Original article

Impact of preload changes on positive and negative left ventricular dP/dt and systolic time intervals: preload changes on left ventricular function

Peiman Jamshidi¹, Richard Kobza¹, Stefan Toggweiler², Patti Arand³, Michel Zuber⁴, Paul Erne^{5*}¹Attending Physician, ²Assistant Physician, ⁴Professor, Medical Consultant, ⁵Professor and Head, Division of Cardiology, Luzerner Kantonsspital, Lucerne, Switzerland, ³Director of Research, Inovise Medical, Inc., Beaverton, Oregon, USA.

KEYWORDS

Acoustic cardiography
Haemodynamics
Heart failure

ABSTRACT

Aim/objectives: Previous work has shown that the electromechanical activation time (EMAT) is prolonged in patients with abnormally low left ventricular (LV) dP/dt. In the present study, we investigated whether EMAT was responsive to rapid changes in LV systolic function induced by abrupt increases in LV preload.**Methods and results:** A total of 116 patients were assessed before and after LV angiography with a bolus injection of 40 mL of non-ionic contrast dye. Left ventricular end-diastolic pressure (LVEDP) increased from 18 ± 7 mmHg to 20 ± 8 mmHg ($P < 0.01$). In patients with a baseline dP/dt < 1500 mmHg/sec, dP/dt increased from 1098 ± 213 mmHg/sec to 1146 ± 306 mmHg/sec ($P = 0.02$) and EMAT decreased from 106 ± 29 ms to 103 ± 18 ms ($P = 0.02$). In patients with a baseline dP/dt ≥ 1500 mmHg/sec, dP/dt decreased from 1894 ± 368 mmHg/sec to 1762 ± 403 mmHg/sec ($P = 0.01$) and EMAT increased from 88 ± 13 ms to 93 ± 16 ms ($P = 0.02$). Changes in negative dP/dt were similar to changes in dP/dt.**Conclusion:** Electromechanical activation time is a non-invasively measured parameter that allows accurate and rapid detection of changes in LV contractility.

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Introduction

The ability to measure abnormalities of left ventricular (LV) function is important for both the initial detection of heart failure (HF) and for monitoring changes in severity. The availability of an accurate, convenient and cost-effective method to detect changes in ventricular function would be a helpful tool to optimise the effects of medical therapy, interventions, or in the adjustment of cardiac resynchronisation therapy.

Acoustic cardiography has been proposed as such a cost-effective method to assess cardiac function in a wide spectrum of patient care.¹ In previous studies, we demonstrated that acoustic cardiography (Audicor®, Inovise Medical Inc., Portland, Oregon, USA) was superior to LV ejection fraction (LVEF) for detecting abnormally low LV maximum dP/dt² and that this technology can be used in patients with atrial fibrillation,³ HF diagnosis,⁴ during stress testing⁵ as well as ambulatory Holter monitoring.⁶ Acoustic cardiography consists of

the recording and automated algorithmic interpretation of digital electrocardiogram (ECG) and cardiac acoustic data. It obtains these data by using the same array of electrodes used for a standard ECG, but employs proprietary dual-purpose sensors in the V3 and V4 positions. These sensors acquire simultaneous ECG and heart sound data. In prior work, we showed that the acoustic cardiography parameter—the electromechanical activation time (EMAT) was particularly useful for detecting abnormal LV function. Electromechanical activation time is the interval in milliseconds from the onset of the QRS to the first heart sound, and therefore, measures the time required for the LV to generate sufficient force to close the mitral valve. Electromechanical activation time has been shown to be prolonged in patients with impaired LV systolic function.^{7,8}

The purpose of the present study was to determine the responsiveness of EMAT to rapid changes in the haemodynamic status of patients across a wide spectrum of baseline LV functional states. To induce rapid haemodynamic changes, we collected diagnostic data immediately before and immediately after LV angiogram. In this model, each patient underwent

*Corresponding author.

E-mail address: paul.erne@ksl.ch

a sudden increase in LV preload induced by the injection of angiographic dye. We tested the hypothesis that EMAT would accurately reflect any serial changes in invasively measured maximum LV dP/dt that might result from these abrupt increases in preload.

Methods

Subjects

The study was approved by the local Medical Ethics Committee and informed consent was obtained from each patient. We evaluated a sample of 116 patients (33 females, mean age 62 ± 12 years) who underwent diagnostic cardiac catheterisation for the evaluation of heart disease.

