High blood pressure at old age : The Leiden 85 plus study

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Chapter 5

Low blood pressure in the very old, a consequence of imminent heart failure. The Leiden 85-plus Study

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Abstract

Low blood pressure in the very old has been associated with organ dysfunction and excess mortality but the underlying mechanism has yet to be elucidated. We hypothesized that cardiac dysfunction contributes to low blood pressure in the very old. We invited a convenience sample consisting of 82 participants all aged 90 years from a population based cohort study in the very old. Blood pressure was measured twice and all but one underwent echocardiography to assess cardiac dimensions and functional cardiac parameters. Some 47 participants were free from hemodynamically significant valvular disease and were included in the present analyses. There were low values for mean cardiac output (2.04 l/min/m2, SE 0.40) and mean stroke volume (31.4 ml/m2, SE 7.7). For every 10-mmHg decrease in systolic blood pressure, cardiac output was 0.09 L/min/m2 lower (SE 0.04, p=0.019) and stroke volume was1.58 ml/m2 lower (SE 0.68, p=0.024). Mean left ventricular ejection fraction was normal and 2.39% (SE 1.16, p=0.046) higher for each 10-mmHg decrease in systolic blood pressure. Mean left ventricular dimensions were normal but the E/A ratio was reduced (0.68, SD 0.21), indicating diastolic dysfunction. In conclusion, among the oldest old, low systolic blood pressure correlates with low cardiac output. Systolic ventricular function is not impaired.

Introduction

There is a wide range of observational data on the relation between blood pressure and mortality in the very elderly but the outcomes are not unanimous. [1-6]. Some of the studies have shown the expected correlation between high blood pressure and increased mortality risk [6]. Some, however, did not find these associations [2-4]. Moreover, others reported the mortality risk to be higher in those with a relatively low blood pressure [1,5, 7]. In line with these unexpected findings we have recently shown low blood pressure to be associated with organ failure, for example loss of renal function [8].

In general, both diastolic and systolic blood pressure gradually increases up to middle age. From the sixth decade onwards, in most people, diastolic blood pressure tends to decrease, whereas the systolic blood pressure further increases [9]. This increase in 'pulse pressure' is generally interpreted as a consequence of arterial stiffening. At very old age, however, systolic blood pressure eventually decreases again and it is this decline in systolic blood pressure that is associated with a worse prognosis [1, 10].

If low blood pressure at very old age was a reflection of cardiac dysfunction, the increased mortality risk in those with low blood pressure would be easier to understand. To evaluate whether cardiac dysfunction may in part underlie the lower blood pressure in the very old we performed a comprehensive transthoracic echocardiographic examination in a population-based sample of older people all aged 90 years.

Material and Methods

Study population

The Leiden 85-plus Study is a prospective population-based study of all 85-year old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort were described in detail previously [11,12]. In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in the month after their eighty-fifth birthday. There were no selection criteria related to health or demographic characteristics. At baseline and yearly thereafter, the 85-year old participants were visited at their place of residence up to age 90 years. During these visits blood pressure was measured, a venous blood sample drawn, an electrocardiogram recorded and face-to-face interviews and performance tests conducted. At 90 years of age, participants were invited for an echocardiographic examination.

All participants in the study gave informed consent, and when people were severely cognitively impaired, a guardian provided informed consent. The Medical Ethics Commission of the Leiden University Medical Center approved the study.

Echocardiography

All patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system /Vivid Seven; General Electric-Vingmed, Milwaukee, WI, USA). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parasternal (standard long and short axis) and apical views (two- and four-chamber images, long-axis view). The left ventricular dimensions (end-systolic and end-diastolic diameter) were determined from parasternal M-mode acquisitions; fractional shortening and left ventricular ejection fraction were derived [13]. Left ventricular stroke volume (assessed from pulsed-wave Doppler flow through the left ventricular outflow tract times the cross-sectional area of the outflow tract) and cardiac output (stroke volume times heart rate) were calculated. Left ventricular dimensions, stroke volume and cardiac output were subsequently corrected for body surface area.

