Non-invasive Determination of Arterial. Stiffness and Its Relationship to Orthostatic Hypotension in an Elderly Outpatient Population

Rose S. Cohen

A. Study Purpose and Rationale

The prevalence of orthostatic hypotension (defined as a drop in 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure on immediate change from supine to upright posture) in the elderly outpatient Poriulation (older than 65 years) has been cited to range from 5% to 30% (Ooi eta], 1997).

Orthostatic hypotension has been related to morbidity in the elderly Population. Tinetti et al. noted that reduction of systolic blood pressure by 20 mmHg or more by three minutes of assuming an upright position conferred a significant risk for fall and syncope. Davis et al. showed a link between orthostatic hypotension and mortality ill the Hypertension Detection and Follow up Program. Study sub~jects with 20 or areater fall in systolic blood pressure with postural change were a considerable higher risk of 5 year mortality (Davis et al, 1987).

Given this link between orthostatic hypotension and risk for morbidity, elucidating the pathophysiology of orthostatic hypostension would yield insight into disease prevention. Several mechanisms have been proposed and validated, indicating Multiple factors contributing to orthostatic hypotension. Apparently with aging, there is a reduction in the baroreceptor-reflex stimulated heart rate response to hypotensive stimuli (Lipsitz. NEJM, 1989). Other mechanisms include increased sensitivitv to volume reduction, medications, autonomic insufficienc,y (Bradbury-Eggleston syndrome, Shy-Drager Syndrome).

Another key mechanism proposed in the development of orthostatic hypotension results frorn the increase in stiffness of both the heart and the vasculature with normal ageing. Physiologic changes in the vasculature with age that have been described include elevations of systolic blood pressure, increased pulse wave velocity, possible increase in left ventricular wall thickness, and interestingly, arterial stiffness, which will be the primary focus of this study. In a prevalence study performed by Ool et al, among nursing home residents, orthostatic hypotenslon was related to elevated blood pressure (Ool et al, 1997). It has been proposed that sustained elevations in blood pressure reduce the vascular and ventricular compliance, lead ironically to a greater tendency to develop orthostatic hypotension (Lipsitz el al.).

A measurement of vascular stiffness has been described in animal suibJects is effective arterial elastance (Ea), a steady state parameter of arterial properties including peripheral resistance, total vascular compliance, impedance, systolic and diastolic time intervals during cardiac contraction. This parameter is estimated by Ea=TPR(HR)/60, approximately equivalent to Ea = End Systolic Pressurc/Stroke Volume. Ea has been found to assess vascular loading of the ventricle in limited cohorts of human subjects (Kelly et a], 1992). This is determined invasively by obtaining left ventricular pressures and volumes in the setting of preload reduction (by use of an obstructive balloon catheter in the inferior vena cava) to measure the left ventricular end-systolic pressure-volume relation. Ea has been measured in humans, both young normotensive subjects as well as elderly hypertensive subjects (Kelly et al, 1992). Ea was found to be a better index of arterial load than mean arterial resistance in older hypertensive subjects. This was attributed to the fact that Ea is derived by the pressure volume loop of cardiac contraction, which incorporates the pulsatile load on the ventricle.

Both invasive and non-invasive measurements in hrmled populations of both healthy and hypertensive patients confirm that vascular stiffness increases with advancing age, Chen et al. showed by invasive measurements of the pressure volume relationship by conductance catheter in 57 adults between

19 to 93 years o1d that arterial stiffening (Ea) is increased with age, in tandem with ventricular stiffening (Ees). Moreover, as Ea increased, systolic pressure was more sensitive to changes in preload, Suggesting that arterial stiffening could enhance pressure lability with postural shifts, theoretically predisposing to orthostatic, hypotension. These data have been interestingly confirmed by noninvasive studies.

The invasive nature of these physiologic measurements limits their use clinically. However, noninvasive measurements of these indices have been used to determine arterial stiffness and ventricular-vascular coupling. Slotminer et al noted that pulse pressure/stroke volume (determined by 2D Doppler calculation of stroke volume) strongly Increased with age in a population of 162 asymptornatic adults between 25 and 80 years old with complicated essential hypertension (SBP >=140/90). They concluded that while cardiac index and TPR index are preserved across a range of age in patients with mild hypertension, vascular stiffness rises significantly.

Non-invasive estimates of end-systolic pressure in the elderly population have been described and have been generally accepted as 0.9xSBP (Scandrett et al, in press). Measurement of left ventricular volumes can be obtained in both two and three dimensions, though volume measurement in three dimensions has been enhanced by the availability both MR1 and 3D echocardiography. Gopal et al. have shown that EF determined by 3 dimensional echocardiography were comparable to equilibrium radionuclide anglography and was more reliable (less inter-observer variability) than two-dimensional measurements (Gopal et al., 1995).

