

Influence of Aging on Cardiac Function Examined by Echocardiography

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SACHIKO ABE,² MICHIKO SUZUKI,² SINJI KOMATSU,² YOSHIFUMI SAIJO³ and
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WATANABE, S., SUZUKI, N., KUDO, A., SUZUKI, T., ABE, S., SUZUKI, M., KOMATSU, S., SAIJO, Y. and MURAYAMA, N. *Influence of Aging on Cardiac Function Examined by Echocardiography*. Tohoku J. Exp. Med., 2005, **207** (1), 13-19 — We assessed the influence of aging on cardiac function by means of parameters measured by echocardiography. The study group consisted of 494 normal subjects aged 13 to 87 years. We measured the ratio of early filling (E) and atrial contraction (A) transmitral flow velocities (E/A) of left and right ventricular inflow (LV E/A and RV E/A) for assessment of diastolic function. We also measured left ventricular ejection fraction (LVEF), and the ratio of pre-ejection period (PEP) and ejection time (ET) of the left ventricle (PEP/ET) for assessment of systolic function. Both LV E/A and RV E/A decreased significantly with aging while LVEF and PEP/ET remained normal range. The decline rate as aging was greater in LV E/A than in RV E/A. These results showed that both left and right ventricular diastolic function deteriorated with aging while left ventricular systolic function was not noticeably affected by aging. We suggest that indexes of diastolic function are more sensitive than those of systolic function when the natural course is studied in a large population. ——— aging; diastolic function; doppler echocardiography; systolic function

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In cardiac evaluation, parameters of systolic function index such as stroke volume, cardiac output and ejection fraction are very useful in diagnosis and prognosis of patients with cardiac diseases and in evaluating their response to medical treatment. On the other hand, even though the meanings of systolic and diastolic function of heart are different, it is clear that the diastolic function may contribute to the heart failure in some degree (Braunwald and Ross 1963; Bristow

et al. 1970; Gaasch et al. 1976; Grossman and McLaurin 1976; Brutsaert et al. 1985). Echocardiography can easily measure ejection fraction (EF) which is a major index of left ventricular systolic function, by M-mode and B-mode analysis and other parameters of cardiac function from Doppler velocity patterns.

The ratio of early filling (E) and atrial contraction (A) transmitral flow velocities (E/A) measured by Doppler technique is used as a sim-

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ple and good index of diastolic function. Recently, E/A is recognized as being useful for the presumption of left ventricular hemodynamics (Appleton et al. 1988; Giannuzzi et al. 1994), classification of cardiac functional (Vano-verschelde et al. 1990), and prognostic value (Klein et al. 1991; Shen et al. 1992; Pinamonti et al. 1993; Werner et al. 1994; Xie et al. 1994; Yamamuro et al. 1996). However, left ventricular filling pattern receives strong influence from aging factor seen even in healthy normal subjects which inverse the E/A (Takenaka et al. 1986; Gardin et al. 1987; Graettinger et al. 1987; Klein et al. 1989; Kitzman et al. 1991; Cacciapuoti et al. 1992). In this study, we investigated the relationship between age and some of the parameters in left ventricular systolic and diastolic function using echocardiography.

As right ventricular diastolic function can also be assessed by transtricuspid flow velocity patterns (Klein et al. 1990; Pye et al. 1991; Gatzoulis et al. 1995; Komaki et al. 2003), we also extended our investigation to discuss the correlation of left and right ventricular diastolic functions.

MATERIALS AND METHODS

Subjects

The study populations were 494 patients (13 – 87 years old) without significant cardiac disease who came to our hospital for echocardiographic examination from

May 2000 until March 2002. Patients with atrial fibrillation were excluded. The breakdown is as follow: 232 men (56.4 ± 14.9 years old) and 262 women (59.4 ± 15.8 years old).

