Ventral cardiac denervation reduces the incidence of atrial fibrillation after coronary artery bypass grafting

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Objectives: Because the autonomic nervous system is an important determinant in the appearance of atrial fibrillation, we have assessed the role of ventral cardiac denervation for its prevention.

Methods: Patients undergoing low-risk coronary artery surgery were enrolled. No routine antiarrhythmic drugs were administered before or after the operation. Ventral cardiac denervation was performed in 207 patients, and 219 patients were used as control subjects. Denervation was performed before cardiopulmonary bypass. The groups were comparable regarding demographic, clinical, and operative variables.

Results: The additional time for the denervation was 5 ± 2 minutes, and there were no associated complications. Postoperative atrial fibrillation was present in 15 (7%) patients undergoing ventral cardiac denervation (95% confidence interval, 4%-12%) and in 56 (27%) control subjects (95% confidence interval, 18%-35%). Patients submitted to ventral cardiac denervation had fewer and less severe episodes of atrial fibrillation, and no patient had atrial fibrillation after discharge. Ventral cardiac denervation was the most significant predictor of postoperative atrial fibrillation (odds ratio, 0.42; confidence interval, 0.23-0.78; $P = .006$). Age of greater than 65 years (odds ratio, 1.67; confidence interval, 0.96-2.9; $P = .067$) was a highly suggestive predictor. The analysis of the effect of ventral cardiac denervation correlated with the patient's age showed a more pronounced effect in patients younger than 70 years (odds ratio, 0.43; confidence interval, 0.22-0.86; $P = .022$).

Conclusions: Ventral cardiac denervation is a fast and low-risk procedure. Its use significantly reduces the incidence and severity of atrial fibrillation after routine coronary artery bypass surgery. Patients younger than 70 years of age are expected to have a higher success rate than those older than 70 years.

Atrial fibrillation is the most common morbid event after coronary artery bypass grafting. Its incidence ranges from 19% to 27%, as reported by the Society of Thoracic Surgeons database. Many groups have tried to understand and treat this difficult problem and have formulated different hypotheses to explain its origin. An imbalance of the autonomic nervous system after surgical intervention has been accepted as a major determinant for this phenomenon.¹⁻³

We designed a study to assess the role of partial ventral cardiac denervation in reducing the incidence of postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting.

Material and Methods

Four hundred twenty-six patients from 3 different institutions were enrolled in a prospective nonrandomized study. Eligible patients were those submitted to coronary artery bypass grafting and presenting a Euroscore of less than 5. Patients with a previous history of atrial arrhythmias were excluded from this study.

The criteria used for the definition and classification of atrial fibrillation were those recently proposed by the Committee for the Development of Guidelines for the Management of Patients with Atrial Fibrillation.⁴

Prophylactic medication for the prevention of atrial fibrillation was not given before or after surgical intervention. Patients who had been receiving β -blockers before the operation did not interrupt the treatment, which was resumed immediately after the operation.

The demographics and hemodynamic characteristics of the 2 groups are described in Table 1.

Surgical Technique

After median sternotomy, the heart was exposed, and ventral cardiac denervation was performed. Ventral cardiac denervation is achieved by removing the nerves around the large vessels of the base of the heart that run from the right side of the superior vena cava and end at the level of the midportion of the anterior pulmonary artery. This was done by excising the fat pads that surround the superior vena cava, the aorta, and the anterior and right lateral aspects of the main pulmonary artery (Figure 1).

The dissection started at the right side of the pericardial cavity, and the superior vena cava was completely dissected and freed from the right pulmonary artery. Then the fat pad around the aorta was entirely dissected. Finally, all the fatty tissues in the aorta-pulmonary groove and the inner half of the adventitia of the anterior pulmonary artery up to its left border were cut.

Ventral cardiac denervation was performed in 207 patients who provided informed consent, and 219 patients were used as control subjects.

After this procedure, conventional coronary artery bypass grafting was performed either with or without cardiopulmonary bypass under normothermia or moderate hypothermia. Myocardial protection was achieved by using either blood or crystalloid cardioplegia.

