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 $\pm$ 5.8 months). Stratified analysis (high vs low homocysteine) was based on the cutoff value for the last quartile of homocysteine concentration (16 μmol/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 μmol/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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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication May 24, 2012; revisions received July 11, 2012; accepted for publication July 31, 2012; available ahead of print Sept 3, 2012.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2012.07.099

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/m^2 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 $\geq$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 μmol/L). Patients with plasma Hcy 16 μmol/L or greater were included in the high Hcy group, and patients with plasma Hcy less than 16 μmol/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/m^2 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 categoric variables are presented as percentages. Intergroup comparison was performed using the Student t test (continuous variables) and the chi-square test (categoric 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.

Comparison between opposed ROC curves was obtained through the Hanley and McNeil statistic (MedCalc software, Mariakerke, Belgium). The alpha level was 0.05. The analyses were conducted using the Statistical Package for the Social Sciences version 13.0 (SPSS, Inc, Chicago, Ill).

RESULTS

A total of 104 patients were treated with minimally invasive epicardial ablation for nonvalvular AF. Table 1 summarizes the main baseline features of these patients. There were no cases of operative mortality and 3 cases of perioperative morbidity (2.9%; 1 case of intraoperative bleeding, 2 cases of stroke/transient ischemic attack [TIA]). Twenty patients (19.2%) required cardioversion before discharge because of AF/supraventricular tachycardia. All patients but 1 were discharged in sinus rhythm. Multiple logistic regression identified persistent type of AF (odds ratio, 6.57; $P < .001$) and increased Hcy level (odds ratio, 2.7; $P = .0021$) as factors independently associated with the need of predischarge cardioversion.

During the follow-up (average duration, 18.5 ± 5.8 months), 11 clinical relapses of AF were recorded (freedom from AF, 90.4% at 6 months and 89.4% at 12 months). In the present series, there were no patients presenting sinus rhythm on ECG tracings and absence of atrial transport function on pulsed Doppler. The rate of recurrence of AF was 5.9% among the patients with paroxysmal AF versus 15.1% among the patients with persisting AF. There were no thromboembolic events during the follow-up; 2 patients died of noncardiac causes. In the overall population, we recorded a higher mean Hcy level among patients who later had arrhythmia recurrence during the follow-up (18.6 ± 4.7 μmol/L) compared with patients who remained in stable sinus rhythm (13.5 ± 5.9 μmol/L). The difference was statistically significant ($P = .007$). In addition, patients with an enlarged left atrium had a significantly higher mean Hcy level than patients with a normal left atrial dimension ($P < .01$). Likewise, patients with paroxysmal AF demonstrated a 12.9 ± 6.2 μmol/L Hcy concentration versus 15.3 ± 5.6 μmol/L in patients with persistent AF ($P = .043$). After dividing the patients into 2 strata according to the circulating Hcy level, it emerged that the patients included in the high Hcy subgroup were characterized by a statistically higher rate of previous cerebrovascular event (stroke or TIA) and of need of postoperative cardioversion. The average duration of AF was not statistically different among groups (Table 2). Twenty-eight patients (26.9% of the overall population) entered the high Hcy group according to the described criteria. Eighteen of these patients (64.3%) had required early postoperative cardioversion before hospital discharge because of AF or supraventricular tachycardia immediately after the intensive care unit stay. These represented the 90% of the patients who required early cardioversion in the entire study population; the difference versus patients who were included in the low Hcy group was statistically significant ($P < .001$). Recurrence of AF was observed in 9 patients in the high Hcy group (32%) versus 2 patients in the low Hcy group (2.6%) ($P < .001$). Table 3 shows the stratified incidence of AF recurrence according to the type of AF (paroxysmal or persisting) and the Hcy level group (high or low). The results of the Cox proportional hazards regression are shown in Table 4. An elevated Hcy value is identified as an independent predictor of recurrence of AF. Thus, this conclusion is not biased by the association of elevated Hcy level with both enlarged left atrium and persistent type of AF, which appear as the other 2 independent predictors of AF recurrence. Kaplan–Meier analysis confirmed that patients with elevated

