



Evaluation of the relationship between left atrial volume and myocardial ischemia: a systematic review

Ali Azari (MD), Leila Bigdelu (MD)*, Afsoon Fazlinezhad (MD), Marzie Farazandeh (MD), Somaye Bakefayat (MD)

Division of Cardiovascular, Vascular Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

ARTICLE INFO

Article type

Systematic review article

Article history

Received: 9 Mar 2015

Revised: 12 Apr 2015

Accepted: 14 Jul 2015

Keywords

Cardiac volume

Left Atrial Functions

Myocardial ischemia

ABSTRACT

Introduction: The pathophysiology of ischemia involves the cellular effect of myocardial ischemia, reactive oxygen species, and reactive inflammatory enzymes. Left atrial (LA) ischemia has been shown to have several mechanisms through which it can lead to abnormalities in left ventricular filling in early diastole and thus reduces LA passive functional reserve. In this review, we evaluated the physiological mechanisms of LA during myocardial ischemia, as previously demonstrated in experimental and clinical studies.

Methods: Several databases were searched in order to find related articles. The outcome of interest included LA function measurements (measurement of LA volume) during ischemia. By applying a standardized protocol, reviewers independently extracted and assessed the studies.

Results: The literature review indicated 50 publications, among which 15 studies were eligible for analysis. Assessment of LA dimension and function is essential for clinical evaluation and prognostic purposes.

Conclusion: The present article revealed that LA passive emptying volume and LA emptying volume significantly increased in myocardial ischemia. Further researches could provide a better understanding of pathophysiological mechanisms behind LA enlargement and help to predict clinical outcomes in many cardiovascular disorders.

Please cite this paper as:

Azari A, Bigdelu L, Fazlinezhad F, Farazandeh M, Bakefayat S. Evaluation of the relationship between left atrial volume and myocardial ischemia: a systematic review. *Rev Clin Med.* 2017;4(3):97-101.

Introduction

Ischemia occurs when an organ is deprived of blood flow, resulting in inadequate oxygen and nutrient supply (1). Ischemia has been implicated in the pathology of peripheral vascular insufficiency (1), angina, myocardial infarction, and stroke (2).

Ischemic preconditioning (with brief intermittent periods of ischemia, followed by reperfusion prior to prolonged ischemia) and ischemic post-conditioning (immediately after a period of ischemia before the onset of reperfusion) have been shown to reduce myocardial ischemic injury (3). Myocardial reperfusion injury has been postulat-

ed to partially explain these outcomes. The ischemic myocardium reduces its metabolic needs and tends to adopt itself to survive with minimal requirements by reducing its own contractility and the mechanisms responsible for the development of myocardial hibernation in which the heart reduces the contractile function in proportion to reduced blood flow are yet to be identified (1).

Several recent studies have assessed the structure and function of left atrium (LA). Particular attention has been paid to LA and changes of LA structure, caused by a wide range of pathologies

*Corresponding author: Leila Bigdelu.

Department of Cardiology, Ghaem hospital, School of Medicine, Mashhad University of Medical Science, Mashhad, Iran.

E-mail: Bigdelul@mums.ac.ir

Tel: 985138012739

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

(4). LA function has been traditionally described in three phases: reservoir (the filling phase during ventricular systole), conduit (passive emptying phase during early diastole), and contraction (the pumping phase in late diastole) (5). Moreover, LA impairment has been associated with heart failure, aging, and other cardiovascular disorders such as atrial fibrillation, hypertension, and hypertrophic cardiomyopathy (6).

LA ischemia has been shown to have several mechanisms through which it can lead to abnormalities in left ventricular filling in early diastole and thus reduces passive LA functional reserve (7). Myocardial relaxation is an exquisitely energy-dependent process, which is highly sensitive to the effects of ischemia; moreover, subendocardial longitudinal fibers are particularly sensitive to ischemia. This leads to incoordination or asynchronicity between circumferential and longitudinal fibers in ischemic areas, as well as a reduction in longitudinal contractile function that may not be initially detectable but could lead to diminished ventricular suction (8).

The present systematic review aim to discuss the pathophysiological mechanisms of LA during myocardial ischemia, as demonstrated by previous experimental and clinical studies.

