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Brachial Artery Stiffness Testing as an Outcomes Measurement for EDTA-Treated Patients With Vascular Disease

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ABSTRACT: Brachial artery stiffness testing is a well-accepted screening test for vascular disease and correlates well with the degree of atherosclerosis and endothelial dysfunction in the coronary and carotid arteries. In this study, the authors tested patients before and after EDTA-chelation therapy to see if this testing would be a good outcome measurement for patients with occlusive vascular disease. For each patient, the arterial stiffness index was calculated before and after treatment. Of the 18 patients in the study, 12 had a decrease in the arterial stiffness index, which averaged 29%. Of the 13 patients who had abnormal tests prior to treatment, 12 of 13 had a decrease in the arterial stiffness index with the posttreatment testing. None of the 5 patients with normal stiffness prior to treatment had a posttreatment decrease in the arterial stiffness index. The authors conclude that brachial artery stiffness testing appears to be a good outcome measurement for patients treated with EDTA-chelation therapy and that the testing might document an improvement in vulnerable plaques. (*Clinical Practice of Alternative Medicine* 1(4):225-228, 2000)

The importance of thrombosis in coronary and cerebral ischemic events has been described by Falk,[1] among others, with the concept of "lesion activation," which begins with plaque fissure, leads to rupture, and results in massive clotting that occludes the vessel. Levine and associates[2] discussed the mechanism of this process, which they called "endothelial dysfunction." Endothelial dysfunction refers to a general abnormality involving vasomotor tone, inhibition of platelet aggregation, an imbalance between thrombosis and fibrinolysis, and recruitment of inflammatory cells into the vessel wall. Endothelium-derived relaxing factor along with other vasoactive and platelet-regulating substances work together to normalize vascular tone and platelet activity. Oxidative stress and nitrous oxide production play important roles in endothelial dysfunction.[3]

Endothelial dysfunction results in "vulnerable plaques," which are prone to sudden total or near-total occlusion from arterial lesion activation. Two thirds of ischemic episodes occur in arteries with stenosis of less than 50%, and 97% occur in arteries with a stenosis of less than 70%.[4] With this new concept of the pathophysiology of ischemic events, there should be a movement away from surgical therapy toward aggressive medical therapy.

Atherosclerosis and endothelial dysfunction are commonly found in the brachial artery. The degree of disease in the brachial artery correlates well to that found in the coronary and carotid arteries.[5]

Brachial artery endothelial dysfunction is often measured by the responsiveness of the artery on ultrasound after compression with a blood pressure cuff. Arterial stiffness can also be accurately estimated by electronically measuring thousands of readings of the compliance of the brachial artery within a few seconds by an oscillometric blood pressure cuff.[6] A rapid computer analysis converts these readings into a score called the arterial stiffness index (ASI). This system is approved by the Food and Drug Administration as a screening device for early detection of coronary artery disease and arrhythmias and as an objective measurement of blood pressure.

EDTA-chelation therapy has been utilized for 45 years by a minority of physicians for the treatment of vascular disease.[7,8] Because this therapy has both antioxidant effects and antiplatelet activity,[9] it could be a good medical treatment to prevent rupture and thrombosis of the vulnerable plaque.

Lamas and associates[10] have recently stressed the need for more research on the use of chelation therapy to treat cardiovascular disease. One of the problems in performing acceptable outcomes research on the effectiveness of chelation therapy is that there has not been an easily reproducible, inexpensive test for clinicians in an office-based practice to assess whether patients were improving as a result of treatment. The authors hypothesized that the measurement of the brachial ASI with the equipment described in this paper in patients with vascular disease would demonstrate whether each

patient improved. The hypothesis was that the ASI measured after treatment would be less than the ASI measured prior to treatment, which might indicate that the plaque of the treated artery had less endothelial dysfunction and was less "vulnerable" to rupture, thrombosis, and occlusion.