Measurement methods

E/A of mitral and tricuspid valves. Transmitral flow velocities at the center position between the tips of anterior and posterior mitral leaflets in apical four-chamber view were recorded by pulsed Doppler technique. Transtricuspid flow velocities at the center position between the tips of anterior and septal leaflets were recorded in a same manner. The peak velocities of early diastolic filling (E) and atrial contraction (A) of both transmitral and transtricuspid valves were measured and E/A ratio for both valve were calculated (Fig. 1).

Left ventricular ejection fraction. Left ventricular wall motion was recorded using M-mode method. Left ventricular internal dimension at end-diastole (LVDD) and left ventricular internal dimension at end-systole (LVDs) were measured and left ventricular EF was calculated based on Teichholz method.

PEP/ET. The opening and closure of aortic valve were recorded using M-mode method. The time from Q wave of electrocardiography until aortic valve opening was considered as pre-ejection period (PEP) and the time from starting of left ventricular ejection until aortic valve closure was considered as ejection period (ET). Both values were measured and PEP/ET ratio was calculated (Fig. 2). We used conventional ultrasound apparatuses (Toshiba SSH-260A, SSH-160A Toshiba, Tokyo) for the echocardiographic examination. Central frequency was

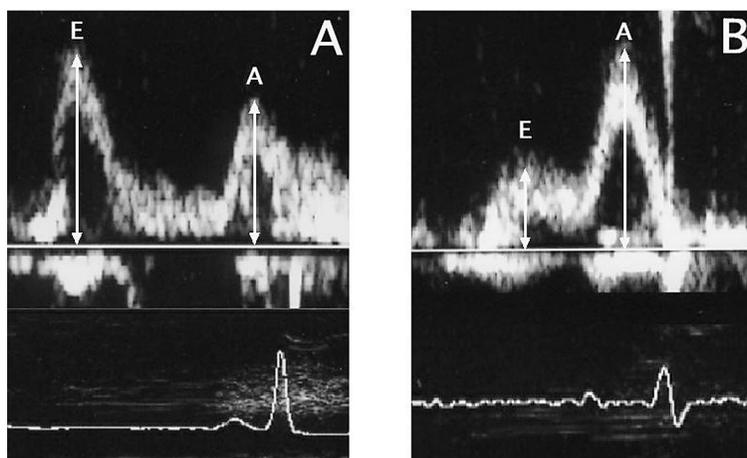


Fig. 1. Examples of left ventricular inflow pattern. A: Normal relaxation pattern ($E > A$). B: Abnormal relaxation pattern ($E < A$).

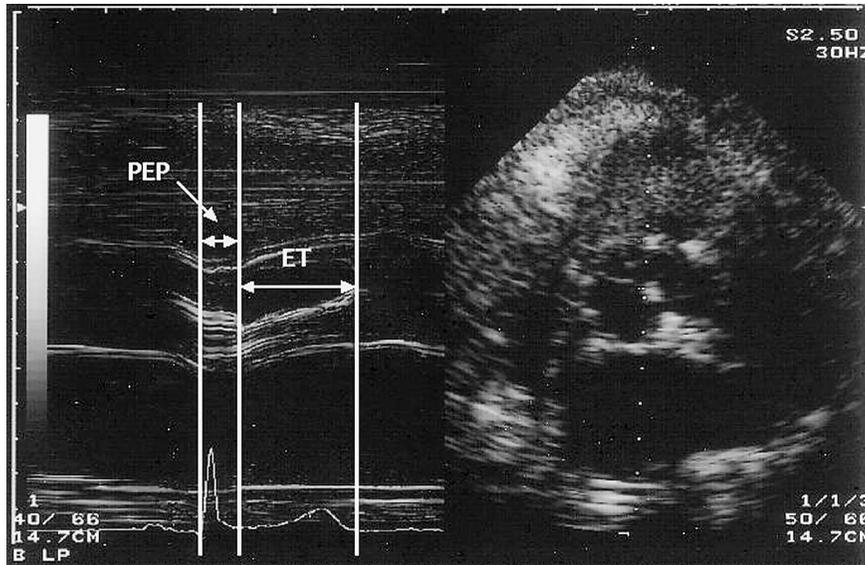


Fig. 2. Measurement of PEP/ET. PEP, pre-ejection period; ET, ejection time.

