European Heart Journal (2002) **23,** 162–171
doi:10.1053/euhj.2001.3032, available online at http://www.idealibrary.com on IDEAL®

Tissue Doppler analysis of age-dependency in diastolic ventricular behaviour and filling

A cross-sectional study of healthy hearts (the Umeå General Population Heart Study)

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Background Much in the diagnosis of diastolic ventricular dysfunction is dependent upon the filling pattern, and most patients diagnosed with diastolic heart failure are elderly. Data from healthy asymptomatic individuals across a range of ages are rare. We sought to find an age-related variation in normal diastolic physiology, specifically the filling pattern and segmental myocardial longitudinal velocities.

Methods and Results To assess the effect of normal ageing on left ventricular longitudinal function, we studied myocardial shortening and lengthening velocities using the tissue Doppler technique in 60 healthy subjects who were randomly selected from the Umeå (Sweden) General Population Register, which represents a wide range of ages (23–88 years). Myocardial velocities were documented at four left ventricular sites (anterior, left, posterior and septal) and at three levels (basal, mid-cavity and apical). Transmitral, transtricuspid and pulmonary venous flow velocities were recorded using pulsed-wave Doppler. While systolic myocardial velocities were conserved across ages, there was a marked decrease in early diastolic velocities with age (from 16 cm . s^{-1} at 30 years to 9 cm . s^{-1} at 80 years at the basal segment) and a corresponding significant increase in late diastolic velocities (from 10 to 16 cm . s^{-1}). Although these findings were most marked at the basal level, they were also clearly manifested at the apical level. Myocardial lengthening velocities were related to transmitral flow velocities, showing a correlation of 0·64 ($P<0·0001$) in early diastole and 0·68 ($P<0·0001$) in late diastole. Finally, diastolic pulmonary venous flow velocity was found to correlate with early diastolic myocardial velocities (at the basal level, $r=0·53$, $P<0·0001$).

Conclusions Normal ageing causes a decrease in early diastolic and a substantial increase in late diastolic myocardial lengthening velocities. These changes explain the known trends in the transmitral flow pattern with age. In contrast, systolic myocardial velocities do not change significantly with age. These findings should be considered when evaluating diastolic function, especially in the elderly.

(Eur Heart J, 2002; 23: 162–171, doi:10.1053/euhj.2001.3032)

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Introduction

Although heart disease becomes progressively more common with increasing age, the dependence of normal cardiac physiology on age has not received as much attention as the physiology of symptomatic subjects. This applies not only to hypertension, ischaemic heart disease[1] and chronic systolic heart failure[2] but also to clinical heart failure with apparently normal systolic function 'diastolic heart failure[3,4]. The distinction between normal physiology and pathological processes presupposes adequate knowledge of the pattern of normality in the population being studied. Yet studies of normal physiology, upon which this distinction is based, have frequently concentrated on healthy controls who are young. Such an approach can only be adequate if normal physiology does not vary substantially with age.

Revision submitted 6 September 2001, accepted 12 September 2001, and published online 22 November 2001.

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0195-668X/02/020162+10 $35.00/0

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Studies of healthy individuals frequently recruit subjects on an ad-hoc basis for reasons of organizational simplicity. The disadvantage of such a recruitment policy is that the age distribution will not be even across the age spectrum studied, but instead typically sparse at both extremes. This has two inter-related adverse consequences. First, the degree of precision with which the normal ranges can be quoted at the extremes of age is poorer. Second, age-dependencies of physiological measurements can easily be missed because relatively few data points are available at the extremes assuming that age dependence is linear.

In this study, therefore, we set out to measure regional ventricular myocardial velocities (using the tissue Doppler technique[5,6]) and diastolic blood flow velocities (using conventional Doppler) in a random sample of healthy individuals whose ages ranged widely and were evenly distributed. Such a representative sample of volunteers was available to us from the Umeå County Population Register.

Methods

Subjects

Sixty normal subjects aged 23 to 88 years were randomly selected from the general population register of Umeå, 26 were male. No subject had hypertension, angina, heart failure or any cardiac-related or other systemic disease. No subject was taking medication. All subjects gave informed consent for this study, which was approved by the local ethics committee. Subjects were coded and codes were broken after the investigation and analysis.

Echocardiography

Subjects were studied with the transducer at the cardiac apex and the patient in the partial left lateral decubitus position. A digital ultrasound scanner (Accuson, Mountain View, CA, U.S.A.) equipped with a multifrequency imaging transducer and Doppler tissue imaging programme was used. This programme was set to the pulsed wave Doppler mode and filters were set to exclude high frequency signals. Gains were minimized to allow for a clear coloured myocardial signal with minimal background noise. All recordings were obtained with superimposed ECG and phonocardiogram, at a speed of $50\ \mathrm{mm}\ .\ \mathrm{s}^{-1}$. All measurements were made from paper printouts.

Myocardial tissue Doppler

Myocardial systolic and diastolic velocities were recorded using the tissue Doppler technique, with the gain adjusted to delineate an optimum velocity envelope. Measurements were made at three left ventricular levels; mitral ring (basal, papillary muscles (mid cavity) and apical and in four axial segments (left (free wall) and septal from the apical four-chamber view, and anterior and posterior from the apical two-chamber view), all from the basal part of the segment. Thus 12 segments of the left ventricle were studied. An average value for each of the four axial segments was obtained by averaging the velocities from the three levels in that segment; similarly an average value for each of the three levels was obtained by averaging the velocities from the four axial segments at that level. From each of the 12 ventricular segments, three peak velocities were measured: systolic, early diastolic and atriogenic. Likewise, from the right ventricular free wall two segments were studied; basal at the lateral angle of the tricuspid ring and mid cavity.

