusion reservoir. Perfusion pressure was set at 90 mm Hg and monitored with a Statham transducer, while blood flow was measured with a Biotronix extracorporeal electromagnetic flowmeter positioned in the perfusion line. The gracilis vein was also cannulated and venous blood returned to the right femoral vein.

The proximal upper aponeurosis of the muscle was securely clamped to a rigid steel bar positioned over the long axis of the muscle. The distal aponeurosis was clamped to a tension transducer that was also coupled to the steel bar. The distance between the distal and proximal muscle clamps was then adjusted to retain the resting muscle length.

The gracilis nerve was ligated, divided and attached to bipolar electrodes. The nerve was stimulated with 8 ms supramaximal monophasic square wave impulses using a Grass stimulator. Such stimuli have been shown (18) to recruit all motor units without exciting autonomic nerve fibers.

The muscle was wrapped with Saran wrap to prevent drying and heat loss. Gracilis muscle surface temperature was monitored and maintained at 34 to 36°C with a heat lamp. The blood perfusion reservoir was surrounded by a water bath that was kept at 37°C. The dog temperature was kept at 37°C with a heat lamp. Ventilatory variables were adjusted to maintain partial pressure of oxygen (Po_2), partial pressure of carbon dioxide (PCo_2) and pH within normal range and arterial oxygen saturation at 95% or greater.

Measurements. Muscle tension, perfusion pressure and gracilis blood flow were recorded. Calibration of the electromagnetic flow meter was checked by timed collection of venous blood. Arterial and venous blood samples were analyzed for functional hemoglobin and hemoglobin oxygen saturations with an Instrumentation Laboratories co-oximeter. Blood samples for lactate determination were immediately deproteinized with iced perchloric acid and analyzed using a spectrophotometric technique (19).

Arterial oxygen content was calculated as arterial saturation × hemoglobin × 1.34 ml oxygen/g of hemoglobin. Oxygen consumption ($\dot{V}O_2$) was calculated as the arteriovenous oxygen difference × blood flow. Oxygen extraction was calculated as the arteriovenous oxygen difference ÷ arterial oxygen content. Muscle vascular resistance, expressed as units, was calculated as 90 mm Hg ÷ blood flow. Developed tension/min was calculated as (contractions/min) × (tension/contraction).

Experimental protocol. Measurements at rest of flow and gracilis arterial and venous oxygen saturations and lactate concentrations were taken when all variables were determined to be in a steady state, usually at least 1 hour after instrumentation. The muscle was then stimulated to contract progressively at rates of 1, 3 and 6/s with each stage of work lasting 3 minutes. At the end of each stage, all measurements were repeated, except for arterial lactate which was measured at rest, between the first and second work stage and at peak exercise.

The muscle was then allowed to rest (recover) for 60 minutes. At the end of this time, prehydralazine measurements were made. Hydralazine in normal saline solution (0.3 mg/ml) was then infused directly into the arterial perfusion line at 0.02 mg/min for 20 minutes. If no effect on blood flow was noted, the infusion rate was increased by 0.02 mg/min increments every 10 minutes until flow increased by 20% or more or a peak infusion rate of 0.12 mg/min, or both, was achieved. Peak hydralazine infusion rates averaged 0.05 mg/min (range 0.02 to 0.12). The infusion rate was then maintained constant for a total of 30 minutes before obtaining measurement at rest and repeating the exercise protocol.

Reproducibility studies. Two gracilis muscle preparations were studied to establish reproducibility of the response to exercise. Studies were performed exactly as just described, including the infusion of saline solution during the second exercise period. However, hydralazine was not added to the saline solution. Measurements at rest before the first and second exercise periods were reproducible: flow 4.9 versus 4.5 ml/min, respectively, $\dot{V}O_2$ 9.2 versus 12.9 μl/min, respectively, venous lactate 30.3 versus 30.4 mg/dl, respectively and arterial lactate 28.4 versus 28.1 mg/dl, respectively. Exercise data at a contraction rate of 6/s were also reproducible: flow 11.2 versus 11.1 ml/min, $\dot{V}O_2$ 137 versus 128 μl/min, developed tension 720 versus 725 kg·min, venous lactate 52.0 versus 55.2 mg/dl and change in venous lactate 23.0 versus 24.9 mg/dl. Measurements at stimulation rates of 1 and 3/s were similarly reproducible.