TABLE 1. Demographics and clinical characteristics of the patients

	VCD group	Control group	P value
Age (y)	60 $\pm$ 10	62 $\pm$ 8	.190
Male sex (%)	76	75	.899
EuroSCORE	1.3 $\pm$ 0.4	1.5 $\pm$ 0.8	.068
Hypertension (%)	36	40	.458
COPD (%)	3	2	.729
Diabetes (%)	26	27	.902
Left main disease (%)	14	16	.663
Three-vessel disease (%)	72	66	.222
Two-vessel disease (%)	14	18	.325
LV function (%)			.121
Good >50	89	87	
30 < moderate < 50	8	5	
Poor <30	3	8	
AA medication (β -blockers) (%)	75	81	.176
Magnesium level (mmol/L)	0.86 $\pm$ 0.03	0.8 $\pm$ 0.07	.003

VCD, Ventral cardiac denervation; COPD, chronic obstructive pulmonary disease; LV, left ventricular; AA, anti-arrhythmic.

The 2 groups were comparable regarding the operative data (Table 2).

Detection of atrial fibrillation after surgical intervention was based on patients' complaints and on daily electrocardiograms obtained for all patients. Telemetry was used in 34% of patients (35% in the ventral cardiac denervation group and 33% in the control group) for the first 4 postoperative days and for the whole hospital admission period in 15% of the patients in both groups.

Statistical Analysis

Variables were expressed as frequencies and percentages for discrete factors, mean values for normally distributed continuous factors, and median values (25th and 75th percentiles) for continuous factors of nonparametric distribution.

Statistical comparison of baseline characteristics and outcomes was performed by using the 2-tailed χ^2 test with the Yates correction or the Fisher exact test for categorical variables and the 2-tailed Student *t* test for continuous variables. Unpaired nonparametric variables were compared by using the Mann-Whitney test.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the occurrence of postoperative atrial fibrillation in relation to treatment group (ventral cardiac denervation vs control).

Multivariate logistic regression analysis was used to identify the independent predictors of postoperative atrial fibrillation among the following factors: age, sex, diabetes, hypertension, chronic obstructive pulmonary disease, extent and severity of coronary artery disease, left ventricular systolic function, treatment group, hospital, surgeon, use and type of cardiopulmonary bypass, type of cardioplegia, duration of myocardial ischemia, number and type of grafts, preoperative antiarrhythmic medication, and preoperative and postoperative blood magnesium levels.

A subgroup analysis was performed to evaluate the interaction between patient age and the effect of ventral cardiac denervation on the prevention of postoperative atrial fibrillation. The same was done to test for an interaction between prior use of β -blocker drugs and the effect of the surgical procedure.

Figure 1. Diagram of the technique of ventral cardiac denervation. Arrows show the areas of dissection.

Statistical analysis was performed with the SPSS system 9.0 (SPSS Inc, Chicago, Ill).

Results

In-hospital mortality occurred in 5 patients, 2 in the denervation group and 3 in the control group, resulting from sepsis ($n = 2$), low cardiac output ($n = 1$), and cerebrovascular accident ($n = 2$).

The additional length of time required for the denervation was, on average, 5 ± 2 minutes, and there were no complications associated with the procedure.

There was no significant excess bleeding, and the postoperative blood drainage was similar in both groups (see Table 3).

A total of 71 patients experienced postoperative atrial fibrillation. This occurred in 7% (95% CI, 4%-12%) of patients in the active treatment group versus 27% (95% CI, 18%-35%) in the control group ($P < .001$).

The episodes of atrial fibrillation were either paroxysmal or persistent. All patients in whom atrial fibrillation was diagnosed were treated with amiodarone or β -blocking agents.

In the denervation group postoperative atrial fibrillation was paroxysmal in 3 patients and persistent in the remaining 12. After discharge, no patient required readmission for the treatment of atrial fibrillation.