The mitral inflow (assessed by pulsed-Doppler echocardiography, with the sample placed at the tip of the mitral leaflets) was used to assess the peak velocity of the early rapid filling wave (E) and late filling wave (A); the E/A ratio was used as a marker of diastolic function. The presence and severity of mitral and aortic regurgitation were graded semi-quantitatively from colour-flow Doppler images obtained from the conventional parasternal long-axis, apical four-chamber and apical long-axis views [14-16]. To avoid the influence of significant valvular disease in the relations between echocardiographic measurements and blood pressure, participants with hemodynamically significant valvular disease were excluded from the analyses.

Blood pressure

Blood pressure was measured twice with an interval of two weeks. Blood pressure was measured, using a mercury sphygmomanometer, in seating position after at least five minutes rest without having performed vigorous exercise during the preceding 30 minutes. The systolic value was measured at the onset of phase 1, and the diastolic value was measured at the onset of phase 5 of the Korotkoff sounds. For the analysis of blood pressure we used the mean of the assessed systolic values and diastolic values.

Demographic and clinical characteristics

At baseline, a research nurse collected information concerning the demographic characteristics. The Mini-Mental State Examination (MMSE) was administered to screen for cognitive impairment [17]. Disability in basic activities of daily living (ADL) was assessed with the Groningen Activity Restriction Scale (GARS) [18]. The presence of cardiovascular disease was defined as a previous history of cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischaemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) [19].

Statistical analysis

The clinical characteristics were presented with the mean and standard error for normal distributed, continuous variables and with the median and interquartile ranges for not normal distributed variables. Differences between participants were tested with the two-sided independent T-test, the Mann Whitney test and Chi-square test respectively. All associations between blood pressure and echocardiographic characteristics were analysed with linear regression and adjusted for gender. All analyses were performed with software SPSS version 12.0.

Results

Study population

Our initial cohort consisted of 599 participants (87% response) at age 85 years. Some 257 participants survived up to age 90 years on 1 April 2004 and were in principle eligible for the study. The study nurse invited a convenience sample consisting of 82 participants. All but one underwent echocardiography. The clinical characteristics of the study cohort and the 176 participants who did not undergo echocardiography are shown in table 1. Participants who underwent echocardiography had better cognitive function (higher MMSE scores) and less disability (lower ADL scores). They also had a significant higher systolic blood pressure.

Table 1: Clinical characteristics of participants aged 90 years

	Echocardiograpic examination		
	Yes [n=81]	No [n=176]	p value
Female subjects [%]	66.7	76.1	0.11*
MMSE (IQR) [points] †	28 (26-29)	22 (16-27)	<0.001‡
ADL (IQR) [points] §	10 (9.0-13.5)	16.0 (10-24)	<0.001‡
History of cardiovascular disease [%] ‖	48.1	55.1	0.30*
DBP (SE) [mmHg]	72.9 (8.9)	71.1 (9.9)	0.16¶
SBP (SE) [mmHg]	154.7 (16.0)	150.0 (18.8)	0.04¶

SE, Standard Error. IQR, Inter Quartile Range. †, Mini Mental State Examination. §, Activities in Daily Living. ‖, Including cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischemia or infarction at age 85. ‡, *, Independent T-test. ‡, Mann Whitney test. ¶, Chi Square test. N, number of participants. DBP, Diastolic Blood Pressure. SBP, Systolic Blood Pressure.