3.5 MHz for M-mode. Central frequency was 2.5 MHz and pulse repetition rate was 4 kHz for the Doppler measurement.

Statistical analysis

Patients were classified according to the age. We calculated the mean \pm S.D. (standard deviation) for the transmitral and transtricuspid E/A ratios, EF and PEP/ET ratio according to groups. We also calculated the difference in mean value using analysis of variance (ANOVA). Regression analysis of linear function and secondary function were examined. Correlation coefficient value of transmitral and transtricuspid E/A ratios were higher in the second function but the difference is not significant,

for that we used the linear function of regression analysis as it can respond enough and easy to apply to clinical study.

RESULTS

Table 1 shows the average (mean \pm S.D.) of each parameter according to age. We also analyzed each parameter according to sex and found that there was no significant difference between male and female for all parameters. Therefore, we only separated the results between male and female for the transmitral and transtricuspid E/A ratio (mean \pm S.D.) (Fig. 3).

TABLE 1. Mean and standard deviations of transmitral E/A, transtricuspid E/A, LVEF, and PEP/ET by age group

| Age (years) | Number | Transmitral E/A | Transtricuspid E/A | LVEF (%) | PEP/ET |
|-------------|--------|-----------------|--------------------|----------------|-----------------|
| < 20 | 9 | 2.28 \pm 0.69 | 1.92 \pm 0.63 | 63.6 \pm 5.2 | 0.31 \pm 0.06 |
| 20~29 | 19 | 1.75 \pm 0.45 | 1.60 \pm 0.37 | 65.4 \pm 5.6 | 0.30 \pm 0.07 |
| 30~39 | 33 | 1.62 \pm 0.45 | 1.69 \pm 0.64 | 67.0 \pm 4.5 | 0.32 \pm 0.05 |
| 40~49 | 74 | 1.31 \pm 0.32 | 1.42 \pm 0.39 | 66.0 \pm 5.0 | 0.32 \pm 0.06 |
| 50~59 | 114 | 1.06 \pm 0.29 | 1.25 \pm 0.36 | 68.1 \pm 5.2 | 0.32 \pm 0.05 |
| 60~69 | 108 | 0.86 \pm 0.26 | 1.15 \pm 0.32 | 68.5 \pm 6.1 | 0.30 \pm 0.05 |
| 70~79 | 114 | 0.76 \pm 0.19 | 1.07 \pm 0.27 | 68.2 \pm 5.8 | 0.31 \pm 0.06 |
| > 79 | 23 | 0.73 \pm 0.14 | 0.98 \pm 0.25 | 68.6 \pm 4.3 | 0.30 \pm 0.06 |

