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EDITORIAL

# Editorial on hemoglobin A1c, blood pressure, and low-density lipoprotein cholesterol goals in diabetics

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## Abstract

The American Diabetes Association (ADA) 2013 guidelines state that a reasonable hemoglobin A1c goal for many nonpregnant adults with diabetes is less than 7.0% a hemoglobin A1c level of less than 6.5% may be considered in adults with short duration of diabetes, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment. A hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, extensive comorbidities, and long-standing diabetes in whom the hemoglobin A1c goal is difficult to attain despite multiple glucose-lowering drugs including insulin. The ADA 2013 guidelines recommend that the systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg. These guidelines also recommend use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the treatment of hypertension in diabetics unless they are pregnant. Diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol lowered to less than 70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL. Combination therapy of a statin with either a fibrate or niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not recommended. Hypertriglyceridemia should be treated with dietary and lifestyle changes. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis.



**Key words:** Diabetes mellitus; Blood pressure; Hemoglobin A1c; Serum low-density lipoprotein cholesterol; Statins; Lipid-lowering drugs

**Core tip:** 2013 guidelines state that a reasonable hemoglobin A1c goal for diabetics is less than 7.0% a hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, and extensive comorbidities. The systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg. Diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol lowered to less than 70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL. Combination therapy of a statin with either a fibrate or niacin is not recommended.

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## INTRODUCTION

The American Diabetes Association (ADA)/American Heart Association (AHA) 2007 scientific statement recommended that diabetics should have a hemoglobin A1c level less than 7.0% and as close to normal (less than 6.0%) without causing significant hypoglycemia[1]. This scientific statement also recommended that diabetics with hypertension should have their blood pressure lowered to less than 130/80 mmHg[1]. In addition, this scientific statement recommended that combination therapy of statins with fibrates or niacin may be necessary to achieve lipid targets. This editorial will discuss clinical trial data showing why these recommendations needed to be changed.

## HEMOGLOBIN A1C GOALS

The action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation trial randomized 11140 type 2 diabetics, mean age 66 years, to intensive glucose control with a hemoglobin A1c of 6.5% reached or to standard glucose control with a hemoglobin A1c of 7.3% reached[2]. At 5-year median follow-up, death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke and all-cause mortality were similar in both treatment groups. Severe hypoglycemia occurred in 2.7% of the intensive glucose control group *vs* 1.5% in the standard glucose control group (hazard ratio = 1.86; 95%CI: 1.42-2.40; $P < 0.001$)[2]. However, major microvascular events (new or worsening nephropathy or retinopathy) were reduced from 10.9%-9.4% by intensive glucose control (hazard ratio = 0.86; 95%CI: 0.77-0.97; $P = 0.01$), primarily because of a reduction in nephropathy[2].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group randomized 10251 type 2 diabetics, mean age 62.2 years, to intensive glucose control with a hemoglobin A1c of 6.4% reached or to standard glucose control with a hemoglobin A1c of 7.5% reached[3]. At 3.5-year mean follow-up, the incidence of cardiovascular death, nonfatal MI, or nonfatal stroke was not significantly different between both treatment groups. However, all-cause mortality was 5.0% in the intensive glucose control group *vs* 4.0% in the standard glucose control group (hazard ratio = 1.22; 95%CI: 1.01-1.46; $P = 0.04$). Hypoglycemia requiring medical assistance occurred in 10.5% of the intensive glucose control group *vs* 3.5% in the standard glucose control group ($P < 0.001$)[3].

The Veterans Affairs Diabetes Trial randomized 1791 type 2 diabetics, mean age 60.4 years, to intensive glucose control with a hemoglobin A1c of 6.9% reached or to standard glucose control with a hemoglobin A1c of 8.4% reached[4]. At 5.6-year median follow-up, cardiovascular death, nonfatal MI, nonfatal stroke, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease, or amputation for ischemic gangrene and all-cause mortality were not significantly different between both treatment groups. Microvascular complications were not significantly different between both treatment groups. Adverse events, predominantly hypoglycemic episodes were more frequent in the intensive glucose treatment group (24.1% *vs* 17.6%, $P < 0.001$)[4].

The ADA 2013 guidelines state that a reasonable hemoglobin A1c goal for many nonpregnant adults with diabetes is less than 7.0%[5]. A hemoglobin A1c level of less than 6.5% may be considered in adults with short duration of diabetes, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment. A hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, extensive comorbidities, and long-standing diabetes in whom the hemoglobin A1c goal is difficult to attain despite multiple glucose-lowering drugs including insulin[5].

The American Geriatrics Society website on February 21, 2013 stated that reasonable glycemic targets would be hemoglobin A1c levels of 7.0%-7.5% in older adults with long life expectancy, 7.5%-8.0% in older adults with moderate comorbidities and a life expectancy of less than 10 years, and 8.0%-9.0% in older adults with multiple comorbidities and shorter life expectancy. Tight control of blood sugar causes higher rates of hypoglycemia in older adults.

## BLOOD PRESSURE GOALS

The 2009 European Society of Hypertension guidelines recommended that lowering the blood pressure to less than 130/80 mmHg in patients at high risk for cardiovascular events was unsupported by prospective trial data, and that the systolic blood pressure should be lowered to less than 140 mmHg in these patients[6]. The American College of Cardiology Foundation/AHA 2011 expert consensus document on hypertension in the elderly recommended that the blood pressure should be reduced to less than 140/90 mmHg in adults younger than 80 years at high risk for cardiovascular events[7]. On the basis of data from the Hypertension in the Very Elderly trial[8], these guidelines recommended that the systolic blood pressure should be reduced to 140-145 mmHg if tolerated in adults aged 80 years and older[7].

In the International Verapamil SR-Trandolapril Study, 6400 patients had diabetes mellitus and coronary artery disease[9]. These patients were categorized as having tight control of their blood pressure if they could maintain their systolic blood pressure below 130 mmHg and their diastolic blood pressure below 85 mmHg, usual control if they could maintain their systolic blood pressure between 130-139 mmHg, and uncontrolled if their systolic blood pressure was 140 mmHg or higher. During 16893

patient-years of follow-up, a cardiovascular event rate (all-cause mortality, nonfatal MI, or nonfatal stroke) of 12.6% occurred in patients with usual control of blood pressure *vs* 19.8% in patients with uncontrolled hypertension (adjusted hazard ratio = 1.46; 95%CI: 1.25-1.71; $P < 0.001$) [9]. The incidence of cardiovascular events was 12.6% in patients with usual control of blood pressure *vs* 12.7% in patients with tight control of blood pressure (*P* not significant). The all-cause mortality rate was 11.0% with tight control of blood pressure *vs* 10.2% with usual control of blood pressure ($P = 0.06$). When extended follow-up to 5 years following the close of INVEST was included, the all-cause mortality rate was 22.8% with tight control of blood pressure *vs* 21.8% with usual control of blood pressure (adjusted hazard ratio = 1.15; 95%CI: 1.01-1.32; $P = 0.04$)[9].

The ACCORD blood pressure trial randomized 4733 patients with type 2 diabetes mellitus to intensive blood pressure control with a target systolic blood pressure of less than 120 mmHg or to standard blood pressure control with a target systolic blood pressure less than 140 mmHg[10]. After 1 year, the mean systolic blood pressure was 119.3 mmHg in the intensive blood pressure control group *vs* 133.5 mmHg in the standard blood pressure control group. Mean follow-up was 4.7 years. The primary composite outcome of nonfatal MI or nonfatal stroke or cardiovascular death and the annual rate of death from any cause were not significantly different between both treatment groups. The annual stroke rate was 0.32% in the intensive blood pressure control group *vs* 0.53% in the standard blood pressure control group (hazard ratio = 0.59; 95%CI: 0.39-0.89; $P = 0.01$) (number needed to treat to reduce 1 stroke = 476 patients). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive blood pressure control group *vs* 1.27% of the standard blood pressure control group, $P < 0.001$ (number needed to treat to increase 1 serious adverse event = 49 patients)[10].

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint trial included 9603 diabetics, mean age 66.1 years, and 15981 nondiabetics, mean age 66.6 years, with hypertension at high risk for cardiovascular events[11]. Mean follow-up was 4.6 years. The primary endpoint was cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure. Compared to nondiabetics, diabetics had a 48% significant increase in the primary endpoint (hazard ratio = 1.48; 95%CI: 1.38-1.57). In patients with and without diabetes, antihypertensive drug treatment reduced the primary outcome if the baseline systolic blood pressure was 143 to 155 mmHg. The lowest incidence of death from cardiovascular causes in diabetics occurred with a systolic blood pressure of 135.6 mmHg (range 130.6 to 140.5 mmHg). The lowest incidence of death from cardiovascular causes in nondiabetics occurred with a systolic blood pressure of 133.1 mmHg (range 128.8 to 137.4 mmHg). For the primary outcome, the highest risk in those with and without diabetes occurred in patients with the lowest or highest in-trial diastolic blood pressures (67.2 and 86.7 mmHg, respectively)[11].

The ADA 2013 guidelines recommend that the systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg[5]. These guidelines also recommend use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the treatment of hypertension in diabetics unless they are pregnant[5].

## DYSLIPIDEMIA

Numerous studies have demonstrated that statins reduce cardiovascular events including stroke and mortality in diabetics[12-15]. A meta-analysis was performed of 14 randomized trials of statins used to treat 18686 diabetics (1466 with type 1 diabetes and 17220 with type 2 diabetes)[14]. Mean follow-up was 4.3 years. All-cause mortality was reduced 9% per mmol/L reduction in serum low-density lipoprotein (LDL) cholesterol, $P = 0.02$. Major cardiovascular events were reduced 21% per mmol/L reduction in serum LDL cholesterol, $P < 0.0001$. Statins caused in diabetics a 22% reduction in MI or coronary death ($P < 0.0001$), a 25% reduction in coronary revascularization ($P < 0.0001$), and a 21% reduction in stroke ($P = 0.0002$). After 5 years, 42 fewer diabetics per 1000 diabetics treated with statins had major cardiovascular events[15].

In the Fenofibrate Intervention and Event Lowering in Diabetes study, 9795 type 2 diabetics (2131 with cardiovascular disease) were randomized to fenofibrate or placebo[16]. Mean follow-up was 5.0 years. The primary outcome of coronary events was not significantly reduced by fenofibrate. Fenofibrate insignificantly increased CAD mortality 19%[16].

In the ACCORD trial, 5518 type 2 diabetics at high risk for cardiovascular disease were randomized to simvastatin plus fenofibrate or to simvastatin plus placebo[17]. Mean follow-up was 4.7 years. Compared with simvastatin plus placebo, simvastatin plus fenofibrate did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke. Among 3414 patients with atherosclerotic cardiovascular disease and low serum high-density lipoprotein (HDL) cholesterol levels treated with simvastatin plus ezetimibe if needed to maintain the serum LDL cholesterol less than 70 mg/dL, at 36-mo follow-up, patients randomized to niacin had improvements in serum HDL cholesterol and triglyceride levels but no clinical improvement compared to patients randomized to placebo[18].

Professor Jane Armitage presented on March 9, 2013 at the Annual Scientific Meeting of the American College of Cardiology in San Francisco, California the results of $HPS_2$-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events). In this study of 25673 patients at high risk of cardiovascular events, adding extended-release niacin plus the anti-flushing agent laropriprant to treatment

with simvastatin or simvastatin/ezetimibe did not reduce at 3.9-year follow-up cardiovascular events. However, there were 31 serious adverse events among every 1000 niacin-treated patients including 3.7% excess diabetic complications ($P < 0.0001$) and 1.8% excess new onset diabetes ($P < 0.0001$).

Diabetics at high risk for cardiovascular events should have their serum LDL cholesterol lowered to less than 70 mg/dL with statins[5]. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL[5]. Combination therapy of a statin with either a fibrate or niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not recommended[5]. Hypertriglyceridemia should be treated with dietary and lifestyle changes[5]. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis[5].

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BRIEF ARTICLE

# Gender differences related to the presence of atrial fibrillation in older hypertensive patients

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## Abstract

**AIM:** To determine whether there are gender differences in the epidemiological profile of atrial fibrillation (AF) and to characterise the clinical, biochemical, and therapeutic factors associated with AF.

**METHODS:** Each investigator (primary care physicians or physicians based in hospital units for hypertension treatment) recruited the first 3 patients with an age of ⩾ 65 years and a clinical diagnosis of hypertension (ambulatory blood pressure monitoring and an electrocardiogram, were performed) on the first working day of the week for 5 wk and identified those individuals with atrial fibrillation. A binary logistic regression was performed, including all of the variables that were significant in the univariate analysis, to establish the variables that were associated with the presence of arrhythmia.

**RESULTS:** A total of 1028 patients were included in the study, with a mean age of 72.8 ± 5.8 years. Of these patients, 47.3% were male, 9% were smokers, 27.6% were diabetics, 48.3% had dyslipidaemia, 10.9% had angina, and 6.5% had experienced a myocardial infarction. Regarding gender differences, the men exhibited a larger waist circumference, a lower body mass index, less obesity, and a more extensive history of diabetes, smoking, ischaemic heart disease, kidney failure, peripheral arterial disease and carotid disease than the women. There were no differences, however, in the prevalence of AF between the men and the women (11.5% *vs* 9.2%, respectively; *P* = no significant). Regarding treatment, the women received antiplatelet agents and diuretics less frequently, but there were no other differences in the use of antihypertensive and antithrombotic therapies. In the multivariate analysis, AF in the total study population was associated with age, alcohol consumption, the presence of heart disease, and decreased glomerular filtration. In the women, AF was associated with all of the factors included in the overall analysis, as well as the presence of left ventricle hypertrophy. In contrast, in the men, the only risk factors associated with AF were age, the presence of heart disease and alcohol consumption.

**CONCLUSION:** In patients with hypertension over 65 years of age, there are relevant gender differences in the factors associated with AF.



**Key words:** Atrial fibrillation; Hypertension; Gender differences

**Core tip:** The presence of atrial fibrillation (AF) in hypertensive patients with an age of ⩾ 65 years was associated with age, alcohol consumption, the presence of heart disease, and decreased glomerular filtration. In women, AF was associated with all of the factors included in the overall analysis, as well as the presence of left ventricle hypertrophy, whereas in men, the only risk factors associated with AF were age, the presence of heart disease and alcohol consumption. Thus, in patients with hypertension who are over 65 years of age, there are relevant gender differences in the factors associated with AF.

Fácila L, Pallarés V, Morillas P, Cordero A, Llisterri JL, Sánchis C, Gorriz JL, Castillo J, Gil V, Redon J. Gender differences related to the presence of atrial fibrillation in older hypertensive patients. *World J Cardiol* 2013; 5(5): 124-131 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i5/124.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i5.124

## INTRODUCTION

Although cardiovascular disease (CVD) has historically been considered to affect mainly men, we now know that CVD is the main cause of death in both men and women worldwide[1]. However, a number of occasionally significant gender differences can be observed in the morbidity, mortality, risk-factor profiles, and clinical presentation of CVD. These differences are consistent between all of the populations and regions analysed and are thus relevant to the development of programmes for the prevention and treatment of CVD.

The INTERHEART study found that, on average, women experience their first myocardial infarction 9 years later than men[2]. Similarly, a recent review reported that men experience their first stroke 4.3 years before women, on average[3]. However, as the prevalence of atrial fibrillation (AF) has increased in recent years due to the ageing of the population, the longer survival of patients with heart disease and, of course, more frequent diagnosis, among other factors, AF has become a major public health problem, particularly due to the associated risk of stroke and mortality[4]. Women are not exempt from this disease, as in addition to presenting several cardiovascular risk factors, their life expectancy is longer. The incidence in women is thus not negligible, and the probability of complications, and particularly cerebrovascular problems, is relatively high. This phenomenon is likely due to the prevalence of hypertension in women, which is the most important risk factor for both AF and stroke.

The purpose of this sub-study is to establish whether there are any gender-related epidemiological, clinical, biochemical, or therapeutic differences or differences in the factors associated with AF in hypertensive patients over 65 years of age.