TABLE 2. Operative data

	VCD group	Control group	P value
Operation with CPB (%) and normothermia	58	52	.258
moderate hypothermia	24	27	.554
Cardioplegia (%)			.586
Blood	76	73	
Crystalloid	24	27	
Off-pump (%)	18	21	.512
Grafts per patient	3.2 ± 0.4	2.9 ± 0.1	$<.001$
Arterial grafts per patient	1.1 ± 0.3	1 ± 0.2	$<.001$
Myocardial ischemia (min)	53 ± 18	50 ± 20	.105
Duration of CPB (min)	95 ± 19	99 ± 19	.030

VCD, Ventral cardiac denervation; CPB, cardiopulmonary bypass.

TABLE 3. Postoperative data

	VCD group	Control group	P value
Mortality (%)	0.9	1.3	.947
Denervation (min)	5 ± 2	—	
Blood drainage (mL)	946 ± 157	941 ± 124	.706
CPK-MB	$855 \pm 103/34 \pm 6$	$750 \pm 98/50 \pm 6$	.001
Troponin (ng/mL)	0.6 ± 0.4	0.7 ± 0.2	.001
Magnesium (mmol/L)			
Day 1	0.73 ± 0.05	0.8 ± 0.04	$<.001$
Day 3	1.2 ± 0.02	1.3 ± 0.03	$<.001$
Hospital stay (d)	8 ± 2.5	8 ± 3	.624

VCD, Ventral cardiac denervation; CPK-MB, creatine phosphokinase MB fraction.

Fifty-six patients in the control group had atrial fibrillation: 2 had paroxysmal and 54 had persistent atrial fibrillation. Eleven of the 54 patients with persistent atrial fibrillation required additional electrical cardioversion for rhythm control. Five patients were readmitted after discharge because of atrial fibrillation. Three of these had experienced either paroxysmal ($n = 2$) or persistent ($n = 1$) atrial fibrillation during hospitalization.

Of all the potential predictors of postoperative atrial fibrillation, only age of greater than 65 years (OR, 1.73; 95% CI, 1.02-2.93; $P < .05$) and ventral cardiac denervation (OR, 0.40; 95% CI, 0.23-0.74; $P = .004$) were significant prognostic factors for the development of postoperative atrial fibrillation. Ventral cardiac denervation remained an independent predictor of postoperative atrial fibrillation after adjustment for the effects of all the variables tested (OR, 0.42; 95% CI, 0.23-0.78; $P = .006$) and was the most significant negative predictor of postoperative atrial fibrillation. Age of greater than 65 years (OR, 1.67; 95% CI, 0.96-2.9; $P = .067$) showed an important trend for predicting postoperative atrial fibrillation.

A significant interaction was observed between patient age and the protective effect of ventral cardiac denervation.

In patients younger than 70 years of age, the overall postoperative incidence of atrial fibrillation was 16.6%. In this age group ventral cardiac denervation was associated with a significant reduction in the incidence of postoperative atrial fibrillation: 10.5% versus 21.4% for patients in the control group (OR, 0.43; 95% CI, 0.22-0.86; $P = .022$). In patients 70 years or older, ventral cardiac denervation determined a nonsignificant reduction in the incidence of postoperative atrial fibrillation ($P = .142$).

No significant interaction was observed between the treatment effect of ventral cardiac denervation and prior medication with a β -blocking drug ($P = .847$ for the interaction test). Patients previously treated with a β -blocker derived significant benefit from ventral cardiac denervation for the prevention of postoperative atrial fibrillation (OR, 0.45; 95% CI, 0.23-0.87; $P = .025$). The relatively small group of patients not receiving a β -blocking drug before surgical intervention seemed to derive similar benefit from ventral cardiac denervation (OR, 0.29; 95% CI, 0.09-1.01; $P = .083$).