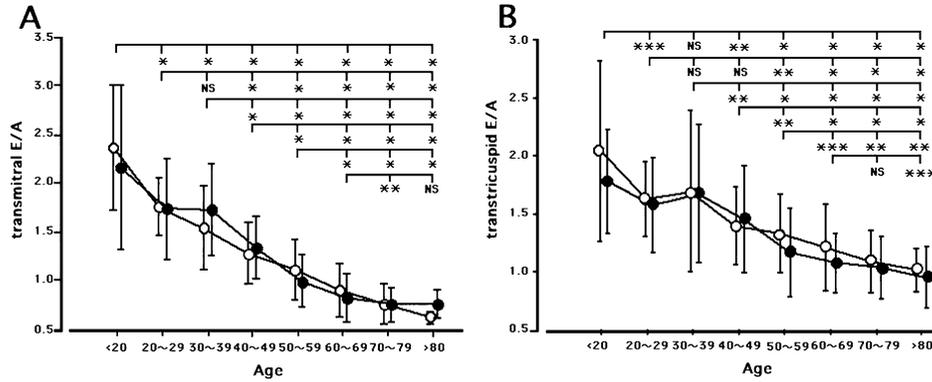


Fig. 3. A: Graph showing the decrease in transmittal E/A with increase in age. B: Graph showing the decrease in transtricuspid E/A with increase in age. Empty circles is male, filled circles is female. Empty and filled circles indicate mean; vertical bars, standard deviation. ANOVA between each group is shown. * $p < 0.001$, ** $p < 0.01$, *** $p < 0.05$.

Parameters related to diastolic function

Average value of an E/A ratio for the transmittal flow was 2.28 ± 0.69 which was more than 2.0 for subjects below 20 years old and 1.06 ± 0.29 which was more than normal average value 1.0 for subjects who were in their 50's. However, we found that E/A ratio for subjects who were in their 60's was 0.86 ± 0.26 which was below 1.0. The inversion of E wave and A wave was apparent in subjects who were in their 40's and increase rapidly to the percentage of 45% and 73% for sub-

jects who were in their 50's and 60's, respectively, and increase further to more than 90% for subjects who were in their 70's and 80's. The correlation coefficient (r) for the transmittal E/A ratio and age was -0.615 ($p < 0.001$) and was recognized for having weak negative correlation (Fig. 4A).

As for average value of an E/A ratio for the transtricuspid flow, the average value was 2.12 ± 0.70 which was more than 2.0, similar to the transmittal E/A ratio for subjects below 20 years

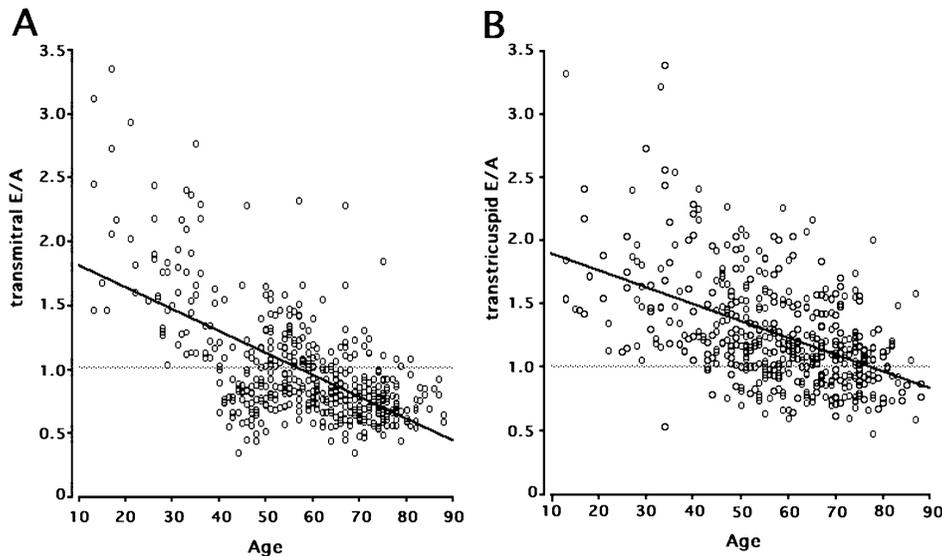


Fig. 4. A: Scattergram showing correlation between transmittal E/A and age. Simple regression line is drawn. $y = 1.983 - 0.017x$, $r = -0.615$ ($p < 0.001$). B: Scattergram showing correlation between transtricuspid E/A and age. Simple regression line is drawn. $y = 2.033 - 0.013x$, $r = -0.497$ ($p < 0.001$).

old and showed tendency to decrease as age increases. However, compared to the transmitral flow, the E/A ratio of transtricuspid flow decreased slowly where for subjects who were in their 70's, the average value of E/A ratio was 1.06 ± 0.29 , which was not below 1.0 and the inversion of E wave and A wave was 40% from overall result. For subjects who were in their 80's, the inversion of E and A waves was 57% and the average value again was not below 1.0. The correlation coefficient (r) for the transtricuspid E/A ratio and age was -0.497 ($p < 0.001$) and was recognized for having weak negative correlation (Fig. 4B).

