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Case Report

NobleStitch Patent Foramen Ovales Closure for Recurrent Strokes in a Patient with COVID-19 on Extracorporeal Membrane Oxygenation

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SEVERE HYPOXEMIA, secondary to the SARS-COV-2 (COVID-19) pneumonia, is a significant contributor to morbidity and mortality.[1] Patent foramen ovales (PFOs) can exacerbate hypoxemia through an intracardiac shunt, slowing recovery and worsening outcomes.[2-4] Cryptogenic stroke is a complication commonly associated with PFOs; however, current guidelines do not address PFO management in COVID-19 patients who experience recurrent paradoxical emboli, especially in the setting of COVID-19 pneumonia, increased right-sided pressures, and a hypercoagulable state.[3,4]

This report describes a challenging case of an unvaccinated patient with recurrent strokes and refractory hypoxemia secondary to COVID-19 pneumonia. The patient subsequently was found to have a PFO and underwent a PFO closure using NobleStitch EL (Heartstitch, Fountain Valley, CA).

Approved by the Food and Drug Administration in 2019, NobleStitch is a suture-mediated approach enabling deviceless PFO closure (Fig 1).[5,6] Using percutaneous access, NobleStitch approximates the septum primum and the septum secundum using 2 polypropylene sutures and a single polypropylene knot, thereby avoiding the risks associated with septal occluders, such as infection, prolonged dual- antiplatelet therapy, arrhythmias, device erosion/dislodgment, and hindered left atrial access.[5,6]

Case Presentation

A previously healthy 42-year-old unvaccinated male presented to the hospital with a 2-day history of dyspnea, fever, and chills, and was diagnosed with COVID-19 infection. Initially, his condition was stable on high-flow nasal cannula, intravenous steroids as per protocol, and antiviral therapy including one 200-mg dose of remdesivir, one 810-mg dose of tocilizumab, and a 14-day course of 4 mg of baricitinib.[7] On inpatient day 4, the patient's oxygenation worsened, requiring escalation of respiratory and pharmacologic support. He subsequently was placed on bilevel positive airway pressure ventilation followed by endotracheal intubation on 100% FIO_2 and positive end-expiratory pressure of 10 cmH_2O. Due to refractory hypoxemia, the patient was transitioned to prone ventilation, inhaled epoprostenol therapy, and eventually

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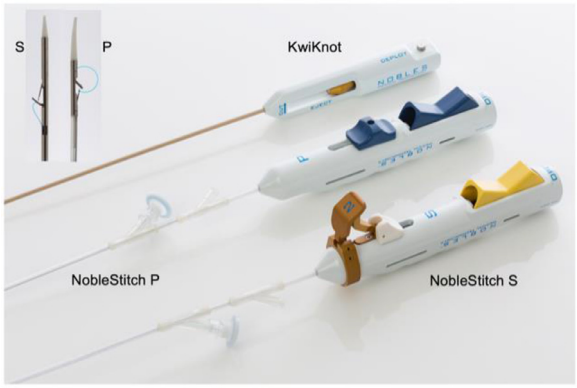

Fig 1. The NobleStitch delivery system consisting of 3 catheters: the NobleStitch S for capturing of the septum secundum, the NobleStitch P for capturing of the septum primum, and the KwiKnot catheter for knot application and trimming of excess suture material.

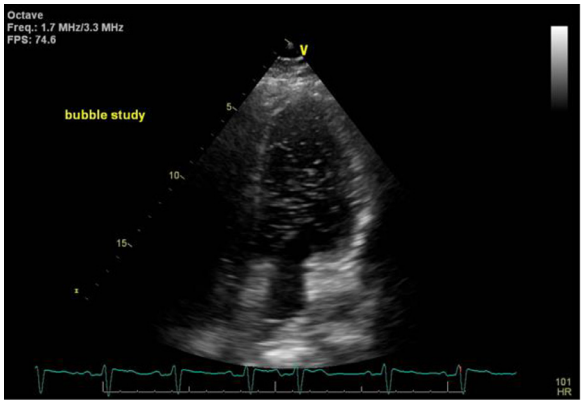

Fig 3. Transthoracic echocardiography bubble study demonstrating the presence of saline contrast (bubbles) in the left ventricle, diagnostic of a right-to-left intracardiac shunt through a patent foramen ovale.

placed on venovenous extracorporeal membrane oxygenation (VV-ECMO) support.