Methods

Data sources and search strategy

The present systematic review was carried out in accordance with the preferred reporting items for systematic reviews and analysis guidelines (9). We searched the literature using the method of keyword search in databases including PubMed, Scopus, Web of Science (WOS), and Google Scholar.

The following MeSH, Emtree, and keyword search terms were used in combination: ischemia, myocardial infarction, and left atrium (LA) to identify further articles.

Data extraction

The reviewers independently extracted the data from the evaluated populations, patient characteristics, and relevant measured outcomes. We did not specify the definitions of prior outcomes, and they were accepted as defined in individual studies. The measured outcomes were markers of ischemia, myocardial ischemia, and indices of regional LA function. Regional atrial functions were determined by LA function during myocardial ischemia.

Quality assessment

Quality assessment Analysis of data and quality evaluation of the literature were performed independently by two investigators. Two investigators read the titles, abstracts, full texts and made final

decisions on study inclusion and proceeding to data collection. For methodological quality evaluation of RCT, the Cochrane Collaboration tool was used.

Results

The literature review identified 50 publications, among which 15 studies were eligible for analysis. Duplicated articles were omitted in the first step. The Figure 1 shows the PRISMA flowchart of the study. Overall five systematic reviews were included (4,8).

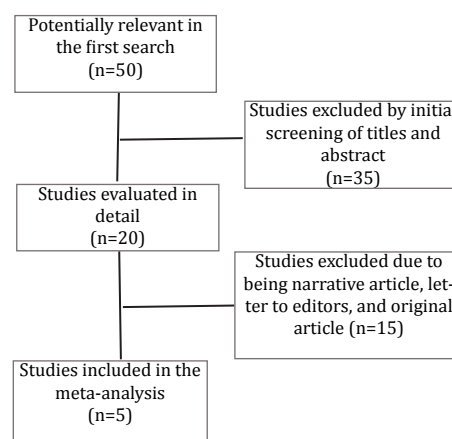


Figure 1. PRISMA flowchart of the study

Discussion

LA has a complex morphology (10,11) and current echocardiographic techniques, which allow surface and volume assessment of LA, are not entirely accurate (10). Moreover, the close coupling between LV pressure and LAV highlights the somewhat artificial distinction between these two properties (12).

As a consequence of LA behavior, the flow through the mitral valve exhibits a biphasic behavior during a cardiac cycle; when the ventricles are relaxed (before the contraction of the atrium); the transmitral flow is nearly zero (13). During LV systole, the downward movement of the mitral annulus stretches the atrium so that the atrial and ventricular volumes reciprocate. This is also the case during early diastolic LA emptying, when ventricular relaxation and elastic recoil move the mitral annulus upward, contributing to LV filling. This has led some to suggest that these LA functional properties should be considered as LV properties (5). Therefore, LA physiology and physiopathology is highly dependent on LV function, as the atrium is exposed to intraventricular pressure, particularly during diastole. As a consequence, any change in intraventricular pressure or volume is reflected on LA function; pathophysiological mechanisms of LV during ischemia leads to abnormalities of ventric-

ular filling in early diastole and thus to a diminution of LA passive functional reserve (7).

Based on the previously discussed volumetric measurements, several indices corresponding to the three basic functions of the LA can be derived:

1. LA reservoir function: LA total emptying volume = LAVmax - LAVmin LA total emptying fraction = (LAVmax - LAVmin)/LAVmax.

2. LA conduit function: LA passive emptying volume = LAVmax - LAVpreA LA passive emptying fraction = (LAVmax - LAVpreA)/LAVmax Conduit Volume = stroke volume - total emptying volume.

3. LA booster pump function: LA active emptying volume = LAVpreA - LAVmin LA active emptying fraction = (LAVpreA - LAVmin)/LAVpreA (8).

Clinical characteristics demonstrated in previous studies indicated the median level of absolute percent increase in LA passive emptying fraction (Δ LAPEF) (8,14,15). Some studies reported that LAPEF deteriorated with stress, resulting in a negative value for Δ LAPEF. In fact, patients with Δ LAPEF below the median value had lower baseline LV ejection fraction at rest and larger LV end-diastolic and end-systolic volume indices (16,17). These results showed the increasing deterioration of inducible wall motion during progressive dobutamine stress.

