Perspective

Retrograde femoral arterial perfusion and stroke risk during minimally invasive mitral valve surgery: is there cause for concern?

Paul Modi[1], **W. Randolph Chitwood Jr**[2]

[1]Liverpool Heart and Chest Hospital, Liverpool, UK; [2]East Carolina Heart Institute, Greenville, NC, USA

Corresponding to: Mr. Paul Modi, MD, FRCS, Consultant Cardiac Surgeon. Liverpool Heart and Chest Hospital,Thomas Drive, Liverpool, UK. L14 3PE. Email: paulmodi@doctors.org.uk.

Recent data have suggested that retrograde arterial perfusion (RAP) during minimally invasive mitral valve surgery (MIMVS) is associated with a higher stroke rate than sternotomy approaches. To assess whether there is genuine cause for concern, we examine the strengths and weaknesses of this data. A multitude of confounding factors obfuscate interpretation of the data including imprecise definitions of MIMVS, the effect of the substantial learning curve, retrospective comparisons of small historic cohorts with baseline differences and differing risk profiles for atherosclerosis, different methods of aortic occlusion and lack of reporting of peripheral vascular disease (PVD)/aortic assessment in patient populations. In patients with severe (grades IV and V) aortic arch/ascending aortic atherosclerosis, RAP has clearly been shown to be associated with an increase in risk of cerebral embolic complications. It would be reasonable to assume that grades IV/V atheroma anywhere along the aorto-iliac axis (from femoral cannulation site to carotid arteries) may also increase the risk of stroke. Hence those *at risk* of severe atherosclerotic vascular disease should be screened to fully assess the aortoiliac axis. Apart from this patient group, there is no convincing evidence (without confounding variables) that retrograde perfusion *per se* during minimally invasive mitral surgery increases the risk of stroke. This may be due to the largely differing aetiologies of vascular and mitral degenerative disease.

Keywords: Surgical procedures, minimally invasive; thoracic surgery, video-assisted; mitral valve insufficiency; stroke; cardiopulmonary bypass

Submitted Nov 11, 2013. Accepted for publication Nov 25, 2013.
doi: 10.3978/j.issn.2225-319X.2013.11.13

Introduction

Conventional median sternotomy as a surgical approach to the mitral valve yields excellent short- and long-term results and has set an extremely high standard (1). More recently, less invasive approaches have been introduced, including the right anterolateral minithoracotomy (4-6 cm), with or without robotic assistance, in order to reduce the surgical trauma and hasten recovery. Compared to a sternotomy, it has been shown to be associated with comparable short- and long-term mortality but reduced pain, transfusions and post-operative atrial fibrillation (AF); duration of ventilation, intensive care unit (ICU) and hospital stay are also shortened, and there are obviously fewer sternal complications (2). However, perhaps the greatest benefit is one that is most difficult to measure and that is speed of recovery once the patient leaves hospital, with return to normal activity in 3 weeks rather than 2½ to 3 months with a sternotomy (3-5).

Limited intraoperative exposure requires extensive modification of the surgical technique. The standard set-up utilises retrograde arterial perfusion (RAP) through the femoral artery, although several centres have evolved to central cannulation with antegrade aortic perfusion (AAP) due to concerns about the risk of stroke with RAP (6-8). Central cannulation requires some modification of the incision location with a more anterior, superior (3rd intercostal space rather than 4th) and larger incision facilitating this, which critics claim may negate many of the benefits of the small non-rib spreading minithoracotomy used in robotic and video-assisted approaches. Certainly, the ascending aorta is not readily accessible with these latter procedures.

Critique of data suggesting a higher stroke risk with retrograde arterial perfusion

In 2010, an analysis of 28,143 isolated primary MV operations for mitral regurgitation (MR) from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgical Database (ACSD) over a 5-year period from 2004-2008 suggested that there was a 1.96 fold increase in the risk of stroke with less invasive mitral valve (LIMV) surgery despite a lower risk profile for these patients (9). This was partly driven by a threefold increase in stroke with a beating or fibrillating heart although once these patients were excluded, the risk of stroke still remained higher in the LIMV group albeit less so (1.52% *vs*. 0.92%, LIMV *vs*. sternotomy, P=0.0002). However, if we look critically at this paper, there were several confounding variables:

(I) There was no field in the STS data set for incision location during this time period. Therefore the authors used femoral cannulation as a *surrogate* for LIMV surgery. A previous version of the dataset [2002-2004] included both incision type and cannulation strategy and the authors found that in this dataset over 5% of patients having femoral cannulation did not have a thoracotomy approach. This could clearly have confounded their results.

