Left Atrial Relaxation and Left Ventricular Systolic Function Determine Left Atrial Reservoir Function

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Left Atrial Relaxation and Left Ventricular Systolic Function Determine Left Atrial Reservoir Function

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Background—Determinants of left atrial (LA) reservoir function and its influence on left ventricular (LV) function have not been quantified.

Methods and Results—In an open-pericardium, paced (70 and 90 bpm) pig model of LV regional ischemia (left anterior descending coronary constriction), with high-fidelity LV, LA, and RV pressure recordings, we obtained the LA area with 2D automated border detection echocardiography, LA pressure-area loops, and Doppler transmitral flow. We calculated LV τ, LA relaxation (a−x pressure difference divided by time, normalized by a pressure), and stiffness (slope between x and v pressure points of v loop). Determinants of total LA reservoir (maximum−minimum area, cm^2) were identified by multiple regression analysis. Different mean rates of LA area increase identified 2 consecutive (early rapid and late slow) reservoir phases. During ischemia, LV long-axis shortening (LAS, LV base systolic descent) and LA reservoir area change decreased (7.3±0.3 [SEM] versus 5.6±0.3 cm^2, $P<0.001$) and LA stiffness increased (1.6±0.3 versus 3.1±0.3 mm Hg/cm^2, $P=0.009$). Early reservoir area change depended on LA mean ejection rate (LA area at ECG P wave minus minimum area divided by time; multiple regression coefficient=0.9; $P<0.001$) and relaxation (coefficient=4.9 $cm^2\times$ms/s; $P<0.001$). Late reservoir area change depended on LAS (coefficient=8 cm/s; $P<0.001$). Total reservoir filling depended on LA stiffness (coefficient=−0.31 cm^4/mm Hg; $P=0.001$) and cardiac output (coefficient=0.001 $cm^2\times$min/L; $P=0.002$). The strongest predictor of cardiac output was LA reservoir filling (coefficient=301 L/min$\times cm^2$; $P<0.001$). The v loop area was determined by cardiac output, LV ejection time, τ, and early transmitral flow.

Conclusions—Two (early and late) reservoir phases are determined by LA contraction and relaxation and LV base descent. Acute LV regional ischemia increases LA stiffness and impairs LA reservoir function by reducing LV base descent. **(*Circulation*. 1999;100:427-436.)**

Key Words: hemodynamics ■ mechanics ■ atrium

Left atrial (LA) function includes 3 phases: reservoir (inflow during ventricular systole), conduit (passive emptying during ventricular relaxation and diastasis), and contraction (active emptying near ventricular end diastole). LA relaxation,[1] stiffness,[2–4] and contractility[5] influence LA reservoir, conduit, and contraction function. Historically, LA function has been expressed by its booster pump contribution to cardiac output.[5–10] LA reservoir function is influenced by LA relaxation,[7,11,12] left ventricular (LV) contraction through the descent of the base during systole,[12,13] LA chamber stiffness,[2–4,8] and right ventricular (RV) systole through pulmonary venous (PV) inflow.[14,15] The relative contributions of these factors have not been quantified.[11,15]

The influence of LA chamber stiffness,[2,8] and thus LA reservoir function, on cardiac output has been inferred, but no in vivo data exist to support the hypothesis that the LA reservoir phase determines cardiac output.

This study quantifies the relationship between LA reservoir function, LV systolic function, and the transmitted RV systolic pressure pulse. We use a model of acute LV regional supply ischemia during right atrial pacing in open-pericardium pigs to measure the independent effects of acute changes of LV systolic function and heart rate on LA reservoir function (chamber dimension changes and stiffness). LA relaxation and systolic descent of the cardiac base are the main determinants of 2 (early and late) distinct LA reservoir phases, respectively. The systolic descent of the cardiac base has a stronger influence on the LA dimension changes during reservoir than the transmitted RV systolic pressure pulse. The LA reservoir function is the main determinant of cardiac output in this model of regional LV ischemia.

Methods

With the approval of the University of California, San Francisco, Animal Research Committee, we studied 12 juvenile Yorkshire pigs (42.3±0.4 [SEM] kg) in an open-chest, open-pericardium model of