We also investigated the relationship between E/A ratio of transmitral and transtricuspid flow velocities and found positive correlation with correlation coefficient (r) equal to $+0.588$ ($p < 0.001$) (Fig. 5).

Parameters related to systolic function

In relation to EF, we found no significant difference in the average values of all age groups although we could see a slight increase in average value of EF as age increases. We also found no significant correlation between EF and age from the correlation coefficient (r) was $+0.168$ (Fig.

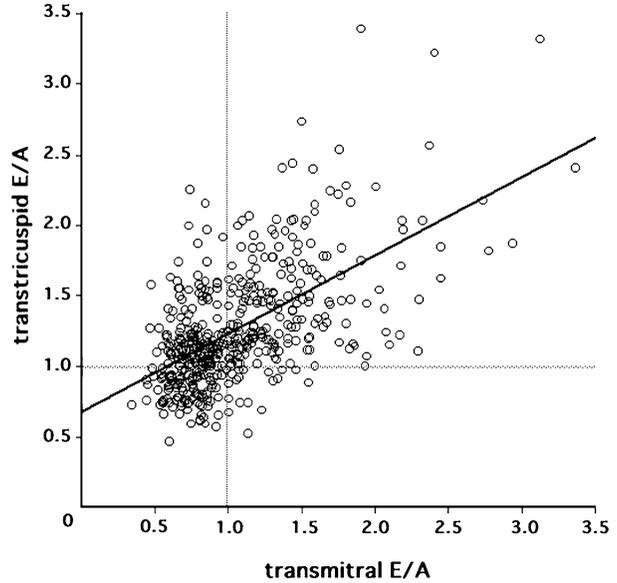


Fig. 5. Scattergram showing correlation between transmitral E/A and transtricuspid E/A. $y = 0.671 + 0.553x$, $r = +0.588$ ($p < 0.001$).

6A).

As for PEP/ET ratio, we found no significant difference in all age groups and the average was around 0.3. We also found no significant correlation between PEP/ET and age and the correlation coefficient (r) was -0.041 (Fig. 6B).