Catheterisation data

All patients were studied in the post-absorptive state and sedated using routine pre-catheterisation medication. Cardiac medications were withheld on the day of the study. Left and right cardiac catheterisation was performed using the Seldinger technique and LV angiogram was performed once in each patient. The left ventriculogram was obtained in the 30° right anterior oblique position with the tip of the catheter positioned in the mid-LV cavity. For the ventriculogram, each patient received a rapid injection of 40 mL of iopromide (Ultravist 370®, Bayer Schering Pharma AG, Berlin, Germany). Single-plane ejection fraction (EF) was determined using Simpson's rule.^{9,10} Following LV angiography, coronary angiography was performed, and significant coronary artery disease (CAD) was diagnosed if a 75% or greater reduction in the transluminal diameter of at least one coronary artery was present.

Both before and after the left ventriculogram, the LV pressure was measured using a manometer-tipped catheter (Volcano Inc., Parker, TX, USA) in 102 patients and a fluid-filled catheter was used in the remaining 14 patients. Positive maximum LV dP/dt max was automatically calculated by the Mac-Lab 6H system (1996 version: Marquette Medical Systems Inc., Milwaukee, WI, USA). Since the measurement system did not store the LV pressure curves electronically, the negative maximum LV dP/dt max was calculated offline through reconstruction of the LV pressure curves using a scientific data reconstruction program (Un-Scan-It 6.0, Silk Scientific Inc., Orem, UT, USA).

In addition, heart rate, LVEDP, pulmonary arterial systolic pressure, and acoustic cardiography parameters were recorded simultaneously before and after the left ventriculogram. We defined reduced LV contractility as a maximum LV dP/dt < 1500 mmHg/sec. We considered an LVEDP ≥ 18 mmHg to be abnormally elevated and LVEDP < 15 mmHg as normal, and an LVEDP between 15 mmHg and 18 mmHg was considered a gray zone. An LVEF of < 45% was *a priori* considered to be abnormally low, while an LVEF of 55% or greater was seen as normal. An LVEF between 45% and 50% was considered a gray zone.

Statistical analysis

Histograms of LVEF, heart rate, LVEDP, positive and negative dP/dt max, and EMAT revealed that their values had Gaussian distributions. Therefore, we chose the parametric two-tailed paired *t*-test to test the null hypothesis concerning differences between the pre- and post-LV angiographic data. We *a priori* selected *P* values < 0.05 to indicate statistically significant differences. The analyses were performed using SPSS Version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Table 1 shows baseline haemodynamics and clinical data. Of the 116 subjects, 80 (69%) had reduced LV contractility.

Figures 1 and 2, respectively, show the correlation of positive and negative LV maximum dP/dt before and after left ventriculography.

Table 2 reveals the haemodynamic changes that occurred following LV angiography in patients with normal vs. elevated baseline LVEDP. In this and all subsequent tables, mathematical means $\pm$ standard deviation (SD) are shown and the post-ventriculography data are located immediately below the pre-ventriculography data. Table 2 shows that regardless of the baseline LVEDP, there was a significant increase in the LVEDP following the LV angiogram. There was no significant change in either dP/dt, $-dP/dt$, or EMAT.

Table 3 shows that in patients with LVEF < 45%, LV angiography resulted in significantly increased LVEDP.

Table 4 shows that LV angiography significantly increased LVEDP, regardless of whether the patient had an abnormally low or a normal LV maximum dP/dt.

Table 1
Demographics and baseline values.

Parameter	Mean $\pm$ SD
Age (yr)	63 $\pm$ 10
Heart rate (bpm)	79 $\pm$ 19
PAS pressure (mmHg)	38 $\pm$ 14
End-diastolic volume (mL)	148 $\pm$ 54
End-systolic volume (mL)	88 $\pm$ 54
LVEF (%)	45 $\pm$ 18
LVEDP (mmHg)	18 $\pm$ 7
LV maximum dP/dt (mmHg/sec)	1345 $\pm$ 457
LV maximum $-dP/dt$ (mmHg/sec)	−1491 $\pm$ 548
EMAT (ms)	101 $\pm$ 20
Hypertensive heart disease	7%
Coronary artery disease	44%
Mitral regurgitation	12%
Aortic regurgitation	6%
Aortic stenosis	8%
Arterial hypertension	15%
Dilated cardiomyopathy	4%
Other cardiomyopathies	9%

n = 116

EMAT: electromechanical activation time, LV: left ventricular, LVEDP: left ventricular end-diastolic pressure, LVEF: left ventricular ejection fraction, PAS: pulmonary arterial systolic, SD: standard deviation.