Transmitral and pulmonary venous flow velocities

Transmitral and transtricuspid Doppler flow velocities were recorded from the apical four-chamber view with the sample volume positioned at the tips of the mitral and tricuspid valve leaflets, respectively. The peak early diastolic and peak atriogenic velocities were measured on the two sides. Pulmonary venous flow velocities were recorded from the same view with the sample volume 1 cm below the orifice of the right pulmonary vein into the left atrium. Peak systolic and diastolic velocities were measured.

Statistical analysis

A standard statistical package, Statview 4.5 (Abacus Concepts, CA, U.S.A.) was used. The Pearson product-moment correlation coefficient and least-squares linear regression were used to assess the strength and slope of the relationships between one continuous variable and another. A P value of $<0{\cdot}05$ was considered significant. Where a large number of comparisons are made (Fig. 2), a stricter criterion for P of $0{\cdot}001$ was used.

Results

Tissue Doppler velocities

All subjects had adequate windows and all data were analysable. The mean systolic, early diastolic and atriogenic myocardial velocities in each of the 12 segments are shown in Table 1.

Age-dependency

There was no significant dependence of systolic velocities on age. The lack of a significant trend with age in

Table 1 Mean velocities at each position in each phase of the cardiac cycle, given in cm . s^{-1}. SEM=standard error of the mean

	Basal		Mid		Apical	
	Mean	SEM	Mean	SEM	Mean	SEM
Systolic						
Left	14·4	0·6	9·6	0·5	7·6	0·3
Septal	10·1	0·2	8·0	0·2	6·0	0·2
Anterior	9·6	0·3	7·7	0·2	5·4	0·2
Posterior	10·8	0·3	8·0	0·2	6·1	0·3
Early diastolic						
Left	17·3	0·7	12·8	0·5	8·1	0·5
Septal	10·8	0·5	11·4	0·4	7·4	0·3
Anterior	10·9	0·4	9·3	0·3	6·5	0·3
Posterior	13·4	0·5	11·4	0·6	7·7	0·4
Atriogenic						
Left	15·9	0·6	11·1	0·7	7·8	0·5
Septal	12·3	0·4	10·9	0·4	6·8	0·4
Anterior	10·9	0·5	9·5	0·5	6·2	0·3
Posterior	11·7	0·4	10·7	0·4	7·2	0·3

All measurements are given in cm . s^{-1}.

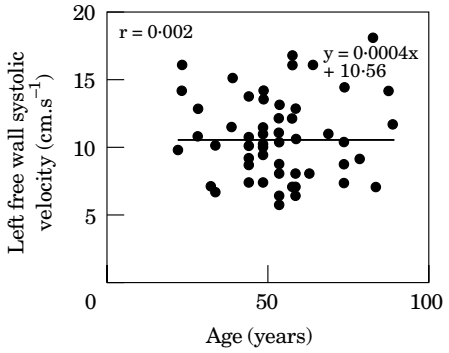

***Figure 1* Relationship of systolic velocity of the left ventricular free wall with age.**

the average velocity in the left free wall is shown in Fig. 1. Similarly, regional measurements at all 12 left ventricular positions and two right ventricular positions showed no trend with age (Fig. 2(a)).

In contrast, diastolic velocities were strongly dependent on age, as shown in Fig. 2(b) and (c). The left free wall early diastolic velocity decreased with age, showing a regression slope of $-60{\cdot}16$ cm . s^{-1} year^{-1} (r$=-0{\cdot}63$, $P<0{\cdot}0001$), as shown in Fig. 3(a). Meanwhile atriogenic velocities increased with age, showing a regression slope of $0{\cdot}18$ cm . s^{-1} year^{-1} (r$=0{\cdot}71$, $P<0{\cdot}0001$), as shown in Fig. 3(b).

Early diastolic and atriogenic velocities were inversely correlated in the left free wall, r$=-0{\cdot}56$ ($P<0{\cdot}0001$, Fig. 4), in the septum, r$=-0{\cdot}43$ ($P<0{\cdot}001$), and in the posterior wall, r$=-0{\cdot}52$ ($P<0{\cdot}0001$), although not significantly in the anterior wall, r$=-0{\cdot}19$ ($P>0{\cdot}05$).

Differences between axial segments of the heart

Myocardial velocities were broadly similar between different axial segments of the heart (at comparable times in the cycle), as shown in Table 1. The left ventricular free wall showed the highest velocities at all levels and at all time points. In systole, its mean velocity (averaged across all three levels) was 10·6 (SE 0·4) cm . s^{-1} which was 34% higher than that of the other three walls, which averaged 7·9 (SE 0·2) cm . s^{-1}; in the basal segment alone, the effect was more prominent 14·4 (SE 0·5) cm . s^{-1} vs 10·1 (SE 0·3) cm . s^{-1}, a 43% difference. Similarly, in early diastole, this difference was 30% as an average across levels but 48% in the basal segment. The atriogenic velocity was also higher at the left (free wall), by 21% across all levels or 35% in the basal segment. These differences were significantly different.

