Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve

Parla Astarci a,*, David Glineur a, Joelle Kefer b, William D’Hoore d, Jean Renkin b, Jean-Louis Vanoverschelde b, Gébrine El Khoury a, Cécile Grandin c

a Cardiovascular and Thoracic Surgery Department — University Hospital Saint-Luc, Brussels, Belgium
b Cardiology Department — University Hospital Saint-Luc, Brussels, Belgium
c Radiology Department — University Hospital Saint-Luc, Brussels, Belgium
d Statistical Department — University Hospital Saint-Luc, Brussels, Belgium

Received 2 September 2010; received in revised form 17 November 2010; accepted 23 November 2010; Available online 20 January 2011

Abstract

Objective: Cerebral embolization during trans-catheter aortic valve implantation (TAVI) has not been assessed clearly in the literature. Therefore, we compared the rate of cerebral embolisms with diffusion-weighted magnetic resonance imaging (DWI) in transfemoral (TF) and trans-apical (TA) approaches.

Method: Eighty patients benefited from TAVI between January 2008 and June 2010. Out of these, 35 were included in the study. Twenty-one were TF (group 1) and 14 TA (group 2). During the same period, 285 patients benefited from a conventional aortic valve surgery (aortic valve replacement (AVR)). Thirteen of these were also analyzed and considered as the control group (group 3). We systematically performed a DWI the day before the procedure and 48 h after. DWI studies were blindly analyzed by a neuroradiologist, and all patients had a clinical neurological assessment before and after the procedure, according the National Institutes of Health Stroke Scale (NIHSS).

Results: Thirty-two patients in the TAVI group had new cerebral lesions: 19 in the TF group and 13 in the trans-apical group (p = NS). Mean number of embolic lesions per patient was 6.6 in group I and 6.0 in group II (p = NS). Mean volume of embolic lesions was 475.0 mm³ in group I and 2170.5 mm³ in group II (p = NS). In group III, one patient had one new cerebral lesion (p < 0.05 vs TAVI) of 36.5 mm³ (p = NS vs TAVI). All patients were neurologically asymptomatic.

Conclusions: The incidence of silent cerebral embolic lesions after TAVI is significantly higher compared with the standard surgical AVR. The number of emboli is similar in the TF and TA groups but the volume tended to be higher in the TA group. However, there is no clinical impact of those lesions.

# 2010 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Diffusion-weighted magnetic resonance; Trans-catheter aortic valve; Cerebral embolization

1. Introduction

Cardiac surgery is increasingly performed on elderly patients. This population has more co-morbidities such as impaired ventricular function, coronary disease, peripheral vascular disease and renal insufficiency. These co-morbid factors have been described as independent factors of mortality in this older population [1].

Neurological complication is a dramatic postoperative event, especially in this population with poor life expectancy [2,3]. Indeed, cerebral damage after conventional aortic valve replacement (AVR) ranges from 0.21% to 2.0% for neurological death rate and from 1.1% to 6.6% for clinical stroke rate [4,5]. Therefore, from 1.1% to 6.6% (trans-catheter aortic valve implantation, TAVI) was first proposed to this very frail population with the expectancy to decrease the mortality and morbidity related with the procedure.

Magnetic resonance imaging (MRI), and especially diffusion-weighted imaging (DWI), is nowadays the most powerful tool for diagnosing acute ischemic brain lesions, and has become a surrogate marker for clinical and sub-clinical brain embolism [6]. DWI has already been used to evaluate the incidence of silent infarcts after angiographic procedures and carotid endarterectomy or stenting [7].

Therefore, we analyzed clinical and sub-clinical brain embolism by DWI in a single-center, prospective, non-randomized study to evaluate per procedural embolic events in patients undergoing TAVI. We compared the cerebral
embolic events between the transfemoral (TF) and the transapical (TA) approach. We also compared the TAVI group to a conventional AVR group.

2. Materials and methods

From January 2008 to June 2010, we performed 355 isolated aortic valve surgery. Eighty were TAVI procedure using Edwards Sapiens (Edwards Lifesciences Inc, Irvine, CA, USA) and 275 were conventional AVR.

The TAVI were divided as 50 TF and 30 TA. All patients were screened for inclusion into this prospective study. Exclusion criteria were: carotid artery stenosis >70% on duplex, presence of permanent pacemaker or defibrillator, patients who refused to participate in the study. Indication for TAVI was in concordance with the recent consensus statement [8].

Concomitantly, we included in the study 13 patients undergoing conventional AVR defined as the control group (CG). Patients’ characteristics are listed in Table 1. The study population was divided in three groups: group 1 TF, group 2 TA, and group 3 CG.