TABLE 1. Baseline characteristics of the study population

Characteristic	
Age (y)	63.9 ± 8
Sex (male/female)	39/65
Left atrial dimension (mm)	41.9 ± 5
Left ventricular ejection fraction (%)	58.1 ± 2.8
Diabetes mellitus (n, %)	21 (20.2%)
Hypertension (n, %)	54 (51.9%)
Creatinine (mg/dL)	0.9 ± 0.3
Previous transcatheter ablation (n, %)	24 (23.1%)
Previous stroke/TIA	9 (8.6%)
Duration of AF (y)	2.6 ± 1.4
Paroxysmal-to-resisting AF ratio	49%-51%
CHADS score	
CHADS 0	29 (27.9%)
CHADS 1	50 (48.1%)
CHADS 2	17 (16.3%)
CHADS 3	8 (7.7%)

TIA, Transient ischemic attack; *AF,* atrial fibrillation; *CHADS,* Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or transient ischemic attack.

TABLE 2. Variable-based comparison of the high homocysteine group versus the low homocysteine group

Characteristic	High Hcy group N = 28	Low Hcy group N = 76	*P*
Previous stroke/TIA	7 (25%)	2 (2.6%)	<.001
Duration of AF (y)	3.4 ± 1.5	3.1 ± 1.4	.21
Postoperative cardioversion	8 (88.9%)	17 (40.5%)	.022

Inclusion into subgroups was based on the cutoff valve of Hcy (16 μmol/L). *TIA,* Transient ischemic attack; *AF,* atrial fibrillation.

TABLE 3. Results of Cox proportional hazards regression: Predictors of recurrence and time to recurrence of atrial fibrillation

	Paroxysmal AF N = 51		Persisting AF N = 53	
Characteristic	High Hcy	Low Hcy	High Hcy	Low Hcy
Recurrence of AF	3	0	6	2
No recurrence AF	8	40	11	34

Hcy, Homocysteine; *AF,* atrial fibrillation.

TABLE 4. Results of Cox proportional hazards regression: Predictors of recurrence and time to recurrence of atrial fibrillation

Characteristic	Standard error	Hazard ratio	*P*	95% hazard ratio confidence limits
Hcy level (continuous variable)	0.063	3.1	.0029	2.06-4.55
Elevated Hcy (categoric variable)	0.051	4.0	<.001	3.2-4.93
Type of AF: persistent	0.074	1.36	.004	0.97-2.05
Left atrial dimension	0.058	3.7	<.001	2.59-4.48

Hcy, Homocysteine; *AF,* atrial fibrillation.

Hcy levels are affected earlier and more frequently by recurrence of AF during the follow-up (log-rank $P < .001$) (Figure 1).

In our population, the cutoff value of plasma Hcy = 16 μmol/L, corresponding to the cutoff for the last quartile for Hcy concentration, yielded a good diagnostic performance in predicting the recurrence of AF at any time during the follow-up (ROC AUC = 0.807) (Figure 2). Such an AUC value was statistically higher than that obtained for different potential cutoff values; to such a purpose, we tested the cutoff for each decile of the distribution of Hcy in the present population (ROC curves not shown).