Transmission of systolic and diastolic velocities along the long axis

The highest velocities were recorded at the basal level both in systole and diastole. There was a remarkable degree of preservation of velocities at sites distant from the base. Systolic velocities averaged 11·2 (SE 0·2), 8·3 (SE 0·2) and 6·2 (SE 0·2) cm . s^{-1} at the basal, mid-cavity and apical levels, respectively. Early diastolic velocities averaged 13·1 (SE 0·5), 11·2 (SE 0·4) and 7·4 (SE 0·3) cm . s^{-1}, respectively. Atriogenic myocardial lengthening velocities averaged 12·8 (SE 0·4), 10·5 (SE 0·4) and 7·1 (SE 0·3) cm . s^{-1}, respectively. On the right side, systolic velocities averaged 16·5 (SE 0·3) and 15·7 (SE 0·4) cm . s^{-1} at the basal and mid-cavity levels. Early diastolic velocities were 17·3 (0·4) and 14·2 (0·4) cm . s^{-1} and atriogenic velocities 14·8 (0·3) and 17·4 (0·4) cm . s^{-1}, at the two levels, respectively.

Age-related changes in transmitral and transtricuspid flow velocities

Transmitral E-wave velocities fell with age ($-0{\cdot}66$ cm . s^{-1} year^{-1}, r$=-0{\cdot}63$, $P<0{\cdot}0001$) while the A-wave velocities rose with age ($0{\cdot}67$ cm . s^{-1} year^{-1}, r$=0{\cdot}60$, $P<0{\cdot}0001$). In contrast, on the right side, the tricuspid flow velocities showed a fall in E wave velocity with age which was less marked ($-0{\cdot}22$ cm . s^{-1} year^{-1}, r$=-0{\cdot}40$, P=ns) and no significant rise in A wave velocity (r$=0{\cdot}15$).

Relationship between transmitral Doppler velocities and myocardial velocities

The peak myocardial early diastolic lengthening velocity was significantly associated with peak early mitral inflow

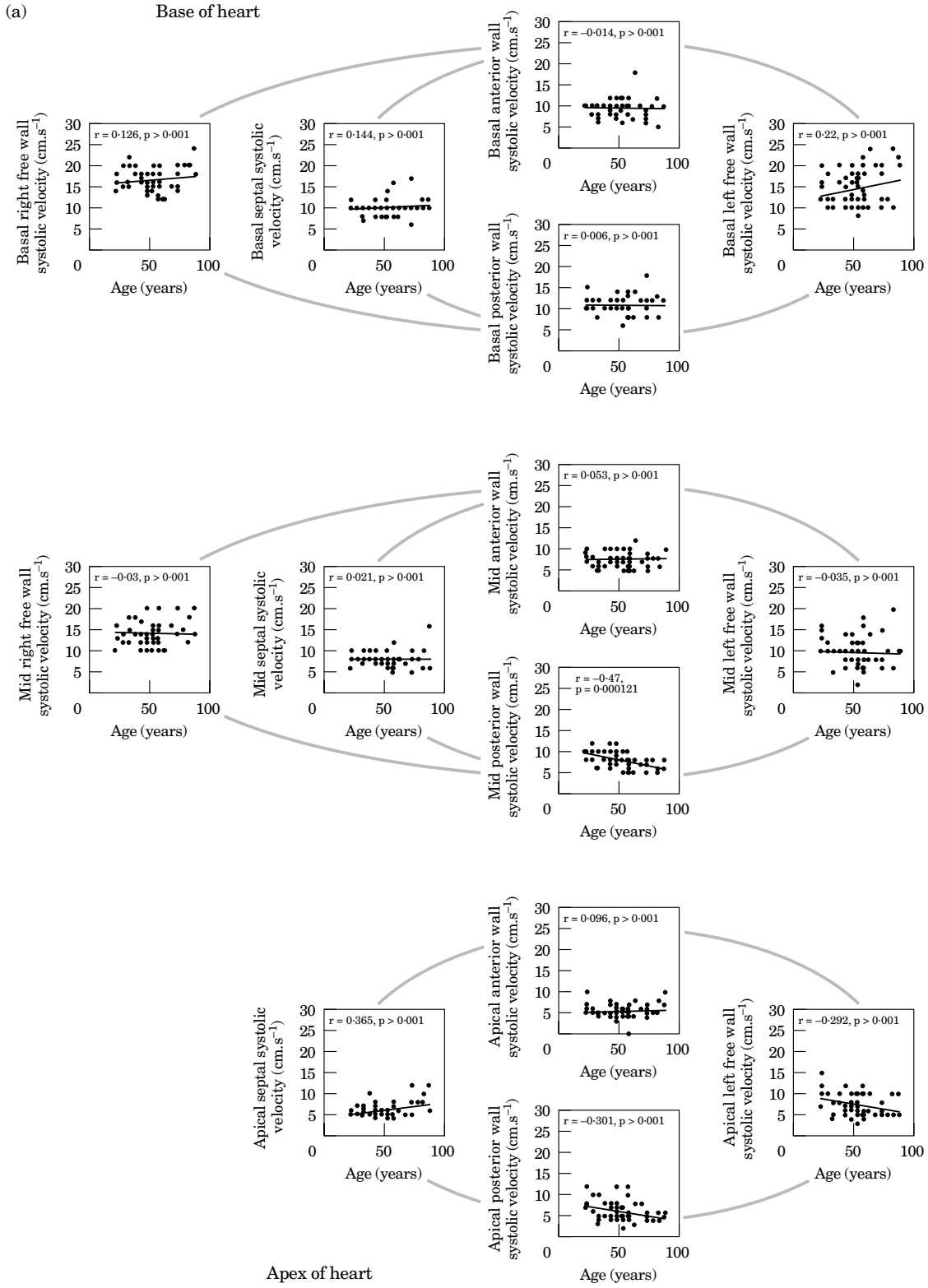
(a)
Base of heart
Basal right free wall systolic velocity (cm.s^{-1})
r = 0·126, p > 0·001
Basal septal systolic velocity (cm.s^{-1})
r = 0·144, p > 0·001
Basal anterior wall systolic velocity (cm.s^{-1})
r = –0·014, p > 0·001
Basal posterior wall systolic velocity (cm.s^{-1})
r = 0·006, p > 0·001
Basal left free wall systolic velocity (cm.s^{-1})
r = 0·22, p > 0·001
Mid right free wall systolic velocity (cm.s^{-1})
r = –0·03, p > 0·001
Mid septal systolic velocity (cm.s^{-1})
r = 0·021, p > 0·001
Mid anterior wall systolic velocity (cm.s^{-1})
r = 0·053, p > 0·001
Mid posterior wall systolic velocity (cm.s^{-1})
r = –0·47, p = 0·000121
Mid left free wall systolic velocity (cm.s^{-1})
r = –0·035, p > 0·001
Apical septal systolic velocity (cm.s^{-1})
r = 0·365, p > 0·001
Apical anterior wall systolic velocity (cm.s^{-1})
r = 0·096, p > 0·001
Apical posterior wall systolic velocity (cm.s^{-1})
r = –0·301, p > 0·001
Apical left free wall systolic velocity (cm.s^{-1})
r = –0·292, p > 0·001
Age (years)
Apex of heart