Data analysis. Statistical comparison of measurements were made using the Student's *t* test for paired data. A probability value of less than 0.05 was considered statistically significant. All data are presented as mean ± standard error of the mean.

Results

Effect of exercise on skeletal muscle flow and metabolism (Fig. 1 and 2). The average values at rest were: blood flow 6.4 ± 0.7 ml/min, resistance 15.1 ± 1.4 × 10^2 units, $\dot{V}O_2$ 18 ± 1 μl/min, oxygen extraction 19.6 ± 2.5% and arteriovenous lactate difference across the muscle 4.1 ± 1.8 mg/dl (Table 1).

Exercise resulted in a progressive increase in developed tension to 188 ± 20 kg/min at a stimulation rate of 1/s and to 293 ± 30 kg/min at 3/s. No further significant increase in tension occurred at a stimulation rate of 6/s. Flow increased to 14.3 ± 0.9 ml/min at a stimulation rate of 1/s and to 17.2 ± 1.2 ml/min at 3/s but did not increase further at 6/s, suggesting achievement of maximal oxygen delivery. $\dot{V}O_2$ increased at 198 ± 18 μl/min at a stimulation rate of

Table 1. Effect of Hydralazine on Muscle Flow, Vascular Resistance, Developed Tension and Metabolism at Rest and at Contraction Rates of 1, 3 and 6/s

		Contraction Rate		
	Rest	1/s	3/s	6/s
Flow (ml/min)				
Control	6.4 ± 0.7	14.3 ± 0.9	17.2 ± 1.2	16.6 ± 1.0
Hydralazine	11.4 ± 1.2†	15.9 ± 0.8*	16.2 ± 1.1	15.7 ± 0.8
Resistance ($\times 10^2$ units)				
Control	15.1 ± 1.4	6.6 ± 0.5	5.4 ± 0.3	5.6 ± 0.5
Hydralazine	8.6 ± 0.9†	5.8 ± 0.3*	5.8 ± 0.4	5.9 ± 0.4
Developed tension (kg/min)				
Control	—	188 ± 20	293 ± 30	353 ± 90
Hydralazine	—	175 ± 24	284 ± 33	344 ± 74
Oxygen extraction (%)				
Control	19.6 ± 2.5	83.7 ± 3.3	95.1 ± 0.6	92.6 ± 1.5
Hydralazine	9.7 ± 1.9†	71.2 ± 5.4*	89.9 ± 2.5*	91.1 ± 1.7
$\dot{V}O_2$ (μl/min)				
Control	18 ± 1	198 ± 18	270 ± 23	254 ± 18
Hydralazine	17 ± 2	186 ± 20	238 ± 21	236 ± 19
Venous lactate (mg/dl)				
Control	26.5 ± 4.4	27.2 ± 3.8	41.5 ± 4.1	47.1 ± 3.3
Hydralazine	23.1 ± 3.1	24.1 ± 4.1	40.4 ± 4.9	41.2 ± 3.5*
Δ Venous lactate (mg/dl)				
Control	—	0.7 ± 1.5	15.0 ± 2.8	20.6 ± 2.3
Hydralazine	—	3.0 ± 1.4	17.3 ± 3.9	18.1 ± 2.0
Arterial lactate (mg/dl)				
Control	22.7 ± 3.0	22.3 ± 3.3		21.2 ± 3.7
Hydralazine	23.1 ± 3.4	22.5 ± 3.8		21.4 ± 3.8
AV lactate difference (mg/dl)				
Control	4.1 ± 1.8	4.9 ± 1.5	19.2 ± 2.6	24.8 ± 1.5
Hydralazine	0.8 ± 0.9	3.8 ± 1.3	18.1 ± 3.9	18.9 ± 1.9*

*$p < 0.05$; †$p < 0.01$ compared with control. AV = arteriovenous; $\dot{V}O_2$ = oxygen consumption.