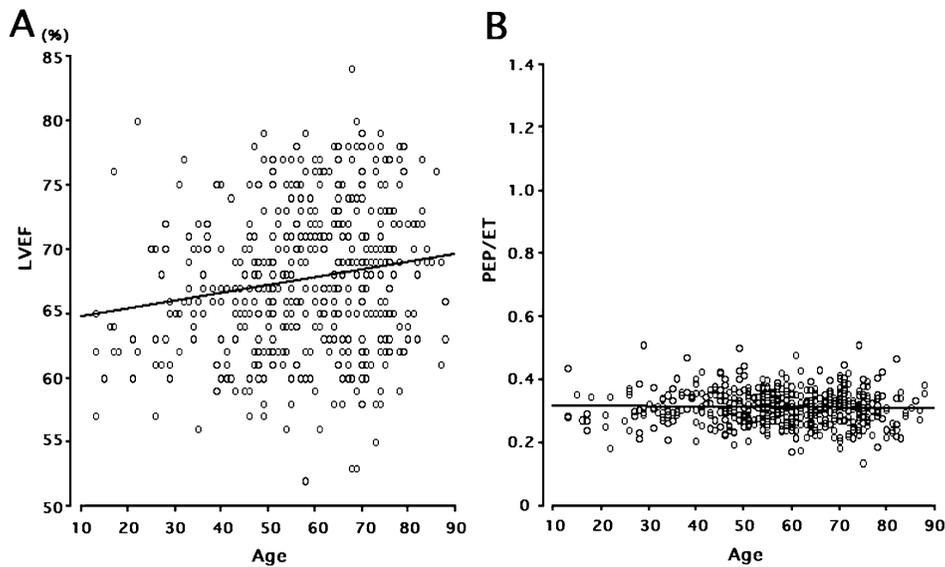


Fig. 6. A: Scattergram showing correlation between LVEF and age. Simple regression line is drawn. $y = 64.157 + 0.060x$, $r = +0.168$ B: Scattergram showing correlation between PEP/ET and age. Simple regression line is drawn. $y = 0.320 - 0.00015x$, $r = -0.041$.

The relationship between LVEF and PEP/ET had weak negative correlation with correlation coefficient (r) equal to -0.168 ($p < 0.001$).

DISCUSSION

In previous studies, evaluation of left ventricular diastolic function has been useful for an early diagnosis of patients with early stage heart failure because diastolic function was often altered when systolic function was preserved (Klein et al. 1991; Shen et al. 1992; Pinamonti et al. 1993; Werner et al. 1994; Xie et al. 1994; Yamamuro et al. 1996). However, diastolic function altered as aging even in healthy subjects. Young healthy subjects showed the ratio around 2.0 but the ratio gradually decreases as aging. At 60 years old, the ratio becomes below 1.0 which is believed as the normal value (Takenaka et al. 1986; Gardin et al. 1987; Graettinger et al. 1987; Appleton et al. 1988; Hatle et al. 1989; Klein et al. 1989; Kitzman et al. 1991; Cacciapuoti et al. 1992). This phenomenon is known as the aging factor in the atonic characteristic of left ventricle.

In this study, we also found that the average ratio showed below 1.0 at the age 60's. However, the population of the patients with greater A wave than E wave, showing the deterioration of left ventricular diastolic function, was 18% and 45%, at the age 40's and 50's, respectively. The percentage rose rapidly to 73% at the age 60's. Considering individual performance, we believe that the deterioration of left ventricular diastolic function starts as early as age 40's. An increase in collagen in the pressure-overloaded ventricle is known to cause myocardial stiffness (Conrad et al. 1995; Ho et al. 1996). Thus diastolic dysfunction in aging is due to the increase of interstitial collagen fiber in left ventricular wall.

The same phenomenon was found in the right ventricular diastolic function where one of the parameters, transtricuspid E/A inversion at the age 40's and deteriorated as aging. However, the inversion was slower than the transmitral flow. The average was above 1.0 even older than age 70's. In fact, in age 70's, the patients with inverted E/A transtricuspid flow was 40% and it means more than half people maintained normal right

ventricular diastolic function at 70's.

Since E/A ratio of transmitral and transtricuspid flow had correlation, it is thought that both left and right ventricular diastolic function deteriorate from age 40's. The difference of degree on diastolic dysfunction may be caused by the effect of pressure-overload was more prominent in left ventricular wall than right ventricle.

Regarding systolic function, aging did not influence EF and thus left ventricular systolic function which is the basis of cardiac pump function is preserved even as age increases.

Recently, tissue Doppler measurement of mitral or tricuspid annular velocity is considered more sensitive and stable method of assessing diastolic function (Tighe et al. 2003). The influence of afterload or valvular disease is smaller in tissue Doppler measurement than conventional flow measurement. In the present study, we evaluated the diastolic function of normal population without cardiac disease. We need to evaluate diastolic function using tissue Doppler technique.

CONCLUSION

We found that diastolic function of both left and right ventricles deteriorated as aging while systolic function was not influenced by aging factor. Furthermore, the rate of deterioration was more prominent in left ventricle compared to right ventricular diastolic function.