## MATERIALS AND METHODS

The FAPRES registry is a healthcare, teaching and research project sponsored by the Valencian Society of Hypertension and Vascular Risk and supported by the Spanish Society of Hypertension-Spanish League for the Fight Against Hypertension (SEH-LELHA). The current study was designed to establish the prevalence of AF in patients of ⩾ 65 years of age with a clinical diagnosis of hypertension (HT) in the region of Valencia, Spain. This study involved the participation of 69 primary care physicians and physicians based in HT hospital units, a proportion similar to the population census of each of the three provinces. Written informed consent was obtained from all of the patients, and the study was performed following the principles of the Declaration of Helsinki (Edinburgh Amendment, 2000) and after approval by a hospital ethics committee (Clinical Research Ethics Committee of the Hospital General Universitario of Castellon). The general study methods and the determination of the sample size were described in previous publications[5,6]. This study is a subanalysis of these data, focusing on differential issues based on gender.

### *Patients*

Each investigator recruited the first three patients who attended the outpatient clinic on the first working day of the week for 5 wk during the recruitment period and who met all of the inclusion criteria and none of the exclusion criteria. The inclusion criteria were as follows: (1) over 65 years of age; (2) a previous diagnosis of HT, at least 3 mo before the start of the study, according to the Good Clinical Practice (GCP) guidelines[7]; and (3) consent to participate in the study. The exclusion criteria were an arm circumference greater than 42 cm, the presence of conditions ineligible for the study or for performing ambulatory blood pressure monitoring (ABPM), and the inability to understand and sign the consent form.

Clinical blood pressure (BP) measurement was performed following the GCP recommendations[8,9], using a validated automatic electronic device. The patient was considered to have good HT control when the mean systolic BP (SBP) and diastolic BP (DBP), based on the two measurements obtained at the visit, were below 140 and 90 mmHg, respectively.

The 24-h ABPM was performed using SpaceLabs 90207 devices (SpaceLabs, Inc. Richmond, WA, United States) specifically supplied for the project. The monitors were scheduled to perform a BP measurement every 20 min during the activity period and every 30 min during the night rest period. Each period was defined individually in each registry according to the bedtime and wake-up time reported by the patient. Registries not meeting the pre-established quality standards were excluded[10]. According to the guidelines of the European Societies of Cardiology and Hypertension (ESH/ESC)[8], a good ambulatory control was defined as having BP values of <

130/80 mmHg (SBP/DBP) in a 24-h period.

### Variables

The variables collected *via* clinical interview were age; gender; weight; height; body mass index (BMI) (obesity was defined when this parameter was ⩾ 30 kg/m$^2$); waist circumference (abdominal obesity was defined when this parameter was ⩾ 102 cm in men or ⩾ 88 cm in women)[11]; time from the onset of HT; excessive alcohol intake (over 30 g/d)[12]; and known cardiovascular risk factors (CVRFs), such as smoking, diabetes, dyslipidaemia (total cholesterol > 250 mg/dL, low-density lipoprotein (LDL)-cholesterol > 155 mg/dL, high-density lipoprotein (HDL)-cholesterol < 40 mg/dL in men or < 48 mg/dL in women, or receiving lipid-lowering treatment), and a family history of early cardiovascular disease (< 55 years of age in men or < 65 years of age in women).

All of the patients underwent an electrocardiogram that was sent by regular mail to a reference centre, where two expert cardiologists who were not familiar with the patients' clinical data analysed the heart rhythm independently. In the case of a disagreement between the experts, another specialist was asked to participate. Data on lesions in the target organs and associated clinical conditions were also collected, as follows: the presence or absence of left ventricular hypertrophy (Sokolow or Cornell electrocardiographic criteria), renal damage (increased serum creatinine from 1.3-1.5 mg/dL in men or 1.2-1.4 mg/dL in women), microalbuminuria, an albumin/creatinine ratio of 22-300 mg/g in men or 31-300 mg/g in women or albuminuria of 30-300 mg/24 h, and a glomerular filtration rate (GFR) estimated from the serum creatinine values according to the abbreviated formula from the Modification of Diet in Renal Disease study[13] (renal disease was defined for a GFR of < 60 mL/h peer m$^2$). Further data were collected on carotid disease (when the patient was diagnosed with an intima-media thickness > 0.9 mm or plaque) and previous heart disease (defined as the presence of ischaemic heart disease, heart failure or both). Additionally, we recorded the presence of previous cerebrovascular disease and peripheral arterial disease. The class and number of therapeutic subgroups of antihypertensives used for the treatment of HT were also recorded. AF was defined as having a history of arrhythmia beginning at least 3 mo before the study, as determined by medical records), even if the patients were now experiencing sinus rhythm or were diagnosed by the ECG performed on all of the patients.

An external audit of 10% of the questionnaires was performed randomly to verify the reliability of the data included in the study.

### Statistical analysis

The results were expressed as frequencies and percentages for the qualitative variables and as averages with standard deviations for the quantitative variables. The 95%CI was calculated for the variables of interest assuming normality using a Kolmogorov-Smirnov test. For the comparison of means, a Student's t test for independent data was used; when comparing quantitative data not following a normal distribution, the nonparametric Mann-Whitney test was used; and for the possible association between qualitative variables, the $\chi^2$ test was implemented, establishing statistical significance at $P < 0.05$. Finally, to establish the variables that were associated with the presence of AF, a binary logistic regression was performed that included all of the variables that were significant in the univariate analysis. The presence of confounding factors was evaluated by the analysis of interactions. The calibration of the multivariate model was tested using the Hosmer-Lemeshow statistic and the discriminative power using the area under the receiver operating characteristic (ROC) curve obtained by analysing the probability of the prognosticated value of the multivariate model. A general analysis and an analysis for each gender were conducted. All of the analyses were performed using the SPSS statistical package, version 15.0 (SPSS Inc., Chicago, Illinois, United States).

## RESULTS

During the period from June to December 2008, 1028 patient records were included in this study, 954 of which (92.8%) met the pre-established quality standards for evaluation (lacking incomplete data and protocol deviations, for example)[10]. The mean age of the patients was 72.8 ± 5.8 years, and 486 (47.3%) were men, 48.3% had dyslipidaemia, 27.6% were diagnosed with diabetes mellitus, 36.2% performed physical exercise at least twice a week, 3.7% reported regular alcohol intake, 10.9% had a history of angina, 6.5% presented with myocardial infarction, and 5% experienced coronary revascularisation. Other associated diseases were heart failure in 7.3% of patients, stroke in 7.5%, and renal failure in 6.1%. Of the patients included in the study, 37.4% were obese based on BMI, and 75.8% were obese based on waist circumference. The prevalence of AF was 10.3% (9.2% in women and 11.5% in men), with 6.7% evidencing AF when an electrocardiogram (ECG), was performed and the other 3.6% having a history of AF, but at the time of analysis, experiencing sinus rhythm. Additionally, 1.7% of patients had no history of AF but were currently experiencing this arrhythmia. The laboratory, electrocardiographic and treatment data are included in Table 1.

### BP control and treatment in the study population

The mean duration of HT in the overall sample was 10.9 ± 8.2 years, and 35.3% of the patients were treated according to the BP measured at the clinic, whereas 50.9% were treated according to the BP determined by ABPM. The mean BP measured at the clinic was 146.7/81.1 mmHg and determined by ABPM was 128.5/70.8 mmHg. Only 6% of the patients were not being treated with antihypertensive drugs, 35.6% were taking a single drug, 35.6% were taking two, and 22.7% were taking three or more.

**Table 1 Baseline characteristics of the study population, including biochemical, electrocardiogram and treatment data (mean ± SD) *n* (%)**

| Characteristics | Data |
|---|---|
| WBC, mm$^3$ | 6727 ± 1774 |
| Haemoglobin, g/dL | 13.6 ± 1.8 |
| Glucose, mg/dL | 108 ± 31 |
| LDL-cholesterol, mg/dL | 118 ± 34 |
| Triglycerides, mg/dL | 129 ± 73 |
| Uric acid, mg/dL | 5.2 ± 1.1 |
| Creatinine, mg/dL | 0.97 ± 0.28 |
| Glomerular filtration rate, mL/min | 75 ± 22.5 |
| Albumin/creatinine ratio | 39.4 ± 109.8 |
| Heart rate, bpm | 71.7 ± 14 |
| Normal QRS | 794 (77.2) |
| Q waves | 25 (2.4) |
| Sokolow LVH | 15 (1.5) |
| Cornell LVH | 103 (10) |
| Strain | 84 (8.2) |
| Global LVH | 177 (17.2) |
| Measurement of anti-HT | 1.7 ± 0.87 |
| Diuretics | 535 (52.1) |
| Beta-blockers | 240 (23.4) |
| Calcium antagonists | 199 (19.4) |
| ACEI | 265 (25.8) |
| ARB | 611 (59.5) |
| Antiplatelet agents | 196 (19.1) |
| VKA | 72 (7.0) |
| No anti-HT drugs | 62 (6) |
| Monotherapy | 366 (35.6) |
| 2 drugs | 366 (35.6) |
| 3 or more anti-HT drugs | 234 (22.7) |

WBC: White blood cell; LVH: Left ventricle hypertrophy; HT: Hypertension; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; VKA: Vitamin K antagonist; LDL: Low-density lipoprotein.

**Table 2 Epidemiological, clinical and therapeutic differences between genders (mean ± SD) *n* (%)**

| | Females (*n* = 542) | Males (*n* = 486) | *P* value |
|---|---|---|---|
| Mean age, yr | 72.7 ± 5.8 | 72.8 ± 5.8 | NS |
| Abdominal circumference, cm | 96.6 ± 11.8 | 100.4 ± 11.0 | < 0.001 |
| Weight, kg | 71.4 ± 11.5 | 79.5 ± 11.5 | < 0.001 |
| Mean height, cm | 155.2 ± 6.7 | 166.7 ± 6.7 | < 0.001 |
| BMI | 29.6 ± 4.5 | 28.6 ± 3.6 | < 0.001 |
| Obesity | 224 (41.4) | 160 (32.9) | 0.005 |
| Years from the onset of HT | 11.0 ± 8.2 | 10.8 ± 8.1 | NS |
| Diabetes mellitus | 134 (24.7) | 150 (30.9) | 0.03 |
| Dyslipidaemia | 267 (49.3) | 230 (47.3) | NS |
| Smokers | 17 (3.1) | 76 (15.6) | < 0.001 |
| Sedentariness | 352 (70.5) | 274 (56.4) | < 0.001 |
| Regular alcohol intake | 5 (0.9) | 33 (6.8) | < 0.001 |
| History of stroke | 32 (6.0) | 32 (6.7) | NS |
| History of IHD | 55 (10.1) | 124 (25.5) | < 0.001 |
| History of HF | 35 (6.5) | 39 (8.1) | NS |
| History of renal insufficiency | 24 (4.5) | 38 (7.9) | 0.025 |
| Peripheral arterial disease | 15 (2.7) | 37 (7.7) | 0.001 |
| Carotid disease | 2 (0.4) | 13 (2.8) | 0.003 |
| Atrial fibrillation | 50 (9.2) | 56 (11.5) | NS |
| CHADS ⩾ 2 | 275 (50.7) | 272 (56.0) | NS |
| LVH by ECG | 111 (20.5) | 66 (13.6) | 0.004 |
| LVH_Sokolow | 6 (1.1) | 9 (1.9) | NS |
| LVH_Cornell | 91 (16.8) | 12 (2.5) | < 0.001 |
| Mean HR, bpm | 75.4 (10.7) | 72.1(10.7) | < 0.001 |
| Mean number of anti-HT | 1.7 ± 0.87 | 1.8 ± 1.0 | NS |
| Diuretics | 304 (56.1) | 226 (46.5) | 0.002 |
| Beta-blockers | 105 (19.4) | 98 (20.2) | NS |
| Calcium antagonists | 93 (17.2) | 80 (16.5) | NS |
| ACEI | 118 (21.8) | 128 (26.3) | NS |
| ARB | 318 (58.7) | 294 (60.5) | NS |
| Antiplatelet agents | 90 (16.6) | 112 (23.0) | 0.012 |
| VKA | 33 (6.1) | 32 (6.6) | NS |

BMI: Body mass index; IHD: Ischaemic heart disease; HF: Heart failure; LVH: Left ventricle hypertrophy; HR: Heart rate; HT: Hypertension; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; VKA: Vitamin K antagonist. NS: No significant.

### Gender differences

Table 2 shows the differences between the men and the women in epidemiological, biochemical, BP and therapeutic characteristics. The women exhibited more obesity, greater sedentariness, a higher systolic and diastolic BP in the first clinic measurement, a higher heart rate, a higher percentage of BP control during ABPM (55.7% in women *vs* 45.7% in men, $P < 0.001$), and higher HDL-cholesterol values (56.1 ± 13.5 in women *vs* 49.4 ± 15.1 in men, $P < 0.001$). In addition, the women had a higher percentage of LVH, as determined by ECG (Cornell voltage criterion), and more frequently used diuretics than the men. In contrast, the men exhibited a greater abdominal circumference and a higher prevalence of a history of diabetes, active smoking, alcohol consumption, ischaemic heart disease, peripheral arterial disease, renal disease, and carotid disease. Regarding the control of BP at the clinic, this parameter was higher in the men (39.9% in men *vs* 31.2% in women, $P = 0.004$), who also had higher uric acid values and more frequently used anti-aggregation drugs. There were no differences in the presence of AF; the use of other antihypertensive treatments, such as beta-blockers, ARA-2, and ACEIs; or other biochemical data, including blood sugar, total cholesterol, LDL-cholesterol, triglycerides and creatinine levels and GFR.

### AF-related risk factors

No significant interactions were determined between gender and other clinical features in AF patients (Table 3). However, the presence of AF in the total study population was associated with age, with a 10% increase in AF prevalence per year; alcohol intake; previous heart disease; and GFR reduction.

In the gender-specific multivariate analysis, the presence of AF in the women was related to all of the overall analysis factors, in addition to the presence of strain in the ECGs (associated with LVH). In contrast, there was no association between AF and regular alcohol intake. In the men, unlike in the women, AF was only associated with age, the presence of heart disease (ischaemic or heart failure or both), and regular alcohol intake. The multivariate analysis was accurately calibrated [$P$ = no significant (NS) and $\chi^2 = 16.5$] and had discriminative power (for the total study population, an area under the curve of 0.78, 95%CI: 0.74-0.83, and $P < 0.01$; for the analysis of the men only, an area of under the curve of 0.75,

**Table 3 Independent predictors of global atrial fibrillation in the total study population and in subgroups according to gender**

| Variable | Total OR (95%CI) | Females OR (95%CI) | Males OR (95%CI) |
|---|---|---|---|
| Age, yr | 1.1 (1.1-1.1) $P < 0.001$ | 1.1 (1.1-1.1) $P = 0.010$ | 1.1 (1.03-1.13) $P = 0.003$ |
| Alcohol abuse | 5.2 (2.1-12.2) $P = 0.001$ | 7.0 (0.6-82.9) NS | 4.2 (1.5-11.4) $P = 0.005$ |
| Heart disease | 4.7 (3.0-7.5) $P < 0.001$ | 6.1 (3.1-12.4), $P < 0.001$ | 3.4 (1.9-6.2) $P < 0.01$ |
| GFR, mL/min per $m^2$ | 0.98 (0.97-0.99) $P = 0.027$ | 0.98 (0.96-0.99) $P = 0.039$ | 0.99 (0.9-1.0) NS |
| Strain on ECG | 1.8 (0.9-3.4) $P$ = NS | 2.97 (1.1-8.1) $P = 0.032$ | 1.2 (0.53-2.81) NS |

Multivariate analysis: Age, gender, body mass index, physical exercise, alcohol use, time from the onset of hypertension, clinical blood pressure, 24-h ambulatory blood pressure monitoring result, family history of early cardiovascular disease, diabetes, smoking, obesity, dyslipidaemia, abdominal obesity, left ventricular hypertrophy, atherosclerotic plaque, renal damage, coronary disease, heart failure, renal disease, and treatment type. GFR: Glomerular filtration rate; ECG: Electrocardiogram; NS: No significant.