DISCUSSION

AF, one of the most common cardiac rhythm disturbances in adults, is a major determinant of cardiovascular morbidity and mortality, mainly due to thromboembolism.[12] Currently, the rate of failure of medical rhythm-control strategies may reach 77% at 36 months,[13] whereas the rate of AF recurrence after the second-line treatment (transcatheter ablation) in patients with drug-refractory AF may reach 37% even after repeated ablation procedures.[14] The traditional Maze treatment offered by cardiac surgery, despite better success rates and contained morbidity, is limited by its invasiveness and the need for cardiopulmonary bypass. These latter features make its application scarcely accepted by the patients affected by nonvalvular AF. Therefore, a therapeutic gap exists for patients with isolated AF. Notwithstanding, it is currently possible to perform an AF ablation surgery on the beating heart and through a 4-cm minithoracotomy. Such a concept is based on thoracoscopy-assisted surgery and RF energy delivery through a dedicated suction-assisted probe to obtain electrical isolation of the pulmonary veins. Such a strategy has been conceptually validated for nonvalvular AF,[15] because the electrical trigger is located within the pulmonary veins cuff in the majority of cases of nonvalvular AF.[16] Our previous clinical data indicate that the presented surgical procedure is safe and that it may yield optimal recurrence-free survival during the follow-up, but also that factors such as increased atrial dimension and persistent type of AF are associated with increased likelihood of recurrence.[2,7] Nonetheless, such elements are insufficient to prompt rational algorithms for the indications and contraindications to minimally invasive ablation of nonvalvular AF.

Evidence is accumulating that circulating Hcy, an amino acid metabolite of cysteine and methionine, is pathophysiologically linked with left atrial enlargement and the likelihood to develop AF (both valvular and nonvalvular AF).[17] Hyperhomocysteinemia occurs under the condition of oxidant stress and is the expression of depleted circulating glutathione;[18] on the other hand, it is accepted that increased oxidant stress represents a trigger of atrial myocardial

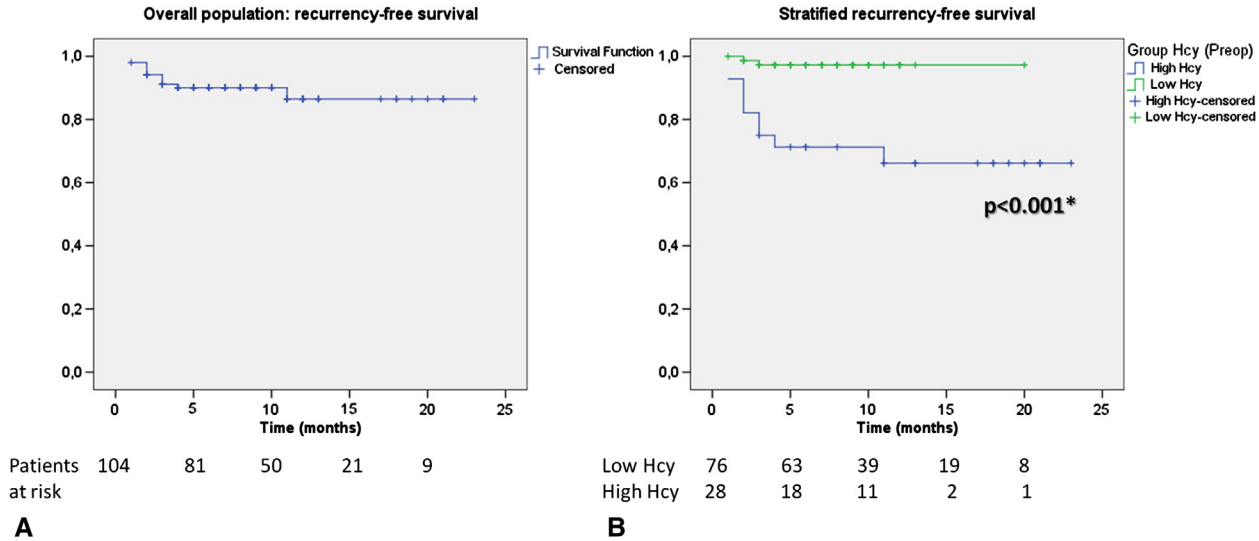

FIGURE 1. Kaplan–Meier curves for recurrent AF-free survival in the overall study population (A) and the high Hcy group versus the low Hcy group (B). The difference between the 2 curves reported in B is statistically significant. *Log-rank *P* value. *Hcy,* Homocysteine.