One week later, the patient's hospital course was further complicated by an acute ischemic cerebrovascular accident. At that time, he was noted to have left arm and leg weakness with a right facial droop. Computed tomography (CT) of the head showed a hypodensity in the left medial cerebellum consistent with a subacute cerebellar infarct (Fig 2). The CT angiography revealed a thrombus occluding the V4 segment of the left vertebral artery, which is associated with the occlusion of the left posterior inferior cerebellar artery. Three days later, a repeat head CT revealed a hypodensity at the parietal-occipital junction raising concern for the evolution of the suspected infarction. Transthoracic echocardiography was performed, and a saline contrast injection revealed right-to-left shunting through a PFO, which was found to be <5mm (Fig 3 and Video 1). The patient's Risk of Paradoxical Emboli score was calculated to be 8, correlating to a causal risk of 84% from his PFO, with a 6% estimated risk of stroke recurrence at 2 years.[8] Interventional cardiology subsequently was consulted for PFO closure due to repeated paradoxical thromboembolic events.

The patient was taken to the hybrid operating room for a transesophageal echocardiography assessment of his PFO. After an evaluation of the patient's PFO, it was concluded that closure with the suture-mediated deviceless NobleStitch would be the best course of action. This decision was made after considering multiple factors, including the patient's young age, the defect's likely amenability to repair based on prior publications, and his hypercoagulable state.[6] If the patient were to require a transseptal puncture for a future procedure, the presence of a traditional closure device could be problematic.

After femoral venous access was obtained, guidewires were placed into the superior vena cava and across the fossa ovalis into the left superior pulmonary vein (Video 1). Next, the NobleStitch secundum catheter (Fig 1) was advanced into the fossa ovalis, and the septum secundum was engaged and grasped. The needle was delivered through the septum secundum, and the device was withdrawn. The septum primum grasping arm was then advanced into the LA, the septum primum was grasped, and the needle was delivered. The grasping arm was then withdrawn, leaving behind 2 polypropylene sutures. Finally, the KwiKnot was advanced over the sutures and tension was applied using the catheter, effectively closing

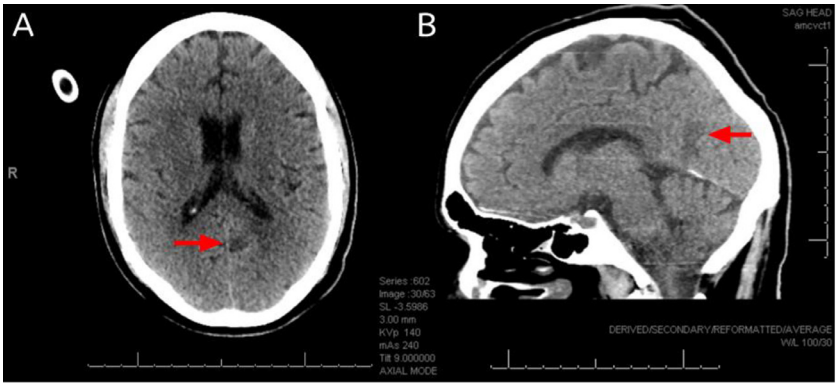

Fig 2. Head computed tomography demonstrating a wedge-shaped area of low attenuation within the inferomedial aspect of the left cerebellar hemisphere with loss of gray-white differentiation in the axial (Inset A) and sagittal views (Inset B), consistent with subacute infarction.

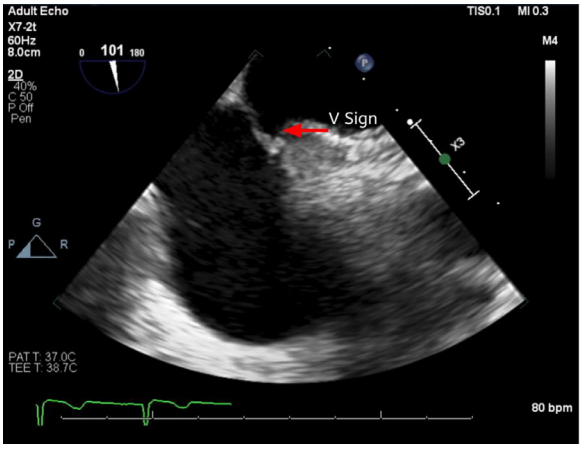

Fig 4. Transesophageal echocardiography demonstrating V-sign, a V-shaped indent on the septum primum, which reflects tension due to the NobleStitch KwiKnot.

the PFO and resulting in a V-shaped indent or the "V sign" (Fig 4). The KwiKnot was deployed subsequently, the sutures were cut, the catheter was removed, and the knot was left behind in the right atrium. A schematic representation of these steps can be seen in Figure 5.