Figure 2 **(a).**

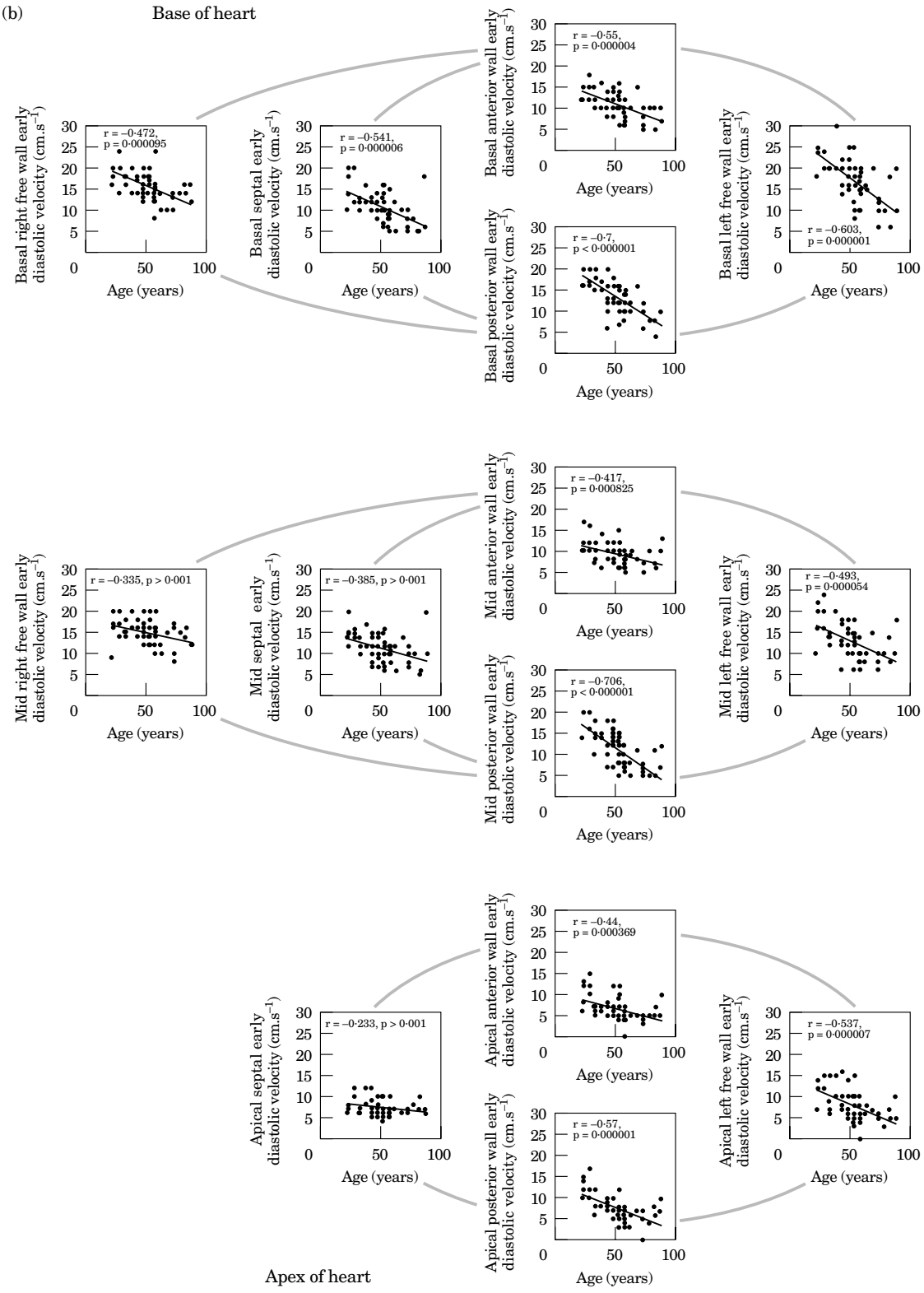
(b)
Base of heart
Basal right free wall early diastolic velocity (cm.s⁻¹)
r = –0·472, p = 0·000095
Basal septal early diastolic velocity (cm.s⁻¹)
r = –0·541, p = 0·000006
Basal anterior wall early diastolic velocity (cm.s⁻¹)
r = –0·55, p = 0·000004
Basal posterior wall early diastolic velocity (cm.s⁻¹)
r = –0·7, p < 0·000001
Basal left free wall early diastolic velocity (cm.s⁻¹)
r = –0·603, p = 0·000001
Mid right free wall early diastolic velocity (cm.s⁻¹)
r = –0·335, p > 0·001
Mid septal early diastolic velocity (cm.s⁻¹)
r = –0·385, p > 0·001
Mid anterior wall early diastolic velocity (cm.s⁻¹)
r = –0·417, p = 0·000825
Mid posterior wall early diastolic velocity (cm.s⁻¹)
r = –0·706, p < 0·000001
Mid left free wall early diastolic velocity (cm.s⁻¹)
r = –0·493, p = 0·000054
Apical septal early diastolic velocity (cm.s⁻¹)
r = –0·233, p > 0·001
Apical anterior wall early diastolic velocity (cm.s⁻¹)
r = –0·44, p = 0·000369
Apical posterior wall early diastolic velocity (cm.s⁻¹)
r = –0·57, p = 0·000001
Apical left free wall early diastolic velocity (cm.s⁻¹)
r = –0·537, p = 0·000007
Age (years)
Apex of heart