95%CI: 0.68-0.81, and $P < 0.01$; and for the analysis of the women only, an area under the curve of 0.82, 95%CI: 0.76-0.88, and $P < 0.01$).

### *Treatment differences in patients with AF*

Regarding the treatment of patients diagnosed with AF (Table 4), statistically significant differences were observed between the men and the women in their use of calcium antagonists (8.9% *vs* 30%, respectively; $P = 0.007$) and antiplatelet agents (26.8% *vs* 8%, respectively; $P = 0.01$). The rates of use of antiplatelet agents and anticoagulants was higher in the men than in the women, although this disparity was also not significant (71.4% *vs* 66%, respectively; $P$ = NS).

After stratification according to the $CHADS_2$ calculated score in patients with AF, we observed that the women and men had a similar rate of using oral anticoagulation therapy in all degrees of $CHADS_2$, except in $CHADS_2 = 2$, in which the use of anticoagulation therapy in the women was nearly double the use in the men (Figure 1).

## DISCUSSION

This study is one of the few in our country that analysed the prevalence of AF[5] and epidemiological differences by gender in a hypertensive population of over 65 years of age visiting outpatient clinics. The AF prevalence determined here (10.3%) is the same as the prevalence in another national registry, the CARDIOTENS 2009, which reported AF in 10.22% of patients with cardiovascular disease or other risk factors and in 6.22% of patients in the overall sample of the registry[14]. These data are equal to twofold the prevalence reported in 1999[15], which did not include patients diagnosed "*de novo*" by ECG, and are

**Table 4 Treatment differences between genders in patients with atrial fibrillation ($n = 106$) $n$ (%)**

| | Females ($n = 50$) | Males ($n = 56$) | $P$ value |
|---|---|---|---|
| Diuretics | 34 (68.0) | 30 (53.6) | NS |
| Beta-blockers | 16 (32) | 17 (30.4) | NS |
| Calcium antagonists | 15 (30) | 5 (8.9) | 0.007 |
| ACEI | 12 (24) | 14 (25) | NS |
| ARB | 32 (64) | 31 (55.4) | NS |
| Antiplatelet agents | 4 (8) | 16 (26.8) | 0.010 |
| VKA | 29 (58) | 25 (44.6) | NS |
| ATG or VKA | 33 (66) | 41 (71.4) | NS |

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; VKA: Vitamin K antagonist; ATG: Anti-aggregants. NS: No significant.

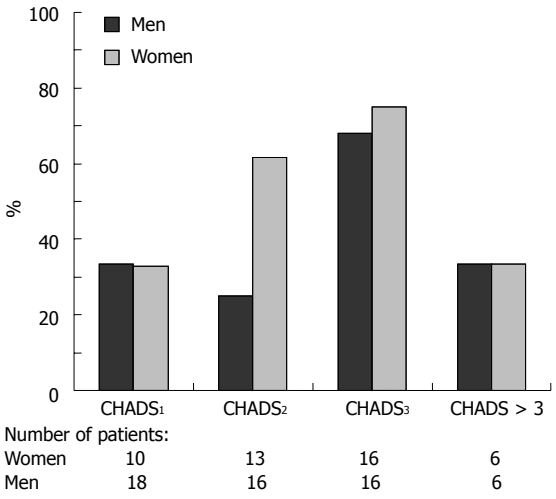


**Figure 1 Gender differences in the use of anticoagulation therapy between groups according to $CHADS_2$ score.**

slightly higher than the AF prevalence of 8.5% reported for the PREV-ICTUS registry, which analysed 7108 subjects of over 60 years of age[16]. The higher AF prevalence reported in the current study is likely due to the different mean age of the two study populations (72.8 years in the current study *vs* 71.9 years in the PREV-ICTUS study), the origin of the recruited patients (here, primary care and hypertension units), and the method of AF detection (here, presence in ECGs and history of AF).

Furthermore, in our study, we noted gender differences between the classic epidemiological factors. Women exhibited a higher prevalence of non-abdominal obesity, whereas men more frequently presented a history of diabetes; smoking; alcohol use; target-organ lesions; and established cardiovascular disease, such as ischaemic heart disease, peripheral arterial disease, and stroke. However, unlike in other studies[16], no significant differences were detected in the presence of AF between men and women, although a slight disparity was noted (11.5% in men *vs* 9.2% in women).

Regarding the risk factors related to the presence of AF in women, the involvement of the target organ, as in

the cases of LVH and renal dysfunction, and heart disease are significant conditions associated with this arrhythmia. In contrast, in men, excessive alcohol intake has a strong association with this condition, possibly due to the toxic effect of alcohol on the myocardium[17]. This knowledge can help clinicians to develop strategies to prevent AF in the hypertensive population. In women, our effort should be aimed at a greater control of BP to prevent the occurrence of lesions in target organs and of cardiovascular disease, whereas in men, the reduction of alcohol intake should be an additional objective, as described in other recent studies[18,19].

Moreover, an important finding of our study is the treatment differences between genders in patients with AF, and particularly differences in the use of antiplatelet agents and anticoagulants. Although the data were is not significant, we observed greater use in men, in contrast to the results obtained by Riesgo *et al*[20], who reported more frequent use in women. However, the patient profile of this prior study was different, as the subjects were recruited only from primary care, and the results were also not significant. Our results are similar to the findings of another recent report indicating higher rates of anticoagulation therapy use in men but no significant gender-related differences for other treatments[21]. Yet, when the population was stratified into groups based on $CHADS_2$ score, women with a score of 2 had a nearly twofold higher rate of using oral anticoagulants than men. One potential reason for this discrepancy is the perception that women have a higher incidence of stroke as a complication of the evolution of AF[22,23]. This perception could lead to the expectation that women receive anti-aggregation and anticoagulation more frequently than men, as recommended in the most recent practice guidelines published[24], in which the female gender is assigned one point on the new $CHADS_2$-$VAS_2C$ scale. Thus, hypothetically, if the practice guidelines were applied to this study, the rate of anticoagulant use in women should approach 100% if there is no contraindication (the $CHADS_2$-$VAS_2C$ score in the women included in this study was 3). One of the main limitations of this sub-study is that it was not specifically designed to analyse differences between genders. Additionally, the sub-study did not analyse the initial reason for a consultation to diagnose arrhythmia, which would have contributed to a better interpretation of the results. There also may be other unknown confounding factors related to practitioner preferences and guideline adherence, which could explain the presence or absence of gender-related differences. Finally, the nonrandomised selection of physicians and patients may reduce the external validity of the study.

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### *Appendix: fapres study researchers*

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## COMMENTS

### *Background*

The incidence of atrial fibrillation (AF) is important in the general population but is even more so in hypertensive patients. As atrial fibrillation increases cardiovascular risk, knowledge of the factors that are associated with this condition is highly clinically relevant. Furthermore, the incidence of atrial fibrillation in women is different than in men, and therefore, the factors associated with atrial fibrillation in women may also be different.

### *Research frontiers*

Risk factors related to the presence of atrial fibrillation are under investigation, as knowledge of these factors can aid the development of preventive strategies. The difference in risk between men and women is also being studied in the field of cardiovascular medicine.

### *Innovations and breakthroughs*

It is possible that the more aggressive treatment of these patients, particularly by administering cardiovascular drugs, could improve the patients' prognosis.

### *Applications*

The main application of this registry is to determine the risk factors associated with atrial fibrillation. By targeting these factors, we can avoid the development of this disease in both men and women, which has been little studied in large clinical trials.

### *Terminology*

AF is the most common cardiac arrhythmia (irregular heart beat). It may cause no symptoms, but it is often associated with palpitations, fainting, chest pain, or

congestive heart failure. However, in some people atrial fibrillation is caused by otherwise idiopathic or benign conditions. Hypertension or high blood pressure, arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. ROC curve, is a graphical plot which illustrates the performance of a binary classifier system as its discrimination threshold is varied. It is created by plotting the fraction of true positives out of the positives true positive rate (TPR) *vs* the fraction of false positives out of the negatives false positive rate (FPR), at various threshold settings. TPR is also known as sensitivity (also called recall in some fields), and FPR is one minus the specificity or true negative rate. Univariate analysis is the simplest form of quantitative (statistical) analysis. The analysis is carried out with the description of a single variable and its attributes of the applicable unit of analysis. For example, if the variable age was the subject of the analysis, the researcher would look at how many subjects fall into a given age attribute categories.

### Peer review

This study is one of the few in our country that analyses the prevalence of AF and the epidemiological differences by gender in a hypertensive population of over 65 years of age attended in outpatient clinics.

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BRIEF ARTICLE

# Association of the level of heteroplasmy of the 15059G>A mutation in the MT-CYB mitochondrial gene with essential hypertension

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## Abstract

**AIM:** To examine whether the heteroplasmy level for 15059G>A mutation in the mitochondrial genome might be associated with essential hypertension.

**METHODS:** This cross-sectional study involved 196 unrelated participants randomly selected from general population (90 males and 106 females) who underwent a regular medical check-up at the Institute for Atherosclerosis Research (Moscow, Russia). One hundred and twenty of them (61%) had essential hypertension, and 76 (39%) were apparently healthy normotensive persons. The level of heteroplasmy for 15059G>A mutation occurring in the coding region of cytochrome b gene (*MT-CYB*) of mtDNA isolated from the blood leukocytes, was quantified using DNA pyrosequencing method.

**RESULTS:** The 15059G>A heteroplasmy level ranged between 4% and 83%, with a median level of 31%. Between the upper and lower quartiles of 15059G>A heteroplasmy distribution, significant differences were observed for patients' age, systolic blood pressure, and triglyceride levels. 15059G>A heteroplasmy correlated both with age ($r$ = 0.331, $P$ < 0.001) and the presence of hypertension ($r$ = 0.228, $P$ = 0.002). Regression analysis revealed that the age explains 12% variability of 15059G>A heteroplasmy, and hypertension independently explains more 5% variability. The 15059G>A heteroplasmy exceeding 31% was found to be significantly associated with a higher risk of essential hypertension (odds ratio 2.76; $P$ (Fisher) 0.019]. The study participants with high 15059G>A heteroplasmy level were found to have significantly higher age ($P$ < 0.001) and the prevalence of essential hypertension ($P$ = 0.033), as compared to those with low 15059G>A heteroplasmy level. These observations suggested a positive correlation between the level of 15059G>A heteroplasmy and essential hypertension.

**CONCLUSION:** This study provides the evidence of association of mtDNA 15059G>A mutation heteroplasmy with essential hypertension.



**Key words:** Essential hypertension; Heteroplasmy; Mi-

tochondrial DNA; 15059G>A mutation

**Core tip:** The pathophysiology of essential hypertension (EH) is insufficiently understood; in particular, the impact of mitochondrial DNA mutations on the development of EH is poorly investigated. We undertook this study in order to see whether the level of heteroplasmy for the 15059G>A mutation in the mitochondrial cytochrome b gene might be associated with EH. The 15059G>A heteroplasmy level in mtDNA in blood leukocytes obtained from 196 study participants, randomly selected from general population (120 of whom had EH), exceeding 31%, was found to be significantly associated with a higher risk of EH.

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## INTRODUCTION

It is known that mutations in mitochondrial DNA (mtDNA) cause a variety of hereditary disorders with complex phenotypes including those that have hypertension as one of their clinical outcomes (such as the HUPRA syndrome comprising hyperuricemia, metabolic alkalosis, pulmonary hypertension, and progressive renal failure in infancy)[1].

Essential hypertension (EH), that represents a common form of hypertension, is a highly polygenic pathological condition which is caused by a combination of small-scale changes in the expression of many genes, in conjunction with a variable collection of environmental factors[2-4]. To the date, in total, 14 independent chromosome loci have been recognized for blood pressure traits that reached genome-wide significance including replication in independent cohorts[2]. Nevertheless, these variants explain just a very small fraction of the heritability of blood pressure traits[2]. Because chromosomal DNA variants exhibit only a modest effect in EH[2], it is impossible to exclude that, in contrast, somatic mtDNA mutations might importantly contribute to the development of hypertension and that a genetic predisposition to EH may be influenced by a ratio between mutated and wild-type mtDNA, *e.g.*, by heteroplasmy level. In support of this possibility, a non-redundant role of mtDNA heteroplasmy has been reported in human aging[5] and several age-related pathologic conditions including atherosclerosis[6,7], Alzheimer's disease[8], and diabetes[9]. It has been also reported that the entire mtDNA sequencing in United States pedigrees of African and European descent allowed to identify significant changes in the mtDNA sequence of hypertensive probands, which implies a potential role of mtDNA mutations in EH[10]. To the date, the role of somatic mtDNA mutations in EH is poorly studied and poorly understood. Therefore, it is obvious that any report dealing with the consideration of the involvement of mtDNA sequence alterations in hypertension may represent interest for further understanding of "genetic roots" and the mechanisms of the development of EH.

Initially, a G-to-A mutation at nucleotide 15059 of the mtDNA sequence was described in a patient with mitochondrial myopathy[11]. It has been established that G-to-A mutation occurs as a result of replacement of glycine at amino acid position 190 of mitochondrial cytochrome b with a stop codon leading to a truncated protein that misses 244 amino acids at the C-terminus of cytochrome b[12]. Earlier it was shown that 15059G>A heteroplasmy is associated with fibro-fatty atherosclerotic plaques which suggests a potential involvement of 15059G>A heteroplasmy in atherosclerosis[6,7]. In the present report, we proved the results of a study that involved an analysis of 196 randomly selected individuals which indicate an association of this mtDNA mutation with EH.

## MATERIALS AND METHODS

### Patients

This study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. All participants gave their written informed consent prior to their inclusion in the study, and the protocol was approved by the ethics committee of the Institute for Atherosclerosis Research, Moscow, Russia.

The study involved 196 unrelated patients (90 males and 106 females) who underwent a regular medical check-up at the Institute for Atherosclerosis Research, Moscow. On admission, a careful analysis of history was taken with special attention to cardiovascular risk factors, including a family history of cardiovascular diseases.

EH was diagnosed according to the European Society of Hypertension and the European Society of Cardiology classifications[13]. The presence of concomitant coronary heart disease (CHD) was evaluated according to American College of Physicians/American College of Cardiology Foundation/American Heart Association guidelines[14]. Standard 12-lead echocardiography was used for the diagnosis of left ventricular hypertrophy (LVH)[13]. Myocardial infarction (MI) was diagnosed according to the joint criteria of the Expert Consensus Document[15].

### Biochemical measurements

The venous blood for lipid analysis was taken after overnight fasting. To obtain serum, the blood was incubated for 1 h at 37 ℃ and centrifuged for 15 min at 1500 *g*, and serum was stored at -70 ℃. Serum concentrations of cholesterol and triglycerides were measured by enzymatic method using commercially available kits (Analyticon Biotechnologies AG, Germany)[16]. High density lipoprotein (HDL) cholesterol was measured enzymatically in

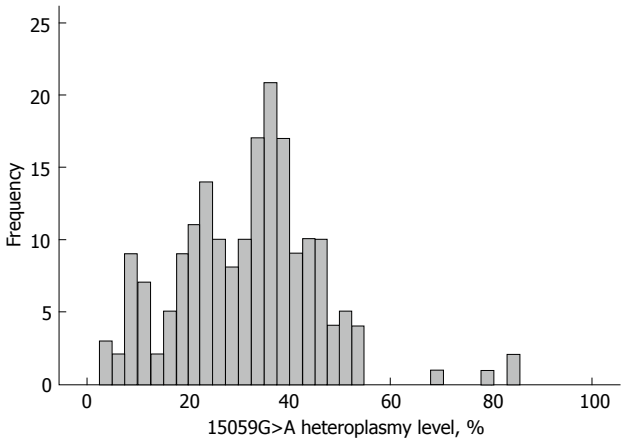


**Figure 1 A frequency distribution histogram of the mtDNA 15059 G>A mutation heteroplasmy level in 191 studied individuals.** The bell-shaped curve represents the expected normal frequency distribution of the mutated allele.

the supernatant after the precipitation of apolipoprotein B-containing lipoproteins[17], and low density lipoprotein (LDL) cholesterol were calculated using the Friedewald formula[18].