Cardiac parameters

Some 20 participants had hemodynamically significant valvular disease. Blood pressure, both systolic and diastolic was not different between subjects with and without hemodynamically significant valvular disease (all p>0.06). As functional parameters could not be assessed unequivocally: participants with hemodynamically significant valvular disease were excluded in the present analyses. An additional 14 participants were excluded because no reliable estimation of the left ventricular outflow could be assessed (not allowing for assessment of stroke volume). Table 2 shows the echocardiography findings of the remaining 47 participants. The cardiac index (mean 2.04 L/min/m2, SE 0,40) and stroke volume index (mean 31,4 ml/m2, SE 7.7) were lower than considered normal [20,21]. Moreover, a low systolic blood pressure was significantly associated with lower stroke volume index. For every 10-mmHg lower systolic blood pressure, stroke volume index was 1.58 ml/m2 (SE 0.68, p=0.024) lower (Figure 1a). The mean left ventricular ejection fraction was 66.9% (SE 10.8%) and for every 10-mmHg decrease of systolic blood pressure, ejection fraction was 2.39% (SE 1.16, p=0.046) higher (Figure 1b). Similar but nonsignificant associations were observed between diastolic blood pressure and functional characteristics of the heart. For every 10-mmHg decrease in diastolic blood pressure, stroke volume index was 1.54 ml/m2 (SE 1.22, p=0.21) lower whereas ejection fraction was 3.59% (SE 2.04, p=0.09) higher.

Left ventricular end-diastolic and end-systolic dimensions were within reference values [20,21]. The left ventricular end-diastolic diameter was above 2.8 cm/m2 in 21 participants and four participants had a diameter beneath 2.0 cm/m2. The left ventricular end-systolic diameter was above 2.1 cm/m2 in five participants and beneath 1.3 cm/m2 in eight participants. The left ventricular dimensions were not related with diastolic or systolic blood pressure (all p>0.14). The average E/A ratio was low (mean 0.68, SE 0.22), indicating a high prevalence of diastolic dysfunction. However, the E/A ratio was not associated with systolic/diastolic blood pressure or cardiac output (all p>0.28).

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Table 2: Echocardiograpic characteristics in 47 participants without hemodynamically significant valvular disease.

	Mean (SE)	Range	Reference values
Cardiac Index [L/min/m2]	2.04 (0.40)	1.24-2.80	2.4-4.0
SV Index [ml/m2]	31.4 (7.7)	17.4-53.0	40-70
Heart rate [beats/min]	66.4 (10.8)	46-101	
LVEF [%]	66.9 (12.8)	32-87	
LVEDD Index [cm/m2]	2.73 (0.49)	1.86-3.86	2.0-2.8
LVESD Index [cm/m2]	1.70 (0.42)	0.58-2.59	1.3-2.1
E/A ratio	0.68 (0.21)	0.38-1.46	

LVEF, Left Ventricular Ejection Fraction. LVEDD, Left Ventricular End Diastolic Dimension corrected for BSA (Body Surface Area). LVESD, Left Ventricular End Systolic Dimension corrected for BSA. SV, Stroke Volume. BP, Blood Pressure. SE, Standard Error.