Methods

The authors studied 18 patients with vascular disease from one author's (LTC) family practice who opted for EDTA-chelation therapy. Each patient was tested with 3 to 5 readings of the ASI. If the first 3 ASI readings were within 10% of each other, no further reading was taken during a testing session. If there was variation greater than 10%, 2 more readings were obtained. For all cases, the pretreatment ASI score was determined by the mean of the 3 to 5 readings.

Each subject was treated with 30 treatments of EDTA-chelation therapy, according to the published protocol.[11] Then, a posttreatment ASI score was obtained using the same technique and calculation. A paired sample *t* test on the differences of the pretreatment ASI minus the posttreatment ASI was obtained to analyze the data statistically.

Results

The results are illustrated in the Table. All 18 patients had symptoms of vascular disease. There were 9 women and 9 men with ages ranging from 45 to 79 years. All patients had symptoms of vascular disease and 14 had Doppler ultrasound testing for either carotid and/or peripheral circulation, all of which showed mild to severe decreases in arterial blood flow.

After 30 treatments with EDTA-chelation therapy, 17 of 18 patients had an improvement in their symptoms. Of the 14 patients who had pre- and posttreatment Doppler testing, 13 of 14 had some degree of objective improvement on their Doppler strip-chart recordings.

Twelve of the 18 patients had improved ASI scores, indicating decreased arterial stiffness after treatment. One patient had identical ASI scores pre- and posttreatment. Five patients had higher scores after treatment than before treatment. The average improvement in ASI scores for the 18 patients was 24.25%.

Upon closer examination of the data, the authors observed that all 5 of the patients who had higher scores after treatment than before had normal ASI scores prior to chelation therapy. Of the 13 patients who had abnormal tests (ASI>70) before treatment, 12 of 13 had lower ASI scores after treatment, 1 had no change. For the 12 patients who had reduced stiffness after treatment, the improvement percentages ranged from 12% to 79% (Table), and the average improvement in the ASI score was 42.5% for the entire group of 13.

Statistics

The appropriate statistical analysis of the data presented in this paper is the paired *t* test on the brachial artery stiffness differences of each of the patients. The difference of each paired sample chosen was pre-post, or the initial reading minus the final reading. This means that when the initial reading is larger than the final reading, the datum has a positive value and vice versa. Physically, then, a positive value of the datum indicates an improvement in endothelial function of the artery, whereas a negative value indicates deterioration in the same.

Eighteen subjects were tested. The paired *t* test indicated that the test on the data of this group was significant with $P=.0058$ for the alternative hypothesis $m > 0$; ie, the probability of obtaining a sample mean this high by chance is 0.58%. One outlier in the group had an initial ASI of 649. The *t* test without the outlier had a probability of .012. Therefore, the measurement of endothelial function, by measuring brachial artery stiffness, was an effective outcome measurement for chelation therapy.

An examination of the data indicates that further analysis is appropriate. When the original group was divided into 2 subgroups, unexpected results were obtained. Group A, the subset of the 13 subjects with initial brachial artery stiffness, was high or abnormal, whereas group B, the subset of the 5 subjects with initial stiffness, was normal (<70). The results of group A, the subjects with abnormal stiffness prior to treatment, showed the expected decrease in the ASI after treatment. The results of group B, those with normal stiffness prior to treatment, showed an increase in the ASI after treatment, although the posttreatment results for these subjects continued to be in the normal range. The *t* tests for the data of both of these subsets were significant but in opposite directions; this situation calls for further study.

The *t* test results for the data of the subjects of group A, with and without the outlier, were both significant, with $P=.0015$ and $P=.0036$ for the alternative hypothesis, $m > 0$; ie, the probability of obtaining a sample mean this high by chance is 0.15% or 0.36%, respectively. Thus, for patients with initial abnormal brachial ASIs, measuring endothelial function by measuring brachial artery stiffness was an effective outcome measurement for chelation therapy.

The *t* test results for the data of group B were significant for the alternative hypothesis, $m < 0$, with $P=.0043$. The probability of obtaining a sample mean this low by chance is 0.43%. For patients with initial brachial artery stiffness readings in the normal range, measurement of endothelial function by measuring brachial artery elasticity was an ineffective outcome measurement for chelation therapy.