(II) The median number of LIMV cases per centre per year submitting data to the STS ACSD was three. We have learnt from Prof Mohr's group in Leipzig that this is an operation with a long learning curve (75-125 cases) with better results achieved in surgeons who do more than one case per week (10). Thus, on average, it would take only one surgeon in each unit a whole career to traverse the learning curve. Assessing results of a procedure performed by surgeons still in their learning curve will clearly bias the results.

(III) The authors state in their manuscript that "femoral cannulation was not independently related to increased risk for stroke in the LIMV operations". If LIMV is defined as "femoral cannulation", why is the first term predictive and not the second?

Nevertheless, this was followed in 2011 by a consensus statement from the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) based on a meta-analysis of 35 studies (only two of which were randomised trials) (2). This documented a 1.79 fold increase in the risk of stroke with a minimally invasive approach, but on subgroup analysis this appeared driven by a higher stroke risk in those studies reporting endoaortic balloon occlusion (relative risk 1.72, P=0.09) and not transthoracic clamping (relative risk 0.80, P=0.85). This introduces another confounding variable in interpreting data from studies which include both external and endoaortic clamping. However, any meta-analysis is limited by the quality of the available studies and for the analysis of stroke risk there were only 11 of 35 studies suitable for inclusion, five of which were published prior to 2003 on data going back to 1996, that is, on data from right at the start of the learning curve. And again we come back to the confounding variable of the learning curve for this operation. Clearly the writing committee were concerned about the data quality as they concluded that "the available evidence consists almost entirely of observational studies and must not be considered definitive until future RCTs address the risk of stroke".

The New York University (NYU) group, who have moved from retrograde to antegrade perfusion, then published three important papers in successive years from 2010. In the former, they reported on 905 high-risk reoperative mitral procedures, two-thirds of which had concomitant procedures and half of which were greater than 70 years of age (11). The risk of stroke with retrograde arterial perfusion was 4.4 times higher than with antegrade perfusion for the whole cohort. However, this data needs to be interpreted with the knowledge that for isolated mitral valve reoperations there was no significant difference in the stroke rate. In the conference discussion that followed the authors acceded that these were very high-risk atherosclerotic patients and that it is only in these patients that retrograde perfusion carries an increased risk.

The following year, they looked at a heterogenous group of 3,180 *primary* isolated minimally invasive mitral and aortic operations and noted a 3.4 fold increase in risk of stroke with RAP, lower than their previous publication presumably because reoperations were excluded (12). Importantly there was no difference in patients <50 years old, presumably due to a lower atherosclerosis burden. Thus, one begins to appreciate that the common mechanism in all these papers reporting stroke risk is the *burden of atherosclerosis* of the study population.

Glauber's group in Massa, Italy, have recently documented a 4.28 fold increase in stroke risk with RAP in 1,280 patients undergoing primary minimally invasive mitral valve surgery (MIMVS) (8). Retrograde perfusion was used at the start of their learning curve and one-third of these had endoaortic balloon occlusion, whereas all patients who were perfused antegradely had external aortic clamping. The ISMICS meta-analysis suggested that the majority of strokes occurred in studies using endoaortic cross-clamping (2). Thus, we come back again to confounding variables, in this case the learning curve and aortic occlusion technique.

However, for every study that reports a higher stroke risk with MIMVS, there are studies reporting no difference in this. The only other meta-analysis on this subject published in 2008 concluded that of six eligible studies, there was no significant difference in neurological event rate [odds ratio 0.66, 95% confidence interval (CI) 0.23-1.93, P=0.45] (5). The following year, the combined Chitwood/Hargrove series of almost 1,200 patients undergoing non-robotic MIMVS reported a stroke rate of only 1.2% for transthoracic clamping (13). Also from the Chitwood group, the stroke rate was only 0.6% in 540 consecutive robotic MV repairs and this was *without* pre-operative aortic CT screening (14). In comparison, the data from all units in the UK from 2004-2008, where over 95% of isolated mitral valve operations are still performed through a sternotomy, revealed a stroke rate of 1.4% (www.bluebook.scts.org). Three propensity matched studies from high-volume institutions (Cleveland, Leipzig, Mayo/UPenn) have all shown no difference in stroke risk with RAP compared to antegrade perfusion (15-17).

How can we make sense of this conflicting data?