In patients with a baseline $dP/dt < 1500$ mmHg/sec, dP/dt increased from 1098 ± 213 mmHg/sec to 1146 ± 306 mmHg/sec ($P=0.02$) and EMAT decreased from 106 ± 29 ms to 103 ± 18 ms ($P=0.02$). In patients with a baseline $dP/dt \geq 1500$ mmHg/sec,

dP/dt decreased from 1894 ± 368 mmHg/sec to 1762 ± 403 mmHg/sec ($P=0.01$) and EMAT increased from 88 ± 13 ms to 93 ± 16 ms ($P=0.02$). Changes in negative dP/dt were similar to changes in dP/dt .

Figure 1 Relationship between positive and negative maximum LV dP/dt prior to the left ventriculogram $n=116$. LV: left ventricular.

Figure 2 Relationship between positive and negative maximum LV dP/dt following the left ventriculogram $n=116$. LV: left ventricular.

Table 2

Normal versus elevated left ventricular end-diastolic pressure before and after ventriculography.

	EF%	Heart rate	LVEDP	dP/dt max	$-dP/dt$ max	EMAT
All	45 ± 18	79 ± 18	18 ± 7	1345 ± 457	-1494 ± 548	101 ± 20
$n=116$		80 ± 20	20 ± 8	1337 ± 443	-1430 ± 401	100 ± 18
P		0.73	<0.001	0.72	0.06	0.34
LVEDP < 15	48 ± 18	82 ± 17	11 ± 3	1271 ± 370	-1414 ± 377	101 ± 18
$n=42$		82 ± 14	14 ± 5	1273 ± 345	-1343 ± 326	100 ± 17
P		0.93	<0.002	0.96	0.14	0.63
LVEDP ≥ 18	40 ± 17	78 ± 22	24 ± 5	1381 ± 556	-1509 ± 655	102 ± 22
$n=53$		79 ± 19	26 ± 7	1336 ± 518	-1422 ± 412	101 ± 20
P		0.68	0.01	0.2	0.11	0.74

dP/dt max: maximum left ventricular dP/dt , EF: ejection fraction, EMAT: electromechanical activation time, LVEDP: left ventricular end-diastolic pressure.

Discussion

The present study shows that the acoustic cardiography parameter EMAT reflects the changes in LV maximum dP/dt associated with acute increases in LV volume. The positive and negative LV maximum dP/dt correlated significantly, both before and after LV angiography. This relationship may result from the coexistence of systolic and diastolic LV dysfunction exhibited in many patients.¹¹

The ability of EMAT to detect these changes, even when they occur very rapidly, suggests that this acoustic cardiography parameter can be utilised for monitoring haemodynamic changes that result from therapeutic interventions such as pharmacological therapy, optimisation of cardiac resynchronisation therapy, and ultrafiltration.^{12–15} Our results also suggest that EMAT can be used to detect rapidly occurring impairment of LV function, e.g. in acute myocardial infarction (AMI) and inadvertent fluid overload.

In Table 3, the trend in dP/dt and the significant reduction in EMAT in patients with abnormally low LVEFs was the result of the increase in preload produced by the injection of iopromide. The different response in patients with vs. without abnormally low LVEF is consistent with the observation that patients with impaired ventricular function depend more heavily on the Starling mechanism than do patients whose LV function is intact.

Evidence of the operation of the Starling mechanism was also demonstrated in Table 4. These data show an increase in LV maximum dP/dt in the patients whose baseline dP/dt was abnormally low. A directionally opposite change occurred in the patients with a normal baseline dP/dt , probably because of negative inotropic effect of iopromide.^{16–18} Both sets of alterations in LV maximum dP/dt were mirrored by significant and directionally appropriate changes in EMAT. Table 4 also demonstrates a significant decrease in negative LV maximum dP/dt in patients with normal baseline LV systolic function, probably, due to the negative lusitropic effect of iopromide. Such a decrease in negative dP/dt did not occur in patients

Table 3

Normal versus reduced versus low left ventricular ejection fraction.