TABLE

The use of brachial artery stiffness testing as an outcomes measurement for patients treated with EDTA-chelation therapy

	ID #	Age	Sex	Complaint	Symptom improvement	ASI Pre	ASI Post	% change
A.	46-70	57	M	Elevated blood pressure Carotid vascular disease	Lower blood pressure Increased blood flow	140	67	52% +
	171-02	79	M	Peripheral vascular disease	Decrease in symptoms	277	176	36% +
	157-46	75	M	Carotid vascular disease Peripheral vascular disease	Decrease in symptoms Decrease in symptoms	267	56	79% +
	137-20	72	M	Carotid vascular disease Peripheral vascular disease	Increased blood flow Icreased blood flow	174	58	67% +
	169-15	70	M	Carotid vascular disease Peripheral vascular disease	Increased blood flow Increased blood flow	138	49	64% +
	142-32	64	M	Carotid vascular disease Chest pain	Increased blood flow Decrease in symptoms	88	27	69% +
	129-98	48	F	Leg cramps	Decrease in leg cramps	176	176	0%
	94-72	77	F	Carotid vascular disease	Increased blood flow	369	190	49% +
	164-74	78	M	Carotid vascular disease Dizziness	Increased blood flow Decreased dizziness	78	30	62% +
	145-62	66	M	Carotid vascular disease Peripheral vascular disease	Increased blood flow Decrease in symptoms	253	166	34% +
	160-87	73	M	Peripheral vascular disease Bilateral ankle edema	Increased blood flow Decreased bilateral edema	147	124	16% +
	169-41	60	F	Peripheral vascular disease	Decrease in symptoms	649	543	16% +
	158-29	49	F	Carotid vascular disease Intermittent claudication	Increased blood flow Decreased claudication	122	107	12% +
B.	170-12	45	F	Carotid vascular disease Dizziness Headaches	No change Decreased dizziness Decreased headaches	59	78	32% -
	167-82	50	F	Carotid vascular disease Peripheral vascular disease Intermittent claudication	Increased blood flow Increased blood flow Decreased claudication	36	42	17% -
	166-94	79	F	Peripheral vascular disease Syncope	Increased blood flow No change	46	60	30% -
	170-20	58	F	Carotid vascular disease Chest pain Intermittent claudication	Increased blood flow Less frequent and severe Decreased claudication	19	26	37% -
	169-12	54	F	Carotid vascular disease Peripheral vascular disease Dizziness	Increased blood flow No change Decreased dizziness	53	70	32% -

ASI indicates arterial stiffness index; +, decreased stiffness; -, increased stiffness.

With regard to bias, the research method utilized in this paper can be considered statistically marginal. In order to substantiate these preliminary results, a well-structured clinical trial should be pursued in the future.

Discussion

Brachial artery stiffness measurement has the potential to be a useful tool for measuring the results of chelation therapy in patients with vascular disease. A statistically significant decrease in arterial stiffness existed for the 18 patients with vascular disease treated with chelation therapy in this study. Not all patients had abnormal ASI readings prior to treatment, even if they had vascular disease documented by other methods. In this study, 12 of 13 patients with abnormal ASI scores had documented improvement in their scores after treatment. One had no change. Of the 12 patients in this subgroup who improved, 9 had Doppler testing pre- and posttreatment, and all 9 had improvement in both their Doppler readings and their ASI scores.

In this small study, patients with symptoms of vascular disease but normal ASI scores apparently could not be reassessed accurately after treatment by repeat brachial artery stiffness measurement. Their scores might have gone even lower into the normal range, but this did not occur. Four of the 5 patients in this subgroup had improvement in Doppler testing but an increase in their ASI scores. One patient had no change in Doppler testing and had worsening of the ASI. The data indicate that these patients should be reassessed not with brachial artery stiffness testing but with other types of vascular testing.