References

- Appleton, C.P., Hatle, L.K. & Popp, R.L. (1988) Relation of transmitral flow velocity patterns to left ventricular diastolic function: New insights from a combined hemodynamic and Doppler echocardiographic study. *J. Am. Coll. Cardiol.*, **12**, 426-440.
- Braunwald, E. & Ross, J., Jr. (1963) The ventricular end-diastolic pressure: Appraisal of its value in the recognition of ventricular failure in man. *Am. J. Med.*, **34**, 147-150.
- Bristow, J.D., Van Zee, B.E. & Judkins, M.P. (1970) Systolic and diastolic abnormalities of the left ventricle in coronary artery disease: Studies in patients with little or no enlargement of ventricular volume. *Circulation*, **42**, 219-228.
- Brutsaert, D.L., Rademakers, F.E., Sys, S.U., Gillebert, T.C. & Housmans, P.R. (1985) Analysis of relaxation in the evaluation of ventricular function of the heart. *Prog. Cardiovasc. Dis.*, **28**, 143-163.
- Cacciapuoti, F., D'Avino, M., Lama, D., Bianchi, U., Perrone, N. & Varicchio, M. (1992) Progressive impairment of left ventricular diastolic filling with advancing age: A Doppler echocardiographic study. *J. Am. Geriatr. Soc.*, **40**, 245-250.