### DNA analysis

Mitochondrial DNA was isolated with the Aquapure Genomic Tissue Kit (Bio-Rad Laboratories, Hercules, CA, United States) according to the manufacturer's protocols. The heteroplasmy level of the mtDNA mutation 15059G>A was quantified by the pyrosequencing method using the automated pyrosequencing machine PSQ HS96MA (Pyrosequencing AB, Uppsala, Sweden). Briefly, a 450-bp polymerase chain reaction (PCR) fragment of mtDNA was amplified using forward primer 5'-Bio-CATTATTCTCGCACGGACT-3' and reverse primer 5'-GCTATAGTTGCAAGCAGGAG-3' and then sequenced using the primer 5'-TTTCTGAGTAGAGAAATGAT-3'. The quantitative assay of the mutant allele 15059A was performed by peak height analysis of the pyrogram in the studied domain of a single strand PCR fragment of the mitochondrial genome as previously described[6]. Primers were synthesized by Syntol (Moscow, Russia).

### Statistical analysis

Data were analyzed using a software package SPSS 14.0 (SPSS Inc., Chicago, IL, United States). The comparisons of mean values were performed by the Mann-Whitney *U*-test for continuous variables, and by chi-square Pearson's test for categorical variables. The data are presented in terms of mean and SD. The normality of the 15059G>A heteroplasmy distribution was estimated from normal probability plots and by the Shapiro–Wilk *W*-test[19]. Quartiles with their confidence intervals (CI) were computed according to Aczel[20] and Conover[21] and analyzed by *t*-test. Odds ratios (OR) and their 95%CI were calculated using the Calculator for Confidence Intervals of OR[22]. Two-tailed Fisher's exact test was used to examine whether the 15059G>A heteroplasmy level is associated with EH. The significance of differences was defined at the 0.05 level of confidence.

**Table 1 Antropometric, clinical and biochemical characteristics of study participants (mean ± SD) *n* (%)**

| Characteristics | |
|---|---|
| Age, yr | 65.1 ± 9.8 |
| BMI, kg/m$^2$ | 26.2 ± 4.7 |
| SBP, mm/Hg | 138 ± 19 |
| DBP, mm/Hg | 83 ± 9 |
| Cholesterol, mg/dL | 234 ± 49 |
| TG, mg/dL | 125 ± 70 |
| HDL cholesterol, mg/dL | 66 ± 11 |
| LDL cholesterol, mg/dL | 143 ± 47 |
| EH | 120 (61) |
| LVH | 53 (27) |
| CHD | 45 (23) |
| Type 2 diabetes | 23 (12) |
| Myocardial infarction | 8 (4) |
| Family history of EH | 75 (38) |
| Family history of myocardial infarction | 51 (26) |

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; CHD: Coronary heart disease; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

## RESULTS

The characteristics of study participants are presented in Table 1. Of 196 participants, 120 (61%) and 45 (23%) had clinically manifested EH and CHD, respectively. Compared to 76 normotensive subjects, hypertensive patients were significantly older [66.3 (SD 8.7) *vs* 62.1 (SD 9.0) years, $P < 0.001$], had higher systolic blood pressure [systolic blood pressure (SBP) 147 (SD 16) *vs* 127 (SD 13) mmHg, $P < 0.001$], elevated plasma triglycerides [127 (SD 55) *vs* 112 (SD 47) mg/dL, $P < 0.001$], and had a more frequent family history of EH (45% *vs* 28%, $P = 0.034$). Compared to 151 CHD-free study participants, CHD patients exhibited no significant differences in clinical characteristics, except for age [69.9 (SD 8.6) *vs* 63.4 (SD 9.1) years, respectively, $P < 0.001$].

The distribution histogram of the 15059G>A heteroplasmy level in 196 study participants is presented in Figure 1. The heteroplasmy percentage ranged between 4% and 83%, with a median level of 31%. Except for three samples, the 15059G>A heteroplasmy level fitted the normal distribution (Shapiro-Wilk *W*-test; $P = 0.18$), with a mean level of 30.4% (SD 17.9%).

Clinical characteristics of patients were compared using a quartile scale of the 15059G>A heteroplasmy level distribution, with the first quartile being the lowest, and the fourth quartile being the highest. Between the upper and lower quartiles, significant differences were observed for patients' age, SBP, and triglycerides (TG) levels (Table 2). However, there was no significant correlation between age and the level of SBP in the given sample ($r = 0.108$, $P = 0.2$). On the other side, 15059G>A heteroplasmy level correlated both with age ($r = 0.331$, $P < 0.001$) and the presence of hypertension ($r = 0.228$, $P = 0.002$). Regression analysis revealed that the age explains 12% variability of 15059G>A heteroplasmy level, and hypertension independently explains more 5% variability.

**Table 2 Antropometric, clinical and biochemical characteristics of study participants from the 1st and 2nd quartiles of distribution of 15059G>A heteroplasmy level *n* (%)**

| Characteristics | 15059G>A heteroplasmy level[1] | | *P* value |
|---|---|---|---|
| | Quartile 1 (*n* = 49) | Quartile 4 (*n* = 48) | |
| Age, yr | 60.1 ± 7.1 | 66.2 ± 9.9 | 0.001 |
| BMI, kg/m$^2$ | 26.4 ± 4.5 | 27.1 ± 5.1 | 0.41 |
| SBP, mm/Hg | 132 ± 18 | 143 ± 22 | 0.022 |
| DBP, mm/Hg | 83 ± 12 | 84 ± 12 | 0.50 |
| Cholesterol, mg/dL | 228 ± 42 | 243 ± 43 | 0.10 |
| TG, mg/dL | 112 ± 57 | 141 ± 61 | 0.021 |
| HDL cholesterol, mg/dL | 66 ± 14 | 68 ± 19 | 0.69 |
| LDL cholesterol, mg/dL | 140 ± 40 | 147 ± 44 | 0.44 |
| EH | 22 (45) | 30 (63) | 0.17 |
| LVH | 13 (27) | 13 (27) | 0.97 |

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

**Table 3 Antropometric, clinical and biochemical characteristics of coronary heart disease patients from the 1st and 2nd quartiles of distribution of 15059G>A heteroplasmy level *n* (%)**

| Characteristics | 15059G>A heteroplasmy level[1] | | *P* value |
|---|---|---|---|
| | Quartile 1 (*n* = 11) | Quartile 4 (*n* = 10) | |
| Age, yr | 63.2 ± 7.0 | 72.9 ± 8.7 | 0.011 |
| BMI, kg/m$^2$ | 27.2 ± 6.2 | 26.1 ± 5.9 | 0.69 |
| SBP, mmHg | 129 ± 22 | 153 ± 22 | 0.03 |
| DBP, mmHg | 80 ± 12 | 85 ± 13 | 0.32 |
| Cholesterol, mg/dL | 224 ± 54 | 236 ± 49 | 0.59 |
| TG, mg/dL | 130 ± 77 | 121 ± 56 | 0.78 |
| HDL cholesterol, mg/dL | 62 ± 15 | 69 ± 15 | 0.39 |
| LDL cholesterol, mg/dL | 136 ± 47 | 143 ± 42 | 0.69 |
| EH | 7 (64) | 7 (70) | 0.86 |
| LVH | 4 (36) | 4 (40) | 0.68 |

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

In the subgroup of CHD patients, significant differences between the upper and lower quartiles of 15059G>A heteroplasmy level were found for patients' age and SBP (Table 3). In CHD-free patients, significant differences between the upper and lower quartiles of 15059G>A heteroplasmy level remained for patients' age and TG levels (Table 4). Thus, in comparison with study participants who had a lower level of the 15059G>A heteroplasmy, the presence of CHD in those with higher heteroplasmy positively correlated with increased SBP but not with elevated serum TG.

Using a two-step cluster analysis, the 15059G>A heteroplasmy level was classified as "low heteroplasmy" and "high heteroplasmy". In the "high heteroplasmy" group, study participants were found to have significantly higher age ($P < 0.001$) and EH prevalence then those from "low heteroplasmy" group (Table 5). These observations suggest an association between the level of 15059G>A heteroplasmy and EH. The 15059G>A heteroplasmy level exceeding 31% was associated with increased risk of EH [OR =2.76, *P* (Fisher) = 0.019] (Table 6). The relative risk accounted for 1.47 (95%CI: 1.15-1.84; $P = 0.002$). The presence of CHD in study participants with high 15059G>A heteroplasmy seemed to further increase the risk for EH by ~1.2-fold but this association did not reach statistical significance [OR = 3.31, *P* (Fisher) = 0.18], obviously due to insufficient sample size.

## DISCUSSION

The pathophysiology of essential hypertension (EH) is insufficiently understood; in particular, the impact of mitochondrial DNA mutations on the development of EH is poorly investigated. We undertook this study in order to see whether the level of heteroplasmy for the 15059G>A mutation in the mitochondrial cytochrome *b* gene might be associated with EH. The 15059G>A heteroplasmy level in mtDNA in blood leukocytes obtained from 196 study participants, randomly selected from general population (120 of whom had EH), exceeding 31%, was found to be significantly associated with a higher risk of EH.

Compared to the nuclear DNA, mitochondria are known to lack the efficient DNA repair and protection

**Table 4 Antropometric, clinical and biochemical characteristics of CHD-free study participants from the 1st and 2nd quartiles of distribution of 15059G>A heteroplasmy level *n* (%)**

| Characteristics | 15059G>A heteroplasmy level[1] | | *P* value |
|---|---|---|---|
| | Quartile 1 (*n* = 38) | Quartile 4 (*n* = 37) | |
| Age, yr | 59.4 ± 7.2 | 64.7 ± 8.8 | 0.005 |
| BMI, kg/m$^2$ | 26.0 ± 4.0 | 27.4 ± 5.3 | 0.2 |
| SBP, mmHg | 132 ± 14 | 141 ± 21 | 0.17 |
| DBP, mmHg | 84 ± 11 | 84 ± 10 | 0.99 |
| Cholesterol, mg/dL | 231 ± 41 | 246 ± 47 | 0.14 |
| TG, mg/dL | 106 ± 46 | 147 ± 61 | 0.003 |
| HDL cholesterol, mg/dL | 67 ± 14 | 67 ± 18 | 0.99 |
| LDL cholesterol, mg/dL | 143 ± 37 | 150 ± 42 | 0.44 |
| EH | 15 (39) | 23 (62) | 0.19 |
| LVH | 10 (26) | 10 (27) | 0.98 |

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

**Table 5 Comparison of antropometric, clinical and biochemical characteristics of study participants from "low heteroplasmy" and "high heteroplasmy" groups *n* (%)**

| Characteristics | 15059G>A heteroplasmy level[1] | | *P* value |
|---|---|---|---|
| | Low (*n* = 99) | High (*n* = 97) | |
| Age, yr | 60.2 ± 8.4 | 68.6 ± 8.4 | < 0.001 |
| BMI, kg/m$^2$ | 26.3 ± 4.1 | 27.0 ± 5.0 | 0.52 |
| SBP, mmHg | 133 ± 16 | 142 ± 18 | 0.024 |
| DBP, mmHg | 82 ± 11 | 84 ± 11 | 0.39 |
| Cholesterol, mg/dL | 232 ± 48 | 241 ± 48 | 0.27 |
| TG, mg/dL | 118 ± 56 | 135 ± 62 | 0.065 |
| HDL cholesterol, mg/dL | 67 ± 14 | 66 ± 15 | 0.92 |
| LDL cholesterol, mg/dL | 141 ± 42 | 148 ± 44 | 0.49 |
| EH | 51 (52) | 69 (71) | 0.033 |
| LVH | 20 (20) | 33 (34) | 0.1 |

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

**Table 6 Association between the 15059G>A heteroplasmy level and essential hypertension prevalence**

| 15059G>A heteroplasmy level | No hypertension, *n* | Hypertension, *n* | Odds ratio (95%CI) | *P* value |
|---|---|---|---|---|
| Low (< 31%) | 51 | 51 | | |
| High (> 31%) | 25 | 69 | 2.76 (1.45-5.27) | 0.019 |
| Total | 76 | 120 | | |

systems[23]. Because of the large number of mitochondrial genome copies exist within each cell, a ratio of mutated to wild-type mtDNA that represents significant determinant of phenotype[24]. In a number of studies, including the analysis of a large Han Chinese pedigree with suggestively maternally transmitted hypertension, the role of homoplasmic, inherited mtDNA mutations in etiology of familial, maternally inherited forms of hypertension (MIH) has been acknowledged[3,25-29]. It is known that all homoplasmic mtDNA mutations which are associated with MIH cause functional defects[3,25-29]. The 4435A>G mutation which is located at 3' end to the anticodon (corresponding to the conventional position 37 of $tRNA^{Met}$) affects the fidelity of codon recognition, structural formation, and stabilization of functional tRNAs[27]. The 4263A>G mutation resided at the processing site for the $tRNA^{Ile}$ 5'-end precursor results in reduced efficiency of the $tRNA^{Ile}$ precursor 5'-end cleavage catalyzed by RNase P[28]. The 4401A>G mutation that is situated at the spacer immediately to the 5' end of $tRNA^{Met}$ and $tRNA^{Gln}$ genes causes a reduction in the steady-state levels of both mitochondrial tRNAs[25]. The 4295 A>G mutation, which is located at immediately 3' end to the anticodon, corresponding to conventional position 37 of $tRNA^{Ile}$, has a

functional effect similar to that of the 4435A>G mutation[3]. The mitochondrial hypertension-associated ND1 T3308C mutation that locates in two nucleotides which are located to be adjacent to the 3' end of mitochondrial $tRNA^{Leu}$ UUR has been shown to result in a change of the H-strand polycistronic RNA precursor processing as well as in the destabilization of ND1 mRNA[26]. Despite a high penetrance, these mutations are thought to be infrequent as such mutations were identified in just a few families. In relation to the 4263A>G mutation. This mutation was identified only in one family and was not detected in 49 other families with matrilineal hypertension[28].

The fact that we observed higher levels of the 15059G>A mutation heteroplasmy in the elderly is not unexpected and is formally consistent with a theory of aging purports[30]. According to this theory, reactive oxygen species (ROS), normally produced by mitochondrial respiration, affect mitochondria by causing oxidative damage to the mitochondrion membrane components and cytosolic elements[30-34]. This eventually leads to dysfunction and further production of ROS and an increase in mtDNA mutation[30-34]. An increase in the ratio of mutated to wild-type mtDNA in mitochondrial genes encoding the respiratory chain subunits might thus lead to reduced steady-state levels of respiratory chain proteins and respiratory chain deficiency.

It has been reported that the nonsense 15059G>A mutation affecting the mitochondrial cytochrome b results in the formation of an inactive truncated product lacking a pair of ubiquinol/ubiquinone-binding sites that is likely to uncouple the mitochondrial respiratory chain[11]. Practically all homoplastic mutations found in the *MT-CYB* gene have been found to lead to deleterious effects associated with the respiratory chain complex III deficiency in muscles and clinical presentation involving exercise intolerance[31]. For example, truncating mutations 15242G>A and 15761G>A in MT-CYB, which, similar to 15059G>A, result in loss of the last N-terminal amino acids of cytochrome b, were heteroplasmic and abundant (87% and 73% respectively) in affected tissue (skeletal muscle) but were rare (0.7%) or absent in unaffected tissue (blood) of patients with symptoms of mitochondrial myopathy[32,33]. The 15059G>A homoplasmy might lead to pathological consequences, and the severity of clinical outcomes caused by this mutation should correlate with the percentage of the mutated mtDNA[30-34]. However, compared to blood cells, effects of truncating heteroplasmic mutations in *MT-CYB* are likely to be more harmful in tissues involved in active mitochondrial glucose oxidation and high energy consumption such as skeletal muscle[30-34]. The information about the dynamic nature of mitochondria has been outlined in large number original studies and reviews[35-43]. The dynamic nature of mitochondria is a concept that includes the movement of mitochondria along the cytoskeleton, the regulation of mitochondrial architecture (morphology and distribution), and connectivity mediated by tethering and fusion/fission events[35]. This dynamic networks are essential in order to maintain normal mitochondrial functions and participate in key functional processes including development, metabolic efficiency, apoptosis, and aging[36].