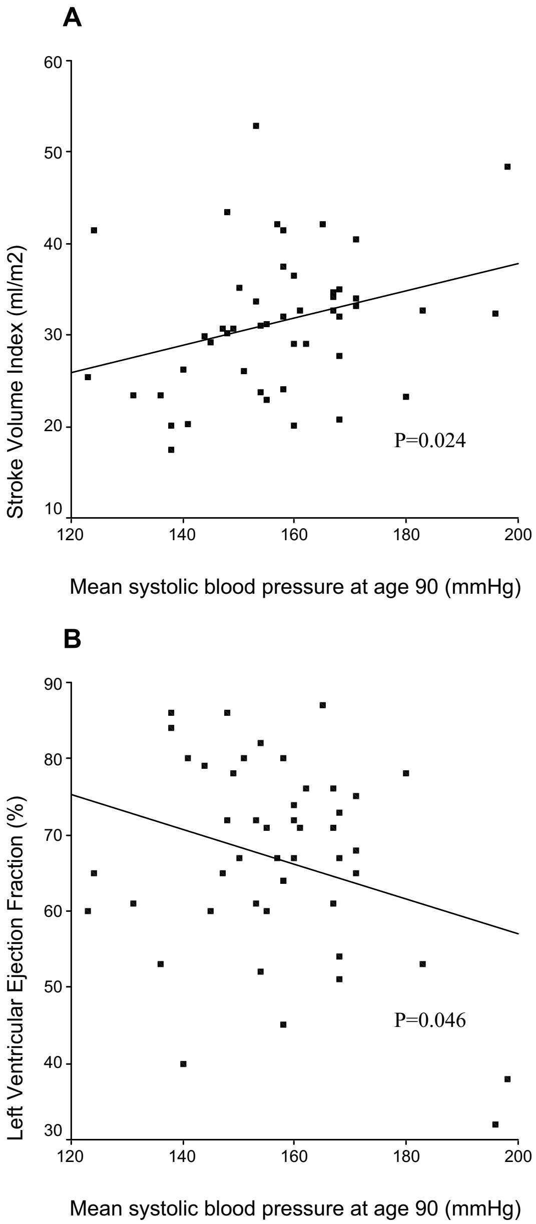

Figure 1: Cardiac performance dependent on systolic blood pressure.
Analyses were done in 47 participants without hemodynamically significant valvular disease at age 90. P-values were obtained with linear regression analyses adjusted for gender.

Systemic parameters

A low systolic and diastolic blood pressure was associated with a lower cardiac index. For every 10-mmHg lower systolic blood pressure, cardiac index was 0.09 l/min/m2 (SE 0.04, p=0.019) lower. For every 10-mmHg lower diastolic blood pressure, cardiac index was 0.12 l/min/m2 (SE 0.06, p=0.06) lower. To study whether low blood pressure, which is associated with low stroke volume and low cardiac index, is appropriate on a systemic level, we have investigated the relation between stroke volume index and heart rate. Figure 2 displays that heart rates were significant higher in participants who had a lower stroke volume (p<0.001).

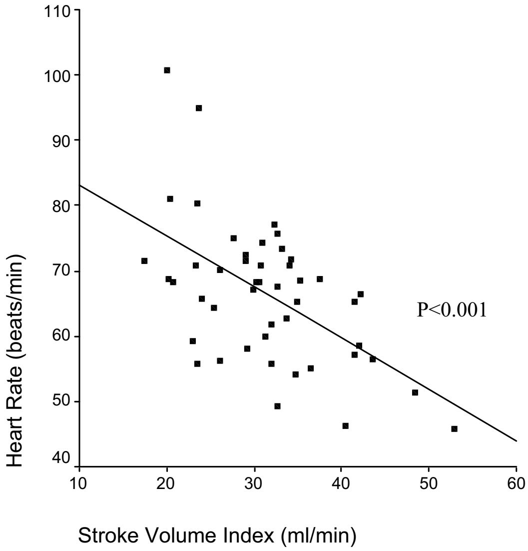

Figure 2: Systemic response to cardiac performance.
Analyses form 47 participants without hemodynamically significant valvular disease P-values were obtained with linear regression analyses adjusted for gender.

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Discussion

The main findings in our population-based study of nonagenarians consisted of fair evidence for an association between low systolic blood pressure and an impaired cardiac function. The cardiac index and the stroke volume index were on average below normal values and both were significantly and inversely related with systolic blood pressure. A low cardiac index and a low stroke volume index correlated with both, a low diastolic and a low systolic blood pressure. The left ventricular dimensions were mostly within normal values and were not related with diastolic or systolic blood pressure. Low blood pressure at very old age may thus reflect imminent heart failure, as defined by a diminished stroke volume and diminished cardiac output. It can be hypothesized that this association may, in part, underlies the association between low blood pressure and increased mortality [1,3-5].

There is only little data on routine echocardiograpic examinations in very old people [22, 23]. These studies have highlighted the presence of impaired left ventricular systolic function and the prevalence of left ventricular hypertrophy among the elderly. Another study analysed cardiac parameters of all clinically performed normal echocardiography examinations among persons who are 90 years and older but did not relate outcomes with clinical signs and symptoms [24]. Only one earlier publication made a link with blood pressure and echocardiography in community dwelling elderly [25]. No association was found between left ventricular ejection fraction and decrease of systolic and diastolic blood pressure. Measurements of cardiac index and stroke volume were not reported. As left ventricular hypertrophy did predict a decrease in blood pressure, these results suggest that diastolic dysfunction is involved in the process of decline in blood pressure in older age [25].