Cerebral DWI was performed in patients 24 h before implantation. For group 1 and 2 post-procedural DWI was performed after 48 h, and for group 3 after 72–96 h because of the external pacemaker leads.

The systematic clinical neurological examination was assessed following a standardized protocol according to the National Institutes of Health Stroke Scale (NIHSS) before and after implantation.

2.1. MRI protocol

A standard protocol using fast spin echo-fluid attenuated inversion recovery sequence (FSE-FLAIR) and diffusion-weighted-spin echo planar imaging (DWI SE-EPI) was applied in all patients before and after the procedure. The MR examination was performed at 1.5T (NT-Philips Healthcare or Intera-Philips Healthcare) in five patients in group 1, five in group 2, and one in group 3. The other patients were examined at 3T (Intera-Philips Healthcare or Verio-Siemens). The DWI sequence consisted of an initial T2-weighted acquisition followed by a second acquisition with the application of diffusion-sensitizing gradients in the three orthogonal directions with a b factor = 1000 s mm⁻². The exact repetition time and echo time differed slightly, according to the scanner.

A 1.5T, 24 axial slices with a thickness of 5 mm and a gap of 0.5 or 1 mm were acquired. The in-plane resolution at the acquisition was 1.9 × 2.4 mm², interpolated to 0.95 mm² at the reconstruction. A 3T, 32 axial slices with a slice thickness of 4 mm, a gap of 0.4 mm, and an in-plane resolution of 1.8 × 2.3 mm² interpolated to 0.9 mm² (Philips) or 1.3 × 1.6 mm² (Siemens) were obtained.

One neuroradiologist blinded to the surgical protocol reviewed all MR examinations and rated the DWI trace images for the presence of acute ischemic parenchymal damage. Lesions were quantified using the following scoring system: number of lesions, location according to the vascular territory (anterior, middle, posterior cerebral arteries, or vertebrobasilar arteries), side and cortical versus subcortical or deep gray matter. Moreover, a planimetry of each lesion was performed by manual contouring, and the lesion volume was calculated by multiplying the surface by the slice thickness and slice gap.

2.2. TAVI procedure

The Edwards Sapiens (Edwards Lifesciences Inc, Irvine, CA, USA) valve consists of a tri-leaflet bioprosthetic bovine pericardial tissue valve mounted and sutured in a balloon-expandable stainless-steel frame. The TF technique was performed as described by Cribier [9]. The TA technique was performed as described previously by Walther [10], and modified by our team [11].

2.3. Conventional AVR procedure

All conventional patients were operated by median sternotomy under classical cardiopulmonary bypass. Arterial cannulation was performed in the ascending aorta and venous cannulation in the right atrium. Myocardial protection was achieved with an intermittent antegrade warm blood cardioplegia every 15 min. Valve implantation was realized with a pledget below the annulus suture.

2.4. Statistical analysis

Descriptive statistics were performed using Statistical Package for Social Sciences (SPSS) statistical software. A p-value less than 0.05 was considered significant. Continuous variables are presented as mean ± standard deviation. One-way analysis of variance (ANOVA) was used to compare continuous variables between the three groups.

To analyze the relationships between the embolic cerebral lesions and type of procedure, we used two strategies. In a first strategy, we used negative binomial regression to model the relationships between the number of embolic cerebral

<table>
<thead>
<tr>
<th>Table 1. Patients characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Log EuroSCORE %</td>
</tr>
<tr>
<td>NYHA class</td>
</tr>
<tr>
<td>Ejection fraction %</td>
</tr>
<tr>
<td>Ao valve area (cm²)</td>
</tr>
<tr>
<td>Peak gradient (mmHg)</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n (%). NYHA: New York Heart Association functional class.
lesions and type of procedure, taking confounders into account. Negative binomial regression was preferred over Poisson regression because of observed overdispersion (variance > mean). The SAS procedure GENMOD was used. In a second strategy, we used logistic regression to model a binary variable (presence of absence of embolic cerebral lesion). Type of procedure was introduced in the form of dummy variables; other covariates were not transformed. The SAS procedure LOGISTIC was used. SAS procedures were run under SunOS (SAS 9.1 release).

3. Results

Forty-eight patients completed cerebral DWI pre- and postoperatively. Procedural success for valve implantation was 100% for all three groups.

3.1. Clinical results

Neurological examination after the procedure was similar to the neurological examination prior to the procedure in all patients. None of them had a clinical neurological deficit.

3.2. DWI results

Of the 48 patients, 33 had new embolic cerebral lesions. The median (mean, SD) number of lesions were four (mean = 5.9, SD = 6.8) in group 1, 4.5 (mean = 6.6, SD = 7.1) in group 2, and 0 (mean = 0.08, SD = 0.28) in group 3. Attack rate (presence of new lesions/number of patients) was 90% in group 1 (19/21), 93% in group 2 (13/14), and 8% in group 3 (1/13).