One cannot exclude that a positive correlation between the high 15059G>A heteroplasmy and increased plasma TG levels in non-CHD patients, found in our study, may reflect an insufficient lipid intake in individuals with increased levels of the mutant allele 15059A. This may result from the reduced capacity of mutant mitochondria to metabolize fatty acids. Elevated plasma TG itself and a high TG/HDL-cholesterol ratio indicate an atherogenic lipid profile that predisposes to atherosclerosis and CHD[42,43]. Increased plasma TG were shown to predispose to CHD more strongly in the subsets of hypertensive patients[44,45]. This is in accordance with our observations that showed a high frequency of EH subjects in CHD-free patients who had the highest 15059G>A heteroplasmy levels.

There are no doubts that the present study has limitations. First of all, the sample size was rather small in order to detect significant differences in the level of 15059G>A heteroplasmy between EH-free individuals and EH patients. Secondly, the study participants with known EH were on treatment; and thirdly, although not all of them reached treatment goals, blood pressure levels were affected anyway. We have found an association of heteroplasmy both with the prevalence of EH and SBP, but not DBP. This difference was observed for the whole group of study participants; on the subdivision into CHD patients and CHD-free subjects, the difference in EH prevalence was not significant. The observed findings are not extremely big, and reliable statistical hints were applied: two-step cluster analysis was able to demonstrate an association of EH and G15059A heteroplasmy. It should also be noted that the sample was taken from ethnically heterogeneous population of Moscow inhabitants of senior and elderly ages. Therefore, at present there is insufficient evidence to interpolate the results of this study to other populations and age groups. Finally, the given study was cross-sectional, and the assessment of actual risk of EH due to the presence of a high level of 15059G>A heteroplasmy requires further prospective studies.

The precise mechanism by which 15059G>A mutation might affect in the development of EH is currently unknown. Earlier, Wang *et al*[28] showed that the homoplasmic 4263 A>G mutation in the *MT-T1* gene associated with familial MIH also involved in changes of codon AGA to AGG in *MT-ND1* gene coding for NADH dehydrogenase subunit 1 of the respiratory chain complex I . Functional assays have revealed that this mutation results in a marked reduction in substrate-dependent oxygen consumption reflective of complexes I , Ⅲ, and Ⅳ by 70%-80% and increased ROS levels in the lymphoblastoid cell lines derived from mutation carriers[28]. The 15059G>A mutation associated with a deficiency in the production and activity of mitochondrial cytochrome

b may contribute to EH involving a similar mechanism associated with defects in oxidative phosphorylation, reduced mitochondrial-dependent oxygen consumption, and increased ROS generation[28]. Elevated ROS levels may induce oxidative stress, which represents a ubiquitous risk factor for a variety of vascular diseases including EH[46]. There is a strong possibility that ROS may directly alter vascular function as well as may be responsible for changes in vascular tone by several actions, for example, altering nitric oxide (NO) bioavailability or signaling[46]. It is well known that a reduced bioavailability of NO represents one of the key processes by which endothelial dysfunction is manifested in hypertension[46]. As a result, an imbalance of counteracting mechanisms, designed to maintain vascular homeostasis, occurs and this leads to vasoconstriction, impaired vascular function, and chronic hypertension[47].

It is well known that a variety of cell types, including endothelial cells, smooth muscle cells, pericytes and dendritic cells reside in the intact vascular wall[48,49]. However, it is currently unknown in which cell type(s) of the vessel wall the mitochondrial 15059G>A mutation may exert its effects associated with EH. A quantification of the 15059G>A heteroplasmy in different vascular cells in autopsy samples derived from patients with chronically manifested EH should help with unraveling this puzzle. It is worth to noting here that an ultrastructural examination of arterial cells in a variety of vascular pathologies allowed to reveal that marked alterations in the structural appearance of mitochondria occur[50-52]. These alterations include a reduction in number of mitochondrial cristae and changes in electron density of mitochondrial matrix[50-52]. However, the question whether the structural alterations of mitochondria might reflect the presence of mitochondrial mutation(s) in these organelles requires further investigation.

In conclusion, the present study provides the evidence of mtDNA 15059G>A mutation heteroplasmy association with EH.

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BRIEF ARTICLE

# Mechanical breakdown and thrombolysis in subacute massive pulmonary embolism: A prospective trial

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Author contributions: Mohan B conceived the idea and performed mechanical breakdown and thrombolysis in these patients and guided the project; Chhabra ST involved in case selection, data analysis, procedural assistant and review of literature initially as a fellow in cardiology and then as assistant professor during the follow up phase; Verma S involved in case selection and review of literature as a medical intern; Sharma S involved in statistical analysis of data as an associate professor in department of social and preventive medicine; Aslam N, Sood NK and Wander GS associated team of interventional cardiologists who were actively involved in assisting the procedures and supervised the study; Mehra AK visited interventional cardiologist who assisted the cases and guided data analysis and the completion of the project.
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## Abstract

**AIM:** To assess role of combined modality of mechanical fragmentation and intralesional thrombolysis in patients with massive pulmonary embolism presenting subacutely.

**METHODS:** Eight of 70 patients presenting in tertiary care centre of North India with massive pulmonary embolism within 4 years had subacute presentation (symptom onset more than 2 wk). These patients were subjected to pulmonary angiography with intention to treat basis *via* mechanical breakdown and intra lesional thrombolysis. Mechanical breakdown of embolus was accomplished with 5-F multipurpose catheter to re-establish flow, followed by intralesional infusion of urokinase (4400 IU/kg over 10 min followed by 4400 IU/kg per hour over 24 h).

**RESULTS:** Eight patients, mean age 47.77 ± 12.20 years presented with subacute pulmonary embolism (mean duration of symptoms 2.4 wk). At presentation, mean heart rate, shock index, miller score and mean pulmonary pressures were 101.5 ± 15.2/min, 0.995 ± 0.156, 23.87 ± 3.76 and 37.62 ± 6.67 mmHg which reduced to 91.5 ± 12.2/min ($P$ = 0.0325), 0.789 ± 0.139 ($P$ = 0.0019), 5.87 ± 1.73 ($P$ = 0.0000004) and 27.75 ± 8.66 mmHg ($P$ = 0.0003) post procedurally. Mean BP improved from 80.00 ± 3.09 mmHg to 90.58 ± 9.13 mmHg ($P$ = 0.0100) post procedurally. Minor complications in the form of local hematoma-minor hematoma in 1 (12.5%), and pseudoaneurysm (due to femoral artery puncture) in 1 (12.5 %) patient were seen. At 30 d and 6 mo follow up survival rate was 100% and all the patients were asymptomatic and in New York Heart Association class 1.

**CONCLUSION:** Combined modality of mechanical fragmentation and intralesional thrombolysis appears to be a promising alternative to high risk surgical procedures in patients with subacute massive pulmonary embolism.



**Key words:** Mechanical breakdown; Subacute; Thrombolysis; Thromboembolic; Intra pulmonary; Catheter directed

**Core tip:** Patients with massive pulmonary embolism presenting subacutely (> 2 wk) have high mortality and older clots in these patients may be less amenable to thrombolysis with increased likelihood of recurrence and thromboembolic pulmonary hypertension. Eight of 70 patients with massive pulmonary embolism presenting subacutely were subjected to mechanical breakdown and intra lesional thrombolysis with urokinase (4400 IU/kg over 10 min followed by 4400 IU/kg per hour over 24 h). Post procedurally, patients documented significant improvement in hemodynamic parameters with 100% survival at 30 d and 6 mo followup. This modality appears to be a promising alternative to high risk surgical procedures in such patients.

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## INTRODUCTION

Massive pulmonary embolism (PE) is a life-threatening condition with a high early mortality rate due to acute right ventricular failure and cardiogenic shock[1-3]. In addition to the rapid initiation of anticoagulation therapy with intravenous (IV) unfractionated heparin, potentially life-saving therapy includes thrombolysis, surgical embolectomy, or catheter thrombectomy. The traditional window period for thrombolysis in patients presenting with acute massive pulmonary embolism is two weeks[4]. In the present review we propose another subset of patients with massive pulmonary embolism presenting subacutely (> 2 wk) who appear to benefit maximally with mechanical breakdown and thrombolysis. These patients presenting subacutely have high mortality and may not respond to standard anticoagulant or thrombolytic therapy with high likelihood of recurrence and development of thromboembolic pulmonary hypertension[5].

## MATERIALS AND METHODS

The present study has been conducted as an open non comparative prospective trial in the department of cardiology of our institution, a tertiary care centre in North India over a time span of four years (2007-2011). Approval for the same was obtained from ethical committee of the institute.

Eight of the 70 patients presenting with massive pulmonary embolism had subacute presentation with presenting symptoms of two to four weeks duration. Massive pulmonary embolism was defined as pulmonary arterial occlusion of more than 50% as confirmed by pulmonary angiographic score (Miller Index) and/or presence of hemodynamic impairment *i.e.*, mean pulmonary artery pressure > 25 mmHg and/or shock index > 1. Shock index equals heart rate divided by systolic systemic blood pressure.

After obtaining bed side transthoracic echocardiography to confirm the suspicion of pulmonary embolism, to estimate pulmonary arterial pressure and to exclude right atrial or ventricular thrombi, patients underwent emergent right heart catheterization and pulmonary angiography. Patients who showed a rapid deterioration of their cardiopulmonary condition were put on oxygen supplementation with noninvasive pressure support or intubation. Positive inotropic and vasoactive support with catecholamines was supplemented according to the patient's hemodynamic condition prior to right heart catheterization and pulmonary angiography.

The criteria for inclusion were patients who received emergency catheter directed intervention due to angiographically confirmed subacute massive PE (miller index > 0.6) with involvement of central pulmonary artery and hemodynamic shock defined as shock index (*i.e.*, heart rate/systolic blood pressure) score of > 0.8. Patients with acute presentation (< 2 wk) and those who were hemodynamically stable (shock index < 0.8) and sub massive PE (Miller index of < 0.6 and central pulmonary artery not involved) were excluded. Echocardiographic criteria for diagnosis of subacute PE were right ventricular (RV) wall thickness > 5 mm; tricuspid regurgitant jet velocity > 3.7 m/s; the occurrence of both a dilated RV cavity with normal interventricular septal motion; an inspiratory collapse of the inferior vena cava[6].

Informed, written consent was obtained. Under local anaesthesia, 5F femoral sheath was introduced in femoral vein for procedure. Initially with 5F multipurpose catheter, right heart study was performed and pulmonary artery pressure recorded. Subsequently, 5F multipurpose (cordis) catheter was used to obtain pulmonary angiogram after injecting 10-15 mL non ionic contrast dye with hand injection (Figure 1A). After confirming the diagnostic criteria, mechanical fragmentation was initiated; 0.35" guide wire was passed; multiple rotatory movements were given in embolus. Further mechanical breakdown was done with 5F multipurpose catheter and pig tail catheter (Figure 1B). The pig tail was kept inside the large significant embolus for urokinase therapy.

After ensuring flow across pulmonary artery; urokinase in dosage of 4400 IU/Kg body weight was given intralesional over 10 min and 4400 IU/kg per hour for 24 h through pig tail catheter kept in pulmonary artery. Follow up angiogram was done 24 h post procedure (Figure 1C). Patient's blood pressure and heart rate were monitored every hour. Clinical follow up and simultaneous hemodynamic data was obtained. Shock index was calculated on hourly basis. Technical success was defined as reduction in baseline miller index following treatment. Clinical success was defined as stabilization of hemodynamic parameters, resolution of shock, complete weaning off of inotropic support and survival until discharge from the hospital.

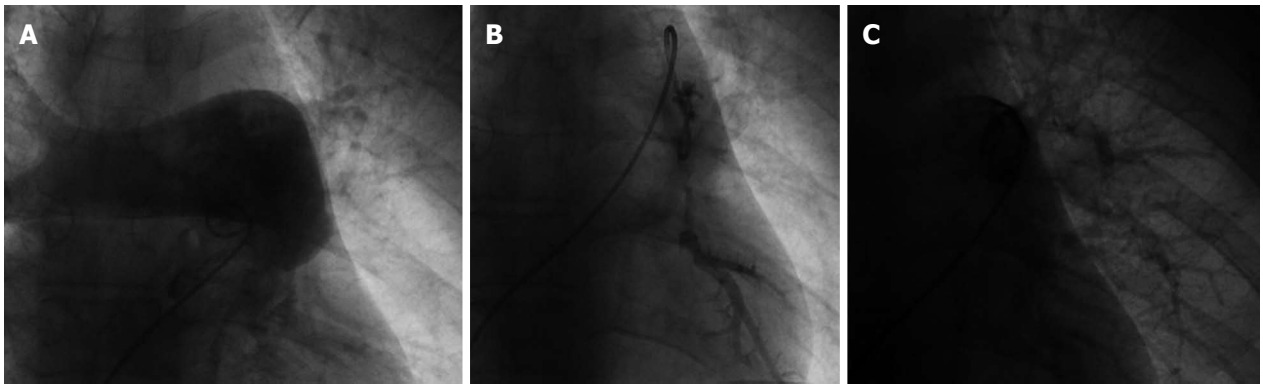


**Figure 1 Pulmonary angiography.** A: Total cut off of right pulmonary artery; B: Mechanical breakdown and intra pulmonary urokinase administration; C: Post procedural pulmonary angiography revealing restoration of pulmonary flow in right pulmonary artery and its branches.

**Table 1 Clinical profile and hemodynamic data of patients with subacute pulmonary embolism at presentation**

| No. | Duration | PA involved | PAP | | Mean PAP | | Heart rate | | BP | | Mean BP | | SI | | Miller score | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After | Before | After |
| 1 | 2 wk | RPA | 88/26/48 | 58/18 | 46 | 30.66 | 84 | 72 | 100/70 | 130/70 | 80 | 90 | 0.84 | 0.55 | 22 | 3 |
| 2 | 15 d | Both PA | 46/24/34 | 28/12 | 31.33 | 17.33 | 102 | 90 | 106/72 | 110/80 | 83.33 | 90 | 0.96 | 0.81 | 26 | 8 |
| 3 | 15 d | RPA occlusion | 70/30 | 60/30 | 43.33 | 40 | 102 | 110 | 110/70 | 120/80 | 83.33 | 93.33 | 0.92 | 0.91 | 22 | 5 |
| 4 | 15 d | B/L PE (TB) | 50/24 | 40/14 | 32.66 | 22.66 | 98 | 94 | 100/70 | 130/90 | 80 | 103.33 | 0.98 | 0.72 | 25 | 5 |
| 5 | 4 wk | B/L PTE | 89/20 | 68/20 | 43 | 36 | 122 | 96 | 100/70 | 100/70 | 80 | 80 | 1.22 | 0.96 | 26 | 8 |
| 6 | 3 wk | Clot at MPA | 50/70 | 28/10 | 30 | 16 | 102 | 90 | 100/70 | 130/90 | 80 | 103.33 | 1.02 | 0.69 | 25 | 7 |
| 7 | 2 wk | B/L main segment | 78/25 | 50/24 | 42.66 | 32.66 | 122 | 102 | 100/70 | 110/70 | 80 | 83.33 | 1.22 | 0.92 | 28 | 6 |
| 8 | 2 wk | B/L | 56/20 | 50/15 | 32 | 26.66 | 80 | 78 | 100/60 | 104/70 | 73.33 | 81.33 | 0.8 | 0.75 | 25 | 5 |

PA: Pulmonary artery; MPA: Main pulmonary artery; RPA: Right pulmonary artery; PAP: Pulmonary arterial pressure; Mean PAP: Mean pulmonary arterial pressure; BP: Blood pressure; Mean BP: Mean blood pressure; SI: Shock index; PE: Pulmonary embolism; B/L: Bilateral; PTE: Pulmonary thromboembolism; TB: Tuberculosis.