Pathophysiological reasoning implies that low blood pressure results from either a normal or high cardiac output with concomitant low peripheral resistance or from a low cardiac output with a high peripheral resistance. We were not informed about the peripheral resistance in our participants but we found low cardiac output to be associated with lower systolic blood pressure, that is impaired cardiac performance. The first physiological adaptation to compensate for a low stroke volume is an increase in heart rate, consequent on stimulation of the sympathetic nervous system via the baro-receptor reflex [26]. It seems unlikely that the elevated heart rate among the study participants has been consequent on autonomous sympathetic activation as under such circumstances, concomitant blood pressure would have been higher also. Therefore we reason that among the oldest old, an elevated heart rate is likely to be a systemic adaptation of cardiac dysfunction. Previously, we have reported on this same cohort that a higher heart rate on annual repeated electrocardiograms was predictive of mortality [27]. The data presented here, higher heart rates reflecting a compensatory response to impaired cardiac function, are an alternative biological explanation of our report.

In our sample the average stroke volume index and the E/A ratio were low: the findings together indicate a high prevalence of diastolic dysfunction [28], especially as significant valvular lesions were excluded. Hence, older people may have a stiff left ventricle with an impaired diastolic filling, which in turn may give a high left ventricular ejection fraction if the systolic function is not disturbed. The fact that in most people the left ventricular dimensions were within the normal range adds weight to our interpretation that systolic function is relatively intact, and left ventricular ejection fraction among very old participants may not provide a valid estimation of cardiac function. Although the E/A ratio is frequently used as an indicator of diastolic function, it is a limitation of our study that we have not assessed other measures of diastolic dysfunction.

One of the strengths of our study is the population-based character. However, the present analysis is limited due to the inclusion of relatively vital participants. The differences in general performance, cognitive performance (MMSE) and activities of daily living between the participants with versus those without an echocardiography underlined this bias towards health. Although the findings can thus not be applied to old people with ill health, one may argue that the adaptive responses as shown for those in good health, are exaggerated in those 90-year-old subjects who are less vital. The relatively small sample size prohibits us from identifying an optimal blood pressure at old age in the population at large.

Perspectives

The clinical consequences of these new unexpected echocardiographic findings have clinical significance. Physicians must be aware that a 'normal' blood pressures in the very old, for example non-hypertensive blood pressure values, does not guarantee a healthy cardiovascular state but may reflect cardiac dysfunction. Furthermore, the assessment of left ventricular ejection fraction only, to mark cardiac failure is insufficient as systolic function in old age is relatively conserved. Stroke volume index and cardiac output, together with heart rate, better identify older people at risk. Proper cardiac evaluation in those patients might open treatment modalities and hence improve prognosis.

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References

1 Lernfelt B, Svanborg A. Change in blood pressure in the age interval 70-90. Late blood pressure peak related to longer survival. Blood Pressure 2002;**11**:206-12

2 Boshuizen HC, Izaks GJ, Van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older. BMJ 1998;**316**:1780-4

3 Rajalo S, Haavisto M, Heikinheimo R, Mattila K. Blood pressure and mortality in the very old. Lancet 1983; **322**:520-1

4 Heikinheimo RJ, Haavisto MV, Kaarela RH, Kanto AJ, Koivunen MJ, Rajala SA. Blood pressure in the very old. J Hypertens 1990;**8**:361-7

5 Bemmel T, Gussekloo J, Westendorp RGJ, Blauw GJ. In a population-based prospective study no association between high blood pressure and mortality after age 85 years. J Hypertens 2006;**24**:287-292

