Population-Based Data on Congenital Heart Disease and Stroke

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Mandelenakis and colleagues present a population-based analysis of the risk of stroke in over 25,000 patients with congenital heart disease (CHD). The investigators identified patients from a Swedish registry, which included almost all cardiothoracic procedures and hospitalizations between 1970 and 1993. Patients were followed through 2011. After a median follow-up of 20.1 years, 0.54% of the CHD patients were diagnosed with ischemic stroke, a figure more than 10-fold higher than observed in an age- and sex-matched control group. As documented by this large data set, only 7.9% of the strokes in CHD patients occurred in the perioperative period. Certain comorbidities were associated with a higher risk of stroke in the CHD cohort: heart failure, hypertension, and atrial fibrillation. Stroke, however, appeared to comprise a modest proportion of overall disease burden and adversity associated with CHD, as evidenced by a cumulative stroke incidence to age 40 of 1.5% compared with a cumulative mortality of ≈15%.

These data complement a recent report on stroke in adults with CHD by Lanz et al using administrative data from Quebec. That report suggests a similar increase in risk for stroke in the subgroup of patients under age 55 years (9- to 12-fold higher than in the general population) and there is notable consistency in risk factors identified in these patients (heart failure and diabetes mellitus). Hypertension and atrial arrhythmia were less robust predictors in the Quebec study, possibly because the population prevalence of these diagnoses was so much higher in that adult sample (eg, hypertension: 22.2% versus 0.5% and atrial arrhythmia: 8.0% versus 0.2% for CHD controls in the Quebec sample and for population based controls in the Swedish report, respectively).

Admittedly, it is not surprising that children and adults with congenital heart disease are at increased risk for stroke. Many CHD subgroups are expected, if not known, to be at increased risk for stroke (Table). Iatrogenic causes include acute surgical and other procedural injury, but also encompass device- and valve-related thromboembolism. Cyanosis also predisposes to stroke because of secondary erythrocytosis, paradoxical embolism, and other mechanisms. CHD patients are at greater risk for atrial arrhythmia and endocarditis, both associated with increased stroke risk. Stroke may also be linked with CHD because of concomitant diseases such as an increased risk for intracranial aneurysms in patients with coarctation.

The reports from Sweden and Quebec clearly highlight the increased risk of stroke in CHD patients and provide perspective on the magnitude of the problem. They also, however, highlight the stark limitations of population-based administrative data, even when well analyzed and thoughtfully considered. Specific to this topic, definitive diagnosis of stroke can be challenging and variable, an issue that persists despite the advent of ubiquitous advanced imaging. Administrative coding of stroke is only moderately accurate. More fundamentally, the data are insufficiently granular and key comorbidities are either missing or undependable. One would never design a study on stroke without collecting data on the presence of mechanical valves or anticoagulant medication, but these data sets have no reliable codes for such key variables. How can we interpret a finding of increased stroke risk without understanding how much of the attributable risk is due to known factors? The current report does not include data on obesity or hypercholesterolemia or tobacco use, perhaps because of known poor documentation of these diagnoses in administrative data sets. For example, in the nested stroke case–control part of the Quebec study only 4% of 12,440 CHD controls, enrolled between 1998 and 2010, were documented tobacco users. In contrast, the province-wide prevalence of tobacco use was 22.2% in 2004. To add to appropriate concern, there is no evidence that these grossly inaccurate variables are unaffected by differential bias (eg, more or less extensive ascertainment and documentation) according to CHD or stroke status.
A thought experiment demonstrates that these comments have more than academic relevance. Imagine that the results had been the converse: Patients with CHD are actually at lower risk for stroke than people without CHD. Would you believe it? We would not; rather, we would be sure the findings reflected an artifact of faulty study design. The findings might be due to unmeasured confounding or survivorship bias or other systematic bias, but they could not be an accurate representation of what exists in the real world. The results are believable only because we already know they are generally true.