Discussion

The intrapericardial epicardic nerves of the heart have been described extensively. However, some aspects of its physiology still remain unclear.⁵⁻⁷

Cardiac denervation is a surgical procedure described by Arnulff in 1936.⁸ It was widely performed in the 1970s for the prevention of coronary artery spasms. There are several published studies reporting results of this surgical technique, and although its safety was well established,^{9,10} no mention was made of the postoperative rhythm of the patients. Amano and colleagues¹¹ studied the effects of intrapericardial cardiac denervation on the flow of coronary artery bypass grafts and showed its beneficial effect on systemic hemodynamics and coronary circulation as a result of vasodilatation of the distal arterioles. The knowledge about the type of axons included in the nerves of the ventral plexus is very limited and requires further clarification to fully understand the pathophysiology of its function.

Performing this operation in a more limited fashion makes it very safe and fast. No procedure-related complications, namely excess bleeding, were observed. The reported incidence of postoperative atrial fibrillation after coronary artery bypass grafting varies from 5% to 40%.³ A limitation of our study is related to the method of detection of atrial fibrillation because events of atrial fibrillation might have been undetected, either because they were asymptomatic or because not all patients were undergoing telemetry control. However, because of the large size of our cohort of patients, this limitation is partially overcome in our study.

The methods used to diagnose atrial fibrillation appear to have a significant influence on this reported incidence. Ap-

proximately 15% of the patients in our series presented with asymptomatic or paroxysmal atrial fibrillation, and only telemetry allowed its diagnosis.

Many factors have been thought to correlate with the incidence of atrial fibrillation. Of these, only age is a consistent independent predictor for the occurrence of atrial fibrillation after coronary artery bypass grafting.^{12,13} Other factors, such as sex, hypertension, the use of β -blocking agents, the duration of cardiopulmonary bypass, off-pump surgery, net fluid balance, magnesium levels before and after the operation, prophylaxis with amiodarone, atrial ischemia, and atrial pacing have been quoted as being determinants of the incidence of postoperative atrial fibrillation. Yet there are conflicting reports on these issues,¹²⁻²³ and in some instances, their documented beneficial effect is limited.²⁴⁻²⁸

Some of the abovementioned factors were present in both groups in our study and were not significant predictors for the occurrence of postoperative atrial fibrillation. The only significant factors for the occurrence of postoperative atrial fibrillation were ventral cardiac denervation and age.

Hogue and associates¹ have shown that patients who have atrial fibrillation after coronary artery bypass graft surgery have reduced heart rate complexity, higher heart rates, and more frequent atrial ectopy before the onset of the arrhythmia.

Previous studies have shown that decreased RR interval variability and premature atrial contractions are associated with an increased incidence of postoperative atrial fibrillation, thus reinforcing the concept that an autonomic nervous system imbalance is at the origin or is a mediator of atrial fibrillation.² It should be noted that some of these mechanisms are related to the stress induced by an operation or caused by cardiopulmonary bypass.^{29,30}

It was also surprising to observe a more pronounced effect of ventral cardiac denervation when performed on patients younger than 70 years of age. Although surprising, this should not be unexpected because it is well known that older persons, although having the same number of nerves as younger persons, have less axons per nerve. Those morphologic features might explain the better results of ventral cardiac denervation when used in younger patients.

Another clinically significant observation was that the incidence and severity of atrial fibrillation episodes after coronary artery bypass grafting was significantly reduced as a result of the denervation procedure. It is noteworthy that in addition to the absolute number of episodes being smaller, they were also less severe. In the group of patients submitted to ventral cardiac denervation, cardioversion was always achieved solely with medical therapy, thus avoiding the need for electrical cardioversion. The fact that no hospital readmissions were required as a result of the late development of atrial fibrillation is also very encouraging.

This experience reinforces the concept that the autonomic nervous system plays an important role in the development of postoperative atrial fibrillation. The mechanisms underlying its action are still to be determined, but it should be pointed out that by performing ventral partial cardiac denervation, we were able to reduce the incidence and severity of atrial fibrillation after routine coronary artery bypass grafting.

In summary, we conclude that ventral cardiac denervation is a fast and low-risk procedure that significantly reduces the incidence of atrial fibrillation after routine coronary artery bypass surgery.