1/s and 270 ± 23 μl/min at 3/s but again reached a plateau at 6/s.

With exercise at a stimulation rate of 1/s, venous lactate was not significantly different from levels at rest. Thereafter, venous lactate increased by 15.0 ± 2.8 mg/dl at 3/s and by 20.6 ± 2.3 mg/dl at 6/s. Arterial lactate remained unchanged throughout exercise.

Effect of hydralazine on skeletal muscle flow and metabolism (Fig. 1 and 2). At rest, hydralazine decreased muscle resistance from 15.1 ± 1.4 to 8.6 ± 0.9 × 10^2 units ($p < 0.001$). Of the nine muscle preparations, six had an increase in flow of more than 50%, two had an increase of 20 to 50% and one had an increase of 8%. Oxygen extraction concomitantly decreased from 19.6 ± 2.5% to 9.7 ± 1.9% ($p < 0.001$), so that $\dot{V}O_2$ remained unchanged (control, 18 ± 1 μl/min versus hydralazine, 17 ± 2 μl/min). Venous and arterial lactate levels were also unchanged.

With hydralazine, flow at a stimulation rate of 1/s was significantly higher than during control exercise (control, 14.3 ± 0.9 ml/min versus hydralazine, 15.9 ± 0.8 ml/min [$p < 0.03$]). However, flow at the other two stimulation rates was not significantly different from control exercise values. Moreover, the minimal vascular resistance achieved was similar before (5.6 ± 5 × 10^2 units) and after hydralazine (5.9 ± 0.4 × 10^2 units).

Oxygen extraction was significantly reduced at a stimulation rate of 1/s (control, 83.7 ± 3.3% versus hydralazine, 71.2 ± 5.4% [$p < 0.05$]) and at 3/s (control, 95.1 ± 6% versus hydralazine, 89.9 ± 2.5% [$p < 0.05$]), but not at 6/s (control, 92.6 ± 1.5% versus hydralazine, 91.1 ± 1.7%). However, developed tension and $\dot{V}O_2$ were not significantly different from control exercise values at all three stimulation rates, maximal $\dot{V}O_2$ being 254 ± 18 μl/min before and 236 ± 19 μl/min after hydralazine.

Changes in venous lactate were not significantly different from control exercise values at rates of 1, 3 and 6/s (control, 20.6 ± 2.3 mg/dl versus hydralazine, 18.1 ± 2.0 mg/dl). The arteriovenous lactate difference during exercise was

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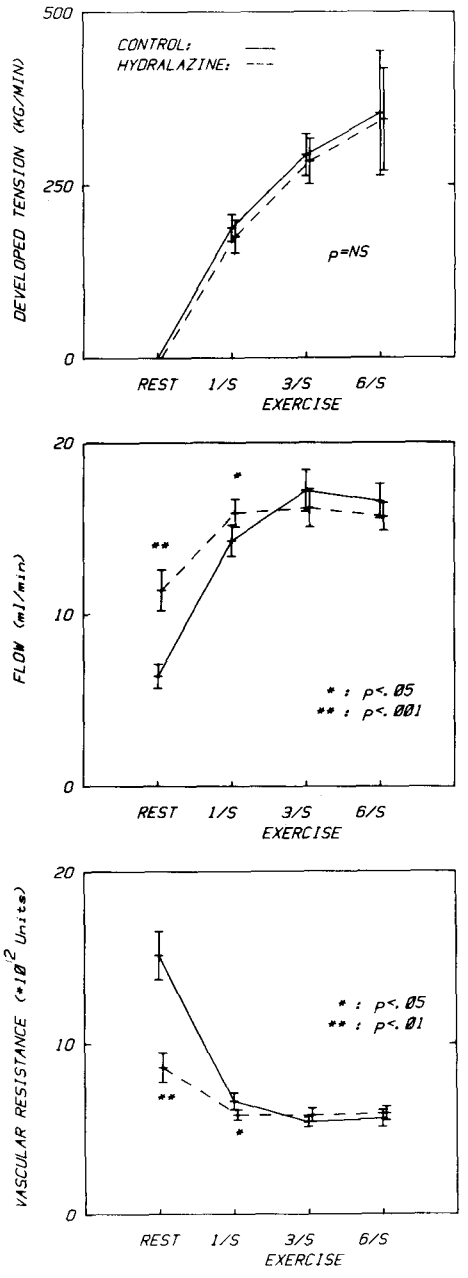

