Vascular Effects of Nylidrine Hydrochloride During Exercise. (25131)

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Various agents are capable of influencing regional blood flow. The vascular system apparently does not react as an entity to these agents; responses produced are neither uniform nor unidirectional in different vascular beds(1,2). The classical example of a drug, exhibiting both vasodilating and vasoconstricting activity at the same time is adrenaline, which dilates blood vessels of skeletal muscle and simultaneously constricts cutaneous vessels(3,4). There are situations in which vasodilation in muscle without vasoconstriction in skin is the desired effect. The first drug, fulfilling above criteria, was nylidrine hydrochloride (phenyl 2 butylnorsuprifen hydrochloride) known commercially as Arlidin,* chemically related to adrenaline and ephedrine. Several workers(5,6,7,8,9) found nylidrine caused dilation of blood vessels in the resting muscle without concomitant effects on skin. Exercise is the specific physiologic stimulus for producing vasodilation in skeletal muscle. Blood flow response is accompanied by little or no change in surface temperature. Consequently it seemed interesting to test the influence of nylidrine upon blood flow response to exercise.

Methods and material. Resting blood flow to foot and leg was measured by a large limb venous occlusion plethysmograph in 10 subjects in 20 experiments. Of these 10 subjects, 3 were without clinical evidence of cardiovascular disease; 7 patients had demonstrable non-gangrenous occlusive arterial disease. Surface temperature was recorded intermittently with a 6 lead Speedomax. All measurements were performed in constant temperature room at 20°C and 55% humidity with subject under basal conditions. After measurements of resting flow had been determined, the subject exercised for 5 minutes by pressing down 60 times/minute on foot board adjusted within the plethysmograph casement(10). Blood flow recordings were made immediately after exercise and every 2 minutes thereafter. When blood flow returned to pre-exercise base line levels, nylidrine (7 mg) was administered intravenously. After 15 minutes the exercise was repeated. Blood flow was measured every 2 minutes for 1 hour thereafter. All experiments were duplicated; in a number of experiments 2 exercise tests were done in succession, without drug administration. In a few experiments, tolazoline hydrochloride (50 mg) and azapetine (10 mg) were used for comparison.

Results. Resting blood flows ranged from 8.3 to 14.6 ml/100 ml tissue/min. in 3 normal subjects and from 4.7 to 8.1 ml/100 ml tissue/min. in 4 patients with occlusive arterial disease; in one sympathectomized patient blood flow was 11.4; in 2 who had been on oral Arlidin medication for several months prior to test, basal flows were 13.1 and 15.6 respectively. In response to first exercise test peripheral blood flow increased in all 10 subjects average 65.5%. Surface temperature rose in 3 subjects, average 4.6°C and did not show any essential change in 7 subjects (less than 2°C). When the exercise test was repeated after intravenous nylidrine (7 mg), 9 of 10 subjects showed average blood flow increase of 112.6%, exceeding that of initial exercise test by 47.5%. Surface temperature showed a small increase in 3, averaging 2.8°C; it decreased in 2 subjects, there was no significant change in surface temperature in 5. One subject with chronic sequelae of frost bite failed to show an increase in exercise response after nylidrine HCl.

Table I lists individual responses in all 10 subjects.

Fig. 1 shows a typical experiment. Control studies using repeated standardized tests without administration of nylidrine did not show any further increase in measured blood flow,

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TABLE I. Blood Flow Response in Lower Extremities to Standard Exercise before and after I.V. Nylidrine HCl 7 mg to 10 Subjects.

Age	ml/100 cc tissue/min. Basal flow	After exercise	%	Surface temp. change, °C	ml/100 cc tissue/min. after exercise and nylidrine	%	Surface temp. change, °C	Remarks
68	8.3	12.9	55	−1	14.9	80	−1.5	Normal
50	12.1	19.0	57	−1	24.0	100	0	"
38	14.6	19.9	36	+4	22.5	54	−2	"
76	8.1	10.8	33	+3	13.0	60	+2.5	Occlusive arterial disease (compensated)
38	11.4	19.4	70	+1	23.0	100	+1.5	Sympathectomized occlusive arterial disease
61	6.7	12.9	92	0	18.7	180	0	Occlusive arterial disease (compensated)
50	6.4	13.5	110	0	14.7	130	0	*Idem*
36	4.7	11.0	130	+1.5	8.7	85	−2	Frost-bite
62	13.1	17.6	34	+1.5	21.8	66	+3	Occlusive arterial disease (4 mo on oral Arlidin, prior to exp.)
64	15.6	31.7	103	+7	53.5	250	+3	*Idem* (9 mo on oral Arlidin, prior to exp.)

above level obtained on initial exercise. When tolazoline and azapetin were used for comparison, only negligible additional increases in rate of blood flow in response to exercise were obtained, while surface temperatures showed a significant rise.