	EF%	Heart rate	LVEDP	dP/dt max	–dP/dt max	EMAT
All <i>n</i> =116 <i>P</i>	45±18	79±18 80±20 0.73	18±7 20±8 0.001	1345±457 1337±443 0.72	–1491±548 –1430±401 0.06	100±20 100±18 0.34
EF≥55 <i>n</i> =34 <i>P</i>	64±10	77±19 77±22 0.59	17±6 19±8 0.08	1727±510 1678±465 0.36	–1856±679 –1702±439 0.065	94±18 96±18 0.22
EF<45 <i>n</i> =60 <i>P</i>	34±10	81±20 81±17 0.59	19±7 22±8 0.001	1100±305 1121±340 0.41	–1226±360 –1221±270 0.89	106±20 102±19 0.03
EF<35 <i>n</i> =33 <i>P</i>	25±6	85±18 86±18 0.72	19±8 23±9 0.001	1032±239 1082±335 0.19	–1152±307 –1167±275 0.74	107±19 101±20 0.03

dP/dt max: maximum left ventricular dP/dt, EF: ejection fraction, EMAT: electromechanical activation time, LVEDP: left ventricular end-diastolic pressure.

Table 4

Low versus normal maximum left ventricular dP/dt.

	EF%	Heart rate	LVEDP	dP/dt max	–dP/dt max	EMAT
All <i>n</i> =116 <i>P</i>	45±18	79±18 80±20 0.73	18±7 20±8 0.001	1345±457 1337±443 0.72	–1494±548 –1430±401 0.06	100±20 100±18 0.34
dP/dt<1500 <i>n</i> =80 <i>P</i>	39±17	78±19 78±16 0.972	18±7 20±8 0.001	1098±216 1146±306 0.02	–1264±309 –1285±310 0.43	106±20 103±18 0.02
dP/dt≥1500 <i>n</i> =36 <i>P</i>	58±14	81±21 82±22 0.42	18±6 20±7 0.04	1894±368 1762±403 0.01	–1997±625 –1746±398 0.002	88±13 93±16 0.02

dP/dt max: maximum left ventricular dP/dt, EF: ejection fraction, EMAT: electromechanical activation time, LVEDP: left ventricular end-diastolic pressure.

with impaired LV systolic function. In these patients, the indirect positive lusitropic effect of increased preload overwhelms the direct negative lusitropic effect of iopromide. To our knowledge, we are the first to report this paradoxical effect of non-ionic contrast agents in patients with and without depressed systolic LV function.

The findings of the present study show that the acoustic cardiography parameter EMAT provides an accurate, convenient, and cost-effective way to assess alterations in LV function, and therefore, augments the well understood third heart sound.¹⁹ This is especially important in the assessment of HF patients, where biomarkers are primarily used in the acute management²⁰ but further low-cost, non-invasive methods are needed for monitoring of patients with chronic HF.²¹ In this study, the acoustic cardiography parameter EMAT was compared with the invasively measured LV maximum dP/dt—a conventional diagnostic standard. Obviously such invasive measurements are not feasible in the routine evaluation of patients in a wide variety of clinical settings. In addition to their cost and relatively limited availability, other tests require too much time to perform to be as responsive to acute changes in haemodynamic status as has been demonstrated for acoustic cardiography.

Conclusion

Electromechanical activation time is a non-invasively measured parameter that allows accurate and rapid detection of changes in LV contractility.

The ability of EMAT to do this suggests its utility in evaluating and monitoring patients with known or suspected abnormalities of LV function. We are reporting for the first time the paradoxical effect of non-ionic contrast agents on dP/dt and –dP/dt in patients with and without depressed systolic LV function.

Limitations of the study

The number of subjects, particularly, those with volume or pressure overload, is rather small and the cardiac disease subgroups had overlapping subjects. Not all the recordings of dP/dt were performed with manometer-tipped catheters. The LVEF was calculated using mono-plane LV angiography. Although short-acting diuretics had been withheld on the morning of the catheterisation, the subjects varied with respect to the types and dosages of the various other cardioactive

drugs that they were receiving. Since drugs such as beta-adrenergic blockers, vasodilators and angiotensin-converting enzyme inhibitors influence ventricular performance, this pharmacological variability may have affected our results.