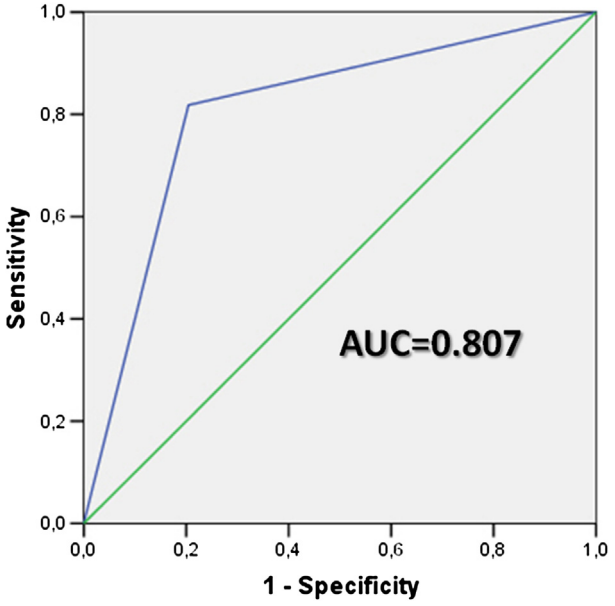

FIGURE 2. ROC curve for the cutoff value of the last quartile of Hcy concentration in our population (16 μmol/L) in the prediction of AF recurrence at any time during the follow-up. *AUC,* Area under the curve.

remodeling and increased likelihood of developing AF.[19] Nonetheless, it is likely that Hcy plays a direct role in the determinism of atrial myocardial remodeling and in influencing the electrophysiologic milieu toward promotion and sustainment of AF.[20] A direct effect of Hcy on potassium currents of atrial human myocytes may be at the root of such finding.[21] In addition, hyperhomocysteinemia is associated not only with increased likelihood of developing AF but also with endothelial dysfunction and higher stroke risk in patients with persistent AF. Such a concept was confirmed by the clinical finding that increased Hcy predicts the recurrence of AF after direct-current cardioversion[11] and the occurrence of adverse cardiovascular events after transcatheter RF ablation of AF.[4]

The present data are consistent with previous evidence that hyperhomocysteinemia is associated with enlarged left atrium and persistent type of AF.[4] In addition, we demonstrate that as for patients who have undergone transcatheter ablation, elevated Hcy is closely associated with recurrence of AF during the follow-up after minimally invasive surgical ablation. Such an association is not dependent on other variables, such as left atrial diameter, type of AF, and coexistence of hypertension, which may be confounding factors (as indicated by the Cox regression model). This concept seems to be consistent with the previous finding that the role played by Hcy in the pathophysiology of cardiovascular disease is independent of interaction with other pathways.[3,10] All of the patients enrolled in our series consistently were free from any heart disease other than AF. Elevated Hcy also represents an independent risk factor for the need for predischarge cardioversion because of onset of AF in the perioperative period (logistic regression), whereas patients demonstrating higher Hcy levels were more likely to have a history of stroke or TIA. Collectively, these findings suggest that elevated Hcy can be regarded as a marker of aggressiveness of the disease and, consequently, of the likelihood of AF recurrence.

We then hypothesized that the assessment of circulating Hcy may become part of the evaluation of potential candidates for minimally invasive ablation, and therefore contribute along with other risk factors for recurrence to the establishment or refusal of surgical indication. We quantified the efficacy of a given cutoff of Hcy (test variable) in predicting the outcome event recurrence of AF during the follow-up (state variable) by means of formal diagnostic performance analysis and ROC curves as the plot of test sensitivity to the false-positive rate. Such an approach facilitates the clinical application of the Hcy assessment in clinical judgment. Nonetheless, although in our population we found that an Hcy concentration of 16 μmol/L displays an adequate diagnostic performance (area under the ROC, 0.807), other authors have proposed different cutoff values to this aim,[4,11] which suggests the existence of a population bias and underscores the need for larger and tailored investigations that also need to take into account the measurement of preoperative Hcy levels. Nonetheless, no formal diagnostic performance analyses have been reported, and we believe that such a conceptual approach may be extended to the future research in this field.