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Discussion

Dr R. Damiano (St Louis, Mo). Postoperative atrial fibrillation remains a vexing clinical problem and a significant source of morbidity and increased hospital costs after cardiac surgery. I congratulate Dr Melo and his group for examining a novel surgical approach, partial cardiac denervation, in an attempt to decrease the incidence of this common complication. This was a beautifully presented study, and I would like to thank Dr Melo for providing me the manuscript in advance to read before this meeting.

I have several questions regarding the study. First, in terms of study design, this was a prospective but nonrandomized trial. How did you exclude selection bias as a variable that might have affected your results, and particularly, were the postoperative caregivers blinded to the intraoperative treatment?

Second, the study does have a weakness in that only 15% of patients had telemetry during their entire hospital stay. Did this

perhaps result in an underreporting of atrial fibrillation? In the manuscript you did state that 15% of patients received diagnoses on the basis of telemetry alone, and thus this small group of patients who had continuous telemetry might have had an undo influence on the study outcome.

My third question is that one of the major complications associated with postoperative atrial fibrillation is its negative effect on both hospital stay and overall costs after coronary revascularization. Did you look at either of these parameters in this prospective study?

Finally, cardiac innervation is extensive, and this limited approach clearly does not completely denervate the heart. Do you think that partial cardiac denervation affects primarily parasympathetic or sympathetic fibers? In any subgroup of patients, were any provocative tests performed to evaluate the extent of denervation? Also, were any of the electrophysiologic manifestations of autonomic imbalance measured, particularly RR variability, P-wave alternans, and premature atrial contractions?

I congratulate you again on a very nice study and your investigation of novel approaches to this old problem. I would also like to thank the Association for the privilege of commenting on this manuscript.

Dr Melo. Dr Damiano, thanks for your comments. I will try to answer all your questions.

The study design was not biased in the sense that even though not being prospectively randomized, actually only in one institution was it prospectively randomized, but in the other institutions not because this was mostly assigned to the surgeons' possibility of doing that, but it was completely blinded regarding the postoperative care. And of course, only 15% of the patients had telemetry during the whole hospital admission, but this happened in both groups, not only in the group of patients who had denervation. Of course, I assume that there might have been some episodes of paroxysmal atrial fibrillation that were not detected, but if so, they were in the 2 groups and not only in one.

The hospital stay, as I pointed out in this presentation, was the same in both groups, 8 days. We were also very puzzled with the

question of what we were removing. Were those sympathetic nerves or parasympathetic nerves? And that is why we decided to undertake a more profound study that is now being done mostly in Leiden. It is very puzzling, but as I showed, the number of nerves is highly variable. When we dissect those nerves off the heart, which we have done for 1 year in specimens, we see that some of the fibers are coming from the vagus, the fibers that are in the plexus of the heart, and some are coming from the sympathetic chains of the spine. And by trying to stain nerves and trying to determine whether the nerve was parasympathetic or sympathetic, we were surprised to see that the axons take some stain or other, but most intriguing, some of the axons do not take any stain, and this is a topic of ongoing research. If you ask me what I believe, I believe at the moment that most nerves or the nerves of so-called ventral plexus, they are mixed: they are fibers that are sympathetic and fibers that are parasympathetic.

It has been well documented, not by ourselves but before us at Washington State by the anesthesia group of Charles Hogue, that all those patients have dispersion of refractoriness, reduced heart rate variability, and often frequent atrial ectopy. In our own groups, we have done tilt tests at 1 and 3 months in selected patients of both groups, and we could find no difference between the 2 groups.

Dr H. Schaff (*Rochester, Minn*). I would like to ask one question of Dr Melo. You had an incidence of atrial fibrillation in the control group of 50%, and yet you did not have a difference in the hospital stay. Was that expected? Was that what you projected?

Dr Melo. No. We had an incidence of 27%, not 50%.

Dr Schaff. And how about the resting heart rate? Was the resting heart rate after the operation different in the patients who were denervated versus those who were not, and did you have a difference in pacing requirements?

Dr Melo. We did not see any difference because this is a limited denervation, and that is our explanation for not seeing any effects from this procedure.