Figure 1. Effect of hydralazine on vascular resistance, flow and developed tension at rest and at muscle contraction rates of 1, 3 and 6/s. Significant differences between control and hydralazine data are noted by **asterisks.**

also not significantly different at a stimulation rate of 1 and 3/s, but was slightly lower at 6/s after hydralazine (control, 24.8 ± 1.5 mg/dl versus hydralazine, 18.9 ± 1.9 mg/dl [$p < 0.02$]). This may have been due to a tendency for the arteriovenous lactate difference at rest to be lower after hydralazine (control, 4.1 ± 1.8 mg/dl versus hydralazine, 0.8 ± 0.8 mg/dl), rather than to a change in the degree of lactate released during exercise. Arterial lactate was unchanged by hydralazine and remained stable throughout exercise.

Discussion

During exercise, nutritive flow to working skeletal muscle is increased by dilation of arterioles, resulting in increased blood flow, and by dilation of precapillary sphincters, invoking a greater functional capillary density in the proximity of working cells (13,14). Normally, these two independent processes act in concert to maximize delivery of oxygen to the most metabolically active cells and thereby optimize muscle function. However, administration of various compounds with vasodilator activity (for example, isoproterenol, histamine and bradykinin) appears to disrupt this normal microcirculatory response to muscular work and thereby depresses muscle force development (15,16). This occurs most strikingly when flow is experimentally held constant. This pharmacologically mediated adverse circulatory response is not associated with changes in the capillary filtration coefficient, making it unlikely that capillary density or filtration is altered (15,16). Consequently, it has been suggested that arteriolar vasodilators can adversely affect the distribution of nutritive blood flow either within the available capillaries or by diverting flow to channels outside the muscle proper, such as connective tissue.

Effect of hydralazine on skeletal muscle nutritive flow in patients with heart failure. To investigate whether hydralazine alters skeletal muscle nutritive flow, we initially undertook a study (20) in patients with heart failure. In that study, we examined the effect of hydralazine on limb blood flow and metabolism during maximal upright bicycle exercise in 10 patients. During exercise, hydralazine increased leg blood flow, but did not change femoral venous lactate, arterial lactate, maximal $\dot{V}O_2$ or maximal exercise capacity. We, therefore, proposed that hydralazine probably does not improve or impair skeletal muscle nutritive flow.

However, in that prior study (20), we could not be certain that our measurements reflected muscle nutritive flow. Maximal systemic $\dot{V}O_2$ and maximal exercise capacity in patients with heart failure are influenced to some extent by motivational factors. Lactate measurements in femoral venous and arterial blood do not necessarily reflect lactate release from maximally exercising muscle; both blood sources contain blood coming not only from maximally exercising muscle, but also from muscle that is not maximally exercising and, therefore, is metabolizing lactate (21). The use of total limb flow and $\dot{V}O_2$ to examine skeletal muscle behavior is similarly limited since these variables reflect the behavior of all tissue in the leg, not just muscle.