Figure 2 **(b).**

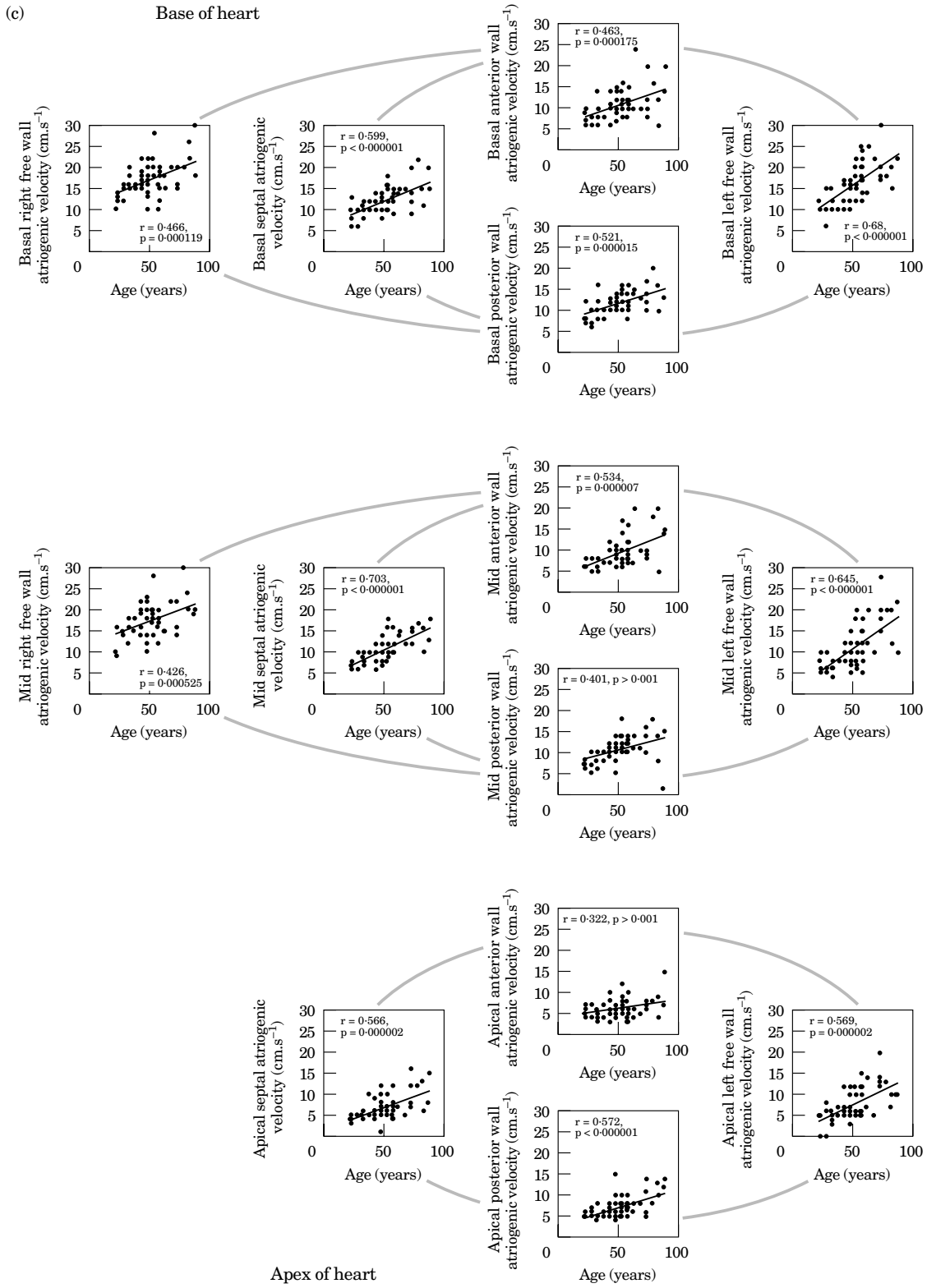

Figure 2 **(c).**

Figure 2 **(a) Relationships of systolic velocities in the ventricular myocardium with age. (b) Relationships of early diastolic velocities in the ventricular myocardium with age. (c) Relationships of atriogenic velocities in the ventricular myocardium with age.**

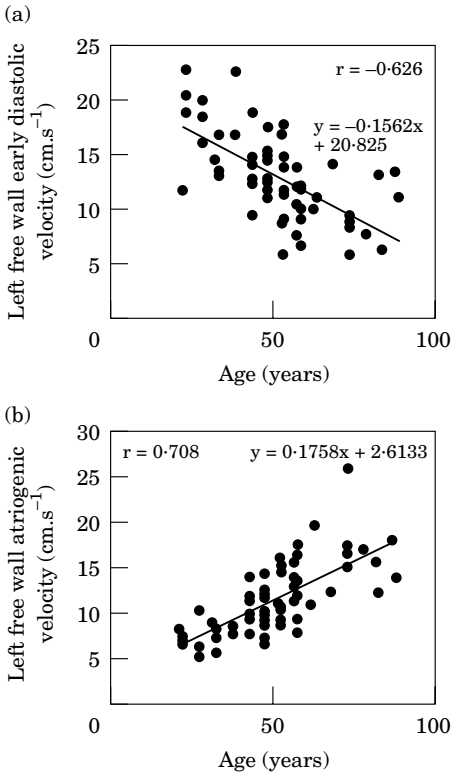

Figure 3 **Relationship of (a) early diastolic and (b) atriogenic myocardial velocity of the left ventricular free wall with age.**

velocity at the basal level (r=0·64, $P<0·0001$) and at the mid-cavity (r=0·69, $P<0·0001$) levels. The relationship was less marked at the apex (r=0·56, $P<0·0001$). Likewise, the atriogenic velocity correlated significantly with late diastolic myocardial velocities at the basal level (r=0·68, $P<0·001$), mid cavity (r=0·59, $P<0·001$) and apex (r=0·58, $P<0·001$).

Relationship of velocities in the pulmonary vein with myocardial velocities

Pulmonary venous diastolic flow velocities were significantly associated with early diastolic myocardial lengthening velocities at the basal level (r=0·53, $P<0·0001$) and at the mid-cavity (r=0·45, $P<0·0001$), with a much weaker relationship at the apex (r=0·35, P=ns), as shown in Fig. 6. Systolic velocities, however, were not related to myocardial systolic velocities but atrial ones (r=0·43, $P<0·005$).

Discussion

Left ventricular minor axis function is poorly predictive of filling pattern because overall ventricular function is contributed to by two perpendicular axes. In contrast, ventricular long axis motion[7] has been shown to correlate with filling velocities, particularly in early diastole. The mechanism of this relationship is the insertion of the