A significant body of experimental studies has shown that during an ischemic insult, changes in LV diastolic function occur before any changes in systolic wall motion (18). Thus, relying on the detection of abnormalities in systolic wall motion alone, may result in missing some patients with early ischemia. Similarly, changes in LA function during angioplasty have been shown to precede changes in LV systolic function (8).

Today, LA area and volume measurements are preferred for assessing LA dimensions, as they are shown to have a better correlation with the increased risk of cardiovascular events (19). Several methods can be applied to measure LAV such as the cube method, the area-length method, the ellipsoid method, and the modified Simpson's rule. The Simpson's rule is preferred by most physicians, since it depends on fewer geometrical assumptions, compared to previous methods, particularly the ellipsoid method (10). Therefore, for reporting LA function during ischemia, cardiovascular magnetic resonance imaging (CMRI), dobutamine stress evaluation of myocardial ischemia, and quantification of LA emptying function have been applied in previous studies (20-22).

There are several possible mechanisms through which ischemia can lead to abnormalities in ventricular filling in early diastole and thus reduces LA passive functional reserve (7). These mechanisms have been described as follows:

1) Myocardial relaxation is an exquisitely energy-dependent process and is highly sensitive to the effects of ischemia, since adenosine triphosphate hydrolysis is required for the release of tightly bound actin-myosin bonds and calcium reuptake into the sarcoplasmic reticulum.

2) Subendocardial longitudinal fibers are particularly sensitive to ischemia. This leads to incoordination or asynchronicity between circumferential and longitudinal fibers in ischemic areas, as well as a reduction in longitudinal contractility that may not be initially detectable but could lead to diminished ventricular suction (8). It would be of interest to know if LA functional parameters (such as Δ LAPEF) are more sensitive to LV ischemia than classical diastolic markers.

Resting LAV and LA function are important parameters in healthy subjects and myocardial ischemic patients. As Farzaneh-Far et al. indicated, Bland-Altman analysis of interobserver variability for VOLmax (left atrial volume at end-systole), VOLbac (left atrial volume before atrial contraction) (53 ± 10 ml/m²), and VOLmin (left atrial volume at end-diastole) had biases ($\pm 95\%$ limit of agreement) of 1.5 ± 7.9 ml, 1.0 ± 7.8 ml, and 3.2 ± 7.6 ml, respectively. In addition, kappa values were calculated to assess interobserver agreement in detecting abnormally low LA function parameters (8).

In a study by Pritchett et al. performed on a population with no cardiovascular diseases and normal systolic and diastolic functions, Doppler echocardiography, along with LA dimension (LAD) and LAV assessments, showed that the median normal value of LAD/body surface area (BSA) was 22 ml/m² in men and 21 ml/m² in women (23); these findings were consistent with the results obtained by Tsang and colleagues (10). Based on the criteria presented by the Standards Committee and the Chamber Quantification Writing Group, LA values may be used to describe LA enlargement as mild (29-33 mL/m²), moderate (34-39 mL/m²), and severe (>40 mL/m²) (24).

As Abhayaratna et al. reported that an LA value of ≥ 34 mL/m² could be an independent predictor of death, heart failure, atrial fibrillation, and ischemia (25). Messika-Zeitoun et al. (26) and Rossi et al. (27) also indicated that cardiovascular events are more likely to occur in patients undergoing cardiovascular surgeries for mitral regurgitation in the presence of LA enlargement. However, a complete assessment of LA size and function may not rely on maximum LA alone, as LA dimensions vary widely during the cardiac cycle.