Effect of hydralazine on skeletal muscle nutritive flow in gracilis muscle. To more precisely establish the effect of hydralazine on skeletal muscle nutritive flow, we undertook the present study using an isolated working skeletal muscle. Total muscle perfusion and vascular resistance were monitored to examine the effect of hydralazine on arteriolar tone. Skeletal muscle oxygen consumption, lactate release

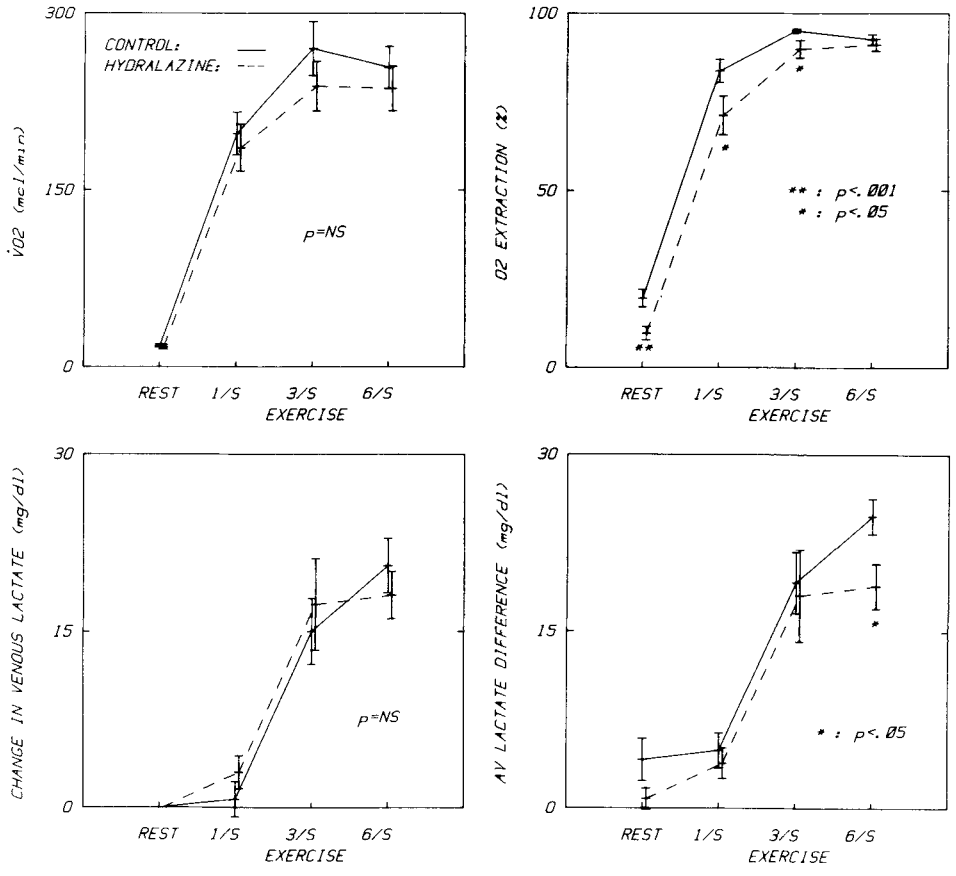

Figure 2. Effect of hydralazine on oxygen consumption ($\dot{V}O_2$), oxygen extraction, the exercise-induced change in venous lactate and the arteriovenous (AV) lactate difference at rest and at muscle contraction rates of 1, 3 and 6/s. Significant differences between control and hydralazine data are noted by **asterisks.**

and tension development were used to indirectly assess muscle nutritive flow. The perfusion pressure of 90 mm Hg was chosen because it is consistent with the reduced perfusion pressure present during exercise in patients with heart failure.