A postprocedural saline bubble study confirmed no residual intracardiac shunt (Video 1). On postoperative day 0, patient's VV-ECMO settings were set to 60% fraction of delivered oxygen (FdO_2), with a flow rate of 3.6 L/min while on 50% FIO_2 via mechanical ventilation. On postoperative day 8, FdO_2 was lowered to 21% with a flow rate of 3.99 L/min and 40% FIO_2. The patient was weaned off VV-ECMO completely on postoperative day 14. He ambulated shortly thereafter while still receiving oxygen therapy through a tracheal collar, and was discharged subsequently to outpatient rehabilitation where he continued to improve.

Discussion

Recent clinical trials have indicated that patients with cryptogenic stroke experience better outcomes and have a reduced risk of recurrent cryptogenic stroke when treated with percutaneous PFO closure in addition to antiplatelet or anticoagulant therapy compared to those treated with medication alone.[9] A randomized controlled study comparing the rate of stroke recurrence in patients who underwent PFO closure with either Gore Helex or Cardioform septal occluders (Gore Medical, Newark, DE), combined with antiplatelet therapy (n = 441), as opposed to those treated with antiplatelet therapy alone (n = 223), discovered that the number needed to treat to prevent 1 stroke in 5 years was approximately 25, favoring PFO closure in patients with a history of cryptogenic stroke.[10] Another randomized controlled trial also compared PFO closure with the Abbott Amplatzer (Abbott Laboratories, Chicago, IL), in addition to medical management with antiplatelet or anticoagulant therapy (n = 60), and showed that PFO closure significantly reduced recurrence of stroke, vascular death, or major bleeding in the 2-year follow-up period compared to the medication group alone (n = 60), reporting a number needed to treat of 8.[11] Although these occluders have shown to be efficacious, they can be complicated by increased device burden, device dislodgement, thrombosis, and can hinder left-sided cardiac procedures that may become necessary later in life, particularly in younger patients.[1,3,4,12,13] This can be especially pertinent in patients in a hypercoagulable state such as COVID-19 pneumonia.

The role of PFO in refractory hypoxemia and cryptogenic stroke in patients with COVID-19 has often been overlooked, and there are currently no evidence-based recommendations regarding the management of these patients.[3,12,14] Although COVID-19 can often present with thromboinflammation and a hypercoagulable state, right-to-left shunting through a PFO further increases the risk for paradoxical embolism, possibly

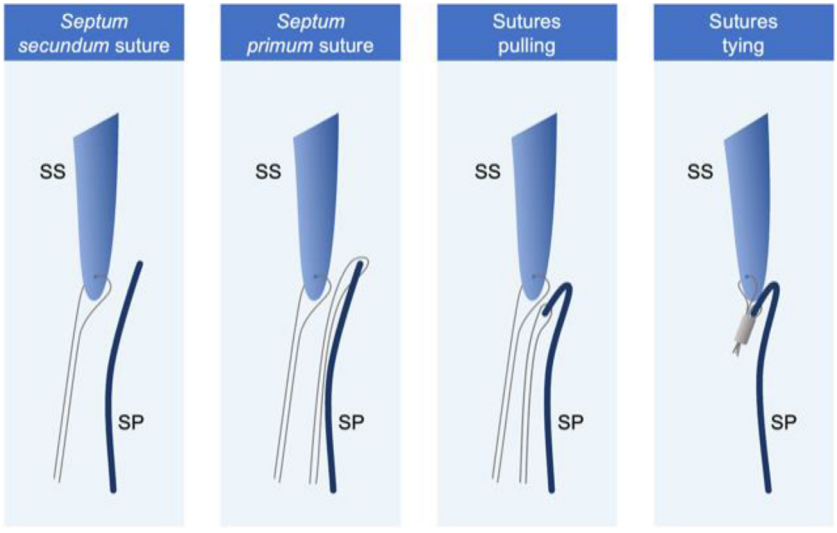

Fig 5. Schematic representation of the NobleStitch in closure of patent foramen ovale, demonstrating suture through the septum secundum, suture through the septum primum, suture pulling just prior to KwiKnot deployment, and suture tying using the KwiKnot.