Comment. Additional increase in blood flow of 47.5% in response to exercise after nylidrine was never accompanied by additional increase in surface temperature; on the contrary, in general, temperature readings were lower compared to response to exercise without nylidrine administration. In subject E. F. *e.g.* surface temperature increased by 4°C on initial exercise, but decreased by 2°C on exercise after nylidrine. It can be reasonably assumed that additional increment in blood flow after nylidrine goes mainly to the muscle. It seems unlikely that shunting of blood from skin bed to muscle bed occurs since surface temperature usually rises slightly in response to exercise, though less after than before nylidrine administration. It has been shown by Barcroft *et al.*(11) that basal flow in resting muscle is regulated by vasomotor centers, but that this neurogenic regulation is not responsible for circulatory changes during muscle activity. Existence of 2 separate sets of minute vessels in skeletal muscle of man, only one of which is in direct connection with vessel branches supplying the skin, has been demonstrated by Saunders *et al.*(12). It seems most likely then, that circulatory changes in resting muscle occur simultaneously with circulatory changes in the skin in response to stimuli(13,14). In contrast, circulatory changes during muscular activity are chiefly dependent on the action of metabolites produced during such activity(15) and the skin bed hardly participates in these responses (10). Wiemers(16) showed in cats and dogs,

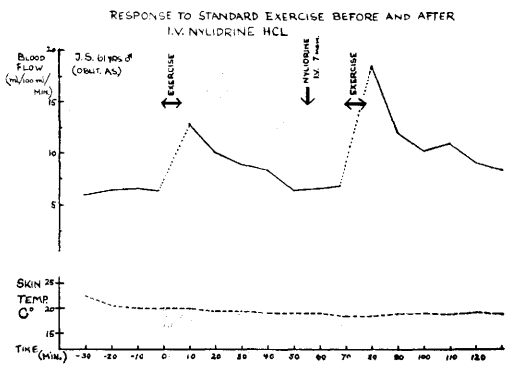

FIG. 1.

that depot blood was released from spleen and liver in response to nylidrine, without altering essentially the blood flow of remaining splanchnic bed. It is conceivable that most of this additional blood went to the periphery. A similar mechanism may perhaps be involved in our experiments.

There were no significant differences between directional and magnitudinal responses of normal subjects compared with patients with non-gangrenous occlusive arterial disease.

Summary and conclusions. Blood flow response to exercise was tested plethysmographically in 3 healthy subjects and 7 patients with non-gangrenous occlusive arterial disease of lower extremities, before and after intravenous administration of nylidrine hydrochloride, an adrenaline analog. Response in blood flow was significantly augmented after administratino of drug in all but one subject, who had severe bilateral frost bite. Since blood flow response to exercise takes place mostly in working skeletal muscles, it is concluded that the primary site of nylidrine action is in the vasculature of skeletal muscle. Nylidrine apparently enhances capacity of muscle vessels to respond to exercise.

1. Redisch, W., Wertheimer, L., Delisle, C., Steele, J. M., *Circulation,* 1954, v9, 68.

2. Steele, J. M., Redisch, W., *J. Chron. Dis.,* 1956, v4, 327.

3. Stein, I. D., Harpuder, K., Byer, J., *Am. J. Physiol.,* 1947, v150, 181.

4. Goodman, M. A., Gilman, A., *Pharmacological Basis of Therapeutics,* McMillan Co., 1941, p404.

5. Riddell, A. G., Steele, J. M., McCoy, J. M., *Angiology,* 1954, v5, 314.

6. Hensel, H., Ruef, J., Golenhofen, K., *ibid.,* 1955, v6, 190.

7. Stein, I. D., *Ann. Int. Med.,* 1956, v45, 185.

8. Klasson, D. H., *J. Am. Geriatric Soc.,* 1958, v6, 33.

9. Murphy, H. L., Klasson, D. H., *N. Y. State J. Med.,* 1957, v57, 108.

10. Redisch, W., de Crinis, K., Antonio, A., Bogdanovics, A., Steele, J. M., *Circulation,* 1959, v15, 579.

11. Barcroft, H., Dornhorst, A. C., McClatchey, H. M., Tanner, J. M., *J. Physiol.,* 1952, v117, 391.

12. Redisch, W., Tangco, F. F., Saunders, R. L., *Peripheral Circulation on Health and Disease,* Grune and Stratton, N. Y., 1957, p113.

13. Wertheimer, L., Lewis, A. J., Steele, J. M., *Circulation,* 1957, v15, 518.

14. de Crinis, K., Redisch, W., Antonio, A., Bogdanovics, A., Steele, J. M., *ibid.,* 1959, v15, 583.

15. Grant, R. T., *Clin. Sci.,* 1939, v3, 157.

16. Weiner, K., *Med. Klinik,* 1950, v45, 453.

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Fresh, Disintegrated Platelets in Radiation Thrombocytopenia: Correction of Prothrombin Consumption without Correction of Bleeding.* (25132)

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Platelets have 2 major functions in the hemostatic mechanism. The first is a mechanical action of intact platelets, the platelet plug(1) being the visible result of this effect, and the second is a complex biochemical role in coagulation. Many factors are involved, but the prothrombin consumption test may be taken to reflect the more important of these factors. It is essential to separate these 2 effects both from a theoretical and a practical point of view. Theoretically it should be known whether a normal clotting system, including platelet factors is able to maintain hemostasis in absence of mechanical effects of platelets. Practically, it should be known whether thrombocytopenic patients may benefit from platelet substitutes. Much and conflicting work is going on in this field(2,3,4), but it is not known whether normalization of the clotting system by disintegrated platelets will stop bleeding in thrombocytopenia. The value of the irradiated thrombopenic dog or rat in evaluating factors concerned with he-

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