

Increased plasma homocysteine predicts arrhythmia recurrence after minimally invasive epicardial ablation for nonvalvular atrial fibrillation

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Objective: Minimally invasive epicardial ablation via right minithoracotomy is an emerging option for patients with drug-refractory nonvalvular atrial fibrillation. To guide the development of rational treatment algorithms, factors predisposing to recurrence of arrhythmia need to be quantified and eventually treated. We addressed the association of the plasma levels of homocysteine and the recurrence of atrial fibrillation after minimally invasive ablation.

Methods: We obtained peripheral blood samples from 104 patients at follow-up after arrhythmia surgery; the homocysteine concentration was expressed as micromoles per liter. Prospective follow-up was conducted through electrocardiogram Holter monitoring (average 18.5 ± 5.8 months). Stratified analysis (high vs low homocysteine) was based on the cutoff value for the last quartile of homocysteine concentration ($16 \mu\text{mol/L}$). Time-to-event and diagnostic performance analyses were performed.

Results: The rate of freedom from atrial fibrillation was 89.4% at the end of follow-up. Elevated circulating homocysteine level, persistent type of atrial fibrillation, and increased left atrial dimension independently predicted the recurrence of atrial fibrillation during the follow-up (adjusted Cox regression). Patients with a high homocysteine level were more likely to have atrial fibrillation recurrence (stratified Kaplan–Meier, $P < .001$). The cutoff value for elevated homocysteine ($16 \mu\text{mol/L}$) yielded a good diagnostic performance in the prediction of atrial fibrillation recurrence (area under the receiver operating characteristic curve, 0.807).

Conclusions: The homocysteine level measured during the follow-up reliably predicts the risk of recurrence after epicardial ablation of nonvalvular atrial fibrillation via minithoracotomy. Specific treatments to reduce plasma homocysteine could be considered in the future in these patients. (*J Thorac Cardiovasc Surg* 2013;146:848-53)

The epicardial off-pump ablation via minithoracotomy is an emerging option for the treatment of patients affected by nonvalvular atrial fibrillation (AF). This approach has been reported to yield superior results in terms of freedom from arrhythmia compared with the established catheter ablation.^{1,2} Several factors have been indicated to predict the recurrence of AF during the postoperative follow-up (including persistent type of AF and enlarged left atrial cavity),

but the criteria to indicate minimally invasive epicardial ablation for nonvalvular AF need to be refined. We aimed to ascertain whether the plasma levels of homocysteine (Hcy), a marker of cardiovascular risk,^{3,4} may predict the recurrence of AF. We also aimed to clarify whether Hcy may work as an additional tool to stratify the risk of recurrence and, therefore, the clinical cost/benefit ratio of minimally invasive epicardial ablation in individual patients.

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MATERIALS AND METHODS

Patients Selection

Starting in June 2008, we selected patients for minimally invasive ablation of nonvalvular AF according to the following criteria: (1) episodes of paroxysmal or persistent nonvalvular AF, refractory to the maximal tolerated doses of class IC and class III antiarrhythmic drugs, alone or in combination; (2) at least 1 failed direct-current or pharmacologic cardioversion during the previous 6 months. Patients had to be free from any other cardiac dysfunction on the basis of the review of recent transthoracic echocardiogram and stress electrocardiogram (ECG) tracings. The coexistence of any valvulopathy graded more than mild and left ventricular ejection fraction less than 55% was considered exclusion criterion. Paroxysmal AF was defined as episodes of AF lasting less than 7 days and self-terminating, whereas persistent AF was defined as AF episodes lasting more than 7 days and requiring termination by direct-current or pharmacologic

Abbreviations and Acronyms

AF	= atrial fibrillation
AUC	= area under the curve
ECG	= electrocardiogram
Hcy	= homocysteine
RF	= radiofrequency
ROC	= receiver operating characteristic
TIA	= transient ischemic attack

cardioversion.⁵ Patients had to report symptoms for AF and have left atrial dimension not exceeding 35 mm/m² of body surface area. The surgical evaluation and the enrollment of patients for surgery were collegially performed by cardiac surgeons and electrophysiology cardiologists, and in compliance with the current guidelines.⁶

End Points

The end points were (1) effects of the plasma Hcy concentration on the rate of maintenance of sinus rhythm after minimally invasive ablation of nonvalvular AF and (2) validation of a cutoff value of plasma Hcy as a tool to stratify the likelihood of long-term success of minimally invasive ablation of nonvalvular AF.

Surgery

The surgical technique has been described in detail.⁷ Briefly, the procedure is conducted via a right minithoracotomy (4 cm) at the third intercostal space. Videoscopic view and long-shafted instruments are used. After entering the pericardium, the ablation probe is advanced into the transverse sinus and the oblique sinus using a dedicated introducer to embrace the left atrium around the origin of the 4 pulmonary veins. The device uses radiofrequency (RF) energy and is suction-assisted to optimize the contact with the myocardium (Cobra Adhere XL Surgical System; Estech Inc, San Ramon, Calif). RF energy is delivered to obtain a midwall temperature of 80°C and electrical isolation of the pulmonary veins (circular box lesion). This lesion set was uniformly applied to all the study patients. All procedures were performed by 2 surgeons (G.N. and G.S.) using established protocols. Two energy applications lasting 150 seconds each were delivered, followed by a 60-second application after the probe was moved circumferentially, to achieve complete closure of the box lesion. Conduction block was verified by pacing of the pulmonary veins (exit block). Complete block was considered to be indicative of effective electrical isolation. When feasible, the patients were extubated in the operative room. The operation is completely off-pump. After discharge from the intensive care unit, electrical cardioversion was performed whenever required. For the purposes of the present analysis, we defined as recurrence any episode of AF that could be demonstrated at any time during the follow-up, after hospital discharge.