This is a critique of administrative “big data” in its contemporary form and most certainly not a criticism of the investigators or their methods. We felt no shame for reporting equally intuitive associations using administrative data. The conclusions are obvious only to clinicians caring for these patients. It is critical to bring attention to these issues and provide quantitative, if imperfect, evidence to make compelling arguments to policymakers and others outside the field. Hopefully, these reports will focus appropriate attention toward improving our understanding of which CHD patients are at greatest risk for stroke, specific mechanisms of stroke in specific groups of patients, and, most important, optimal approaches to minimizing risk.

We expect that most of those who read Mandalenakis and colleagues’ article will be clinicians hoping to better understand their patients and provide better care now. They may not find the results surprising or clinically relevant. Within the field, this kind of research often elicits an “of course” followed by a laundry list of valid criticisms. Our colleagues caring for CHD patients, however, do not comprise the key audience. Paradoxically, these data will only be unexpected and useful to those without prior interest in this topic or group of patients. That does not make the results any less important. Such findings are the foundation of arguments to increase funding.

Table. Characteristic Pathophysiology of Stroke in Patients With Congenital Heart Disease

| Category                               | Subgroup                                                   | Predominant Stroke Pathophysiology                                      | Selected Example(s)                                               |
|----------------------------------------|-------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------|
| Iatrogenic, periprocedural             | Perioperative                                                | Ischemic (watershed hypoperfusion), embolic (athero-, thrombo-, or air) | Watershed infarct in a young patient after cardiac surgery⁴       |
|                                        | Catheterization and electrophysiology studies               | Embolic (thrombo-, air, or cholesterol), dissection                    | Embolism of aortic atheroma debris dislodged by catheter          |
| Iatrogenic, chronic                    | Device related                                               | Embolic (paradoxical thrombo- or septic)                               | Pacemaker leads in right heart with intracardiac shunt⁵           |
|                                        | Prosthetic valves                                            | Embolic (thrombo-)                                                     | Thrombosis of left sided mechanical prosthetic valve              |
|                                        | Created shunts and baffles with leak                         | Embolic (paradoxical)                                                 | Atrial switch operation with residual baffle leak                 |
| Cardiovascular, related to underlying CHD | An rhythmia                                                 | Embolic (thrombo-)                                                     | Atrial fibrillation and flutter in context of any underlying diagnosis |
|                                        | Endocarditis                                                | Embolic (septic)                                                       | Left-sided valve vegetation with systemic embolization            |
|                                        | Residual shunts                                             | Embolic (paradoxical)                                                 | Residual unrepaired patent foramen ovale after surgical repair of other CHD |
|                                        | Abnormal systemic-to-pulmonary venous communication         | Embolic (paradoxical)                                                 | Classic Glenn with pulmonary AVM, venovenous collaterals in Fontan |
|                                        | Hypertension                                                | Ischemic                                                               | Coarctation of the aorta                                         |
|                                        | Congenital or acquired malformations and associated syndromes | Ischemic, hemorrhagic                                                  | Berry aneurysm with coarctation, Moyamoya⁶                        |
| End-organ effects                      | Thrombophilia                                               | Embolic (paradoxical thrombo-), ischemic                               | Eisenmenger syndrome, Fontan circulation⁷                         |
|                                        | Venous stasis                                               | Embolic (paradoxical thrombo-in conjunction with shunt)               | Fontan circulation, others with peripheral venous disease and chronic high venous pressure |
|                                        | Hypoxemia and secondary erythrocytosis                     | Embolic (paradoxical thrombo-), ischemic, infectious (abscess)         | Eisenmenger syndrome and other cyanotic heart disease⁶,⁹           |
| Other unusual associations              | Cerebral venous thrombosis,¹⁰ cervicocephalic arterial dissection¹¹ |                                                                        |                                                                   |

AVM indicates arteriovenous malformation; CHD, congenital heart disease.