The mean number of emboli per patient was 6.0 in group 1, 6.6 in group 2 and 0.1 in group 3 (group 1 vs 3: p = 0.02; group 2 vs 3: p = 0.01 and group 1 vs 2: p = NS).

The mean volume of ischemic lesion was 475.0 mm³ in group 1, 2170.5 mm³ in group 2, and 36.5 mm³ in group 3 (group 1 vs 2 vs 3: p = NS). The majority of the lesions were located in the left brain (Fig. 1). The new embolic lesions were located in supraventricular and infra-tentorial (deep) regions.

Negative binomial regression adjusted for age and European System for Cardiac Operative Risk Evaluation (EuroSCORE) showed that type of lesion was significantly associated with the number of lesions. In comparison with group 3, parameter estimate of group 1 was 3.2 (standard error = 1.09, chi-square = 8.55, p = 0.0035) and parameter estimate of group 2 was 3.4 (standard error = 1.09, chi-square = 9.67, p = 0.0019). EuroSCORE was not significantly associated with the number of events, while age was positively associated.

Logistic regression resulted in similar associations. In comparison with groups 1 and 2, group 3 was strongly associated with the presence of lesions: parameter estimate = −4.85, standard error = 1.2, Wald chi-square = 16.3, p < 0.0001, and odds ratio (OR) = 0.008 (95% confidence limits = 0.001 and 0.083). No other variable was significantly associated with the presence of lesions once group 3 was in the regression model. Model fit was quite acceptable according to likelihood ratio and Hosmer–Lemeshow statistics.

As it can be seen, both strategies led to similar parameter estimates indicating a strong association of TA and TF procedures with new embolic lesions, as compared with the surgical approach.

4. Discussion

This study confirms that silent neurological lesions occur more often after TAVI than after conventional AVR. None of the patients with embolism were symptomatic.

However, in this study, we performed a standard neurological motricity examination before and after the procedure; we did not performed fine neurocognitive testing. Barber described in 2008 [12] that, after cardiac surgery, 63% had embolic events on cerebral DWI. Of those 5% had a clinical stroke, but neurocognitive decline was observed on cerebral DWI in 100% of patients who had silent embolic events. We strongly believe that neurosensitive testing is mandatory in further studies.

Recent articles reported a clinical stroke rate after TAVI less than 72% [13,14]. In this study, there was no incidence of clinical stroke, but we were surprised by the high incidence of the silent ischemic events during TAVI.

Embolization could occur during retrograde or antegrade arch catheterization, during balloon valvuloplasty or during endovascular implantation. We report a rate of new ischemic lesion of 90% in the TF approach compare with 92% in the TA approach. We were expecting a higher rate of emboli in the retrograde TF group because of the manipulation of the stiff devices into the aortic arch but antegrade TA approach did not reveal a lower rate of embolic events. Our results could help to elucidate the potential sources of embolism because there is no statistical difference between antegrade and retrograde approach in terms of mean number of embolic lesions. However, there is a statistical difference (p = 0.02) between TAVI (groups 1 and 2) and conventional surgery (group 3) with a rate of embolism of only 7%. We observed that the volume of the lesions is higher in the TA approach (2170.5 mm³) compared to the TF (475.0 mm³) approach and to conventional surgery (36.5 mm³), but this was not statistically significant.

The localization of the embolic lesions was also preponderant on the left cerebral hemisphere to a greater extent in the TF than in the TA group. We were expecting a
higher rate of right hemisphere embolism in the TA group because, during the antegrade approach, the guiding wire would go often into the right brachiocephalic trunk. Again, there is no difference in terms of the localization of the embolic lesions. Even in CG, the embolic side was the left hemisphere. Ghanem reported exactly the same results [15] with respect to CoreValve (Medtronic Inc, Minneapolis, Minnesota, USA) prosthesis implantation by the TF approach. We developed three hypotheses to understand why embolisms occur in the left hemisphere.

First, position of the left subclavian artery in the arch is in the direct way of the emboli released by the sheath when it runs from the descending thoracic aorta to the aortic arch. The external curve of the device scratches the aortic wall when you push it forwards to reach the aortic valve. The second hypothesis is regarding the total amount of emboli coming from the ascending aorta. We could say that one-third is going in each supraaortic arch vessel. However, the amount of embolus going into the brachiocephalic trunc is divided into three vessels: right carotid, right vertebral, and right axillary arteries. On the other hand, one-third of emboli goes directly into the left carotid and one-third into the left vertebral artery; hence, there are more emboli in the left brain than in the right. This is just our own analysis of the problem. The third hypothesis is based on an experimental fluid mixing model published by Lutz [17] to understand why anticancer drugs do not reach the left brain and the right brain. They propose that there is a stratification of the flow even into the Willis polygone. The drug injected by the left vertebral artery is not mixed into the Willis polygone and only the left brain receives the drug, and not the right brain. So, this means that the phenomenon is complex and we need further analysis of the emboli process using, for instance, an intracranial Doppler during the procedures.