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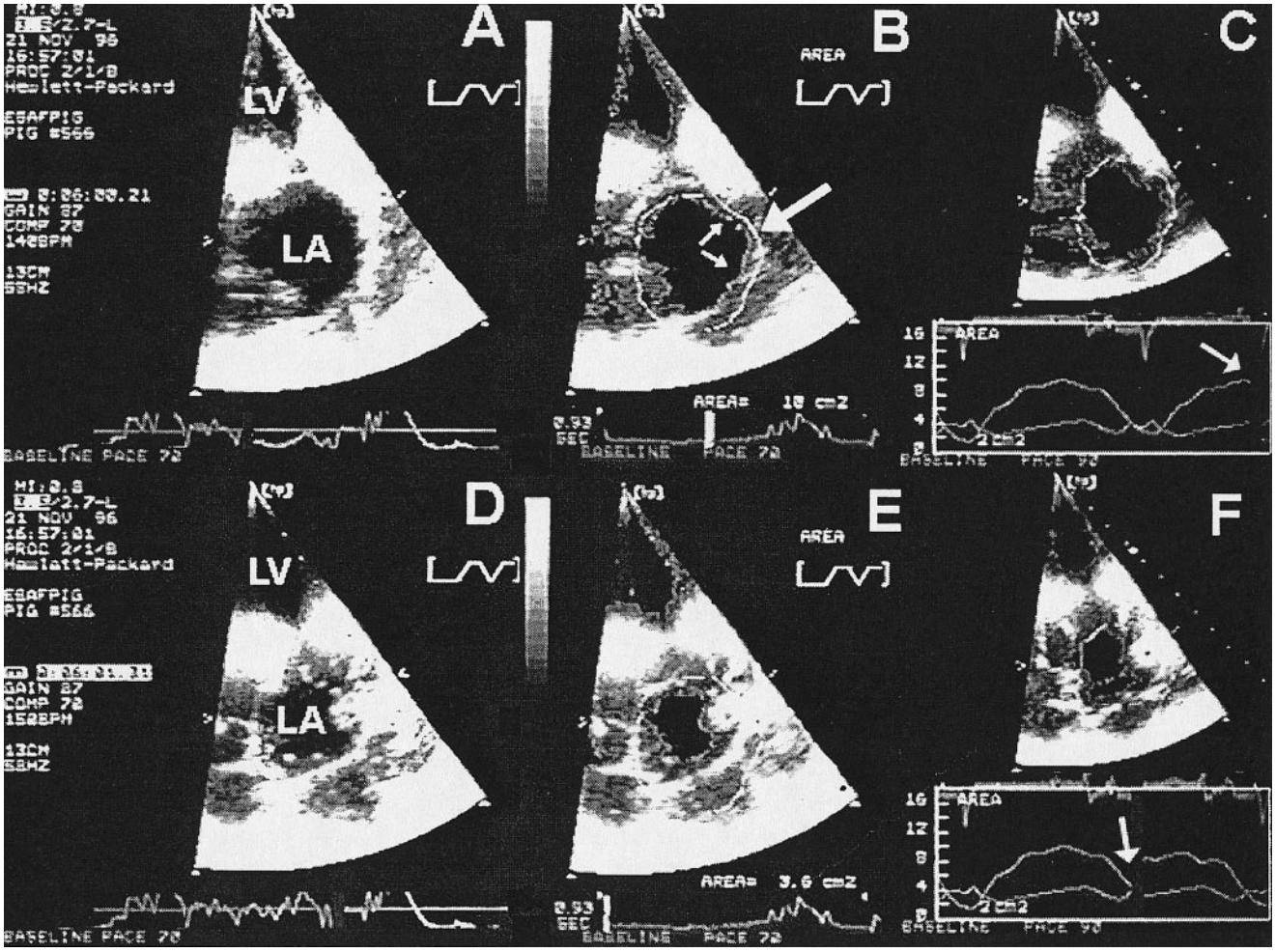

Figure 1. ABD recordings of LA from 4-chamber epicardial apical view (pig 566, baseline paced at 70 bpm). A, Maximum LA area, cross-sectional examination. B, Maximum LA area. Region of interest has been traced just outside LA area (large arrow). Line overlapping LA endocardium is generated along atrial inner border by ABD algorithm of ultrasound machine (small arrows). C, Bottom, Tracing of instantaneous LA area by ABD algorithm (arrow indicates maximum LA area point). D, E, and F, As in A, B, and C but with LA minimum (end-contraction) area. Time of examination at C and F is 5 to 10 minutes later than in B and E.

LV regional supply ischemia at 2 heart rates. Methods have been described in detail previously.[16]

Surgical Preparation and Instrumentation

The pigs were anesthetized with α-chloralose (100 mg/kg IV), then fentanyl (30 mg) and pancuronium (4 mg) as needed, and were mechanically ventilated (room air and oxygen). Animals were placed supine, and a pericardial cradle was created after a midline sternotomy and partial rib excision for epicardial positioning of the ultrasound transducers (Hewlett Packard Sonos 2500, 2.5/3.5 and 5.0 MHz). We placed 5F Millar micromanometer-tipped catheters in the LV through the apical dimple, in the LA through the LA appendage, and in the RV cavity. Pacing electrodes on the right atrial appendage permitted pacing with 1:1 atrioventricular conduction after administration of zatebradine (ULFS 49, 2 mg/kg). A C-clamp constrictor was placed around the left anterior descending coronary artery to reduce flow and regional myocardial shortening, measured with 2 pairs of segment-length crystals (Sonometrics) in the mid anterior wall (ischemic region) and basal lateral wall (reference region). An occluder was placed around the inferior vena cava. A single-lead ECG was recorded to synchronize hemodynamic and echocardiographic measurements. Data were digitized at 200 Hz with the respirator off at end expiration.

Echocardiographic and Doppler Recordings

We recorded biplane LV 4- and 2-chamber views with minimal transducer contact on the apical dimple. In the 4-chamber view, the LA area (including the appendage) was maximized by transducer rotation. A 50-Hz frame rate minimized the LA automated border detection (ABD) pressure signal delay (Figure 1).[17] Diastolic LV filling was recorded from Doppler transmitral annular flow. Cardiac output was calculated from LV outflow tract area and velocities in the apical 5-chamber view. A 5.0-MHz transducer on the posterosuperior LA wall recorded PV flow with the pulsed Doppler sample volume (3 mm^3) in a left lower PV, 5 mm proximal to a PV sinus. We used Doppler color flow to screen for mitral and tricuspid regurgitation (Niquist limit 60 cm/s). Echocardiographic and Doppler recordings were stored in S-VHS tape and measured offline (Tomtec Imaging Systems).

Protocol

Regional LV ischemia was obtained by tightening the constrictor for ≈15 minutes to achieve a 20% decrease in segment-length shortening of the anterior wall crystals. Tracings of LA ABD areas, LV outflow velocities, LV 4- and 2-chamber views, and PV flow velocities were obtained within a 5-minute interval, during baseline and ischemia, each paced at 70 and 90 bpm. Inferior vena cava occlusions were performed to define the LV diastolic pressure-volume curve over a wide range of end-diastolic volumes.

Measurements

Echocardiographic and Doppler measurements were obtained by averaging 3 to 5 consecutive beats. Hemodynamic data were averaged over 15 beats that included these 3 to 5 beats.