The present series confirms the efficacy in maintenance of sinus rhythm at follow-up after minimally invasive surgical ablation (89.4% freedom from recurrence at the 12-month follow-up) compared with state-of-the art catheter ablation.[4,22] We also confirm the increased rate of AF recurrence in patients with preoperative persisting AF. We also underscore that the results of the rate of freedom from recurrence in the paroxysmal patients treated by minimally invasive surgical ablation (followed by 6 months of antiarrhythmics) is excellent (5.9% rate of recurrence). This may prompt a reflection over the efficacy of alternative treatment strategies (catheter vs surgical ablation) even in the patients with paroxysmal AF. Remarkably, the majority of the instances of recurrence in our series occur in the earliest phase of the follow-up (91% of cases within the sixth postoperative month) (Figure 1, *A*). This supports the stability of results over time, despite withdrawal of antiarrhythmic drugs at the sixth postoperative month. Conversely, it is reported that more than 40% of patients who remain in stable sinus rhythm within 1 year after transcatheter ablation will later develop arrhythmia recurrence.[22] One recent randomized trial has suggested that the epicardial surgical ablation may yield better results than transcatheter ablation in patients with coexisting risk factors for arrhythmia recurrence.[1] Under this perspective, the assessment of Hcy

may be considered as an additional tool to balance the expected effectiveness of each strategy and understand whether the more aggressive surgical approach would be advisable. The analysis of recurrence-free survival was conducted according to the Kaplan–Meier methodology. Because ultimately the occurrence of AF during the follow-up is not a definitive outcome event (eg, mortality), the Kaplan–Meier curves may be theoretically misleading. Nonetheless, we decided to address the reliability of minimally invasive surgical ablation in achieving complete freedom from recurrent AF: therefore, even 1 demonstration of recurrence during the follow-up marked a definitive outcome event with respect to our intended purposes, even though the same patient was in sinus rhythm at 1 subsequent time point. Nonetheless, all patients in our series who were in AF at any follow-up time point were found to show AF even at the subsequent time point(s).

Study Limitations

The present investigation must account for some limitations. The study population is limited (104 patients); nonetheless, the estimates of the regression model excluded model overfitting. Moreover, only the Hcy level measured at the sixth postoperative month was available. The measurement of the preoperative Hcy levels would be more useful to help establish the indication for the surgical treatment of nonvalvular AF. The present study design allows us to conclude that even the Hcy levels measured during the postoperative follow-up have a predictive value and may be used to tailor the pharmacologic treatment and the clinical surveillance. To definitely clarify the role of Hcy level measurement in the prediction of recurrent AF, additional investigations focused on the preoperative Hcy level are required and currently ongoing at our Anthea Hospital, GVM Care & Research (Bari, Italy).

CONCLUSIONS

Hcy plays a complex role in the pathophysiology of AF. Although the molecular interplay of Hcy with the atrial myocardium remains to be clarified, the measurement of circulating Hcy level may already have a clinical fallout. This measurement is reliable in stratifying the risk of recurrence after RF ablation of nonvalvular AF via a minimally invasive surgical route, thus opening new avenues of research for the development of novel treatment algorithms for this arrhythmia. Future treatments aimed at reducing the Hcy level may be evaluated as a strategy to further improve the surgical results in these patients.