Acknowledgement

We acknowledge the assistance of Dr. Markus Roos, who lead the registration of acoustic cardiographic data at our institute, and of Dr. Robert Warner and Dr. Peter Bauer, Inovise Medical, Inc., Portland, OR for their data analysis support.

References

- Erne P. Beyond auscultation—acoustic cardiography in the diagnosis and assessment of cardiac disease. *Swiss Med Wkly* 2008; 138:439–52.
- Roos M, Toggweiler S, Jamshidi P, et al. Noninvasive detection of left ventricular systolic dysfunction by acoustic cardiography in cardiac failure patients. *J Card Fail* 2008;14:310–9.
- Dillier R, Kobza R, Erne S, et al. Noninvasive detection of left-ventricular systolic dysfunction by acoustic cardiography in atrial fibrillation. *Cardiol Res Pract* 2010;2011:173102.
- Zuber M, Kipfer P, Attenhofer Jost CH. Usefulness of acoustic cardiography to resolve ambiguous values of B-type natriuretic peptide levels in patients with suspected heart failure. *Am J Cardiol* 2007;100:866–9.
- Zuber M, Erne P. Acoustic cardiography to improve detection of coronary artery disease by stress testing. *World J Cardiol* 2010; 2:118–24.
- Dillier R, Zuber M, Arand P, et al. Assessment of systolic and diastolic function in heart failure using ambulatory monitoring with acoustic cardiography. *Ann Med* 2011;43:403–11.
- Shapiro M, Moyers B, Marcus GM, et al. Diagnostic characteristics of combining phonocardiographic third heart sound and systolic time intervals for the prediction of left ventricular dysfunction. *J Card Fail* 2007;13:18–24.
- Zuber M, Attenhofer Jost CH, Kipfer P, et al. Acoustic cardiography augments prolonged QRS duration for detecting left ventricular dysfunction. *Ann Noninvasive Electrocardiol* 2007;12:316–28.
- Wilson DJ, North N, Wilson RA. Comparison of left ventricular ejection fraction calculation methods. *Echocardiography* 1998; 15:709–12.
- Baim DS, Grossman W. Cardiac ventriculography. In: *Grossman's Cardiac Catheterization, Angiography, and Intervention* Baim DS, Grossman W. Philadelphia: Lippincott Williams & Wilkins 2005.
- Baicu CF, Zile MR, Aurigemma GP, et al. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. *Circulation* 2005;111:2306–12.
- Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol* 2006;48:2243–50.
- Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–49.
- Chan C, Floras JS, Miller JA, et al. Improvement in ejection fraction by nocturnal haemodialysis in end-stage renal failure patients with coexisting heart failure. *Nephrol Dial Transplant* 2002;17: 1518–21.
- Julius S, Nesbitt SD, Egan BM, et al. for the trial of preventing hypertension (TROPHY) study investigators. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med* 2006;354:1685–97.
- Schmid I, Didier D, Pfammatter T, et al. Effects of non-ionic iodinated contrast media on patient heart rate and pressures during intra-cardiac or intra-arterial injection. *Int J Cardiol* 2007;118: 389–96.
- Schröder R, Abel J, Sievert H, et al. Koronararteriographie mit einem plasmatisotonen Röntgenkontrastmittel: Auswirkungen auf EKG, Blutdruck und Koronardurchblutung. *Z Kardiol* 1989;78: 33–40 (in German).
- Wink K. Frühe hämodynamische kardiovaskuläre Reaktionen nichtionischer niederosmolarer Kontrastmittel bei der Koronarangiographie. *Röntgenblätter* 1988;41:384–8 (in German).
- Narain VS, Puri A, Gilhotra HS, et al. Third heart sound revisited: a correlation with N-terminal pro brain natriuretic peptide and echocardiography to detect left ventricular dysfunction. *Indian Heart J* 2005;57:31–4.
- Aernja N, Breidhardt T, Socrates T, et al. Risk stratification for one year mortality in acute heart failure: classification and regression tree analysis. *Swiss Med Wkly* 2011;141:w13259.
- Gariani K, Delabays A, Prenger A, et al. Use of brain natriuretic peptide to detect unknown left ventricular dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease. *Swiss Med Wkly* 2011;141:w13298.