Miller index was used to calculate the angiographic scores for the degree of pulmonary embolism[7]. The Miller score is composed of an objective score for arterial obstruction and a subjectively determined score for reduction of peripheral perfusion. The right pulmonary artery is assigned 9 and the left is assigned 7 segmental arteries. Partial or complete occlusion of a segmental artery receives a point score of 1. Proximal pulmonary embolism is scored equal to the number of segmental arteries arising distally according to the anatomic subdivisions. The maximal score for obstruction is 16. Reduction of peripheral perfusion is scored by dividing each lung into upper, middle and lower zones and using a four point scale. Maximal score of reduced perfusion in both lungs is 18. The maximal Miller score for both lungs is 34. A Miller score of 17 or more indicates a greater than 50% obstruction of pulmonary vascular bed and forms an angiographic definition of a massive PE. The Miller index is Miller score divided by 34 (range 0.0 to 1.0)[8].

The Miller index was recorded in our study at the time of initial pulmonary angiogram and after 24 h of urokinase infusion. Major procedural complications were defined as: hemorrhage requiring transfusion, perforation of cardiopulmonary structures, anaphylaxis from contrast injection, arrhythmias with hemodynamic decompensation (blocks), worsening pulmonary artery hypertension, hypoxia or shock and/or death during the procedure.

Minor complications were defined as transient catheter-induced arrhythmia, mild contrast reactions, catheter-related infection and small hematomas not requiring transfusion. Major hematoma was defined as hematoma requiring one or more blood transfusion. Minor hematoma was defined as spontaneously resolving hematoma not requiring blood transfusion. The data was analyzed using students t test for comparison of paired samples. A $P$ value of $< 0.05$ was considered to be statistically significant.

## RESULTS

Over the span of four years, 70 patients presented with massive pulmonary embolism of whom 8 (11.43%) presented subacutely (2-4 wk). There were 6 males and 2 females and the average age of patients was 47.77 ± 12.20 years. The average duration of symptoms prior to presentation in emergency was 2.4 wk (range: 2-4 wk). All the patients had tachycardia (heart rate > 100/min) and tachypnoea at the time of presentation (Table 1).

Catheter directed mechanical breakdown combined with intraembolus thrombolysis with urokinase was performed in all cases with subacute massive PE. There was a statistically highly significant fall in mean pulmonary

**Table 2 Statistical analysis of hemodynamic parameters of patients**

| | PAP | | HR | | BP | | SI | | Miller score | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After | Before | After |
| mean ± SD | 37.62 ± 6.67 | 27.75 ± 8.66 | 101.5 ± 15.2 | 91.5 ± 12.2 | 80.00 ± 3.09 | 90.58 ± 9.13 | 0.995 ± 0.156 | 0.789 ± 0.139 | 23.87 ± 3.76 | 5.87 ± 10.73 |
| mean ± SE | 37.62 ± 2.4 | 27.75 ± 3.1 | 101.5 ± 5.4 | 91.5 ± 4.3 | 80.00 ± 1.1 | 90.58 ± 3.2 | 0.995 ± 0.055 | 0.789 ± 0.049 | 23.87 ± 1.3 | 5.87 ± 0.61 |
| *t* | 6.346 | | 2.659 | | 3.499 | | 4.809 | | 17.686 | |
| *P* | 0.0003 | | 0.0325 | | 0.0100 | | 0.0019 | | 0.000000 | |
| df | 7 (highly significant) | | 7 (significant) | | 7 (significant) | | 7 (highly significant) | | 7 (highly significant) | |

PAP: Pulmonary arterial pressure; BP: Blood pressure; SI: Shock index; HR: Heart ratio.

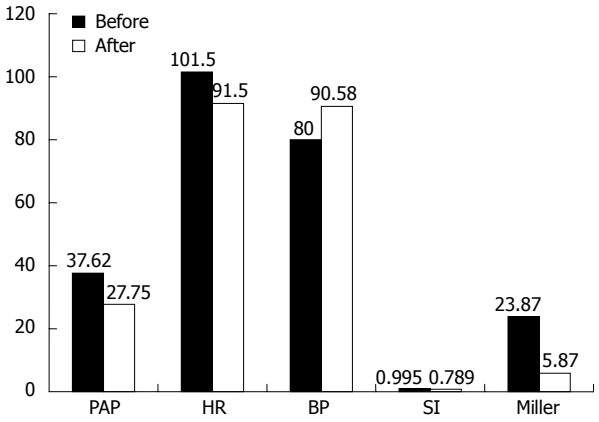


**Figure 2 Hemodyamic parameters of 8 patients with subacute pulmonary embolism at presentation and 24 h post procedure.** Highly significant improvement in mean pulmonary artery pressure (PAP), stroke index (SI) and millers index and significant improvement in heart rate (HR) and blood pressure (BP) post procedure.

artery pressure from 37.62 ± 6.67 to 27.75 ± 8.66 mmHg ($P$ = 0.0003) 24 h post procedure, Mean systemic blood pressure rose significantly from 80.00 ± 3.09 mmHg to 90.58 ± 9.13 mmHg post procedure ($P$ = 0.0100), The arterial oxygen saturation showed significant rise from base line levels 88.5% ± 2.8% to 98.6% ± 2.07% ($P$ < 0.001). The mean heart rate prior to procedure was 101.5 ± 15.2 beats per minute. Twenty-four hours post procedure it showed a significant decrease to 91.5 ± 12.2 bpm ($P$ = 0.0325). There was a highly significant fall in mean shock index from 0.995 ± 0.156 prior to procedure to 0.789 ± 0.139 ($P$ = 0.0019) post procedurally. The 2 hourly change in shock index was also recorded. It was found that shock index continued to decrease up to 24 h with significant abrupt fall within first 8 h. The decrease in Miller score was highly significant when check pulmonary angiography was performed after 24 h [23.87 ± 3.76 to 5.87 ± 1.73 pre procedure ($P$ = 0.0000004)] after 24 h (Table 2 and Figure 2).

Minor complications in the form of local hematoma-minor hematoma in 1 (12.5%), and pseudoaneurysm (due to femoral artery puncture) in 1 (12.5%) patient were seen.

All the patients were discharged on oral anticoagulants. At 30 d and 6 mo of follow up survival rate was 100% and all the patients were asymptomatic and in New York Heart Association class 1.

## DISCUSSION

Pulmonary embolic disease can present in many ways ranging from mild pleuritic pain to sudden fatal collapse. Since the presentation is so varied, classification of these patients into different clinical subgroups using the history, echocardiography and pulmonary angiographic findings is needed before possible differences in clinical course, response to treatment, and late prognosis can be considered[9].

Major pulmonary embolism occurring insidiously over several weeks (subacute massive pulmonary embolism) has a high mortality and may not respond well to standard anticoagulant or thrombolytic treatment[5]. Treated acute massive pulmonary embolism has a good long-term prognosis[3,10-12], and recurrent pulmonary embolism, poor resolution of pulmonary artery obstruction, and the development of pulmonary hypertension are extremely rare[13,14]. This is not surprising since most of these patients have welldefined and often temporary factors predisposing to embolism, the embolus is of recent formation, and it is susceptible to both therapeutic and natural lysis. In contrast, in subacute massive pulmonary embolism the predisposing factor is often unknown and potentially might continue to operate after initial treatment, causing recurrence of emboli. Furthermore, older clot, accumulated in the pulmonary circulation over a period of weeks, might be expected to lyse less easily. If so, thromboembolic pulmonary hypertension ought to be more likely to develop in subacute rather than in acute massive pulmonary embolism. Henceforth in this subset of patients presenting subacutely, mechanical breakdown and intrapulmonary thrombolysis might be more effective than usual intravenous thrombolysis or anticoagulation. In patients with subacute PE, with hypotension and borderline hemodynamics, systemic thrombolysis might not be possible making local thrombolysis with mechanical breakdown an attractive possibility. Moreover, mechanical breakdown might be less invasive and score over the traditional surgical approach (thromboendarterectomy) for these patients.

The thrombolytic employed in our study, urokinase (UK), specifically catalyzes the cleavage of the Arg-Val bond in plasminogen to form plasmin which breaks down the fibrin polymers of blood clots. Among the plasminogen activators, UK provides a superior alternative for the simple reasons of it being more potent

as compared to tissue-plasminogen activator and non-antigenic by virtue of its human origin unlike streptokinase[15]. Weitz *et al*[16] in a study found that UK has direct catalytic activity against fibrinogen and renders it less clottable by thrombin by releasing fibrinopeptide B, a potent chemoattractant. Henceforth they concluded that urokinase may participate in processes extending beyond fibrinolysis, a property which might especially be relevant in our patients with subacute PE and relatively older thrombus in process of organization. Moreover in a randomized controlled multicenter trial of recombinant tissue plasminogen activator[17] (rt-PA) versus urokinase in the treatment of acute pulmonary embolism, Goldhaber *et al*[3] found that despite rapid clot lysis at 2 h by rt-PA; at 24 h both drug regimens had produced equally good reperfusion. Also, in terms of cost and availability in developing nations UK might be a preferred option.

In our study significant reduction in shock index, Miller index and mean pulmonary artery pressure was recorded in 8 patients 24 h post procedure. The hemodynamic improvement recorded was maximum in first 8 h after procedure, though the improvement continued to occur over period of 24 h. At 6 mo of follow up survival rate was 100% and all the 8 patients were asymptomatic. The proposed mechanisms of early rapid hemodynamic improvements in our patients could be increased exposure of fibrin on clot surfaces caused by fragmentation accelerating the thrombolytic action. Also when there is total occlusion of pulmonary artery occlusion by an embolus, any fluid infused will theoretically make only evanescent contact with thrombus and be washed into the non occluded ipsilateral and contralateral pulmonary artery. After fragmentation, infused thrombolytics will have greater contact with the distal thrombus throughout the pulmonary arterial tree. This especially could be helpful in patients with subacute PE in whom older clot, accumulated in the pulmonary circulation over a period of weeks, might be expected to lyse less easily. Moreover 5F multipurpose and then pigtail catheter was employed in our study for mechanical fragmentation of this organizing old clot, which could be an added advantage[18-21].

The consensus statement recommends IV fibrinolytic therapy for patients with massive PE with low risk of bleeding complications (class IIa; level of evidence B) and for patients with submassive PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications (class IIb; level of evidence C). Fragmentation of clot in the main or lobar pulmonary arteries to restore pulmonary perfusion alone or followed by local thrombolysis is an alternative for patients with massive PE and contraindications to fibrinolysis or who remain unstable after receiving fibrinolysis (class IIa; level of evidence C) and emergency surgical thrombectomy is unavailable or not preferred[22].

Patients presenting with systolic pulmonary artery pressures $\geqslant$ 50 mmHg at the time of acute pulmonary embolism are very likely to suffer from chronic thromboembolic pulmonary hypertension (CTEPH) even if the diagnosis has not been established earlier. Beyond 2 wk, patients with subacute massive pulmonary embolism are no longer candidates for traditional thrombolytic therapy and in presence of massive PE the modality of treatment for is pulmonary endarterectomy (PEA). When performed in experienced centers and in carefully selected patients, PEA in patients with CTEPH provides remarkable results with a periprocedural mortality rate of < 5% to 11%, nearly normalized hemodynamics, and substantial improvement in clinical symptoms[23-25]. In a comprehensive review of 1500 PEA procedures performed at a center in California, there was an almost linear relationship between preoperative pulmonary vascular resistance and perioperative mortality. In a series from France[25], the mortality rate was 4% when the preoperative pulmonary vascular resistance was < 900 dyne.s/cm$^5$ but increased to 10% in patients with resistances between 900 and 1200 dyne.s/cm$^5$and to 20% for higher resistances[25]. Postoperative residual pulmonary hypertension has been identified as the most important predictor of death. In the largest series published thus far, patients with a postoperative pulmonary vascular resistance > 500 dyne.s/cm$^5$ had a mortality rate of 30.6% (15 of 49 patients), whereas those with a postoperative resistance < 500 dyne.s/cm$^5$ had a mortality rate of 0.9% (4 of 434 patients)[24]. Taken together, these data suggest that technical operability must not necessarily confer a benefit to every patient with CTEPH. Dartevelle *et al*[25] have suggested that patients should be selected for PEA only if a reduction in pulmonary vascular resistance by > 50% can be predicted.

The 8 patients with massive PE presenting sub acutely who underwent mechanical breakdown and thrombolysis had significant immediate, 30 d and 6 mo improvement in hemodynamics and clinical profile. This technique is less invasive, inexpensive with probably similar if not more mortality benefits than surgical procedure (100% survival at 6 mo in this study). Moreover, it may prevent development of CTEPH in patients presenting with subacute massive pulmonary embolism in whom window period for traditional systemic thrombolysis is over and thrombus is in process of organizing. Larger, multicenter and randomised trials should be performed to further study the role of mechanical breakdown and intrapulmonary thrombolysis in this subset of patients[26,27].

In conclusion, subacute massive pulmonary embolism has a high mortality and may not respond well to standard anticoagulant or thrombolytic treatment, as older clot accumulated in the pulmonary circulation over a period of weeks might be expected to lyse less easily. With survival rate of 100%, improved hemodynamics and clinical profile at 6 mo, in this subset of patients, mechanical breakdown followed by intrapulmonary thrombolysis appears to be an attractive option. Larger, multicenter and randomised trials with longer follow up are required to study the role of this less invasive and inexpensive

technique in terms of immediate mortality benefits and prevention of recurrent PE/progression to CTEPH.

## COMMENTS

### Background

In subacute massive pulmonary embolism older clots accumulated over period of weeks may be less amenable to thrombolysis with increased likelihood of recurrence and development of thromboembolic pulmonary hypertension. In these patients mechanical breakdown of thrombus followed by urokinase infusion may be cost-effective, minimally invasive, and potentially life-saving procedure by accelerating velocity of thrombolysis and increasing surface area of clot being lysed. Moreover, combined modality of mechanical fragmentation and intralesional thrombolysis appears to be a promising alternative to high risk surgical procedures in patients with subacute massive pulmonary embolism.

### Research frontiers

Though not many areas are involved in studying the combined modality of mechanical breakdown and intralesional thrombolysis in patients with subacute massive pulmonary embolism; Kuo *et al*, based on a recent meta-analysis of 594 patients from 35 nonrandomized studies (six prospective with 94 patients, 29 retrospective with 500 patients) reported pooled clinical success rate from catheter based therapy to be 86.5% (95%CI: 82.2-90.2) in patients with massive pulmonary embolism. Moreover, pulmonary endarteractomy is being performed in patients with chronic thromboembolic pulmonary hypertension at specialized centers in California and France and have reported an almost linear relationship between preoperative pulmonary vascular resistance and perioperative mortality.

### Innovations and breakthroughs

This is the first study conducted in the patients of subacute massive pulmonary embolism with mechanical breakdown and thrombolysis as a method of treatment. Prior studies on combined modality of mechanical breakdown and intralesional thrombolysis have involved patients with acute massive pulmonary embolism. Moreover at our tertiary care centre in North India, authors have reported excellent outcomes when this modality was employed in patients with failed thrombolysis as published in *JOIC*.

### Applications

The study highlights the role of combined modality of mechanical breakdown and intralesional thrombolysis in patients with subacute massive pulmonary embolism. This modality is an attractive, less invasive alternative and might help to avoid surgical management (pulmonary endarterectomy) with excellent long term results in these patients. Moreover, in developing nations where cost is an important issue, this technique appears to be cost effective.

### Terminology

Subacute pulmonary embolism: Patients with massive pulmonary embolism presenting subacutely *i.e.*, more than 2 wk from symptom onset. Massive pulmonary embolism: Defined as pulmonary arterial occlusion of more than 50% as confirmed by pulmonary angiographic score (miller index) and/or presence of hemodynamic impairment *i.e.*, mean pulmonary artery pressure > 25 mmHg and/or shock index > 1. Shock index equals heart rate divided by systolic systemic blood pressure.