atrial and ventricular longitudinal fibres around the circumference of the mitral ring[8,9]. Since the ventricular apex and the top of the atrium remain relatively stationary through the cardiac cycle, the longitudinal function of the two chambers depends on the mitral and tricuspid annular movement: in systole towards the apex and in diastole towards the atrium. Therefore, it is quite conceivable that the mitral annular change in velocities directly influences those of ventricular filling, even when the amplitude of motion is maintained. If this is the case a clearer understanding of the known alteration of filling velocities with age can be achieved.

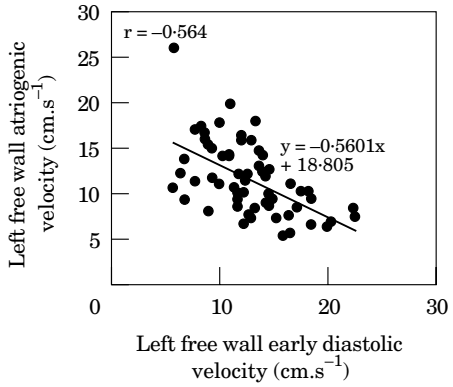

Figure 4 **Relationship of early diastolic velocity of the left ventricular free wall with age.**

Our results show that systolic segmental myocardial velocities are independent of age as is the overall systolic ventricular function as assessed by fraction shortening. In contrast, in diastole, early lengthening velocities decline significantly with age in almost all segments, but to the greatest extent at the basal level. Concomitantly, atriogenic velocities increase, again most prominently at the basal level but nevertheless clearly detectable even at the apex. This change in balance is not merely relative but also absolute, with atriogenic velocities being approximately 60% higher in 80-year-olds than 30-year-olds. Early diastolic velocities correlate directly with transmitral flow velocities as well as with the diastolic component of pulmonary venous flow. Finally, right ventricular velocities and tricuspid flow velocities do not manifest the marked variation with age that is seen in the corresponding left-sided indices.

