Validation of Non-invasive Hemodynamic Estimates of End-Systolic Pressure in An Elderly Patient Population

Rebecca Scandrett

A. Study Purpose

The main goal of this study is to determine if non-invasive hemodynamic measures, i.e. systolic blood pressure (SBP) and mean arterial pressure (MAP), are accurate estimates for left ventricular end systolic pressure (ESP) over a wide range of ages. The study will also determine if there are any intrinsic factors in an aging population which would make one non-invasive estimate more or less accurate than the other. A secondary purpose of the study is to validate the SphygmoCor® Blood Pressure Analysis system as a method to derive ESP in a research setting.

B. Rationale

The le ventricular end-systolic pressure-volume relation (ESPVR) is a load independent measure of ventricular function (i.e. contractility). A multitude of studies have shown that by measuring left ventricular end systolic pressure (ESP) and left ventricular end systolic volume (ESV) during cardiac catheterization, over a wide range of cardiac loading conditions, a linear 'relationship (called the ESPVR) is created. The slope of this line reflects the contractility of the left ventricle independent of preload (the less steep the slope, the worse the contractility)[1,2,3]. The ESPVR is a particularly useful clinical measure in patients who have known valvular regurgitation and/or changes in their baseline volume status, both conditions when traditional non-invasive methods for assessing LV function, i.e. echocardiography, are less accurate. Since invasive measurement of left ventricular pressures and volumes over a wide range of cardiac loading conditions are required to create the ESPVR, this technique has not been widely applied in the clinical setting. In order to simplify the formulation of ESPVR, clinician have Used the assumption that Vo is constant and approximates zero and have therefore used the ratio of ESP/EPV to calculate ESPVR. By using echocardiographic or radionuclide measures of left ventricular volume the second half of the ratio has been able to be determined non-invasively. Non-invasive measures of ESP, however, have been based on SBP and/or MAP as approximations of ESP. [4,5,6,7] Few studies have specifically examined the accuracy of MAP as an estimate of ESP. Among 105 subjects with an average age of 3.2 years (age range of 1 day to 45 years), MAP was an accurate estimate of aortic dicrotic notch pressure measured during cardiac catheterization. The mean difference between MAP and ESP was -0.3 ± 2.9 min Hg, with no apparent systematic variation seen with increasing end systolic pressure. [8] In adults, however, the estimate of ESP from MAP has not been as accurate. In one study, when MAP was compared to invasively measured aortic dicrotic notch pressure in 24 patients (aged 32 to 68 years old), there was a highly significant correlation with dicrotic notch pressure (r 0.82,p=0.001). However; they did not examine the effect of age on the accuracy of this estimation. [4] Another study of 26 patients, whose ages were not specified, found that the mean difference between aortic dicrotic notch pressure and MAP, measured during coronary artery bypass grafting, was 1.1±13 min Hg[9]. In the only other published series of 17 adult subjects (52 ± 13 years), the correlation between MAP and aortic dicrotic notch pressure was 0.93, p = 0.0001. In this study, MAP actually underestimated dicrotic notch pressure with the mean difference between mean and dicrotic notch pressure equal to 9.4 ± 7.6 mmHg and the difference was associated with age.[10] While there is this limited data on as an estimate of ESP, none of these studies have examined the underlying biasing factors in this estimation. In addition, no specific studies to my knowledge have examined the accuracy of SBP as an estimate of ESP.

It is our hypothesis that since aging is characterized by increased central conduit artery stiffness, which affects the accuracy of MAP as an estimate of ESP more than SBP, SBP will be a better estimate of

ESP in the elderly. This hypothesis is supported by the observation made by Kelly et al that there is a discrepancy between MAP and ESP in a hypertensive patient as compared to a young healthy patient, while SBP is a closer approximation in the hypertensive patients. [11]

By validating these non-invasive estimates of ESP, the average clinician will be able to get i a more accurate estimate of a patient's LV contractility with a simple echocardiograrn and manual blood pressure reading. In this manner, the clinician will be able to better tailor a patient's heart failure regimen, especially in the patient with known severe valvular regurgitation. It will also aid the clinician in determining when the appropriate tin ie is to start inotropic therapy in severe heart failure patients and to determine if this therapy is having the appropriate clinical response. In addition, by recognizing potential biases in the non-invasive estimates, especially in the elderly patient population, clinicians will also be more cautious with the use of these estimations in the identified patient populations.