- Conrad, C.H., Brooks, W.W., Hayes, J.A., Sen, S., Robinson, K.G. & Bing, O.H. (1995) Myocardial fibrosis and stiffness with hypertrophy and heart failure in the spontaneously hypertensive rat. *Circulation*, **91**, 161-170.
- Gaasch, W.H., Levine, H.J., Quinones, M.A. & Alexander, J.K. (1976) Left ventricular compliance: mechanisms and clinical implications. *Am. J. Cardiol.*, **38**, 645-653.
- Gardin, J.M., Davidson, D.M., Rohan, M.K., Butman, S., Knoll, M., Garcia, R., Dubria, S., Gardin, S.K. & Henry, W.L. (1987) Relationship between age, body size, gender, and blood pressure and Doppler flow measurements in the aorta and pulmonary artery. *Am. Heart J.*, **113**, 101-109.
- Gatzoulis, M.A., Clark, A.L., Cullen, S., Newman, C.G. & Redington, A.N. (1995) Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot: Restrictive physiology predicts superior exercise performance. *Circulation*, **91**, 1775-1781.
- Giannuzzi, P., Imparato, A., Temporelli, P.L., de Vito, F., Silva, P.L., Scapellato, F. & Giordano, A. (1994) Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J. Am. Coll. Cardiol.*, **23**, 1630-1637.
- Graettinger, W.F., Weber, M.A., Gardin, J.M. & Knoll, M.L. (1987) Diastolic blood pressure as a determinant of Doppler left ventricular filling indexes in normotensive adolescents. *J. Am. Coll. Cardiol.*, **10**, 1280-1285.
- Grossman, W. & McLaurin, L.P. (1976) Diastolic properties of the left ventricle. *Ann. Intern. Med.*, **84**, 316-326.
- Hatle, L.K., Appleton, C.P. & Popp, R.L. (1989) Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation*, **79**, 357-370.
- Ho, S.Y., Jackson, M., Kilpatrick, L., Smith, A. & Gerlis, L.M. (1996) Fibrous matrix of ventricular myocardium in tricuspid atresia compared with normal heart. A quantitative analysis. *Circulation*, **94**, 1642-1646.
- Kitzman, D.W., Sheikh, K.H., Beere, P.A., Philips, J.L. & Higginbotham, M.B. (1991) Age related alterations of Doppler left ventricular filling in normal subjects are independent of left ventricular mass, heart rate, contractility and loading conditions. *J. Am. Coll. Cardiol.*, **18**, 1243-1250.
- Klein, A.L., Hatle, L.K., Burstow, D.J., Seward, J.B., Kyle, R.A., Bailey, K.R., Luscher, T.F., Gertz, M.A. & Tajik, A.J. (1989) Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. *J. Am. Coll. Cardiol.*, **13**, 1017-1026.
- Klein, A.L., Hatle, L.K., Burstow, D.J., Taliercio, C.P., Seward, J.B., Kyle, R.A., Bailey, K.R., Gertz, M.A. & Tajik, A.J. (1990) Comprehensive Doppler assessment of right ventricular diastolic function in cardiac amyloidosis. *J. Am. Coll. Cardiol.*, **15**, 99-108.
- Klein, A.L., Hatle, L.K., Taliercio, C.P., Oh, J.K., Kyle, R.A., Gertz, M.A., Bailey, K.R., Seward, J.B. & Tajik, A.J. (1991) Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: A Doppler echocardiography study. *Circulation*, **83**, 808-816.
- Komaki, K., Sakuma, M., Ishigaki, H., Hozawa, H., Yamamoto, Y., Takahashi, T., Kumasaka, N., Kagaya, Y., Ikeda, J., Watanabe, J. & Shirato, K. (2003) Varieties of right ventricular diastolic function in patients with non-obstructive hypertrophic cardiomyopathy. *Tohoku J. Exp. Med.*, **199**, 49-57.
- Pinamonti, B., Di Lenarda, A., Sinagra, G. & Camerini, F. (1993) Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications: Heart Muscle Disease Study Group. *J. Am. Coll. Cardiol.*, **22**, 808-815.
- Pye, M.P., Pringle, S.D. & Cobbe, S.M. (1991) Reference values and reproducibility of Doppler echocardiography in the assessment of the tricuspid valve and right ventricular diastolic function in normal subjects. *Am. J. Cardiol.*, **67**, 269-273.
- Shen, W.F., Tribouilloy, C., Rey, J.L., Baudhuin, J.J., Boey, S., Dufosse, H. & Lesbre, J.P. (1992) Prognostic significance of Doppler-derived left ventricular diastolic filling variables in dilated cardiomyopathy. *Am. Heart J.*, **124**, 1524-1533.
- Takenaka, K., Dabestani, A., Gardin, J.M., Russell, D., Clark, S., Allfie, A. & Henry, W. L. (1986) Left ventricular filling in hypertrophic cardiomyopathy: A pulsed Doppler echocardiography study. *J. Am. Coll. Cardiol.*, **8**, 1963-1971.
- Tighe, D.A., Vinch, C.S., Hill, J.C., Meyer, T.E., Goldberg, R.J. & Aurigemma, G.P. (2003) Influence of age on assessment of diastolic function by Doppler tissue imaging. *Am. J. Cardiol.*, **91**, 254-257.
- Vanoverschelde, J.L., Raphael, D.A., Robert, A.R. & Cosyns, J.R. (1990) Left ventricular filling in dilated cardiomyopathy: relation to functional class and hemodynamics. *J. Am. Coll. Cardiol.*, **15**, 1288-1295.
- Werner, G.S., Schaefer, C., Dirks, R., Figulla, H.R. & Kreuzer, H. (1994) Prognostic value of Doppler echocardiographic assessment of left ventricular filling in idiopathic dilated cardiomyopathy. *Am. J. Cardiol.*, **73**, 792-798.
- Xie, G.Y., Berk, M.R., Smith, M.D., Gurley, J.C. & DeMaria, A.N. (1994) Prognostic value of Doppler transmitral flow pattern in patients with congestive heart failure. *J. Am. Coll. Cardiol.*, **24**, 132-139.
- Yamamuro, A., Yoshida, K., Akasaka, T., Hozumi, T., Takagi, T., Honda, Y., Okura, H. & Yoshikawa, J. (1996) Prognostic value of serial Doppler echocardiographic follow-up of transmitral flow patterns in patients with congestive heart failure who presented with pulmonary edema. *J. Cardiol.*, **27**, 321-327.