Mechanisms

Our observation that myocardial systolic velocities are constant across ages may at first seem to conflict[10] with existing knowledge that ejection fraction has previously been found to increase slightly with normal ageing[11,12]. Our interpretation is that ejection fraction, being additionally dependent on chamber size and minor axis movement, may rise without any change in shortening velocity, if the chamber becomes smaller[13] or the minor

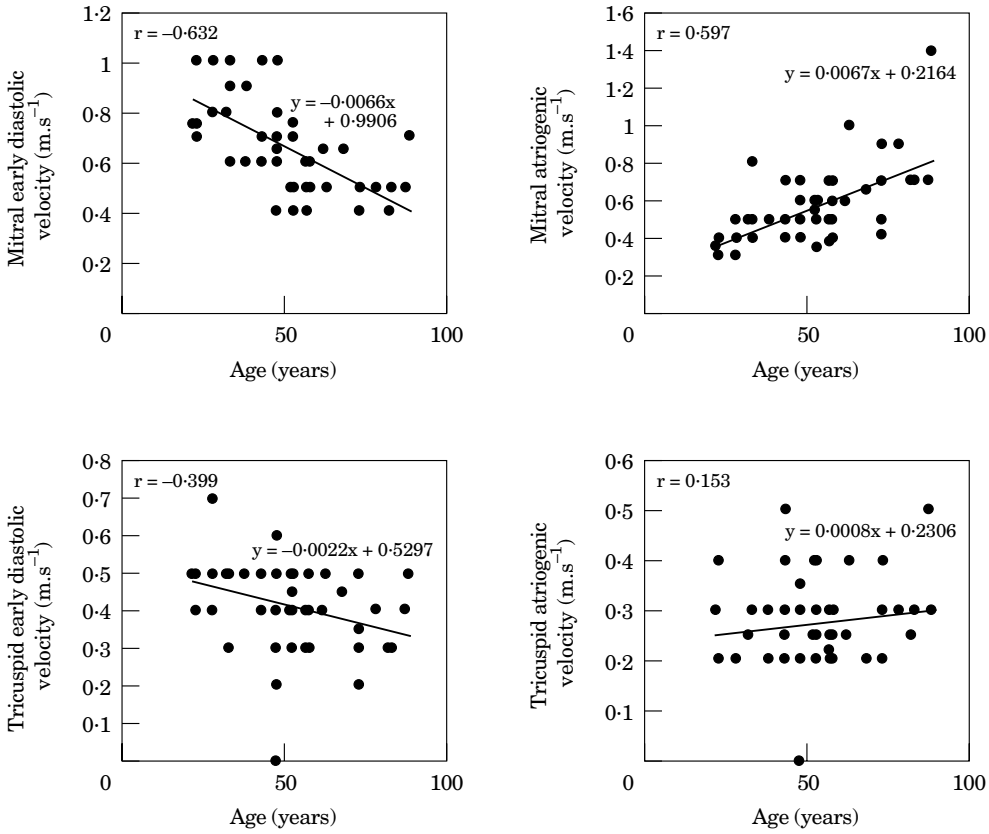

Figure 5 **Relationship between transmitral (upper panels) and transtricuspid (lower panels) Doppler flow and age. E-wave filling is shown on the left and A-wave filling on the right.**

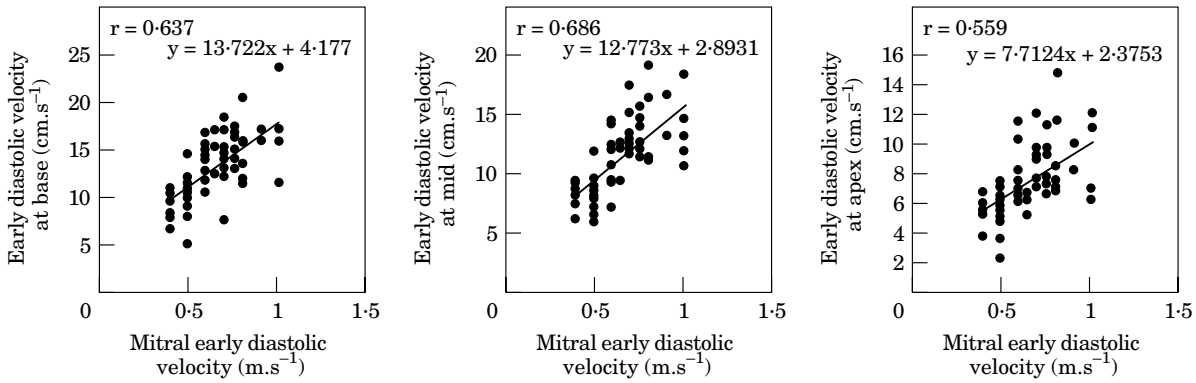

Figure 6 **Relationship between transmitral early filling velocity and myocardial lengthening velocity at the basal (a), midcavity (b) and apical (c) levels of the ventricle.**

axis more active[14]. Indeed there is established clinical evidence for both of these phenomena occurring with increasing age.