due to the increased right atrial pressure in this population.[1,4,12] This is a predicament in patients with a PFO in the setting of COVID-19 pneumonia, during which the increased right-sided pressures induce vascular damage, further activating the coagulation system and exacerbating the risk for paradoxical embolism.[1,4,12] Moreover, the increased pulmonary pressures in these patients may be responsible for the refractory hypoxemia that is often seen.[3,4] In circumstances such as these, procedural correction of the PFO may both decrease right-to-left shunting, thereby improving oxygenation, and help prevent cryptogenic strokes.[1,4,13] NobleStitch provides a novel way of closing a PFO, which represents a significant source of embolic stroke and refractory hypoxemia.[5] To the authors' knowledge, this report highlighted the first case of PFO closure in a COVID-19 patient using NobleStitch.

Although the inclusion and exclusion criteria have not been elucidated explicitly by the device manufacturer or prescribed on FDA or CE mark documentation, the device is indicated broadly for PFO closure in patients with recurrent paradoxical ischemia. The device is not recommended in patients with inadequate septal tissue for the NobleStitch grasping arms/suturing, aortic or carotid artery disease, supraventricular and ventricular rhythm, multifenestrated septum, active endocarditis, atrial septal defect, or autoimmune disease.[6,15] Furthermore, at this institution, PFO closure with NobleStitch is not performed in defect sizes >5 mm; however, previous studies described the potential for successful closure in these cases using multiple KwiKnots.[6,15] Guided by transesophageal echocardiography (Video 1), this technique effectively closes the PFO by applying sutures through the septum primum and septum secundum, subsequently creating a knot between the 2 sutures and removing excess suture material, thereby avoiding many risks that accompany septal occluders.[5] Hypercoagulable patients, such as those with COVID-19, may be at increased risk of thrombotic complications with traditional permanent implanted devices.

Thus far, NobleStitch has shown promising results in terms of effectiveness, safety, and longevity.[6,15,16] To improve patient selectivity, a retrospective observational study of 247 patients who underwent PFO closure with NobleStitch suggested new predictors of residual shunting after intervention. This study revealed improved outcomes with a preoperative PFO <5 mm in width and absence of a spontaneous right-to-left shunt, indicators that were both met in this patient.[15] Another prospective single-center study with a 6-month follow-up period (n = 116) investigated factors that may have contributed to a residual intracardiac shunting grade ≥2 (20%, n = 23), and revealed partial stitch detachment (n = 12), atrial septal tear (n = 3), and KwiKnot embolization (n = 2) as the main causes of right-to-left shunting at follow-up.[17] Although the NobleStitch is not without complications, it has clear advantages over commonly used device PFO closures.[5,6,17]

This case highlighted how the NobleStitch procedure may be used to close a PFO in a COVID-19 patient with refractory hypoxemia and cryptogenic stroke on VV_ECMO. Particularly useful in younger patients, this deviceless system overcomes many of the complications associated with traditional PFO closure devices by averting risk of clot formation, future strokes, and need for long-term anticoagulation.[6,9] Given the ubiquity of COVID-19 and its complications, the early detection and treatment of PFO in patients with severe COVID-19 may prove important for timely recovery and prevention of serious sequelae.[4] This is significant considering that congenital PFO affects approximately 25%-to-34% of the population[3,12], and a recent cross-sectional study (n = 75) of patients under mechanical ventilation secondary to COVID-19 pneumonia found a 15% prevalence of PFOs in these patients.[18] Although most patients with a PFO do not require surgical intervention, selected patients may benefit from PFO closure to prevent recurrent cryptogenic strokes.[19] Initial registry data (n = 192) have demonstrated that NobleStitch is a safe and effective method of PFO closure, revealing complete resolution of the right-to-left shunt in 75%, and a grade 1 residual right-to-left shunt in 14%.[6] Although recent studies have begun to refine the inclusion criteria for this procedure to improve postprocedural residual shunting, long-term outcomes of this device will be better understood with the completion of the prospective multicenter clinical trial slated to conclude in 2026.[15,17,20]

Conflicts of Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2022.10.014.

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