To reduce the risk of cerebral embolism during TAVI, we have to develop and use efficient protection devices. There are already some of them available on the market; but no one has to develop and use efficient protection devices. There is no difference in terms of the localization of the embolic lesions. Even in CG, the embolic side was the left hemisphere. Ghanem reported exactly the same results [15] with respect to CoreValve (Medtronic Inc, Minneapolis, Minnesota, USA) prosthesis implantation by the TF approach. We developed three hypotheses to understand why embolisms occur in the left hemisphere.

One option to reduce the risk of embolism could be the 'no touch' technique described by Bagur [16] using a TA approach to deploy the valve with no wire and no catheter manipulation in the arch. In this article, the authors assume that the embolism occurs during the aortic arch manipulation. This is an isolated case report in which silent embolic lesions were not assessed by DWI. Further studies are mandatory to prove that absence of wire in the aortic arch signifies the absence of cerebral embolization.

4.1. Study limitation

This is not a randomized trial and the number of patients included in the three groups is limited. Regarding the control group 3, we agree that the population is younger than in groups 1 and 2. We had some difficulties to convince old people, who were eligible for AVR, to have preoperative and postoperative DW-MRI. Many of them refused because they had been already into a long preoperative work-up and they were unhappy to have surgical AVR rather than TAVI. On the other hand, old patients selected for TAVI knew that they are going to receive an expensive, less invasive, and new technique; hence, they accepted easily any additional investigations such brain DW-MRI before and after the procedure. Anyway, we still continue to further enroll older patients for further publication.

The neurological examination did not take into account neurocognitive testing. This is a clear weakness of our study, which needs to be assessed in further studies.

5. Conclusions

The incidence of cerebral silent embolic lesions is very high during TAVI and is similar in the TF and TA approaches. The conventional on-pump AVR is still the 'gold standard' treatment with a lesser risk of cerebral embolization. The impact of neurocognitive dysfunction need to be assessed in further studies.

References

Appendix A. Conference discussion

Dr T. Walther (Bad Nauheim, Germany): There is increasing evidence that there are some lesions on MRI, and we do not know what clinical relevance that has. So probably in the future you are very right that we need a multicenter study. We need a broader picture that has neurocognitive function testing pre-, postop, and even at follow-up, to really have a better understanding of the relevance of those lesions.

I would like to congratulate you for a very low rate of such lesions in your conventional group, so this is excellent, whereas it is higher than expected in the trans-catheter group. And the question is, it is kind of disappointing the results are not better than transfemoral. Is it due to case mix that you of course didn’t randomize? You kind of selected sicker patients to the trans-apical cohort? Do you have any assessment on the vascular status of those patients? How much calcification do they have somehow. I think it is a real concern for us, and we should somehow connect the disease to better define incidences of stroke and to reduce the stroke rate somehow. I think it is during the frame deployment, because we don’t touch the aortic arch, really.

Dr Falk: Your findings are in line with the previous presentations in this session. In the British registry we saw a 3.5% stroke rate overall. In the Belgian registry a 5% stroke rate was reported, going up to 10% in the trans-apical group. You are presenting a 90% incidence of new brain lesions. I think this is really of concern.

Dr F. Mohr (Leipzig, Germany): I think this is, again, an example where we need a combined approach with our neurologists and radiologists. There is a parallel study for AF ablation. I don’t know whether you recall these numbers. If the EP guys perform trans-catheter atrial fibrillation ablation, they report an incidence up to 25% of lesions on MRI, and, of course, everything resolves, so we don’t really know the definite neurological outcome.

Peter Kappetein and I are always fighting in terms of coronary artery disease to better define incidences of stroke and to reduce the stroke rate somehow. I think it is a real concern for us, and we should somehow connect with the neurologists to have a kind of objective reading and diagnosis of these incidences, otherwise it may be under-reported.

Dr R. Dion (Genk, Belgium): Maybe just a short question. Wouldn’t it be possible to register all the hits going to the carotid or to the vertebral arteries during the procedure, because then you would at least know when it happens. Maybe during the balloon valvuloplasty?

Dr Astarci: I am sure it is a good suggestion, but it is a new technique and the setup is quite difficult at the beginning, and we did not perform any transcranial Doppler or other investigation. But you are completely right, we have to do something to find out when this embolism occurs.