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and provide other resources for patient-oriented research in CHD. There is a growing breadth of high-quality population-based research showing diverse facets of the substantial burden of premature morbidity and mortality associated with CHD. When will there be enough “of course” research? When policymakers respond “of course” when asked to support initiatives to address the challenges faced by a growing population of increasingly complex CHD patients.

Disclosures

None.

References

1. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Hansson P-O, Dellborg M. Ischemic stroke in children and young adults with congenital heart disease. J Am Heart Assoc. 2016;5:e003071 doi: 10.1161/JAHA.115.003071.
2. Lanz J, Brophy JM, Therrien J, Kaouache M, Guo L, Marelli AJ. Stroke in adults with congenital heart disease: incidence, cumulative risk, and predictors. Circulation. 2015;132:2385–2394.
3. Hoffmann A, Chockalingam P, Balint OH, Dadashev A, Dimopoulos K, Engel R, Schmid M, Schwerzmann M, Gatzoulis MA, Mulder B, Oechslin E. Cerebrovascular accidents in adult patients with congenital heart disease. Heart. 2010;96:1223–1226.
4. Chen J, Zimmerman RA, Jarvik GP, Nord AS, Clancy RR, Wernovsky G, Montenegro LM, Hartman DM, Nicolson SC, Spray TL, Gaynor JW, Ichord R. Perioperative stroke in infants undergoing open heart operations for congenital heart disease. Ann Thorac Surg. 2009;88:823–829.
5. Khairy P, Llandberg MJ, Gatzoulis MA, Mercier LA, Fernandez SM, Cote JM, Lavoie JP, Fournier A, Guerra PG, Fugoudaki A, Walsh EP, Dore A. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts: a multicenter study. Circulation. 2006;113:2391–2397.
6. Lutterman J, Scott M, Nass R, Geva T. Moyamoya syndrome associated with congenital heart disease. Pediatrics. 1998;101:57–60.
7. Cromme-Dijkstra AH, Henkens CM, Bijleveld CM, Hilleges HL, Bom VJ, van der Meer J. Coagulation factor abnormalities as possible thrombotic risk factors after Fontan operations. Lancet. 1990;336:1087–1090.
8. Clark DB, Tyler HR. Incidence of neurological complications in congenital heart disease. AM Arch Neurol Psychiatry. 1957;77:17–22.
9. Opotowsky AR, Landberg MJ, Beghetti M. The exceptional and far-flung manifestations of heart failure in Eisenmenger syndrome. Heart Fail Clin. 2014;10:91–104.
10. Carvalho KS, Bodensteiner JB, Connolly PJ, Garg BP. Cerebral venous thrombosis in children. J Child Neurol. 2001;16:574–580.
11. Schievink WI, Mokri B, Piepgras DG, Gittenberger-de Groot AC. Intracranial aneurysms and cervicocephalic arterial dissections associated with congenital heart disease. Neurosurgery. 1996;39:685–689; discussion 689-690.
12. Connolly HM, Huston J III, Brown RD Jr, Warnes CA, Ammash NM, Tajik AJ. Intracranial aneurysms in patients with coarctation of the aorta: a prospective magnetic resonance angiographic study of 100 patients. Mayo Clin Proc. 2003;78:1491–1499.
13. Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. Stroke. 1998;29:1602–1604.
14. Reid JL, Hammond D, Rynard VL, Burkhalter R. Tobacco use in Canada: patterns and trends. 2014 Edition. Waterloo, ON: Propel Centre for Population Health Impact, University of Waterloo.
15. Opotowsky AR, Siddiqi OK, D’Souza B, Webb GD, Fernandez SM, Landberg MJ. Maternal cardiovascular events during childbirth among women with congenital heart disease. Heart. 2012;98:145–151.
16. Krieger EV, Landberg MJ, Economy KE, Webb GD, Opotowsky AR. Comparison of risk of hypertensive complications of pregnancy among women with versus without coarctation of the aorta. Am J Cardiol. 2011;107:1529–1534.

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