### Peer review

The paper is interesting and well written, my major comment refers to overall presentation of data: this paper is a report of 8 cases and should be presented as is.

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CASE REPORT

# Heart stopping tick

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## Abstract

Although Lyme carditis is relatively rare within 4-6 wk of exposure, it can uncommonly present as the first sign of disseminated Lyme disease. Here we present 17 year old boy who presented to the emergency department with chest discomfort and was later found to have complete atrioventricular block due to lyme carditis. He had uneventful recovery after empiric treatment with ceftriaxone. Our case highlights the importance of considering reversible causes of complete AV block since appropriate therapy can avoid the need for permanent pacemaker insertion.



**Key words:** Lyme carditis; Heart block; Antibiotic; Pacemaker; Disseminated lyme; Borrelia burgdorferi; Tick bite

**Core tip:** Seventeen-year man presented with acute chest discomfort following a tick bite 5 wk back. His hospital course was complicated with the development of first degree AV block which rapidly deteriorated to total AV block. Due to high grade of suspicion of lyme disease and positive lyme enzyme-linked immunosorbent assay and Lyme IgM (Western blotting), treatment with Ceftriaxone and doxycycline was started with complete remission. It is important to consider the reversible causes of complete AV block since appropriate therapy can avoid the need for permanent pacemaker insertion.

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## INTRODUCTION

The incidence of cardiac involvement in Lyme disease has been estimated to be 4%-10% in the adult population in the United States[1,2]. Lyme disease should be suspected as a cause of AV block in a patient living in an endemic area or a recent trip to an endemic area. Our case depicts the importance of starting treatment early awaiting serology in order to prevent serious morbidity and mortality. We also discuss the clinical presentation, diagnosis and treatment.

## CASE REPORT

A 17-year-old man presented to the Emergency Department with acute chest discomfort for 1 d. Two weeks ago, he had developed a febrile illness with headache. At that time he was seen in outpatient clinic and was diagnosed with a viral illness and sent home with supportive care. Over the course of the week his fever resolved, however, he reported some nonspecific chest discomfort which became progressively worse. His social history was significant for living in woody area and being bitten by a tick 5 wk back. However, he denied being tested or treated for lyme disease, history of rash and joint pain. His family history was not significant for any heart disease or sudden cardiac death.

His physical examination was unremarkable with normal vital signs. Electrocardiography (ECG) revealed

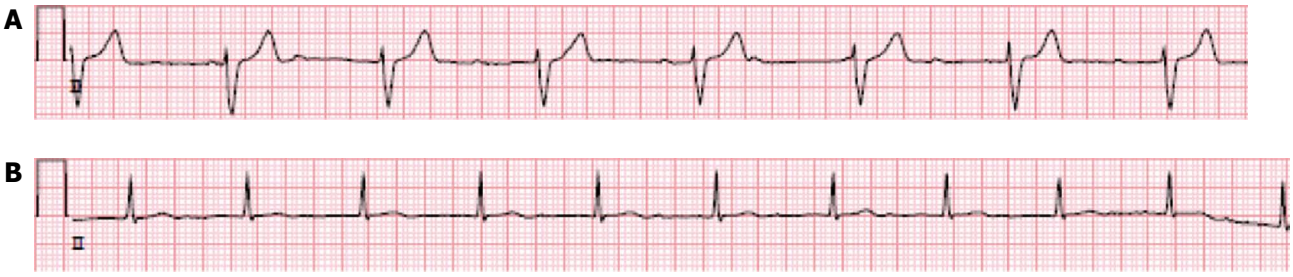


**Figure 1 Electrocardiography.** A: AV-dissociation (Ⅲ degree heart block) in lead Ⅱ; B: first degree AV block in lead Ⅱ following regression of complete heart block 2 d after treatment.

sinus arrhythmia and first degree AV block with a ventricular rate of 97 beats/min. Echocardiogram showed no evidence of structural heart disease. His complete blood count, basic metabolic panel and urine analysis were all within normal limits. Streptococcal throat swab done 2 wk ago was normal. He was placed in observation unit and monitored on telemetry. In the subsequent 24 h he had first degree heart block initially followed by intermittent episodes of complete heart block with AV dissociation (Figure 1A). However he was hemodynamically stable during the whole time. ECG showed sinus tachycardia with an atrial rate in the range of 100 beats/min with complete heart block with narrow escape beat. Empirical treatment with Ⅳ Ceftriaxone 2 g once a day was started and patient was monitored on telemetry. Further tests done including peripheral smear, serological titers for ehrilichiosis, Rocky Mountain spotted fever, streptococcal throat culture blood and urine culture were all negative. Lyme enzyme-linked immunosorbent assay (ELISA) was positive. Lyme IgM through Western blotting was consistent with early infection. After 2 d he had regression of his complete heart block to first degree heart block (Figure 1B). He was discharged on doxycycline to be taken for total of 3 wk. He remains asymptomatic with normal ECG after 3 wk.

## DISCUSSION

Lyme disease, caused by spirochaete Borrelia burgdorferi is transmitted by the bite of Ixodes tick. It constitutes one of the most common tickborne infections in the Northern hemisphere[3] and can involve multiple organs. The clinical manifestations of Lyme disease can be divided into 3 stages. Stage 1 is the acute illness, usually presenting 2 wk after the initial infection with erythema migrans with or without constitutional symptoms. Approximately two thirds of patients progress to stage 2 or dissemination phase, which can involve cardiac or neurologic abnormalities, weeks to months later[4]. Stage 3 or late chronic phase presents months to years later and classically involves the musculoskeletal system with destructive chronic arthritis, with the potential for late neurologic abnormalities[5].

Lyme carditis is defined as myocarditis, pancarditis or acute AV conduction disturbance, usually above the bundle of His[1,2]. It is usually clinically apparent 3 wk after the onset of erythema migrans. Generally, cardiac complications occur in the early disseminated phase. Disturbance of AV nodal conduction is the most common cardiac manifestation of Lyme disease. This is usually self-limited and does not require permanent cardiac pacing[6]. Patients usually complain of dizziness, shortness of breath, substernal chest pain, and palpitations. ECG findings include T-wave flattening or inversions in the lateral and inferior leads[1]. Other conduction disturbances in Lyme disease with unfavourable prognosis are low escape rhythms with severe AV block, which are slow and of wide QRS pattern; transient lack of any escape rhythm, with brief asystoles; and fluctuating bundle branch block depicting either transient His-Purkinje involvement or intranodal AV block[7]. In addition, pericarditis. endocarditis, myocarditis, pericardial effusion, myocardial infarction, coronary artery aneurysm, QT interval prolongation, tachyarrhythmias and congestive heart failure have been reported[8]. Myopericarditis is rare but may lead to transient cardiomegaly or pericardial effusion with non-specific ST and T wave changes on the electrocardiogram[9].

Although the cause of the AV nodal dysfunction in Lyme carditis is unknown, autopsy findings of transmural lymphoplasmacytic infiltrate, necrosis of myocardial fibers, and spirochetes in the endomysial space of myocardial cells[4] have been reported. Direct dissemination of spirochetes into cardiac tissues, the inflammatory response associated with the infection, or both have also been implicated as the cause of AV nodal dysfunction[10].

The diagnosis of Lyme carditis can be challenging if it is the initial presentation of the disease process and patient does not remember having a tick bite. AV block may be the first and only sign of Lyme disease. ELISA testing is preferred for early diagnosis, but most patients are seropositive for IgG antibody only after several weeks. Immunofluorescence assays and Western blotting can also be used[11]. A two-step protocol for the evaluation of *Borrelia burgdorferi* antibodies in sera has been recommended in the United States[12]. The history of tick bite, positive lyme serology, negative serology for babesiosis, ehrlichiosis, in our case helped us to establish the cause of complete heart block.

More than 90% of the patients with Lyme carditis have complete recovery with only up to a third of the patients requiring temporary cardiac pacing[13]. Although

recovery may be delayed and late complications such as dilated cardiomyopathy may occur, the overall prognosis of Lyme carditis is very good. It has recently been demonstrated that, unless meningitis is present, oral doxycycline is as effective as parenterally administered ceftriaxone in preventing the late manifestations of Lyme disease[6]. Patients with minor cardiac involvement (first-degree AV block with PR interval < 0.3 s) could be treated orally with doxycycline, tetracycline, or amoxicillin. Doxycycline is the drug of choice as it is also effective for other tick borne diseases (babesiosis, ehrlichiosis, anaplasmosis) that could be co-transmitted and lead to a more serious outcome[14-16]. Patients with more severe conduction system disturbances (first-degree AV block with a PR interval > 0.3 s, second or third-degree AV block) should be hospitalised in a coronary care unit and treated with either intravenous antibiotics like ceftriaxone or high-dose penicillin G. Insertion of a temporary transvenous pacemaker may be required[5]. As in our case the degree of heart block can fluctuate rapidly from first degree to second degree to complete AV block very quickly in minutes to hours so careful observation is prudent. Treatment with an antibiotic can revert the AV block within 48 h of therapy[1].

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CASE REPORT

# Impact of cardiac magnet resonance imaging on management of ventricular septal rupture after acute myocardial infarction

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## Abstract

A 74-year-old man was admitted to the cardiac catheterization laboratory with acute myocardial infarction. After successful angioplasty and stent implantation into the right coronary artery, he developed cardiogenic shock the following day. Echocardiography showed ventricular septal rupture. Cardiac magnet resonance imaging (MRI) was performed on the critically ill patient and provided detailed information on size and localization of the ruptured septum by the use of fast MRI sequences. Moreover, the MRI revealed that the ventricular septal rupture was within the myocardial infarction area, which was substantially larger than the rupture. As the patient's condition worsened, he was intubated and had intra-aortic balloon pump implanted, and extracorporeal membrane oxygenation was initiated. During the following days, the patient's situation improved, and surgical correction of the ventricular septal defect could successfully be performed. To the best of our knowledge, this case report is the first description of postinfarction ventricular septal rupture by the use of cardiac MRI in an intensive care patient with cardiogenic shock and subsequent successful surgical repair.



**Key words:** Cardiac magnetic resonance imaging; Ventricular septal rupture; Myocardial infarction; surgical repair; Extracorporeal membrane oxygenation

**Core tip:** We report on the case of a 74-year-old man who developed cardiogenic shock and ventricular septal rupture following an episode of acute myocardial infarction. Cardiac magnet resonance imaging (MRI) provided detailed information on size, localization and tissue integrity of the ruptured septum with respect to the myocardial infarction zone, followed by successful surgical repair of the defect. To the best of our knowledge, this case report is the first description of post-infarction ventricular septal rupture by the use of cardiac MRI in an intensive care patient with cardiogenic shock and subsequent successful surgical repair.

Gassenmaier T, Gorski A, Aleksic I, Deubner N, Weidemann F, Beer M. Impact of cardiac magnet resonance imaging on management of ventricular septal rupture after acute myocardial infarction. *World J Cardiol* 2013; 5(5): 151-153 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i5/151.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i5.151

## INTRODUCTION

Ventricular septal rupture after myocardial infarction is

a rare complication but associated with a high mortality rate[1,2]. Cardiac magnetic resonance imaging (MRI) can provide detailed information on size and localization of the ruptured myocardium with respect to the myocardial infarction zone. We present a case of postinfarction ventricular septal rupture that was examined via cardiac MRI prior to surgical repair.

## CASE REPORT

A 74-year-old man presented with a new episode of chest pain to his local general practitioner. Because the on-site electrocardiogram (ECG) showed ST-segment elevations, the patient was referred directly to our cardiac catheterization laboratory.

Physical examination showed hypotension but no dyspnea and no peripheral edema. The 12-lead ECG demonstrated sinus rhythm with a heart rate of 80/min, ST-segment elevation in the inferior leads (Ⅱ, Ⅲ, and aVF), and ST-segment depression in leads V3 to V5. Cardiac catheterization showed an occlusion of the right coronary artery, which was successfully recanalized by angioplasty and implantation of a bare metal stent. It was decided to postpone additional stenosis of the left main artery and the left circumflex artery for intervention in a later session. Afterwards, the patient was initially symptom-free with persistent hypotonic blood pressure. Echocardiography showed inferior wall akinesis with preserved left ventricular function and no aneurysm or ventricular septal defect.

The following day, the patient developed cardiogenic shock with supraventricular tachycardia. Echocardiography showed septal dyskinesia, a ventricular septal rupture basal inferoseptal of about 8 mm, and a left-to-right shunt of about 30%. Medical therapy included a daily dose of 100 mg aspirin, 75 mg clopidogrel, 40 mg simvastatin, and 2.5 mg fondaparinux. Norepinephrine was applied, adapted to the mean arterial blood pressure at a target pressure of 60-70 mmHg. Because the patient was stable at this mean arterial pressure of only 70 mmHg despite administration of norepinephrine and considering the high operative mortality, it was decided to first adopt a conservative approach and gain additional information in order to plan surgical repair.

Therefore, the next day, a cardiac MRI in short axis and four-chamber view was performed on a MAGNETOM® Avanto 1.5 Tesla (Siemens AG Sector Healthcare, Erlangen, Germany). The main questions were size and localization of MI, and whether the rupture was located inside nonviable tissue or surrounded by viable tissue for surgical closure of the myocardial defect. The MRI was performed under emergency conditions and administration of analgesics and sedatives. Heart rate during MRI was 105 beats/min. The ventricular septal rupture first diagnosed by echocardiography was confirmed by cardiac MRI. Although the patient was under mild sedation, there was severe movement of the patient, making fast MRI sequences necessary. Therefore, a fast HASTE 2D for morphologic analysis, a fast SSFP LGE (7 heart beats), and a SSFP cine (not shown) were performed and allowed sufficient discrimination between scar, edema, and movement artifacts. Using these sequences, the rupture previously described by echocardiography was detected in the posterior septum with a defect size of about 2 cm and a surrounding wall edema with a diameter of about 4 cm. Late Gadolinium enhancement (LGE) imaging with PSIR-SSFP revealed an infarction area reaching from basal septal inferior to apical inferolateral, which, with a size of 3-4 cm, was substantially larger than the ventricular septal defect. Furthermore, it showed that the defect was within the infarction area (Figure 1).

As the patient's condition worsened, he was intubated and had an intra-aortic balloon pump (IABP) implanted. Extracorporeal membrane oxygenation (ECMO) was initiated three days after the initial event, bridging the time until surgical repair in order to relieve secondary end organ failure, namely acute renal and liver failure.

During the following days, the patient's situation improved, and surgery could be performed on day six after the onset of the myocardial infarction based on the results of cardiac MRI, knowing the extent of the septal defect, and the fact that viable tissue existed, making surgical repair of the defect possible.

Three target vessels were revascularized utilizing the left internal thoracic artery and saphenous vein grafts. The left ventricle was longitudinally opened posteriorly and parallel to the septum. The excision of the fragile infarction zone resulted in a large septum defect. The myocardial edges were stabilized with Teflon felts in sandwich technique, and the defect was covered with a Dacron patch reaching from the posterior mitral annulus to the left ventricular apex. The anterolateral papillary muscle had to be refixed. The intraoperative echo showed a competent mitral valve and no residual shunt.

The ECMO-support was continued until the first and the IABP-support until the fourth postoperative day. After prolonged weaning, the patient was eventually discharged to rehabilitation in subjective well-being almost two months after the initial event. He is alive and in NYHA class Ⅱ six months after the operation.

## DISCUSSION

In a patient with acute myocardial infarction, cardiac MRI was able to provide detailed information on size, localization, and tissue integrity of the ruptured septum with respect to the myocardial infarction zone.

Cardiac MRI has previously been utilized for characterization of ventricular septal defects, *e.g.*, following chest trauma[3,4]. Nonetheless, none of these patients had been in a critical condition when cardiac MRI was performed. To the best of our knowledge, this case report is the first description of post-infarction ventricular septal rupture by the use of cardiac MRI in an intensive care patient with cardiogenic shock and subsequent successful surgical repair.