The fall in early diastolic myocardial lengthening velocity parallels laboratory experience from senescent myocytes showing that sarcomere relaxation velocity decreases. Since lengthening velocities correlate closely with ventricular filling in early diastole, ageing should result in a significant compromise of early diastolic stroke volume. The increase in atriogenic myocardial lengthening velocity along with filling velocities and consequently volumes seem to be a natural compensatory mechanism. The fact that these alterations in myocardial and ventricular filling behaviour are all age related suggests that it is likely to be a chronic adaptive mechanism. Our previous observations during induction of acute ischaemia, of a fall in early diastolic lengthening and filling velocities, did not result in an immediate increase in atriogenic velocities[15].

Atriogenic velocities in the ventricular myocardium are a direct result of active atrial contraction. The presence of clear atriogenic velocities even near the apex

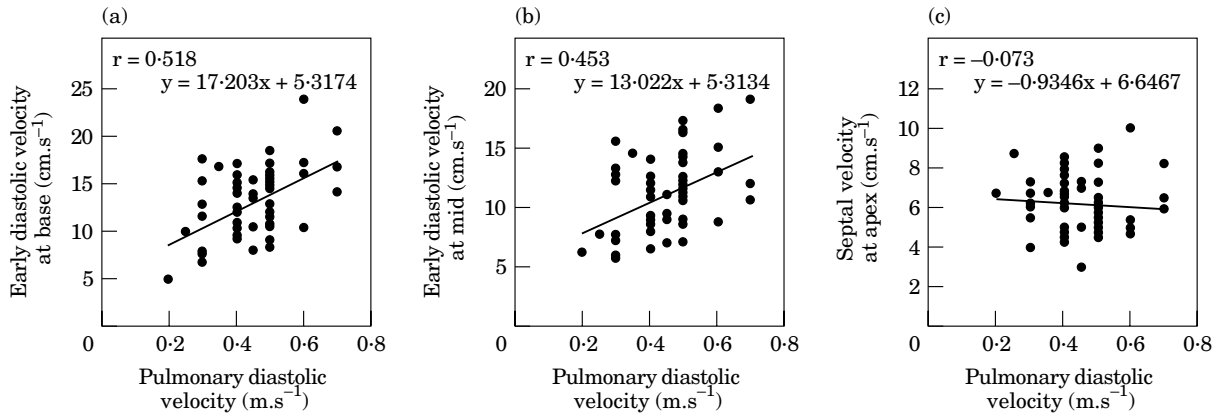

Figure 7 **Relationship between pulmonary venous diastolic velocity and myocardial lengthening velocity at the basal (a), mid-cavity (b) and apical (c) levels of the ventricle.**

shows that energy from atrial contraction is transferred along the myocardial fibrils down to the apical region. Our detection of the accentuation of this atriogenic velocity with age necessarily means that atrial contraction becomes actively more vigorous with normal ageing. The phenomenon cannot be explained by a change in ventricular active properties (because the ventricle is not active) nor the passive properties (because it would have to become extraordinarily compliant).

The close relationship between myocardial early diastolic velocities and the diastolic component of pulmonary venous flow underlines the importance of the activity of the longitudinal fibres, responsible for both of these phenomena[16], in maintaining left atrial stroke volume. The paradox in this relationship is that the increase in atriogenic velocity with age occurs alongside the age-related increase in atrial size and associated increased prevalence of atrial fibrillation[17]. This can be explained by Starling law when the left atrium dilates in order to augment its shortening velocities and stroke volume. There are many areas of physiological control in which the various contributory mechanisms decline at different rates with age, and thus the pattern of predominance may change with time. The peculiarity of myocardial lengthening, however, is that atrial contraction does not merely become relatively more important but rather the active contraction velocity increases absolutely with age.

Clinical implications

Transmitral Doppler flow velocities are frequently used as an index of left ventricular 'diastolic function'. Their normal changes with age should be considered before making interpretations of 'diastolic function', particularly in patients in whom their diagnosis may go as far as diastolic heart failure[4]. This issue may be important not only in the elderly, but also in patients with diseases involving the subendocardium, such as coronary artery disease. Atriogenic myocardial lengthening velocity is a direct measure of active atrial contraction, which may therefore provide complementary information to left atrial dimension, the currently used standard index of left atrial function. Further studies may elucidate whether the two measurements could provide independent predictive value for future atrial arrhythmias. Finally, right ventricular myocardial and tricuspid flow velocities are remarkably stable with ageing, unlike the left side. This suggests that age-related changes are not necessarily an intrinsic property of atrial or ventricular myocardium but reflect the consequence of its being left sided. It also has its clinical benefit when assessing right ventricular function, any observed abnormalities are unlikely to result from normal ageing and therefore are potentially useful age-independent markers of disease. This may explain the surprising value of right ventricular long axis function (a reliable measure of overall right ventricular systolic function[18]) in predicting exercise tolerance[19] and mortality[20] in heart failure.

This study was supported by the Swedish Heart and Lung Foundation, the Swedish Medical Association, The Medical Faculty of Umeå University and Torsten and Ragnar Soderberg's Foundation.

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