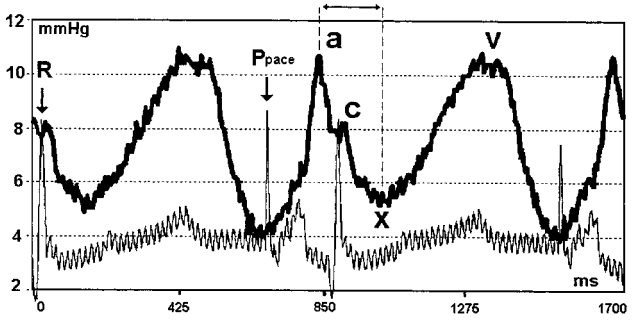

Figure 2. LA high-fidelity pressure tracing (unfiltered data) and simultaneous ECG (pig 564, baseline paced at 70 bpm). Horizontal arrow shows LA relaxation time. P_{pace} indicates right atrial pacing artifact; R, ECG R wave.

We calculated LV end-diastolic pressure and the time constant of isovolumic relaxation, τ.[16] We measured LA peak a (P_a), c, v, and x (P_x) trough pressures (Figure 2), their timings, and mean LA pressure. LA relaxation was defined as the time during which the LA pressure decreased after atrial contraction, between the peak a wave and the x trough and quantified with $[(P_a - P_x)/P_a]/(t_x - t_a)$. Systolic RV−LA transpulmonary pressure gradient was RV peak systolic pressure minus LA peak v pressure difference.

Biplane LV (4- and 2-chamber) end-diastolic (at ECG R wave) and end-systolic (at minimum LV dimension) volumes (area-length method), ejection fraction, and long-axis systolic shortening were calculated. The midsystolic LV outflow tract area and biplane end-systolic mitral annulus area (at basal insertion of the leaflets) were calculated from their diameters, assuming circular orifices. Stroke volume was calculated as velocity-time integral times outflow area, and cardiac output as stroke volume times heart rate. LV ejection time was calculated as time to end minus time to start of LV outflow.

We measured maximum and minimum LA areas (cm^2) and the area occurring before atrial contraction (at ECG P wave) (Figure 3). We calculated total reservoir area change (maximum minus minimum area, cm^2) as an index of reservoir function,[3] duration of the reservoir phase, stroke area (area before atrial contraction minus minimum area, cm^2), fractional shortening (stroke area/area before atrial contraction), and mean LA ejection rate [stroke area/(time of minimum area minus time of area before atrial contraction), cm^2/s]. To synchronize digitized LA pressure and area,[17] we aligned the LA area point before atrial contraction with the beginning of the LA a wave and the end of the ECG P wave (Figure 3).

LA pressure-area curves (Figure 4) have 2 loops. The "a" loop corresponds to LA work during active contraction and relaxation[5,6,8–10,18] and the "v" loop to LA passive filling and emptying. We computed a and v loop areas (mm Hg · cm^2) and an index of LA chamber stiffness as the slope connecting the x and v pressure points of the v loop (Figure 4).

Statistical Analysis

The effects of ischemia and heart rate (and their interaction) were analyzed by 2-way repeated-measures general linear model ANOVA. The tables report the least-squares means and SEMs from the ANOVA. We compared the values of 2 different related variables (eg, LA early and late mean filling rates) using a 3-way repeated-measures ANOVA including a factor to distinguish the 2 variables. We report only the probability value related to this factor and its interactions. ABD variables related to the LA contraction phase were analyzed comparing only baseline paced at 70 bpm with ischemia paced at 70 bpm using a paired *t* test, because LA contraction often overlapped with the preceding conduit phase at 90 bpm.

To test for a linear relationship between 2 variables across the experimental conditions, we used a multiple regression including effects-coded dummy variables for the different pigs. We used stepwise multiple regression forcing dummy variables to account for between-pig effects to identify the independent predictors of the LA reservoir total area change, the mean rates of LA early and late area changes, the LA v loop, cardiac output, and the PV early and late systolic peak velocities and velocity-time integrals (Table 1). Computations were done with SPSS 7.5, with $P<0.05$ considered significant. Results are presented as mean±SEM.

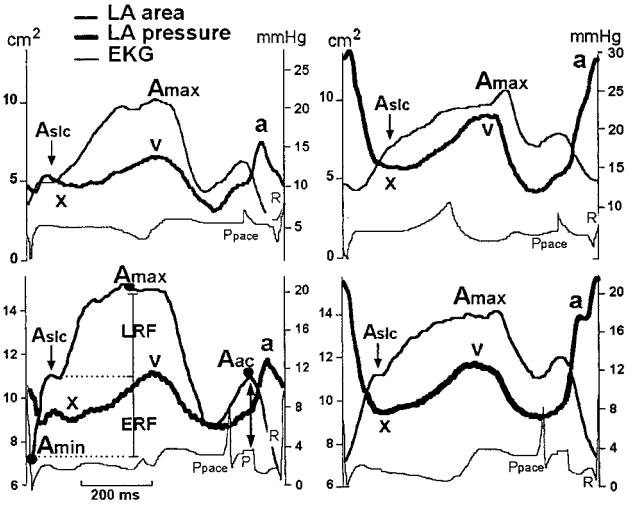

Figure 3. Synchronized LA ABD area curve (thin line), high-fidelity pressure curve (thick line), and ECG (bottom line) in 2 representative pigs (pig 558, top; pig 570, bottom) during baseline (left) and ischemia (right), paced at 70 bpm. Lower left, Black vertical arrow shows alignment of LA area before atrial contraction with beginning of LA pressure a wave and end of ECG P wave. LA area at slope change. A_{slc} divides LA reservoir into early (ERF) and late (LRF) reservoir filling phases and corresponds to LA pressure minimum at x trough. Note increase of LA peak a and v pressures and marked decrease in late reservoir filling slope during ischemia. A_{max} indicates maximum LA area; A_{ac}, LA area before atrial contraction; A_{min}, minimum (end contraction) LA area; A_{slc}, LA area at slope change; c, peak c pressure; P, ECG P wave; P_{ace}, right atrial pacing artifact; and R, ECG R wave.

Results

Baseline

Atrioventricular conduction time was normal (Table 2).

Baseline LV[16] and RV hemodynamics (Table 3), LV volumes, and systolic function (Table 4) were typical for an anesthetized open-chest pig. Mitral regurgitation was absent or trace.