References

1. Boersma L, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, et al. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST). A 2-center randomized clinical trial. *Circulation*. 2012;125:23-30.
2. Nasso G, Bonifazi R, Del Prete A, Del Prete G, Lopriore V, Bartolomucci F, et al. Long-term results of ablation of lone atrial fibrillation through a right minithoracotomy: towards a rational revision of treatment protocols. *J Thorac Cardiovasc Surg*. 2011;142:41-6.
3. May H, Alharethi R, Anderson J, Muhlestein JB, Reyna SP, Bair TL, et al. Increased risk of congestive heart failure in patients with and without coronary artery disease. *Cardiology*. 2007;107:178-84.
4. Shimano M, Inden Y, Tsuji Y, Kamiya Y, Uchikawa T, Shibata R, et al. Circulating homocysteine levels in patients with radiofrequency ablation for atrial fibrillation. *Europace*. 2008;10:961-6.
5. Estes N, Halperin J, Calkins H, Ezekowitz MD, Gitman P, Go AS, et al. ACC/AHA/Physician consortium 2008 clinical performance measures for adults with nonvalvular atrial fibrillation and atrial flutter. *Circulation*. 2008;117:1101-20.
6. Calkins H, Brugada J, Packer D, Cappato R, Chen SA, Crijns HJ, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. *Europace*. 2007;6:335-79.
7. Speziale G, Bonifazi R, Nasso G, Bartolomucci F, Caldarola P, Fattouch K, et al. Minimally invasive radiofrequency ablation of lone atrial fibrillation by monolateral right minithoracotomy: operative and early follow-up results. *Ann Thorac Surg*. 2010;90:161-7.
8. Shemin RJ, Cox JL, Gillinov AM, Blackstone EH, Bridges CR. Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons. Guidelines for reporting data and outcome for the surgical treatment of atrial fibrillation. *Ann Thorac Surg*. 2007;83:1225-30.
9. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry for atrial fibrillation. *JAMA*. 2001;285:2864-70.
10. Sundstrom J, Sullivan L, D'Agostino R, Jacques PF, Selhub J, Rosenber IH, et al. Plasma homocysteine, hypertension incidence, and blood pressure tracking. The Framingham Heart Study. *Hypertension*. 2003;42:1100-5.
11. Naji F, Suran D, Kanic V, Vokac D, Sabovic M. High homocysteine levels predict the recurrence of atrial fibrillation after successful electrical cardioversion. *Int Heart J*. 2010;51:30-3.
12. Ezekowitz M, Netrebko P. Anticoagulation in management of atrial fibrillation. *Curr Opin Cardiol*. 2003;18:26-31.
13. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, et al., STAF Investigators. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690-6.
14. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol*. 2011;57:160-6.
15. Wang J, Meng X, Li H, Cui Y, Han J, Xu C. Prospective randomized comparison of left atrial and biatrial radiofrequency ablation in the treatment of atrial fibrillation. *Eur J Cardiothorac Surg*. 2009;35:116-22.
16. Franz MR, Karasik PL, Li C, Moubarak J, Chavez M. Electrical remodeling of the human atrium: similar effects in patients with chronic atrial fibrillation and atrial flutter. *J Am Coll Cardiol*. 1997;30:1785-92.
17. Marcucci R, Betti I, Cecchi E, Poli D, Giusti B, Fedi S, et al. Hyperhomocysteinemia and vitamin B6 deficiency: new risk markers for nonvalvular atrial fibrillation? *Am Heart J*. 2004;148:456-61.
18. Jacobsen DW. Homocysteine and vitamins in cardiovascular disease. *Clin Chem*. 1998;44:1833-43.
19. Mihm MJ, Yu F, Carnes CA, Reiser PJ, McCarthy PM, Van Wagoner DR, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. *Circulation*. 2001;104:174-80.
20. Law P, Kharche S, Stott J, Zhang H. Effects of elevated homocysteine hormone on electrical activity in the human atrium: a simulation study. *Conf Proc IEEE Eng Med Biol Soc*. 2009;2009:3936-9.
21. Cai BZ, Gong DM, Liu Y, Pan ZW, Xu CQ, Bai YL, et al. Homocysteine inhibits potassium channels in human atrial myocytes. *Clin Exp Pharmacol Physiol*. 2007;34:851-5.
22. Bertaglia E, Tondo C, De Simone A, Zoppo F, Mantica M, Turco P, et al. Does catheter ablation cure atrial fibrillation? Single-procedure outcome of drug-refractory atrial fibrillation ablation: a 6-year multicentre experience. *Europace*. 2010;12:181-7.