Two recent studies have shed some light. Firstly, the NYU group finally looked at a much more homogenous group of 1,280 patients undergoing primary isolated MIMV repair and concluded that the only significant risk factor for neurological events was the use of retrograde perfusion in high-risk patients with aortic disease (odds ratio 8.5, P=0.04) (6). Aortic disease was defined on the basis of grade IV or V disease in the arch or ascending aorta on intraoperative transoesophageal echo. Thus, it would seem likely that it is the characteristics of the NYU patient populations and their decreasing tendency to aortic atherosclerosis in each of their three consecutive manuscripts from 2010 (reoperations), 2011 (primary AV and MV) and 2012 (isolated primary MV repair) that explains their observation of a reduction in the odds ratio for stroke risk with each successive manuscript. This simply elucidates that the risk factors for degenerative mitral valve disease are very different from those of aortic atherosclerosis or aortic valve disease, with the exception of age.

The second study is from the Cleveland Clinic group (18) who screened 141 low-risk patients being worked up for robotic MV surgery with contrast-enhanced multidetector CT (MDCT) of the chest, abdomen and pelvis, and found that one in five patients had significant *subclinical* aorto-iliac atherosclerosis, where significant was defined on the basis of circumferentiality and thickness, not grading as used in the previous paper. Multivariate logistic regression analysis found that significant atherosclerosis and age were associated with a change in operative strategy away from RAP to antegrade perfusion through a complete/partial sternotomy. One patient who was screened did have an embolic event and, as there was no control group, the authors did not demonstrate any association between avoidance of stroke and CT screening. Nevertheless, it would seem that omitting aortic screening may potentially miss subclinical aortoiliac disease in one in five and we know that RAP in the presence of 'severe' aortic atherosclerosis is a risk factor for stroke.

If we now relook at the Chamberlain Memorial paper by Gammie *et al*. in light of this, we see that there is no data on PVD or its extent and it seems unlikely that the LIMV patients were screened during that time period (9). Similarly, in the ISMICS Consensus Statement, only one of the 11 studies included in the stroke analysis either gives data on the incidence of PVD or use of pre-op aortic screening (2). Occult aortoiliac atherosclerosis and lack of assessment of the *whole* aortoiliac system, since the most common location for disease is at the aortic bifurcation, may explain the observations of a higher stroke risk with RAP. There clearly are other considerations when assessing stroke risk with MIMVS compared to sternotomy, such as longer CPB times and adequacy of deairing. However, parity in operative times is achieved with experience and, when CO_2 insufflation is utilised, there is evidence that there is no difference in cerebral microembolic rate as detected using transcranial Doppler even with endoaortic balloon occlusion (19). Flooding the pleural cavity and heart with several hundred litres of CO_2 during a procedure should theoretically displace all the air making air embolisation less of an issue.

Conclusions

Studies reporting higher stroke rates with RAP have multiple confounding factors that need to be borne in mind when interpreting the data. These include imprecise definitions of MIMVS, the effect of the substantial learning curve for the procedure in historic data, retrospective comparisons of small cohorts with baseline differences and differing risk profiles for atherosclerosis, differing methods of aortic occlusion and lack of reporting of PVD/aortic assessment in patient populations.