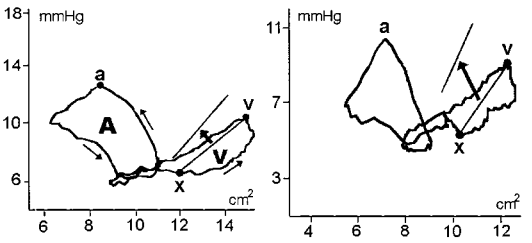

Figure 4. Example of LA pressure-area loops in 2 representative pigs (pig 570, left; pig 568, right) at baseline paced at 70 bpm. Both a (atrial contraction and relaxation) and v (atrial filling and conduit) loops are counterclockwise (left, thin arrows). Slope of line between x pressure trough and peak v pressure points on v loop represents LA stiffness index. Modifications during LV ischemia (paced at 70 bpm) of LA stiffness index are shown by thick arrows, which indicate an upward and leftward displacement and increase in slope of index during LV ischemia.

TABLE 1. Stepwise Multiple Regression Analysis to Identify Important Variables

Dependent	Predictors	b	Units	SE	*P*
LA mean rate of early filling	LA mean ejection rate	0.9		0.1	<0.001
	LA relaxation index	4.9	$cm^2 \times ms/s$	0.8	<0.001
	Constant	1		6	
LA mean rate of late filling	LV long-axis shortening	8	cm/s	1.7	<0.001
	Constant	1.6		2.1	
LA reservoir area change	LA stiffness index	−0.31	cm^4/mm Hg	0.08	0.001
	Cardiac output	0.001	$cm^2 \times$min/L	0.000	0.002
	Constant	10.4		1.2	
LA v loop area	Cardiac output	−0.02	mm Hg$\times cm^2 \times$min/L	0.003	0.001
	LV ejection time	0.21	mm Hg$\times cm^2$/ms	0.09	0.04
	LV relaxation time constant	−1.64	mm Hg$\times cm^2$/ms	0.41	0.001
	Mitral early diastolic flow	0.33	mm Hg$\times cm^2$/mL	0.15	0.05
	Constant	58		21	
Cardiac output	LA reservoir area change	301	L/min$\times cm^2$	73	<0.001
	LA v loop area	−26	L$\times cm^2$/min$\times$mm Hg	8	0.003
	Constant	1472		472	

b indicates unstandardized regression coefficient.

LA peak a pressure was higher than peak c pressure and slightly higher than peak v pressure, as reported in open-pericardium pigs[19] (Tables 3 and 5).

Within 100 ms of the ECG R wave, the ABD tracing slope decreased. This point correlated with the LA x pressure point (coefficient=0.32, SEM=0.13, P=0.02) (Figure 3). The LA area increase to the ABD slope change occurred during LA relaxation, the acceleration of early systolic PV flow and LV ejection, and LV isovolumic contraction (LA pressure c wave) (Table 2 and Figures 3 and 5). The area increase after the slope change occurred during LA pressure increase, to maximum LA area and peak v pressure, including the acceleration of PV late systolic flow. We subdivided LA reservoir area increase into early (time of LA area at slope change minus time of minimum area) and late (time of LA maximum area minus time of LA area at slope change) phases (Table 2 and Figure 3).[7] For each phase, we measured the area change (early=area at slope change minus minimum area; late=maximum area minus area at slope change, cm^2) and mean rate of area increase (early=early area change/duration, cm^2/s; late=late area change/duration) (Table 7). The LA area changes during the early and late reservoir phases were similar (Tables 5 and 7). Because the early phase was shorter than the late phase, the mean rate of LA area change was greater during the early reservoir phase (Tables 2, 5, and 7).

LA stroke area correlated with mean rate of early reservoir area change (r=0.7, P=0.02), and LA mean ejection rate correlated with PV early systolic peak flow velocity (r=0.8, P=0.02), indicating a relationship between LA contraction and LA filling during relaxation. The direction of both the LA a and v pressure-area loops was counterclockwise (Figure 4). The a and v loop areas were similar (Tables 5 and 8).

Effects of LV Ischemia

The atrioventricular conduction time did not change during LV ischemia (Table 2). Mitral regurgitation never exceeded grade II and did not influence LA reservoir function (Table 1).

RV and LV systolic pressures did not change with regional ischemia. LV relaxation slowed, and end-diastolic pressure increased[16] (Table 3). Echocardiography showed severe hypokinesis of mid to apical interventricular septum and apical anterior wall. End-diastolic and end-systolic LV volumes increased, and ejection fraction and long-axis shortening decreased (Table 4). Ischemia reduced early diastolic LV inflow and cardiac output.[16]

All LA pressure values increased during LV ischemia (Table 3), with a pressure increasing more than v pressure (Table 5). The LA relaxation index did not change.

LA minimum area increased during LV ischemia. Total LA reservoir area change, both early and late area changes, and mean rates of area change decreased (Tables 5 and 7). A marked decrease in slope of LA late reservoir and change occurred during ischemia (Figure 3). The mean rate of late area change was related to LV long-axis shortening (coefficient=6.7 cm/s, SEM=1.2, P<0.001). Greater systolic descent of the LV base was associated with increased rate of LA area increase. LV ischemia prolonged LA late reservoir phase duration by delaying both the beginning and end of LV ejection, each positively related to late reservoir duration (coefficient=0.9, SEM=0.3, P=0.004, and coefficient=0.6, SEM=0.2, P=0.002, respectively) (Table 2). LV ischemia decreased PV flow late systolic peak velocity (Table 6), which paralleled its effects on the ABD pattern during the LA reservoir phase.

Mean rate of LA early reservoir area change increased with LA stroke area (coefficient=0.05 s^{-1}, SEM=0.02, P=0.03), fractional shortening (coefficient=0.6 cm^2/s, SEM=0.1, P=0.003), and mean ejection rate (coefficient=0.72, SEM=0.2, P=0.001). During ischemia, as during baseline, LA contraction and relaxation indexes were positively correlated.