C. Study Design and Study Procedures

This will be a prospective observational study. The study subjects will be selected from patients undergoing right and/or left heart catheterization at Columbia Presbyterian Medical Center catheterization lab. Subjects will represent ages ranging between 40 to 90 years old. Twenty subjects in each decade will be studied. The sample size was calculated based on the estimation of the mean, with a 95% confidence interval, a tolerated error of 3 mm Hg, and a standard deviation of 6 mm Hg (based on prior studies examining the correlation between MAP and ESP). Subjects with significant aortic oufflow obstruction will be excluded from the study. All other subjects will be eligible for the study. Clinical information about each subject will be obtained by the physician performing the catheterization. This information will include any medications that the patient is currently taking and any known medical conditions. Baseline non-invasive blood pressure readings using a standard cuff sphygmomanometer will be taken prior to the cardiac catheterization. Three blood pressure measurements will be taken after the patient has been lying down in a quiet room for 15 minutes, 5 minutes apart, and the mean systolic and diastolic blood pressure readings will be used in the final data analysis. Prior to cardiac catheterization the patient will undergo analysis with the SphygmoCor® Blood Pressure Analysis system to measure vascular stiffness via the augmentation pressure. This system non-invasively calculates central aortic pressure waves and pressures using a transformation function previously described in detail [12,13] Briefly, this system employs the technique of radial artery tonometry [14] to obtain a summated peripheral waveform. The peripheral waveform. is calibrated using a standard cuff brachial artery blood pressure measurement. Mean arterial pressure (MAP) is calculated by integrating the area under the summated peripheral arterial waveform. Assuming that mean arterial pressure is constant throughout the arterial tree [15] and using a generalized transfer function [12,16], central aortic waveforms and pressures are determined. Central aortic end-systolic pressure is calculated as the pressure at the end of ejection. The augmentation pressure, the difference in pressure between the primary pressure walveform and the reflected wave, measures central conduit arterial stiffness. As central conduit arteries become stiffer, pulse wave velocity increases and waves reflected from peripheral sites to the ascending aorta occur at an earlier time (e.g. during the ventricular ejection period), merging with the incident (e.g. forward) wave generated by left ventricular ejection, thereby augmenting the central aortic pressure waveform[xii]. This analysis will take about 15 minutes. It does not require any additional interventions and it poses no additional risks to the patient. After this non-invasive arterial tonometer analysis, the patient will undergo routine cardiac catheterization as ordered by their attending physician. At the end of the cardiac catheterization procedure, the ESP will be me i Asured. by conductance catheter technique previously described by Baan et al [17]. Briefly a 7F conductance catheter will be advanced to the LV apex under fluoroscopic guidance. Through this catheter a 2F micromanonmeter catheter will be advanced to me i asure chamber pressure. This measurement will add about 10- 15 minutes onto the procedure time. The measurement in and of itself should not introduce any extra risk to the patient.

D. Statistical, Analysis

Once the data is collected two main analyses will be performed. First, the invasive measurements of LVESP will be compared to the non-invasively measured systolic and mean arterial pressure (calculated from the formula N4AP=DBP+1/3PP). Correlation plots for ESP vs. SBP and ESP vs. MAP will be created. To show the accuracy of the measurement and any systematic error over the range of measurements, a Bland-Altman plot will be created plotting the mean of the two measurements versus the difference between the two measurements. To evaluate the variability between the measures the standard deviation of the differences 18 will be calculated. Univariate and multivariate analysis of the relationship between age, hemodynamic variables, vasoactive medications, and co-morbid medical conditions and the difference between ESP and MAP will be performed. Similar analyses will also be performed comparing ESP to SBP.

Secondly, an analysis comparing the measurement of ESP derived from cardiac catheterization and from the SphygrnoCor® Blood Pressure Analysis system will be performed. The same statistical methods as described above will be used for this analysis.

E. Study Drugs

None

F. Medical Devices

The SphygmoCor® Blood Pressure Analysis system will be used in this study. This device is commercially available. The use in this study will allow for measurements of peripheral vascular stiffness via the augmentation pressure.

G. Study Questionnaires

None

H. Study Subjects

Subjects will be recruited from patients presenting for cardiac catheterization. The only exclusion criteria will be severe left ventricular outflow obstruction. All other patients will be included in this study. Subjects will span the decades from age 40-90 years.