An electrocardiogram-guided echocardiography allows an accurate quantification of LA functions by measuring LAV at different times during the cardiac cycle. Measurements are usually per-

formed as follows:

1) At the end of systole, just before the opening of the mitral valve (at the end of T-wave on ECG)–LAVmax (Figure 2);

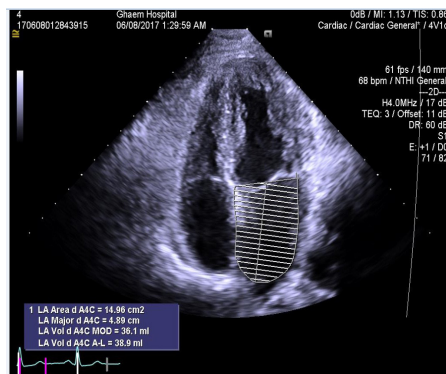


Figure 2. LAVmax measured at the end of systole, using modified Simpson's method from an apical 4-chamber view.

2) At the end of diastole, just before mitral valve closure (at the beginning of QRS complex on ECG)–LAVmin (Figure 3);

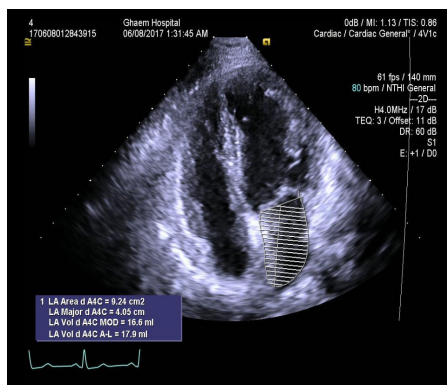


Figure 3. LAVmin measured at the end of diastole, using the modified Simpson's method from an apical 4-chamber view.

3) At the middle of diastole, just before atrial contraction (at the beginning of P-wave on ECG) – pre-atrial contraction volume (LAVpreA) (Figure 4).

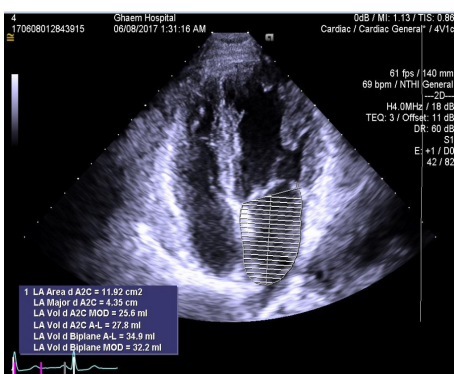


Figure 4. LAVpreA measured in the middiastole using Simpson's modified method from an apical 4-chamber view.

In the present review study, we demonstrated that passive LA emptying volume and total LA emptying volume were significantly increased in myocardial ischemic patients. Ischemia without a well-defined etiology is labeled as cryptogenic and accounts for 30-40% of all ischemic cases.

It has been suggested that cardiac embolism constitutes a major causative mechanism of myocardial ischemia (28). A recent multicenter study demonstrated that almost 20% of patients with myocardial ischemia had occult paroxysmal atrial fibrillation, detected on outpatient cardiac telemetry over a 21-day period (29).

Conclusion

Myocardial ischemic has the drawback of intermittent cross clamping of artery, which may be cause of severe artery disorders in patients. Assessment of LA function is essential for clinical evaluation and prognostic purposes. Augmentation of LA passive emptying fraction is a predictor of cardiovascular prognosis, independent of major clinical or LV imaging predictors. LAV measurement may facilitate atrial remodeling assessment in various pathological conditions, as well as reverse remodeling after medical or invasive therapies (such as cardiac resynchronization therapy or ablation for atrial fibrillation). Although previous studies have demonstrated the clinical and prognostic value of LA assessment, further research could provide a better understanding of pathophysiological mechanisms behind LA enlargement and help to predict clinical outcomes in many cardiovascular disorders.

Conflict of Interest

The authors have no conflict of interest.

References

- Balakumar P, Rohilla A, Singh M. Pre-conditioning and post-conditioning to limit ischemia-reperfusion-induced myocardial injury: what could be the next footstep? *Pharmacol Res.* 2008;57:403-412.
- Buja LM. Myocardial ischemia and reperfusion injury. *Cardiovasc Pathol.* 2005;14:170-175.
- Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med.* 2007;357:1121-1135.
- Lupu S, Mitre A, Dobreanu D. Left atrium function assessment by echocardiography – physiological and clinical implications. *Med Ultrason.* 2014;16:152-159.
- Gerds E, Wachtell K, Omvik P, et al. Left atrial size and risk of major cardiovascular events during antihypertensive treatment: losartan intervention for endpoint reduction in hypertension trial. *Hypertension.* 2007;49:311-316.
- Nistri S, Olivotto I, Betocchi S, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). *Am J Cardiol.* 2006;98:960-965.
- Gibson DG, Francis DP. Clinical assessment of left ventricular diastolic function. *Heart.* 2003;89:231-238.
- Farzaneh-Far A, Ariyarahaj V, Shenoy C, et al. Left Atrial Passive Emptying Function During Dobutamine Stress MR Imaging Is a Predictor of Cardiac Events in Patients With