The areas of the LA pressure-area a and v loops did not change during ischemia. The LA stiffness index increased (Table 8) and was displaced upward and to the left (Figure 4).

TABLE 2. Timings

	Baseline		Ischemia		*P*		
	70 bpm	90 bpm	70 bpm	90 bpm	Heart Rate	Ischemia	Interaction
Cardiac cycle length	836±9	641±2	821±8	642±3	<0.001	0.3	0.39
Atrioventricular conduction time	92±4	97±4	89±5	102±4	0.01	0.96	0.15
Left atrial pressure							
Time to x trough	115±12	110±11	118±12	99±13	0.14	0.66	0.27
Time to v wave	446±14	430±15	463±14	422±10	0.001	0.82	0.19
Left atrial dimensions							
Time to area at slope change	65±6	76±7	99±11	56±6	0.009	0.53	0.03
Time to maximum area	323±19	334±18	374±32	409±24	0.26	0.01	0.26
Duration of early filling	94±6	103±6	116±8	97±7	0.45	0.60	0.07
Duration of late filling	432±15	396±11	436±16	437±13	0.09	0.008	0.008
Duration of total filling	526±14	499±11	552±17	533±11	0.009	0.001	0.01
Pulmonary vein flow							
Early systolic wave, start	22±7	2±9	31±10	−4±14	0.005	0.94	0.14
Early systolic wave, peak	100±10	90±18	116±7	81±11	0.07	0.99	0.18
Early systolic wave, duration	168±5	187±5	183±9	215±13	0.02	0.07	0.17
Late systolic wave, start	190±6	189±10	214±9	211±6	0.92	0.02	0.32
Late systolic wave, peak	321±13	305±11	334±15	327±12	0.11	0.14	0.66
Late systolic wave, duration	294±22	244±56	302±27	233±16	0.03	0.42	0.99
Time to end-systolic flow	485±22	433±22	516±21	444±18	0.005	0.003	0.79
Duration of systolic flow	463±23	432±21	485±24	448±14	0.08	0.02	0.48
Left ventricular outflow tract							
Time to flow start	51±5	58±2	53±4	67±7	0.004	0.31	0.42
Time to peak flow	128±7	131±6	139±5	157±6	0.02	0.003	0.17
Time to end flow	399±9	365±7	409±7	386±8	<0.001	0.01	0.25
Ejection time	348±9	308±7	356±7	315±13	<0.001	0.20	0.81

Values are in ms, least-squares means, and SEM from the ANOVA.

Effect of Increased Heart Rate

The atrioventricular conduction time did not change with increasing heart rate from 70 to 90 bpm (Table 3). LV end-diastolic pressure and τ decreased (Table 2). End-diastolic LV volume decreased, resulting in a lower ejection fraction (Table 4). Long-axis shortening and cardiac output did not change (Table 6). All LA pressure values decreased. Both LA late reservoir phase and total reservoir phase shortened (Table 2). Increasing heart rate did not affect total LA area change (Table 7), PV flow (Table 6), LA loops, or stiffness index (Table 8).

TABLE 3. LA and RV Pressures

	Baseline		Ischemia		*P*		
	70 bpm	90 bpm	70 bpm	90 bpm	Heart Rate	Ischemia	Interaction
LA							
a wave pressure	15±1	11±1	19±2	14±2	0.001	0.009	0.39
c wave pressure	12±1	9±1	18±2	12±2	0.002	0.021	0.21
x trough pressure	8±1	7±1	9±1	8±1	0.004	0.001	0.16
v wave pressure	14±1	11±1	15±1	12±1	<0.001	0.05	0.23
Mean pressure	10±1	9±1	12±1	11±1	0.057	0.001	0.06
a−x pressure difference	7.4±0.5	4.8±0.5	9.3±1	6.3±1	0.001	0.03	0.76
v−x pressure difference	6.1±0.5	4.7±0.3	5.8±0.6	4.4±0.3	<0.001	0.63	0.81
Relaxation index, ms^{-1}	3.8±0.5	3±0.4	3.4±0.4	3.7±0.4	0.54	0.51	0.12
RV							
Systolic pressure	33±1	33±2	34±2	47±14	0.43	0.72	0.38
Systolic pressure−v pressure difference	19±2	22±3	19±3	35±15	0.23	0.33	0.36

Values are mm Hg.

TABLE 4. LV Dimensions and Function

	Baseline		Ischemia		*P*		
	70 bpm	90 bpm	70 bpm	90 bpm	Heart Rate	Ischemia	Interaction
End-diastolic volume, mL	75±4	66±3	83±4	77±3	0.001	<0.001	0.84
End-systolic volume, mL	22±2	22±2	33±2	34±2	0.27	<0.001	0.95
Ejection fraction, %	71±1	67±2	60±2	55±2	0.006	<0.001	0.006
Long-axis systolic shortening, cm	1.4±0.1	1.2±0.1	0.8±0.1	0.6±0.1	0.12	<0.001	0.59

Correspondence Between Dimensional and Doppler Velocity Analysis of LA Reservoir Filling

During baseline paced at 70 bpm, mean rate of early reservoir area change correlated with PV early systolic velocity-time integral ($r=0.6$, $P=0.05$). During ischemia, the mean rate of early area change correlated with early systolic peak velocity and velocity-time integral ($r=0.8$, $P=0.02$ for both). By use of pooled data in a multiple regression analysis, late reservoir LA area change was significantly related to both late PV peak flow velocity (coefficient=7.6 cm · s, SEM=2.8, $P=0.01$) and velocity-time integral (coefficient=2.2 cm, SEM=0.9, $P=0.03$).