I. Confidentiality of Study Data

Any information obtained during this study will be kept confidential. Each patient's chart will be given a unique identifier that will be used for all future evaluations. All of the data will be stored on a secure computer and will only be able to be accessed by the members of the research team.

J. Potential Conflict of Interest

None

K. Location of the Study

The study will take place at the Cardiac Catheterization Laboratory located in Milstein Hospital.

L. Potential Risks

The risks associated with cardiac catheterization (i.e. infection, bleeding, arrhythmias, and death) are present. The patients, however, will not be placed under any additional risk as a result of this study protocol.

M. Potential Benefits

The subjects will not benefit personally from this study. Information obtained as a result of this study may provide insights into the validity of using non-invasive hemodynamic measurements as an estimate of LVESP and, by extension, as a measurement of LV function in the elderly.

N. Alternative Therapies

None

O. Compensation to Subjects

None

P. Costs to Subjects

None

Q. Radiation

None

R. References

1. Grossman W, Braunwald E, Mann T et al. Contractile State of the Left Ventricle in Man as Evaluated from End-systolic Pressure-Volume Relation. Circulation 1977; 56 (5): 845-852.

2. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressurevolume ratio of the canine left ventricle and effect of epinephrine and heart rate on the ratio. Circ Res 1973; 32: 314-322.

3. Grossman W, Baim DS. Grossman's Cardiac Catheterization, Angiography, and Intervention. 6th Edition. New York: Lipincott, Williams & Wilkins; 2000: 374-379.

4. Haedersdal C, Madsen X, Saunamaki K. The left ventricular end-systolic pressure and pressure-volume index. Comparison between invasive and auscultatory arm pressure measurements. Angiology 1993; 44(12): 959-964.

5. Senzaki H, Chen C, Kass D. Single-beat estimation of end-systolic pressure-volume relation in humans; A new method with the potential for noninvasive applications. Circulation 1996; 94(10): 2497-2503.

6. Chen C, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. JAm Coll Card 2001; 38(7): 202812034.

7. Oshita S, Kaieda R, Funatsu N, et al. Assessment of ventriculararterial coupling in humans by transesophageal echocardiography and radial artery pressure tracing. Japn J of Anesth 1995; 44(8): 1147-53.

8. Rowland DG, Gutgesell HP. Use of Mean Arterial Pressure Noninvasive Determination of Left Ventricular End-Systolic Wall Stress in Infants and Children. Am J Cardiology 1994; 74: 98-99.

9. Dah1gren G, Veintemilla F, Settergren G, et al. Left ventricular end-systolic pressure estimated from measurements in a peripheral artery. J of Cardiothoracic and Fasc Anesth 1991; 5(6): 551-553.

10. Hebert JL, Lecarpentier Y, Zamani K et al. Relation Between Aortic Dicrotic Notch Pressure and Mean Aortic Pressure in Adults. Am J Cardiology 1995; 76: 3 01-3 06.

11. Kelly I, Ting C, Yang T, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992; 86(2): 513-521.

12. O'Rourke M F, Gallagher DE. Pulse wave analysis. JHyperten 1996; 14 (suppl 5): S147-S157.

13. Chen C, Nevo E, Fetics B, et al. Estimationof Central Aortic Pressure Wave from by Mathematical Transformation of Radial Tonometry Pressure; Validation of Generalized Transformation Function. Circulation 1997; 95(7): 1827-1836.

14. Stein PD, Blick EF. Arterial tonometry for the atraumatic measurement of arterial blood pressure. JAppl Physiol 1971 Apr; 30(4):593-6.

15. Berne RM and Levy MN. Cardiovascular Physiology. 8 Edition. St. Louis: Mosby, Inc.; 2001: 141-148.

16. Takazawa K, O'Rourke MF, Fujita M, et al. Estimation of ascending aortic pressure from radial arterial pressure using a generalised transfer function. Z Kardiol 1996; 85 Suppl 3: 137-9.

17. Bann J, van der Velde E, de Bruin H, et al. Continuous measurement of left ventricular volume in animals and man by conductance catheter. Circulation 1984; 70: 812-823.

18. Bland J and Altman D. Statistical methods for assessing agreement between two methods of clinical assessment. Lancet 1986; 1: 307-3 10.