This study alms to address whether an index of arteria stiffness measured noninvasively in elderly patients is predictive of the development of orthostatic hypotenslon. This hypothesis will be tested using noninvasive means of determining blood pressure (noninvasive cuff), stroke volume (threc dimensional echo), and tilt table testing.

B. Study Design and Statistical Analysis

This study wi ll be a cohort study looking at a group of elderly outpatients without known cardiac disease, who will undergo three dimensional echocardiography, baseline blood pressure monitoring, and tilt table testing. Blood pressure measurements will be taken at one and three minutes and the outcome measurement will be the development of orthostatic hypotension, defined as a greater than 20 mmHg drop in systolic blood pressure from supine to standing position. The exposure in this study will be Ea, determined for each subject based on their baseline blood pressure multiplied by 0.9 to estimate End Systolic Pressure, as well as stroke Volume determined by three dimensional echocardiography. The number of subjects to he enrolled was largely determined by a power calculation, based on the limited information about the variability of Ea in the population. The variability of Ea in the work of Kass et al. is approximately 2.00±0.57. The prevalence in the elderly outpatient Population of orthostatic hypotension is approximately 20%. Therefore, given the expected distribution of the outcome as 4: 1, and the variability of the exposure (Ea) is roughly between 1.5 to 2.5, the number of study subjects is approximately 64 per outcome group. This is based on a power calculation performed on www.biomath.info for 80% power, testing at p=0.05. Statistical analysis of the relationship between orthostatic hypotension and Ea will be performed by a student's T-test.

C. Study Procedure

Given the noninvasive nature of the measurements made for this study, the patients are unlikely to experience pain, discomfort or inconvenience during blood pressure monitoring (15 minutes, four encounters) by noninvasive blood pressure culf monitoring, or three dimensional echocardiography (30 minutes). The tilt table test (30 minutes) involves lying in the supine position for 10 minutes, followed by a 90 degree rise to standing, with measurements of beat to beat blood pressure hy noninvasive radial artery blood pressure monitoring. The tilt table test confers some risk for developing syncopal symptoms, dizziness, lightheadedness, nausea, and such symptoms will be monitored during the study. The anticipated duration of the patient's participation in the study will not exceed four weeks.

D. Study Drugs

No drugs will be investigated in this study.

E. Medical Device

All devices used in this study are commercially available.

F. Study Questionnaires

No questionnaires will be used in this study.

G. Study Subjects

Inclusion Criteria
Men and women 65 years and older who are community dwelling, ambulatory, with normal ejection fraction by screening 2 dimensional echocardiography.

Exclusion Criteria:
Patients with Parkinson's Disease, patients with known autonomic insufficiency, diabetic patients with HgbA1C greater than 9.0, patients with evidence of end organ damage from hypertension (retinopathy, proteinuria), patients with a history of cardiac disease (specifically valvular, ischernic, ot heart failure of any eliology), stroke, patients on clonidine, phenothiazines, tricyclic antidepressants, prazosin, hydralazine, guanethicline.

H. Recruitment of Subjects

Patients will be recruited for study enrollment from a local senior center by a research coordinator.

I. Confidentiality of Study Data

All data will be coded using a numbering system independent of medical record number, subject initials, phone number, or addresses. Data will be stored in a locked file, accessible only to investigators.

J. Potential Conflict of Interest

There is no conflict of interest in this study on the part of the university or investigators.

K. Location oft he Study

All data collection will occur at within CPMC clinical care areas at both Milstein Hospital (PH-9) and the Allen Pavillion (3rd Floor).

L. Potential Risks

The greatest risk of the trial is syncope or syncopal symptoms with orthostatic hypotension elicited by the tilt table test, though it will be minimized by continuous monitoring by a physician at all times. The outcome measurement will be terminated if the patient is significantly symptomatic. There is no risk to the patient in terms of not receiving optimal treatment or physician follow-up.

M. Potential Benefits

The greatest benefit to study participants includes the benefit to society for the further elucidation of the mechanisms involved in the development of orthostatic hypotension in the elderly, which would ultimately lead to morbidity prevention.

N. Alternative Therapies

There are no alternative therapies involved in this study.

O. Compensation of Subjects

Study participants will be compensated for their transportation costs to and from the medical center, approximately $15 per study participant, to be dispensed after the final outcome measurement is taken.

P. Costs to Subjects

Study participants will not incur any additional financial costs, save the time involved in participating in the study.

Q. Minors as Research Subjects

There are no minors in this study

R. Radiation or Radioactive Substances

There is no radiation/radioactive substances used in this study.

S. References

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