- Suspected Myocardial Ischemia. *JACC Cardiovasc Imaging*. 2011;4:378-388.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
 10. Tsang TS. Echocardiography in cardiovascular public health: the Feigenbaum Lecture 2008. *J Am Soc Echocardiogr*. 2009;22:649-656.
 11. Klein AL, Garcia MJ. Diastology. Clinical approach to diastolic heart failure. Philadelphia: Elsevier Saunders;2008.
 12. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. *Eur Heart J*. 2001;22:22-36.
 13. Saito S, Araki Y, Usui A, et al. Mitral valve motion assessed by high-speed video camera in isolated swine heart. *Eur J Cardiothorac Surg*. 2006;30:584-591.
 14. Takagi T, Takagi A, Yoshikawa J. Elevated left ventricular filling pressure estimated by E/E ratio after exercise predicts development of new-onset atrial fibrillation independently of left atrial enlargement among elderly patients without obvious myocardial ischemia. *J Cardiol*. 2014;63:128-133.
 15. Akil MA, Akil E, Bilik MZ, et al. The relationship between atrial electromechanical delay and left atrial mechanical function in stroke patients. *Anatol J Cardiol*. 2015;15:565-570.
 16. Nazarian S, Bluemke DA, Lardo AC, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. *Circulation*. 2005;112:2821-2825.
 17. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-1463.
 18. Sigwart U, Grbic M, Goy JJ. Left atrial function in acute transient left ventricular ischemia produced during percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery. *Am J Cardiol*. 1990;65:282-286.
 19. Tsang TS, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol*. 2006;47:1018-1023.
 20. Khoo CW, Krishnamoorthy S, Lim HS, et al. Assessment of left atrial volume: a focus on echocardiographic methods and clinical implications. *Clin Res Cardiol*. 2011;100:97-105.
 21. Nattel S, Li D, Yue L. Basic mechanisms of atrial fibrillation-very new insights into very old ideas. *Annu Rev Physiol*. 2000;62:51-77.
 22. Khoo CW, Krishnamoorthy S, Lim HS. Assessment of left atrial volume: a focus on echocardiographic methods and clinical implications. *Clin Res Cardiol*. 2011;100:97-105.
 23. Pritchett AM, Jacobsen SJ, Mahoney DW, et al. Left atrial volume as an index of left atrial size: a population based study. *J Am Coll Cardiol*. 2003;41:1036-1043.
 24. Pironet A, Dauby PC, Paeme S, et al. Simulation of Left Atrial Function Using a Multi-Scale Model of the Cardiovascular System. *PLoS One*. 2013 3;8:e65146 .
 25. Abhayaratna WP, Seward JB, Appleton CP, et al. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol*. 2006;47:2357-2363.
 26. Messika-Zeitoun D, Bellamy M, Avierinos JF, et al. Left atrial remodelling in mitral regurgitation – methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler echocardiographic and electron beam-computed tomographic study. *Eur Heart J*. 2007;28:1773-1781.
 27. Rossi A, Cicoira M, Zanolla L, et al. Determinants and Prognostic Value of Left Atrial Volume in Patients With Dilated Cardiomyopathy. *J Am Coll Cardiol*. 2002;40:1425.
 28. Jickling GC, Stamova B, Ander BP, et al. Prediction of cardioembolic, arterial, and lacunar causes of cryptogenic stroke by gene expression and infarct location. *Stroke*. 2012;43:2036-2041.
 29. Miller DJ, Khan MA, Schultz LR, et al. Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke. *J Neurol Sci*. 2013;324:57-61.