Independent Predictors of LA Reservoir Function

LA Relaxation and LV Systole

LA x pressure timing depended on LA reservoir slope change (coefficient=0.3, SEM=0.1, $P=0.02$) and PV early systolic peak velocity (coefficient=0.4, SEM=0.1, $P=0.02$) timings. LA mean ejection rate and relaxation index were independent predictors of mean rate of LA early reservoir (Table 1). Thus, the rate of LA reservoir dimension increase was proportional to both LA contraction and LA pressure change during relaxation. In contrast, during the late reservoir phase, the mean rate of LA area change depended only on LV long-axis shortening (ie, the systolic descent of the cardiac base).

LA Stiffness and Cardiac Function

Total LA reservoir area change depended on LA stiffness index and cardiac output (Table 1). Thus, increased LA chamber stiffness or decreased cardiac output predicted a decrease in LA reservoir function. LA reservoir phase duration depended on LV ejection time (coefficient=0.4, SEM=0.1, $P=0.009$), consistent with a relation between LV systolic and LA reservoir function. Multiple regression analysis confirmed that LA total area change per se was a determinant of cardiac output[2] (Table 1).

LA Pressure-Dimension Analysis

LA v loop area determinants were related to both LV systolic (cardiac output and LV ejection time) and diastolic (LV and early diastolic flow) function (Table 1). The ascending limb of the v loop reflects LA reservoir, and the descending limb the LV filling.

Discussion

We sought to identify the determinants of LA reservoir function and test Suga's hypothesis[2] that LA reservoir function is a determinant of cardiac output. The reservoir phase is the diastolic phase of the LA. It has been suggested, but not demonstrated, that LA filling is determined initially by LA myocardial fiber relaxation[7,11,12] and later by the combined influence of LA chamber stiffness,[2–4,8,20] descent of the cardiac base,[12,13] and the RV systolic pressure pulse transmitted through the pulmonary circulation.[14] We show that there are 2 LA reservoir phases: an early phase (Figure 3) related to relaxation from the preceding LA contraction and a late phase related to LV longitudinal fiber systolic shortening (the descent of the cardiac base) and LA chamber stiffness. These findings indicate that LA contraction and LV systolic function determine, sequentially, the 2 reservoir phases. LA reservoir function is an independent determinant of cardiac output.

Toma et al[7] used LA x pressure trough timing to identify an early reservoir phase during LA relaxation but did not consider similarities with the biphasic nature of systolic PV

TABLE 5. Comparison of Related Variables

Variables Being Compared (3-Way ANOVA)	Main Effect	Interaction Between Heart Rate and Main Effect	Interaction Between Ischemia and Main Effect	Interaction Between Main Effect, Heart Rate, and Ischemia
Left atrial peak a−peak c pressure, mm Hg	0.001	0.6	0.5	0.02
Left atrial peak a−peak v pressure, mm Hg	0.001	0.06	0.006	0.9
Left atrial early−late filling duration, ms	<0.001	0.5	0.1	0.02
Left atrial early−late area change, cm^2	0.27	0.2	0.6	0.02
Left atrial early−late mean filling rate, cm^2/s	<0.001	0.03	0.1	0.34
Pulmonary vein early−late systolic peak velocity, cm/s	0.04	0.6	0.03	0.5
Pulmonary vein early−late systolic integral, cm	0.004	0.04	0.08	0.8
Left atrial a−v loop area, mm Hg/cm^2	0.72	0.4	0.5	0.05

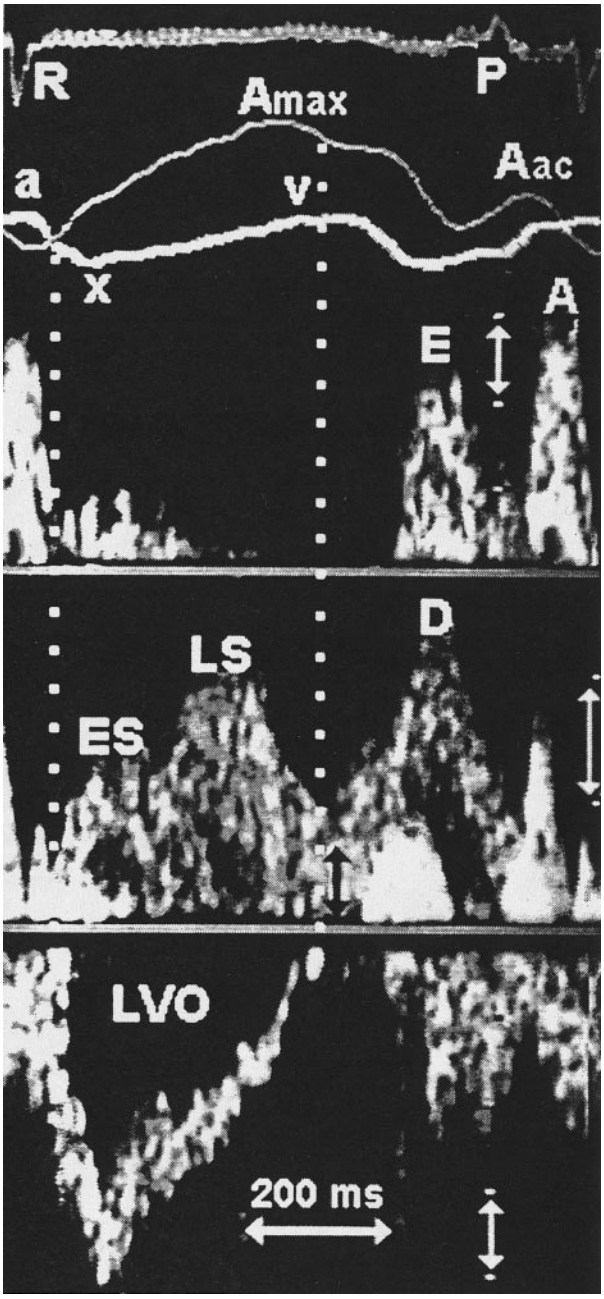

Figure 5. Synchronized LA ABD, pressure, and pulsed Doppler tracings derived from 4 different beats (pig 566, baseline paced at 70 bpm). From top to bottom: ECG, LA ABD area (thin gray line), LA pressure (thick white line), transmitral flow, pulmonary vein flow, and LV outflow velocities. Vertical white arrows indicate 20-cm/s pulsed Doppler velocity scale. White dotted lines indicate start and end of LV outflow (ejection time). Black arrow indicates point of flow velocity variation between late systolic and diastolic pulmonary vein flow velocity waves. a indicates peak a pressure; A, late diastolic transmitral flow velocity; A_{max}, maximum LA area; A_{ac}, LA area before atrial contraction; D, diastolic PVF wave; E, early diastolic transmitral flow velocity; ES, early systolic PVF wave; LS, late systolic PVF wave; P, ECG P wave; R, ECG R wave; v, peak v pressure; and x, x trough pressure.