Interestingly, previous implantation of coronary bare-metal or drug-eluting stents is not a contraindication for cardiac MRI since various studies have confirmed the safety of both in MRI at 3 Tesla or less[5,6]. Operative

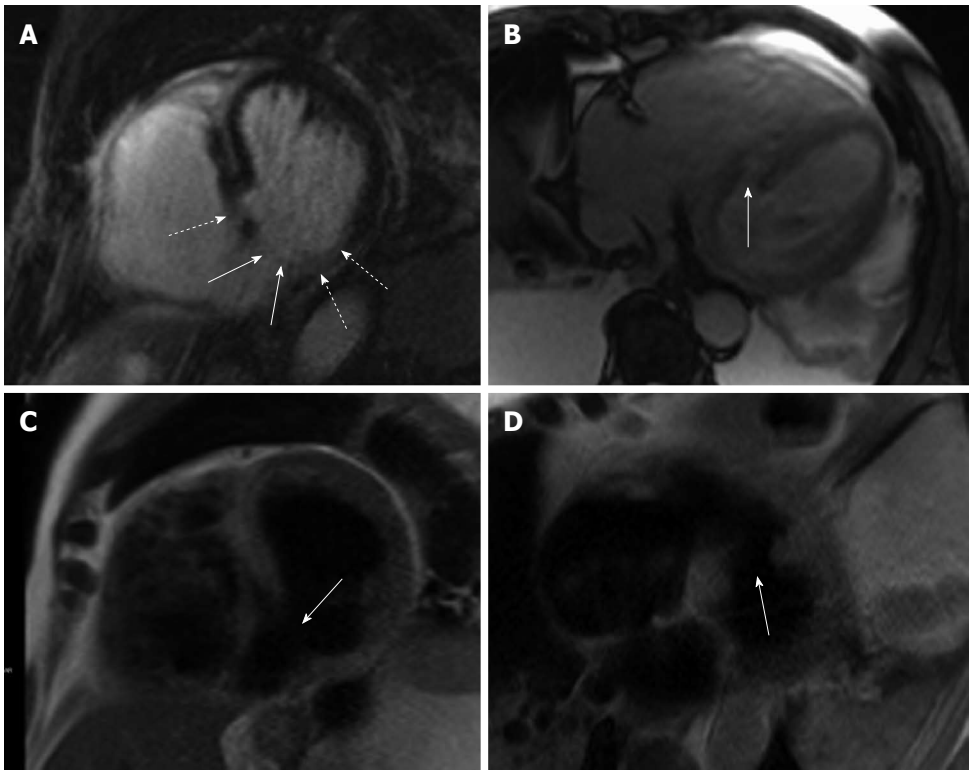


**Figure 1 Cardiac magnet resonance imaging revealed size and localization of the ruptured septum with respect to the myocardial infarction zone.** Ventricular septal rupture in the infarction zone. A: Late Gadolinium enhancement in short axis view; B: On TRUFI localizer; C: On HASTE in short axis view; D: Long axis view. Solid arrows indicate ventricular septal rupture, dashed arrows indicate myocardial infarction zone.

mortality is about 54% if the surgical repair is performed within seven days from acute myocardial infarction[1]. Both timing and method of choice for correction of ventricular septal defect are still being debated[2], and percutaneous closure of ventricular septal defects is a new alternative to surgical repair[7]. However, to date, no studies have compared this new approach to surgical correction.

As postmyocardial infarction ventricular septal rupture is a severe and life-threatening complication, several limitations such as heart rate or circulatory stability exist for performing cardiac MRI in critically ill patients. Therefore, cardiac MRI may not be applicable in all patients, and its overall role in acute postinfarction ventricular septal defect can be considered marginal. However, when being performed, it can provide precise information on localization and size of the defect with respect to the myocardial infarction zone, which is of particular interest before surgical correction.

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CASE REPORT

# Echocardiographic features of an atypical presentation of rapidly progressive cardiac amyloidosis

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## Abstract

We present the case of a 66 year old male who presented with dyspnea and reduced exercise tolerance. Echocardiography demonstrated impaired left ventricular (LV) function and restrictive diastolic function with pronounced concentric left ventricular hypertrophy (LVH) without a history of hypertension and no aortic valve stenosis. Differential diagnostics of concentric LVH are discussed in detail. In the current case, cardiac amyloidosis (AL) amyloidosis was diagnosed and confirmed by serum amyloid P (SAP) scintigraphy and abdominal fat aspiration biopsy. This case shows the rapid decline in clinical condition with progression of cardiac involvement of AL. As discussed in detail, cardiac involvement in AL-amyloidosis generally denotes a poor prognosis, regardless of the method of treatment.



**Key words:** Amyloidosis; Cardiac involvement; Echocardiography; Treatment; Prognosis

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## INTRODUCTION

Amyloidosis is a disease that is characterised by the extracellular deposition of proteinaceous material (amyloid). A distinction has to be made between the (rare) AM-amyloidosis and the more common AL-amyloidosis on which this report will focus.

## CASE REPORT

A 66-year old man was referred to our outpatient clinic for a second opinion because of slowly increasing shortness of breath on exertion, fatigue and reduced exercise tolerance over the previous year. His medical history included a non-ST segment elevation myocardial infarction with preserved left ventricular (LV) function and mild chronic obstructive pulmonary disease. Family history did not reveal any cardiovascular diseases or sudden cardiac death. On physical examination, blood pressure was 130/80 mmHg, a third heart sound was detected but there were no signs of heart failure. Electrocardiography showed microvoltages in the limb leads, a first degree atrio-ventricular block and Q-waves in the anterior and inferior wall leads. Laboratory tests revealed a ferriprive anaemia Hb 6.6; normal (N) = 8.5-11.0 mmol/L), elevated creatinine (150 μmol/L, N < 100 μmol/L), γ-glutamyltransferase (292 U/L, N < 35 E/L) and alkaline phosphatase (200 U/L, N < 120 E/L). Previous echocardiography 8 years before presentation demonstrated preserved LV function with ejection fraction (EF) of 64%, concentric LV hypertrophy with a width of the interventricular septum (IVS) and LV poste-

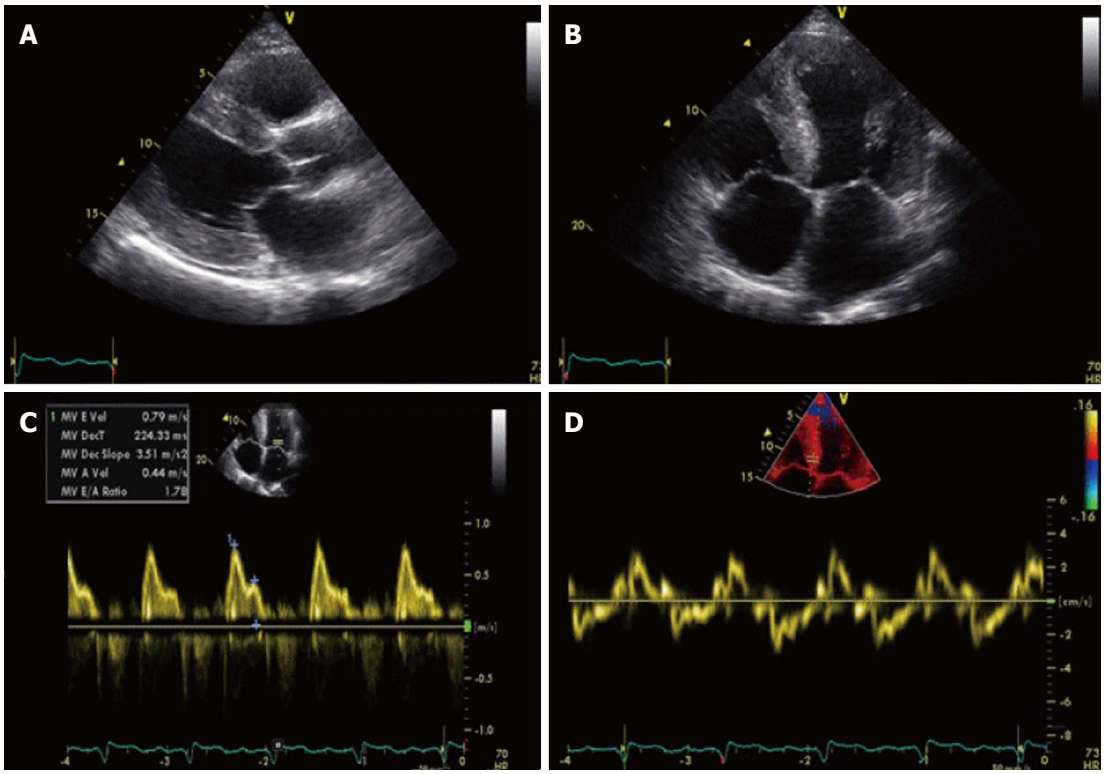


**Figure 1 Transthoracic echocardiography images.** A: Parasternal long axis view diastolic still frame demonstrating thickened myocardium with sparkling of the septum. IVSd 19 mm, LPWd 19 mm; B: Apical four chamber view end diastolic still frame demonstrating thickened myocardium and normal appearance of heart valves; C: PW Doppler measurement of MV inflow. MV E/A ratio 1.8; E-vel 0.80; A-vel 0.57; IVRT 77 ms; dt 224 ms; D: Tissue Doppler Imaging with PW Doppler measurement on medial annulus of MV with E' 3 cm/s E/E' ratio 26.2 confirming the diastolic dysfunction. S' 3.5 cm/s associated with impaired left ventricular function.

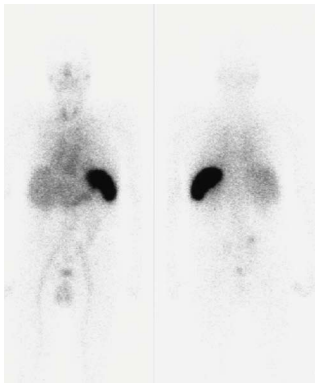

**Figure 2 Serum amyloid P scintigraphy 24 h after intravenous injection of $^{123}$I-serum amyloid P.** Serum amyloid P (SAP) scintigraphy 24 h after intravenous injection of $^{123}$I-SAP. Total body uptake from the side (left image) and back (right image). Normal blood pool activity is present in organs such as liver, heart, and kidneys. Intense uptake is present in the spleen.

rior wall of 18 and 12 mm, respectively. Diastolic function was normal (E/A ratio 0.80; Evel 0.49 m/s; Avel 0.61 m/s) with a normal right ventricular systolic pressure (RVSP). Subsequent echocardiograms demonstrated a progressive decline in EF, progressive diastolic dysfunction to grade Ⅱ and pronounced concentric LV hypertrophy (LVH) without sparkling. During follow-up the patient remained asymptomatic until the year before his appearance at our centre. At presentation, echocardiography showed a moderately impaired LV function (EF 34%) with a sparkling IVS of 19 mm diameter. Diastolic dysfunction had worsened to grade Ⅲ with E/A ratio of 1.8 [E-vel 0.80 A-vel 0.57; S' 3.5 cm/s (N > 5 cm/s); E/E' ratio 26.2 (N < 15)] with an increased RVSP of 41 mmHg with moderate tricuspid insufficiency (Figure 1). Values of S' and E/E' reflected the poor systolic function and raised filling pressures in our patient. The decline in ejection fraction and pronounced concentric LVH without a history of hypertension or aortic valve stenosis on echocardiography with new complaints of exertional dyspnea were reasons for further investigation to rule out or demonstrate other causes of concentric LVH such as amyloidosis, Fabry's disease *etc*.[1,2]. Blood tests showed no para-proteinemia, but free light chains were found in urine (0.06 g/L) and serum samples. Based on the latter finding AL-amyloidosis was suspected[1,2]. This diagnosis was confirmed by serum amyloid P (SAP) scintigraphy (Figure 2) and abdominal fat aspiration biopsy (Figure 3). Bone biopsy revealed mild clonal plasma cell dyscrasia with excess of light chains and total plasma cells of 5 %. Cardiac magnetic resonance imaging (CMR) confirmed cardiac involvement with areas of fibrosis in the inferolateral wall[1,2]. Upon diagnosis, chemotherapy with Melfalan, Thalidomide and prednisolone was initiated according to the Palumbo-schedule[3,4]. Chemotherapy did not have any effect on the clinical condition and nine months after the diagnosis of cardiac amyloidosis, the patient died of heart failure.

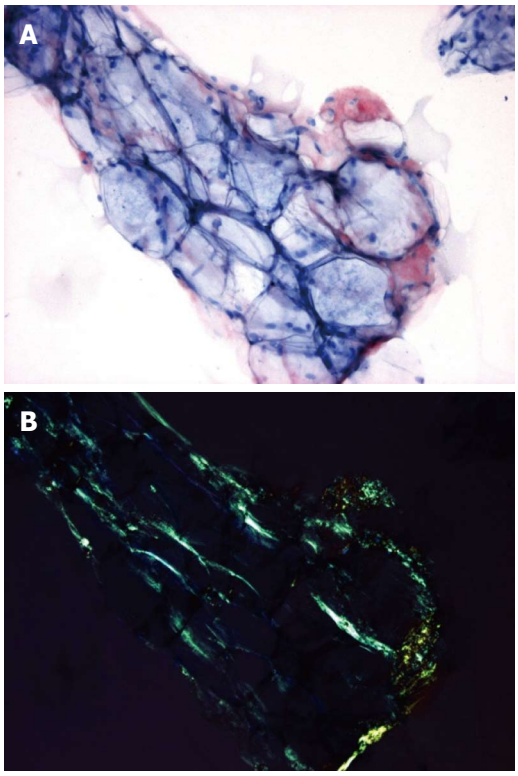


**Figure 3 Abdominal subcutaneous fat aspirate of the patient stained with Congo red, magnification x 30.** Amyloid score 3+ (10%-60% of the surface is occupied by amyloid). A: When viewed in normal light, amyloid is stained red; B:The same specimen viewed in polarised light: amyloid shows apple-green birefringence.

## DISCUSSION

In AL-amyloidosis the amyloid is produced by clonal light chains made by disrupted plasma cells (plasma cell dyscrasia). The extracellular deposition of AL-amyloid can occur in all tissues and organs, but predominates in heart, liver and kidney[3-5]. Cardiac involvement can vary from being absent to severe and is present in approximately 50% of cases. In half of these cases congestive heart failure (CHF) is the presenting symptom and when CHF is present, median survival is less than six months in untreated patients[3-5]. When the heart is involved, amyloid infiltration is generalised: ventricular and atrial myocardium, vasculature, conduction system and valves are equally affected. In 95% of patients with cardiac amyloidosis other organs or tissues are also affected, so signs or symptoms of extracardiac manifestations should not be ignored[3-5].

Electrocardiography usually shows low voltages in the limb leads and poor R wave progression in the precordial leads. Due to amyloid infiltration in the conduction system, several conduction disorders and arrhythmias can occur. Reduced myocardial relaxation is an early echocardiographic finding that usually progresses into restrictive patterns. There may also be left ventricular hypertrophy, granular sparkling, atrial dilation, valvular thickening and pericardial effusion[3-5].

The diagnosis of systemic amyloidosis can be confirmed by SAP scintigraphy and Congo red staining of abdominal fat aspiration biopsy[3-5]. Immunohistochemical staining determines the kind of protein from which the amyloid originates. When abdominal fat aspiration biopsy does not result in diagnosis, endomyocardial biopsy should be considered. The latter has a sensitivity of near 100%. Plasma cell dyscrasia in a bone marrow biopsy and free lambda or kappa (less common) light chains in serum and/or urine samples then confirm the diagnosis AL-amyloidosis[3-5].

This case shows the rapid decline in clinical condition with the progression of cardiac involvement in AL-amyloidosis[5]. Regardless of the method of treatment, cardiac involvement in AL-amyloidosis generally denotes a poor prognosis,. As in our patient, the median survival rate from the onset of symptoms of congestive heart failure is only 6 mo[6].

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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