There is evidence that brachial artery stiffness measurement is a good screening test for the presence of arterial endothelial dysfunction and the presence of atherosclerosis.[12] Preliminary indications from this study are that if a patient begins with an abnormal ASI score, it is reasonable to repeat the testing during the treatment or at the end of the basic course of treatment to have an objective measurement of whether the patient has improved. Arterial stiffness testing appears to be a good outcome measurement to document improvement in patients with occlusive vascular disease treated with EDTA-chelation therapy. Like all tests, the results must be correlated with clinical findings.

Arterial stiffness appears to correlate well with the presence of vulnerable plaques that are prone to rupture and cause myocardial infarctions or strokes in patients with plaque measurements of less than 50% occlusion.[12] If this observation is confirmed, brachial artery stiffness testing might become extremely important not only to determine which patients are at risk but also to measure the effectiveness of various treatment modalities to prevent critical vascular events. The data from this paper indicate that it is probable that the use of brachial artery elasticity testing as an outcome measurement for patients with vascular disease treated with EDTA-chelation therapy is actually documenting a reduced tendency for a vulnerable plaque rupture and subsequent thrombosis.

Other treatments that have been suggested to improve endothelial function and decrease plaque vulnerability include aggressive lipid lowering and the use of antioxidants.[2,3] Chelation therapy might be added to these interventions to form a comprehensive medical therapy, which has the potential to produce far better outcomes than surgical approaches for cardiovascular disease. This is a subject for future research.

Brachial artery stiffness testing has the advantages that it is inexpensive, quick to perform with immediate results, and does not require a large investment or highly skilled technicians. It has good sensitivity and high specificity. The results can give guidance to the practitioner and be cost-effective for patients.

This study is obviously limited because of its small number of patients. Additional research is needed to confirm the findings and better define the role of brachial arterial stiffness testing to monitor results of treatment and determine outcomes for patients with vascular disease treated with various modalities, including EDTA-chelation therapy.

References

1. Falk E. Why do plaques rupture? *Circulation.* 1992;86(suppl III):30-42.
2. Levine GN, Keaney JF, Vita JA. Cholesterol reduction in cardiovascular disease. *N Engl J Med.* 1995;332:512-521.
3. Duffy SJ, Vita JA, Keaney JF. Antioxidants and endothelial function. *Heart Failure.* 1999;Summer/Fall:1-19.
4. Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable angina pectoris. *N Engl J Med.* 2000;343:101-114.
5. Sorensen KE, Kristiansen IB, Celermajor DS. Atherosclerosis in the human brachial artery. *J Am Coll Cardiol.* 1997;29:318-322.
6. Shimazu H, Fukuoka H, Ito H, Yamakoshi K. Noninvasive measurement of beat-to-beat vascular viscoelastic properties in human fingers and forearms. *Med Biol Eng Comput.* 1985;23(1):43-47.
7. Olmstead SF. *A Critical Review of EDTA Chelation Therapy in the Treatment of Occlusive Vascular Disease.* Klamath Falls, Ore: Merle West Center for Medical Research; 1998.
8. Chappell LT, Stahl JP. The correlation between EDTA chelation therapy and improvement in cardiovascular function: a meta-analysis. *J Adv Med.* 1993;6:139-160.
9. Cranton FM, Frackelton JP. Free oxygen radical pathology and EDTA chelation therapy: mechanisms of action. *J Adv Med.* 1998;11:277-310.
10. Lamas GA, Ackerman A. Clinical evaluation of chelation therapy: Is there any wheat amidst the chaff? *Am Heart J.* 2000;140(1):4-5.
11. Rozema TC. The protocol for the safe and effective administration of EDTA and other chelating agents for vascular disease, degenerative disease and metal toxicity. *J Adv Med.* 1997;10:5-100.
12. DeKorte CL, Cespedes EI, van der Steen AFW, Pasterkamp G. Intravascular ultrasound imaging of elastic properties of diseased arteries and vulnerable plaque. *Eur J Ultrasound.* 1998;7:219-224.