flow.[12] We show a consistent decrease of the rate of LA area increase (Figure 3) during the reservoir phase that reflects a transition between the early and late LA reservoir phases and depends on different factors.

Determinants of LA Early Reservoir Function

The early reservoir phase includes ≈50% of LA filling and coincides with LA relaxation (LA pressure fall to the x trough) and early systolic PV flow acceleration (Figures 2, 3, 5, and 6). The mean rate of early area change depends on LA relaxation, a conclusion similar to that reached in Doppler studies[12] based on indirect evidence[21] showing a constant temporal relation between LA contraction and the early PV flow wave. Consistent with a previous angiographic study in humans[7] and the suggestion that LA relaxation depends on the previous LA contraction (as in the LV), we identify LA mean ejection rate as a determinant of the mean rate of early LA reservoir filling and of PV peak early systolic velocity. In contrast, despite the temporal coincidence (Table 2 and Figure 5), we do not find a relation between LA early reservoir filling and LV isovolumic contraction (the LA peak c wave) or LV ejection indexes.

Both extent and rate of LA early reservoir area change were reduced by LV ischemia. The explanation for this finding is that LV ischemia increases LV end-diastolic pressure, which causes an afterload-dependent[9] decrease of LA mean ejection rate. Because LA early reservoir filling is positively related to the LA mean ejection rate, both are decreased by LV ischemia.

Determinants of LA Late Reservoir Function

The late reservoir phase is characterized by a slower rate of LA area increase than the early phase (Figure 3). During this phase, LA area increases in parallel with LA pressure as PV flow distends the relaxed LA chamber. Atrial and ventricular diastolic functions are similar: early diastole is regulated by relaxation, and during late diastole (LA late reservoir phase), both LV and LA chamber characteristics are described by a (passive) pressure-dimension curve[20] (Figure 4). In addition, the LA expands secondary to systolic descent of the cardiac base (Table 1), thus drawing in PV blood like a piston during late systole, as previously suggested.[12,13] In contrast to previous suggestions that the LA inflow pattern is determined either by the transmitted RV systolic pressure pulse alone[14] or in combination with left heart mechanics,[15] we show that the descent of the cardiac base is the only determinant of LA late reservoir area change.

Role of LV Ischemia

Acute regional LV ischemia reduces LV longitudinal fiber shortening and extent and rate of LA late area change (decreasing total LA reservoir filling by 23%), establishing a direct cause-and-effect influence of LV systole on late LA reservoir filling. The upward and leftward displacement of the LA v loop slope indicates that LA chamber stiffness is also increased during LV ischemia (Figure 4). Previous authors have shown that LV ischemia influences LA contraction through the Frank-Starling mechanism.[6] LV ischemia directly affects LA reservoir function, and as a consequence, the dynamics of the cardiac base directly influences LA chamber stiffness.

Pressure-Area v Loop

The LA v loop area has been proposed as an index of LA reservoir work[10,18] or work done on the LA by PV inflow.[10]

TABLE 6. Mitral Valve, Pulmonary Vein, and LV Outflow Velocities

	Baseline		Ischemia		*P*		
	70 bpm	90 bpm	70 bpm	90 bpm	Heart Rate	Ischemia	Interaction
Mitral valve flow							
E wave, mL	44±4	24±3	32±3	17±6	0.005	<0.001	0.87
Pulmonary vein velocities							
Early systolic wave, peak, cm/s	39±6	44±7	47±7	42±7	0.98	0.45	0.39
Early systolic wave, integral, cm	5.3±1	7±1	5.5±1	7±1	0.06	0.69	0.96
Late systolic wave, peak, cm/s	61±11	57±8	48±8	49±8	0.44	0.05	0.84
Late systolic wave, integral, cm	14.5±3	11±1	12±2	9±2	0.08	0.15	0.81
Early/late peak ratio	0.7±0.02	0.8±0.1	1.3±0.4	0.9±0.1	0.71	0.15	0.45
Early/late integral ratio	0.4±0.04	0.6±0.1	0.8±0.3	0.9±0.2	0.45	0.11	0.76
Systolic integral, cm	20±4	18±3	18±3	16±3	0.22	0.30	0.82
LV outflow							
LV outflow mean acceleration, cm/s	919±108	956±114	729±58	617±35	0.95	0.009	0.65
Left ventricular stroke volume, mL	47±2	44±1	44±2	37±2	0.006	0.031	0.3
Cardiac output, L/min	3.3±0.1	3.9±0.1	3.2±0.2	2.6±0.2	0.47	<0.001	<0.001

In contrast, our v loop area is related to both LV systolic work (LV ejection time and cardiac output) and relaxation (LV and early diastolic inflow) but not to LA reservoir function or RV energy delivered through systolic PV flow.[5,6,8–10,18,19] This finding is expected because the v loop represents LA pressure-area changes that occur not only during the late reservoir phase (the v loop ascending limb) but also during the LA early conduit phase (Table 1 and Figures 3 and 4).

