Evaluation of CardioGrip as a Therapeutic Intervention in Hypertension and Vascular Disease. Nicholas A. Flavahan, Ph.D.

Introduction

Hypertension is prevalent in all westernized societies, affecting 15 to 25% of the adult population. The risks associated with long-standing hypertension are multiple and increase in a continuous manner with increasing blood pressure. However, the reduction in risk for both stroke and coronary heart disease associated with control of hypertension through the use of antihypertensive medications is equally impressive. For example, a pharmacological reduction in blood pressure of 3 to 5 mm Hg decreases the risk of stroke by 42% and the risk of coronary heart disease by 14% (1). So far, these benefits have been demonstrated only with medications, but should be observed when the reduction is achieved by other means, including life-style changes. Indeed, given the inherent non-specificity of pharmacological intervention, non-pharmacological treatment could be even more efficacious in risk reduction for any given decrease in blood pressure.

The current 1999 WHO/International Society of Hypertension definition of hypertension is listed in table 1(2). The definition of hypertension and "normal" blood pressure should not obscure the fact that an increased incidence for stroke can be

Table 1: 1999 WHO/International Society of Hypertension Categories (2)

	Systolic Pressure (mm Hg)	Diastolic Pressure (mm Hg)
Optimal	< 120	< 80
Normal	< 130	< 85
High Normal	130-139	85-89
Grade 1 Hypertensive (mild)	140-159	90-99
Subgroup: Borderline	*140-149*	*90-94*
Grade 2 Hypertensive (moderate)	160-179	100-109
Grade 3 Hypertensive (severe)	≥ 180	≥ 110
Isolated Systolic Hypertension	≥ 140	< 90
Subgroup: Borderline	*140-149*	*< 90*

detected at blood pressures below 120/80 (3). Therefore, the potential for a non-pharmacological means of lowering blood pressure, would likely far exceed the already large market-size for antihypertensive medications.

Exercise and Hypertension

Regular exercise is widely recommended as an effective tool in the non-pharmacological treatment of hypertension (1). The current 1999 WHO/International Society of Hypertension guidelines on exercise as a treatment modality in hypertension recommend "modest levels of aerobic exercise on a regular basis, such as a brisk walk, or a swim for 30-45 min three to four times a week" (2). However, the same recommendations suggest that isometric exercise "should be avoided"(2). Isometric exercise is the type of exercise involved with the CardioGrip device. These conservative guidelines reflect the existing state of knowledge in exercise physiology and the apprehension associated with isometric exercise. In cases of intense activity, isometric or static exercises are capable of raising systolic blood pressure to 250 - 450 mm Hg (4).

At present, no prospective, randomized trials have been performed to show that exercise training actually decreases cardiovascular morbidity and mortality in hypertensive patients. However, data from epidemiological and intervention studies have demonstrated that exercise has hypotensive efficacy (1). Meta-analyses of studies on the effects of regular exercise training have demonstrated that aerobic, dynamic exercise reduces resting systolic and diastolic blood pressure (1). The range of mean blood pressure reductions including only randomized trials tends to be smaller than in meta-analysis with less stringent inclusion criteria (reductions in Systolic/Diastolic pressures of 4-5/3-4 mm Hg and 3-10/3-8 mm Hg, respectively)(1). These studies focused on the use of dynamic, aerobic exercises including walking, jogging, cycling or a combination of these activities, but the findings have been extrapolated to other aerobic exercise forms including swimming and cross-country skiing. Furthermore, most of the studies were restricted to measurement of resting blood pressure rather than ambulatory blood pressure, which is more closely related to hypertension-related target organ damage. Subsequent analysis of aerobic, dynamic exercise training has demonstrated significant reduction when blood pressure was measured in this manner (1, 5). Much fewer studies have assessed the role of resistance exercises (usually weight training which involves dynamic/isotonic exercise and isometric/static exercise). Kelley (6) employed meta-analysis of 9 studies that analyzed the effect of weight training and demonstrated similar reductions in resting systolic and diastolic blood pressure compared to aerobic exercise.

The duration of the studies varied from four to 52 weeks. Most of the hypotensive activity of exercise was evident by 10 weeks and there were no indications that the effect of exercise decreased with time during the exercise protocol (1). Furthermore, the existing evidence suggests that low-intensity programs are as effective, if not more effective, than high-intensity schedules.

There has been apprehension about resistance or isometric/static exercises, which is reflected in the1999 WHO/International Society of Hypertension guidelines (2). Concerns about static exercise have focused on the high blood pressures that can be generated during this procedure and the possibility of sudden death (1,7). This is exacerbated by the possibility that these pressure increases cannot be controlled by the patients' medication (9). However, preliminary evidence suggests that a carefully-controlled program can be beneficial (1,4,6,8). Indeed, the American College of Cardiology recommends that "the presence of mild hypertension in the absence of target organ damage / heart disase should not limit eligibility for any competitive sports (dynamic or static)"(1).