In patients with severe arch/ascending aortic atherosclerosis, RAP has clearly been shown to be associated with an increase in risk of cerebral embolic complications. If grade IV or V atheroma in the arch has been shown to be associated with CVA, then it would be reasonable to assume that grades IV/V atheroma anywhere along the aorto-iliac axis (from femoral cannulation site to carotid arteries) would be also. Hence, it is important to understand the atherosclerotic burden in patients being considered for RAP during MIMVS and it would therefore seem prudent to screen patients *at risk* of severe atherosclerosis. Screening *all* patients on the basis of Moodley *et al*. (18) cannot be recommended because no association between a reduction in stroke risk and screening was demonstrated. Whether lesser grades of disease, such as II or III, are associated with a higher risk of stroke remains to be seen. Contrast-enhanced MDCT assesses both the quality of the vessel wall and luminal stenosis, and when combined with TOE provides a thorough assessment of the whole aortoiliac system. Whether ultrasound scanning of the abdominal aorta and iliac system would provide the same data without the radiation/contrast exposure also remains to be seen. In these litigious times, assessment of *atheroma burden* in patients at risk of severe aortoiliac atherosclerosis would seem prudent.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Braunberger E, Deloche A, Berrebi A, et al. Very long-term results (more than 20 years) of valve repair with carpentier's techniques in nonrheumatic mitral valve insufficiency. Circulation 2001;104:I8-11.
2. Cheng DC, Martin J, Lal A, et al. Minimally invasive versus conventional open mitral valve surgery: a meta-analysis and systematic review. Innovations (Phila) 2011;6:84-103.
3. Glower DD, Landolfo KP, Clements F, et al. Mitral valve operation via Port Access versus median sternotomy. Eur J Cardiothorac Surg 1998;14 Suppl 1:S143-7.
4. Casselman FP, Van Slycke S, Wellens F, et al. Mitral valve surgery can now routinely be performed endoscopically. Circulation 2003;108 Suppl 1:II48-54.
5. Modi P, Hassan A, Chitwood WR Jr. Minimally invasive mitral valve surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg 2008;34:943-52.
6. Grossi EA, Loulmet DF, Schwartz CF, et al. Evolution of operative techniques and perfusion strategies for minimally invasive mitral valve repair. J Thorac Cardiovasc Surg 2012;143:S68-70.
7. Chan EY, Lumbao DM, Iribarne A, et al. Evolution of cannulation techniques for minimally invasive cardiac surgery: a 10-year journey. Innovations (Phila) 2012;7:9-14.
8. Murzi M, Cerillo AG, Miceli A, et al. Antegrade and retrograde arterial perfusion strategy in minimally invasive mitral-valve surgery: a propensity score analysis on 1280 patients. Eur J Cardiothorac Surg 2013;43:e167-72.
9. Gammie JS, Zhao Y, Peterson ED, et al. J. Maxwell Chamberlain Memorial Paper for adult cardiac surgery. Less-invasive mitral valve operations: trends and outcomes from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg 2010;90:1401-8, 1410.e1; discussion 1408-10.
10. Holzhey DM, Seeburger J, Misfeld M, et al. Learning minimally invasive mitral valve surgery: a cumulative sum sequential probability analysis of 3895 operations from a single high-volume center. Circulation 2013;128:483-91.
11. Crooke GA, Schwartz CF, Ribakove GH, et al. Retrograde arterial perfusion, not incision location, significantly increases the risk of stroke in reoperative mitral valve procedures. Ann Thorac Surg 2010;89:723-9; discussion 729-30.
12. Grossi EA, Loulmet DF, Schwartz CF, et al. Minimally invasive valve surgery with antegrade perfusion strategy is not associated with increased neurologic complications. Ann Thorac Surg 2011;92:1346-9; discussion 1349-50.
13. Modi P, Rodriguez E, Hargrove WC 3rd, et al. Minimally invasive video-assisted mitral valve surgery: a 12-year, 2-center experience in 1178 patients. J Thorac Cardiovasc Surg 2009;137:1481-7.
14. Nifong LW, Rodriguez E, Chitwood WR Jr. 540 consecutive robotic mitral valve repairs including concomitant atrial fibrillation cryoablation. Ann Thorac Surg 2012;94:38-42; discussion 43.
15. Mihaljevic T, Jarrett CM, Gillinov AM, et al. Robotic repair

of posterior mitral valve prolapse versus conventional approaches: potential realized. J Thorac Cardiovasc Surg 2011;141:72-80.e1-4.
16. Holzhey DM, Shi W, Borger MA, et al. Minimally invasive versus sternotomy approach for mitral valve surgery in patients greater than 70 years old: a propensity-matched comparison. Ann Thorac Surg 2011;91:401-5.
17. Suri RM, Schaff HV, Meyer SR, et al. Thoracoscopic versus open mitral valve repair: a propensity score analysis of early outcomes. Ann Thorac Surg 2009;88:1185-90.
18. Moodley S, Schoenhagen P, Gillinov AM, et al. Preoperative multidetector computed tomograpy angiography for planning of minimally invasive robotic mitral valve surgery: impact on decision making. J Thorac Cardiovasc Surg 2013 Aug;146:262-8.e1.
19. Schneider F, Onnasch JF, Falk V, et al. Cerebral microemboli during minimally invasive and conventional mitral valve operations. Ann Thorac Surg 2000;70:1094-7.

Cite this article as: Modi P, Chitwood WR Jr. Retrograde femoral arterial perfusion and stroke risk during minimally invasive mitral valve surgery: is there cause for concern? Ann Cardiothorac Surg 2013;2(6):E1. doi: 10.3978/j.issn.2225-319X.2013.11.13