Study Measurements, Follow-up, and Collection of Data

Since the introduction of minimally invasive epicardial RF ablation at our Anthea Hospital, GVM Care & Research (Bari, Italy), all clinical data pertaining to the patients undergoing this procedure are prospectively collected and included in an electronic database. The dataset includes baseline characteristics, intraoperative and postoperative results, and follow-up data. The variables were defined and collected according to the current dedicated guidelines.⁸ The preoperative evaluation included the calculation of the Congestive heart failure, Hypertension, Age ≥ 75 , Diabetes mellitus, and prior Stroke or transient ischemic attack score (CHADS), which has been validated for the establishment of the most adequate level of anticoagulation therapy on the basis of the predicted risk of stroke in patients

with nonrheumatic AF.⁹ The database was filled in at the time of the discharge of each patient from the hospital and was periodically checked for errors and omissions. After hospital discharge, patients were followed up by scheduled visits at 3 and 6 months, and every 6 months thereafter to determine the rate of AF recurrence. Visits included physical examination, review of 24-hour Holter ECG tracings, and transthoracic echocardiography. Echocardiography included pulsed-Doppler examination to assess the presence of atrial transport function (defined as evidence of filling A wave with a peak flow velocity of 0.4 m/sec or more). This had to be coupled to the ECG tracing to define the absence of AF recurrence. Telephone contacts were performed on a monthly basis. Unscheduled visits and 24-hour Holter ECG examinations were performed whenever symptoms suggestive of arrhythmia relapse were reported by the patients. The study subjects remained on an antiarrhythmic drug regimen until stable sinus rhythm was demonstrated at both the 3-month and the 6-month follow-up time points. Anticoagulation therapy was withdrawn when stable sinus rhythm was demonstrated up to 9 months after surgery. With respect to time-to-event analysis, prospective event recording (recurrence of AF) was initiated from the day of hospital discharge.

In all patients, a sample of serum was taken from a peripheral vein at the time of the sixth postoperative month follow-up visit. Samples were immediately processed to determine the plasma level of Hcy using a commercially available kit (Mitsubishi Chemical Medience Corp, Tokyo, Japan). Hcy levels were expressed as micromoles per liter. Subsequently, the patients were assigned to 2 groups according to a cutoff value for the last quartile of plasma Hcy concentration in our population (16 $\mu\text{mol/L}$). Patients with plasma Hcy 16 $\mu\text{mol/L}$ or greater were included in the high Hcy group, and patients with plasma Hcy less than 16 $\mu\text{mol/L}$ were included in the low Hcy group. Such methodology is consistent with previous reports in the literature.^{3,10,11} Enlarged left atrial size was defined as a maximum diameter of the left atrium exceeding 22 mm/m² of body surface area in the apical 4-chamber echocardiographic view. All of the measurements were performed using the same echocardiography apparatus in consensus by 2 skilled cardiologists. The local ethical committee approved the study protocol, and the patients provided informed consent to enter the study and to the management of data.

Statistical Analysis

Continuous data are presented as mean \pm standard deviation, and categorical variables are presented as percentages. Intergroup comparison was performed using the Student *t* test (continuous variables) and the chi-square test (categorical variables). All tests were 2-tailed. Multiple logistic regression was used to identify the predictors for the need of predischARGE electrical cardioversion. Multivariable Cox proportional hazards regression was performed to identify the predictors of AF recurrence during the follow-up. All of the available patients' data were included as potential explanatory variables. The assumptions of both regression models were checked and met. All of the variables available in each patient's dataset were entered in the models as potential explanatory variables, including the Hcy level, baseline characteristics (demographics, type and duration of AF, type of preoperative antiarrhythmic therapy, left atrial dimension, New York Heart Association functional class, left ventricular dimension, and ejection fraction), and intraoperative variables (type of ablation pattern, need for early postoperative cardioversion). Left atrial diameter was managed as a dichotomous variable (enlarged vs nonenlarged left atrium). The Kaplan–Meier method was used to build the curves for recurrent AF-free survival during the follow-up. Stratified analysis according to the high Hcy versus low Hcy group was performed, and the corresponding curves were analyzed using the log-rank statistic. The diagnostic performance of serum Hcy cutoff value in predicting the recurrence of AF at any time during the follow-up was evaluated by construction of receiver operating characteristic (ROC) curves. The area under the curve (AUC) was quantified according to a parametric methodology (because it is best suited for smaller samples) and adopted as a measure of diagnostic accuracy.

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