<u>The CardioGrip Device – The "Wiley Study"</u>

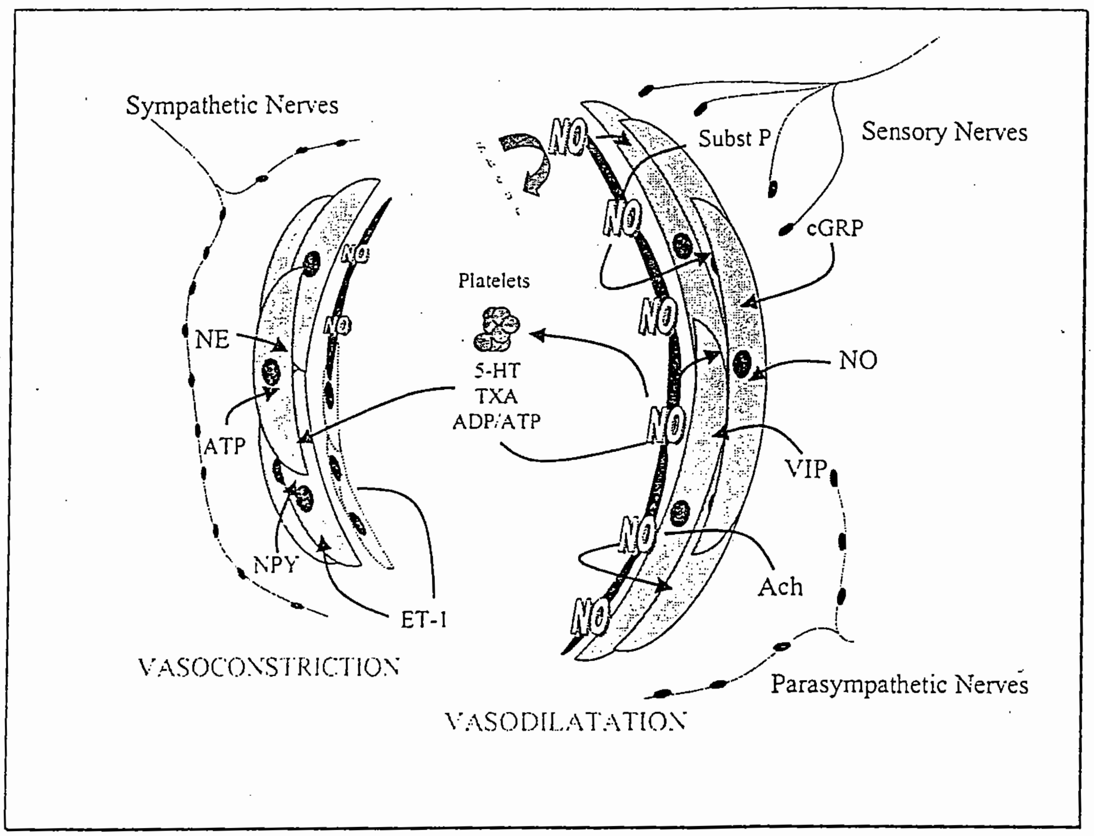
The CardioGrip device is based on the 1992 study by Wiley et al (10). That study demonstrated that a low-intensity training program using an isometric, hand-grip (four 2-min contractions, 3 times/week, 30% effort) for 8 weeks produced a significant and marked reduction in resting blood pressure (systolic/diastolic of 12.5/14.9 mm Hg). The study was performed in 7 to 8 healthy subjects with "high-normal" blood pressure (table 1). These impressive results were obtained despite only small increases in blood pressure during the hand-grip procedure (systolic/diastolic of 16.8/15.9 mm Hg), consistent with the low-intensity nature of the program. The hypotensive effect of the hand-grip program reached significance at four weeks and appeared still to be increasing when the study was terminated at 8 weeks. In unpublished data, the authors (reported in 11) demonstrate in an individual with moderate hypertension that the effect can persist for up to 75 weeks.

This preliminary study indicates that a low-intensity, isometric exercise program using the hand-grip can be a safe and highly effective intervention in reducing blood pressure. Somewhat surprisingly, the study has had a low-impact on the scientific community and has been cited only seven times since its publication in 1992 (Institute for Scientific Information "Citation Database"). A similar study of isometric exercise training in six healthy male using a hand-grip device failed to demonstrate any significant reduction in blood pressure after 4 weeks of training, despite a significant increase in blood flow to the exercising limb (12). The lack of effect in this study may reflect the shorter time-period of observation or the use of higher-intensity exercise (70% effort, usually until fatigue). As described above, low-intensity exercise can outperform high-intensity programs with regard to hypotensive efficacy (1).