6 Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;**360**:1903-13

7 Messerli FH, Mancia G, Conti CR, Hewkins AC, Kupfer S, Champion A, et al. Dogma deputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006;**144**:884-893

8 T van Bemmel, K Woittiez, GJ Blauw, F van der Sman-de Beer, FW Dekker, RGJ Westendorp, et al. Prospective study of the effect of blood pressure on renal function in old age: The Leiden 85-plus Study. J Am Soc Nephrol 2006; **17**:2561-2566

9 Franklin SS, Gustin IV W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. Circulation 1997;**96**:308-15

10 Satish S, Zhang DD, Goodwin JS. Clinical significance of falling blood pressure among older adults. J Clin Epidemiol 2001;**54**:961-7

11 Bootsma-van der Wiel A, van Exel E, de Craen AJ, Gussekloo J, Lagaay AM, Knook DL, et al. A high response is not essential to prevent selection bias. Results from the Leiden 85-Plus Study. Clin Epidemiol 2002;**55**:1119-25.

12 Exel E, Gussekloo J, Houx P, de Craen AJ, MacFarlane PW, Bootsma-van der Wiel A, et al. Atherosclerosis and cognitive impairment are linked in the elderly. The leiden 85-plus Study. Atherosclerosis 2002;**165**:353-9.

13 Isaaz K, Ethevenot G, Admant P, Brembilla B, Pernot C. A simplified normalized ejection phase index measured by Doppler echocardiography for the assessment of left ventricular performance. Am J Cardiol 1990;**65**:1246-5

14 Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, et al. Colour Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 1987;**75**:175–83

15 Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B Evaluation of aortic insufficiency by Doppler colour flow mapping. J Am Coll Cardiol 1987;**9**:952-9

16 Weismann NJ, Tighe Jr JF, Gottdiener JS, Gwynne JT. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. Sustained-Release Dexfenfluramine Study Group. N Engl J Med 1998;**339**:725–32

17 Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A comprehensive review. J Am Geriatrics Soc 1992;**40**:922-35.

18 Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med 1996;**43**:1601-10.

19 Macfarlane PW, Latif S. Automated serial electrocardiogram comparison based on the Minnesota code. J Electrocardiol 1996;**29**:29-34.

20 Feigenbaum. Echocardiography. Williams & Wilkins, Baltimore, Maryland, U.S.A. 1994

21 Marino P.L. The ICU book, second edition. Williams & Wilkins, Baltimore, Maryland, U.S.A. 1998

22 Raymond I, Pedersen F, Steensgaard-Hansen F, Green A, Busch-Sorensen M, Tuxen C, et al. Prevalence of impaired left ventricular systolic function and heart failure in a middle aged and elderly urban population segment of Copenhagen. Heart 2003;**89**:1422-9

23 Lindroos M, Kupari M, Heikkilä, Tilvis R. Echocardiographic evidence of left ventricular hypertrophy in a general aged population. Am J Cardiol 1994;**74**:385-90

24 Dokainish H, Gin K, Lee P, Jue J. Left ventricular filling patterns and pulmonary artery pressures in patients aged 90 to 100 years with normal echocardiography results. J Am Soc Echocardiogr 2003;**16**:664-9

25 Hakala SM, Tilvis RS. Determinants and significance of declining blood pressure in old age. Eur Heart J 1998;**19**:1872-8

26 Guyton AC. Textbook of medical physiology, eighth edition. W.B. Saunders company, Philadelphia, U.S.A. 1991

27 Bemmel van T, Vinkers DJ, Macfarlane PW, Gussekloo J, Westendorp RGJ. Markers of autonomic tone on a standard ECG are predictive of mortality in old age. Int J Cardiol 2006;**107**:36-41

28 Aurigemma GP, Gaasch WH, Mclaughlin M, McGinn R, Sweeney A, Meyer TE. Reduced left ventricular systolic pump performance and depressed myocardial contractile function in patients >65 years of age with normal ejection fraction and high relative wall thickness. Am J Cardiol 1995;**76**:702-5