We described a counterclockwise v loop pattern (Figure 4) and speculate that it is a result of elastic energy stored by the LA during the reservoir phase.[18] This energy comes from stretching by systolic descent of the cardiac base and PV flow and is returned during early LV diastole (during the LA conduit phase) to facilitate LV filling. The discrepancy with previously described clockwise v loops probably is a result of methodological differences. We demonstrate that LV relaxation and early inflow are independent predictors of the v loop area. Early transmitral flow is greater in dogs[22] than in pigs, suggesting a faster early diastolic LA pressure decrease, a steeper pressure-dimension slope during early conduit, and consequently a clockwise v loop in dogs.[5,8] Species-specific differences in relative LA appendage volume compared with its main chamber may affect LA compliance and thus may influence the v loop pattern.[4,20] Previous angiographic studies

TABLE 7. LA Dimensions and Function

	Baseline		Ischemia		*P*		
	70 bpm	90 bpm	70 bpm	90 bpm	Heart Rate	Ischemia	Interaction
Area							
Minimum	5.2±0.5	4.0±0.4	5.9±0.4	5.0±0.6	0.06	0.05	0.29
At slope change	8.6±0.6	8.7±0.4	8.7±0.4	8.1±0.6	0.43	0.92	0.83
Maximum	12.3±0.4	11.4±0.3	11.1±0.4	11±0.6	0.07	0.18	0.1
End-diastolic*	8.6±15	...	9±1.4	...	...	0.52	...
Reservoir							
Total area change	7.1±0.4	7.5±0.4	5.3±0.4	5.9±0.3	0.18	<0.001	0.81
Early area change	3.5±0.4	4.7±0.4	3.0±0.3	3.1±0.4	0.12	0.002	0.09
Early mean filling rate, cm^2/s	37±4	46±3	27±3	33±4	0.07	0.001	0.69
Late area change	3.7±0.4	2.7±0.3	2.3±0.3	2.8±0.4	0.53	0.04	0.01
Late mean filling rate, cm^2/s	14±1	11±1	7±1	8±1	0.05	0.003	0.11
Contraction							
Stroke area*	3.4±0.2	...	3.1±0.3	...	...	0.24	...
Fractional shortening,* %	41±3	...	35±3	...	...	0.18	...
Mean ejection rate,* cm^2/s	47±2	...	40±3	...	...	0.02	...

LA dimensions are in cm^2.

*Statistical analysis performed using paired *t* test and mean±SEM values to compare ischemia 70 bpm vs baseline 70 bpm.

TABLE 8. LA Pressure-Area Loops

	Baseline		Ischemia		*P*		
	70 bpm	90 bpm	70 bpm	90 bpm	Heart Rate	Ischemia	Interaction
a loop area, mm Hg×cm^2	6.4±1.5	11.2±3.6	8±2.2	9.1±3.7	0.52	0.65	0.56
v loop area, mm Hg×cm^2	12±4.8	9.5±5.3	2±4.1	11.6±4.8	0.52	0.56	0.01
Stiffness index, mm Hg/cm^2	1.5±0.1	1.7±0.2	2.9±0.4	2.9±0.7	0.62	0.009	0.95

lacked the higher time resolution of ultrasonic crystals or ABD, and 1-dimensional LA measurements with ultrasonic crystals[6,9] may not adequately represent LA phasic geometric changes because of chamber asymmetry.

Effects of LA Reservoir Function on Cardiac Output

Our multiple regression analysis pointed to LA total reservoir area change as the strongest predictor of cardiac output, together with v loop area (and thus LV systolic and diastolic functions). Suga[2] theorized that LA chamber stiffness during the reservoir phase may have influenced cardiac performance. A direct relation between LA compliance (using an LA pressure-dimension curve) and LA reservoir function (using PV flow) has been demonstrated in dogs[4] and in humans[20] when LA compliance was reduced by LA appendectomy or appendage clamping, respectively. An indirect relation has been shown between cardiac output and LA reservoir function in humans[23] and dogs[24] through the LA Frank-Starling mechanism, which links increased LA end-diastolic volume (at the ECG P wave) and augmented emptying.[4,24] Consistent with our results, Doppler PV systolic flow correlated with cardiac output both in patients with normal LV systolic function during acute pharmacological intervention[25] and in patients with congestive heart failure.[26]

Limitations of the Study

The young age of the pigs may limit the applicability of our findings to understanding the effects of LV ischemia in older humans. However, porcine transmitral and PV flow patterns are more similar to those of adult, middle-aged humans[27] than those of dogs[22] or young humans.[27] Our open-pericardium model differs from the clinical setting with intact pericardium. However, the increase in LV end-diastolic volume with ischemia was clinically negligible, and an intact pericardium would have strengthened our findings by increasing ventriculoatrial interaction.

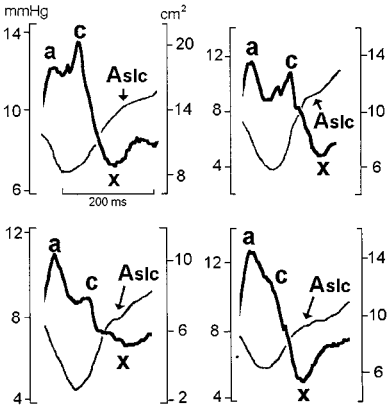

Figure 6. LV cardiac output is determined by both radial (short-axis shortening) and longitudinal (long-axis shortening) systolic fiber function. Longitudinal fiber shortening (ie, descent of cardiac base) is a determinant of LA reservoir filling through influence on LA chamber stiffness. In turn, LA reservoir is an independent predictor of cardiac output. This (pericardium-independent) coupling of LA and LV functions during systole is defined as ventriculoatrial interdependence.

Conclusions

Our findings confirm and extend Suga's hypothesis of a direct relation between LA reservoir function and cardiac performance, broadening the analysis to an in vivo animal model with physiologically complete LA function. We identify 2 (early and late) reservoir phases that are sequentially determined by LA contraction and relaxation and LV systolic function and point to a strong relation between LV systolic and LA reservoir function. The descent of the cardiac base determines LA reservoir function by influencing LA stiffness, whereas LA reservoir function independently predicts LV performance.

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