At rest, we observed that hydralazine significantly decreased vascular resistance and increased muscle blood flow, indicating that it dilates arterioles in skeletal muscle. Åblad and Mellander (22) noted similar changes in cat skeletal muscle, although at somewhat lower doses than required in our study. Such dilation also appears to occur in normal subjects and in patients with heart failure; in both groups, hydralazine increases limb blood flow at rest and decreases limb vascular resistance (7,20,23).

We also observed that hydralazine produced arteriolar dilation during submaximal exercise; at a stimulation rate of 1/s, resistance was significantly decreased by hydralazine while flow increased. At higher work loads, however, flow and resistance were unchanged by hydralazine. During control exercise, arteriolar resistance did not decrease further when the stimulation rate was increased from 3 to 6/s, suggesting that the resistance at 3/s reflected maximal arteriolar vasodilation. The failure of hydralazine to dilate vessels at these stimulation rates, therefore, suggests that it does not augment the normal maximal physiologic vasodilation of arterioles produced by exercise.

In contrast to these effects of hydralazine on arteriolar tone, we found little evidence that hydralazine alters nutritive flow to muscle. At rest, muscle oxygen uptake was unchanged. During exercise, tension increased progressively and to the same extent before and after hydralazine. In addition, metabolic responses to exercise were unchanged. During control exercise, oxygen uptake was increased at a stimulation rate of 1/s without evidence of lactate production, indicating adequate oxygen delivery and consistent with submaximal exercise. At a stimulation rate of 3/s, oxygen uptake increased further but with lactate production, suggesting inadequate oxygen delivery. At 6/s, oxygen uptake reached a plateau and further lactate production occurred, consistent with achievement of maximal oxygen uptake. Administration of hydralazine did not affect oxygen uptake or the change in mixed venous lactate produced by exercise. Only the arteriovenous lactate difference at 6/s was significantly altered by hydralazine. The observed reduction in this difference was most likely due to the lower venous lactate levels at rest observed after hydralazine rather than to any change in oxygen delivery. However, we cannot exclude the possibility that hydralazine improved oxygen delivery to some extent. Such a beneficial effect could be due to the higher flows at rest produced by hydralazine. This may result in more oxygen availability at the start of exercise than during the control exercise period. Such an

increase could reduce the early depletion of creatine phosphate that normally occurs at the start of exercise because of a temporary imbalance between oxygen delivery and energy demands (24). Even if such an effect is operative, however, it is unlikely to be of clinical importance.

Comparison of hydralazine with other vasodilatiors. In any event, on the basis of our finding it is unlikely that hydralazine reduces skeletal muscle nutritive flow. This lack of effect on nutritive flow contrasts with the previously described (15,16) reduction in nutritive flow produced by intraarterial isoproterenol, histamine and bradykinin. This difference may reflect basic differences between the effects of these agents and those of hydralazine on the vasculature. However, it is important to realize that the effect of isoproterenol, histamine and bradykinin on nutritive flow was assessed using an isolated cat gastrocnemius-soleus muscle group, rather than canine gracilis muscle. Moreover, the effect on nutritive flow of each agent was assessed while flow was held constant and muscle was stimulated at 1 to 2 contractions/s. Increasing flow was able to return muscle tension development to normal. Therefore, although it is possible that hydralazine would also interfere with tension development in this muscle preparation, this seems unlikely. In our preparation, flow was, in fact, fixed at contraction rates of 3 and 6/s. We observed no decrease in tension development with hydralazine, although we have observed striking and rapid impairment in tension development at these work loads when flow is reduced (20). In any event, the approach utilized in the present study probably yields information about the impact of vasodilators on muscle nutritive flow that is more relevant to the intact exercising animal than the information provided by constant flow preparations.

Implications. The findings of this experimental animal study suggest that hydralazine dilates arterioles in working skeletal muscle, but has no beneficial or deleterious effect on nutritive flow. This observation is consistent with our previous observations (20) in patients with congestive heart failure and serves to further support our previous conclusion that acute administration of hydralazine to such patients does not alter skeletal muscle nutritive flow.

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