Exercise-Induced Hypotension: Mechanism of Action

Despite the widespread enthusiasm for exercise as a therapeutic regimen in hypertension, the mechanism underlying the hypotensive effect is unknown. Given the complexity of

Figure 1: Mechanisms Controlling Constrictor Activity in Blood Vessels.



vascular regulation (fig. 1), this may not be surprising. Dave Ferguson has elegantly summarized the possible role of elevated shear stress on the endothelial cell surface as a potential regulator of acute (e.g. NO release) and chronic (increased expression of ec-NOS) effects of exercise (11). There is evidence to support a generalized increase in endothelial NO activity from animal studies using dynamic exercise (14,15). However, variable responses have been reported in humans in response to hand-grip exercise (12,16), with one report demonstrating no effect on endothelial function after 4 weeks (12) and one demonstrating increased endothelial dilator function after 8 weeks. This latter effect was restricted to the exercising limb. Other theories regarding the beneficial effects of exercise have proposed that it results from volume depletion or altered activity of sympathetic constrictor outflow, which in turn may reflect altered sensitivity or resetting of baroreceptors (central or peripheral mechanisms) (1,13,17,18,19). Indeed, altered baroreceptor function could occur secondary to changes in endothelial function (20,21).

It is likely that exercise-induced hypotension is mediated by a combination of these mechanisms, which may vary between individual or disease conditions. Most investigations have analyzed the effect of dynamic exercise and there is only sparse information regarding the influence of isometric hand-grip exercise programs on the cardiovascular system. Indeed, the little data that is available indicates that beneficial effects may be restricted to the exercising limb (16,18). Clearly, more research is needed in this area.

Recommendations and Future Directions

Based on the available information, the CardioGrip device and the adoption of an isometric hand-grip exercise program to promote exercise-induced hypotension shows considerable promise. The major advantages of such a program are its potential safety, its apparent remarkable efficacy, and the low-intensity nature of the device which should ensure a high rate of compliance. **I recommend that MD Systems receive full support in order to develop the CardioGrip as a therapeutic device.**

Clearly, more extensive evaluation of the CardioGrip is required before it will be accepted as a therapeutic modality. This is especially relevant given the apprehension associated with isometric exercise. The development should therefore be aimed at:

1) Demonstrating that the device is effective in lowering blood pressure and defining which patient populations (mild to severe hypertensives, with and without other risk factors/diseases) are best suited to this type of intervention. Variations in the exercise program should be evaluated to determine optimal conditions. The device should be assessed as a stand-alone therapy, and as an adjunct to existing pharmacological agents. The efficacy of the device should preferably be demonstrated using ambulatory monitoring rather than resting blood pressure. It would be advantageous to perform a comparison with dynamic aerobic forms of exercise. Although experiments should be aimed at demonstrating the short-term hypotensive efficacy in normal and hypertensive subjects, studies should also be initiated to evaluate the long-term health benefits. If the device has a heterogeneous response, then experiments should be performed to define the characteristics of the responders (including the use of genetic markers). If the therapeutic efficacy can be defined by the initial response to the device, then the device could also be used as a screen within the physician's office. Depending on the mechanism of action of the device, it may also benefit other non-hypertensive patient groups. For example, if it does indeed cause a generalized increase in ec-NOS activity or a decrease in sympathetic outflow, then it may be useful in heart failure and in arteriosclerosis.
2) Demonstrating that the device is safe. Given the apprehension associated with isometric exercise programs, extensive analysis of the acute and chronic effects of the device will need to be assessed in different patient groups, including severe hypertensives, patients with coronary heart disease and heart failure, in the elderly and in the obese. The effects of the prescribed and incorrect exercise program should be evaluated. Furthermore, any potential interactions with pharmacological agents will need to be assessed. From a practical standpoint, certain antihypertensive agents are known to reduce exercise capacity. From a medical standpoint, a synergistic effect between exercise and antihypertensives could produce a hypotensive crisis, or more likely the antihypertensive agents may not be able to control the acute pressor response caused by the exercise. Although this may not be a problem when the device is used as prescribed, it may become a problem if the device is misused.

3) Determining the mechanism of the effect. Extensive characterization of the potential mechanism(s) of action (along the lines of the above discussion) will help convince the medical community of the safety and efficacy of the device. It will also assist in generating high-impact publications on the device.
4) Communicating the beneficial effects of the device to the medical community. From a marketing standpoint, once the device has been proven safe and effective, it would be advantageous to have high-quality and high-impact publications on the device, both in the form of presentations at the American Heart Association's National Meeting and in respected Journals such as Circulation, Lancet, and the New England Journal of Medicine.

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