Internal Aortic Implant to Detect Aortic Root Dissection Before it Occurs

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Background and introduction to Marfan syndrome:

Marfan syndrome is a rare genetic disorder caused by a mutation in the FBN1 gene on the 15th chromosome [1][2]. This mutation leads to a disorder in the connective tissue of the body which leads to physical characteristics including an abnormally tall and skinny stature, long arms and legs, and long slender fingers and toes–a condition called arachnodactyly [1]. Marfan syndrome is found in approximately one in five-thousand to one in three-thousand people and occurs at an equal rate in male and female patients and patients of all ethnicities and racial backgrounds [1]. Although it affects the cardiovascular, ocular, and skeletal systems, Marfan syndrome is usually characterized as a cardiovascular disease because the primary complications and fatalities associated with this syndrome involve the cardiovascular system.

Random mutations resulting in cases of Marfan syndrome account for twenty-five to thirty percent of all Marfan syndrome cases [5]. Marfan syndrome is primarily a genetic disease that is inherited from one or both parents. Marfan syndrome is an autosomal dominant disease meaning that if one copy of the gene is mutated and the other is not, the mutated copy is dominant over the non-mutated copy and the disease still manifests itself. Having both copies of the gene mutated from parental inheritance does not increase the severity of the disease as the dominant nature overrides any healthy copy of the gene.

The mutation in the FBN1 gene found in Marfan syndrome can be the result of many different types of genetic mutations. About two-thirds of the mutations in the FBN1 gene are missense mutations [4]. The missense mutations are usually due to cysteine substitutions. About ten percent of the mutations in the FBN1 gene are nonsense mutations. Another thirteen percent of the FBN1 mutations are small frameshift mutations. The final thirteen percent of FBN1 mutations are various splicing errors.

The FBN1 gene encodes for the protein fibrillin-1. One major function of fibrillin-1 is to bind to a cytokine called Transforming Growth Factor-Beta (TGF-β) to regulate its biological function [4]. When fibrillin-1 is damaged or less prevalent, it can't perform its function and therefore TGF-β levels rise. TGF-β plays a crucial role in cell proliferation, differentiation, and apoptosis. An increased concentration of TGF-β cells can lead to unregulated cell growth. This can be particularly damaging for the structure of the extracellular matrix and the vascular smooth muscle development [4]. Excessive levels of TGB-β also have a role in the development of aortic root aneurysms which is one of the most fatal effects of Marfan syndrome.

The most common fatal complication of Marfan syndrome is aortic root dilatation and dissection [3]. Aortic root dilation is when the section of the aorta closest to the heart is dilated beyond its natural diameter and aortic root dissection is when a rupture occurs in this same aortic section. Fibrillin-1 is an essential protein to the maintenance of microfibrils and elastic lamellae which provide strength and elasticity to the aorta. The mutation in FBN1 causes the fibrillin-1 proteins to be more susceptible to proteolytic degradation. This means that the microfibrils and elastic lamellae become fragmented and the aorta can no longer stretch and recoil properly. This weakened structure causes the aorta to be more susceptible to progressive dilation due to blood flow and pressure. Since the aorta can not stretch properly and there is an abnormal dilation, aorta dissection occurs and blood is able to flow between tissue layers [3].

The current standard of care for Marfan syndrome and its faults:

Marfan syndrome is primarily treated with medication such as beta-blockers [6]. Beta-blockers serve to reduce the heart rate of the patient taking them. A lower heart rate results in lower blood pressure and therefore a lower hemodynamic stress upon the wall of the aorta. A lower hemodynamic stress on the wall of the aorta means that there is a slower rate of aortic root dilation and a reduced chance of aortic root dissection. The goal of the beta-blockers is to reduce the heart rate after submaximal exercise to less than one hundred beats per minute [6]. Another medication called Losartan has also shown promising effects of preventing the progression of aortic dilation in mouse models. Losartan is an angiotensin II receptor blocker. Losartan works by reducing the levels of TGF-β blocking the transcriptions of genes that respond to TGF-β, and its ability to treat hypertension.

Another component of treatment for Marfan syndrome is surgical intervention of the aortic root after the dilation has exceeded a certain threshold in order to prevent the aortic root from dissecting [6]. For most patients with Marfan syndrome, the threshold for surgical intervention in the aortic root is a diameter of fifty millimeters or more. For patients with Marfan syndrome and any of the following risk factors, the threshold is forty-five millimeters. The risk factors are as follows–familial history of aortic root dissection, an aortic root dilation rate of more than three millimeters per year, and possible pregnancy [6]. The survival rate for preventive surgeries is ninety-eight to ninety-nine percent. If preventative surgery is not performed for whatever reason and aortic root dissection does occur, emergency surgery can be performed to fix the dissection and save the patient. The survival rate for emergency surgeries is only eighty percent so it is very important to monitor the dilation of the aortic root in order to prevent dissection completely [6].

In addition to the standard open aortic surgery performed to treat aortic dilation, there is another option. Thoracic endovascular aortic repair or TEVAR is a less invasive option of the same treatment [6]. TEVAR can be performed in emergency situations but in general, it is not recommended for patients with Marfan syndrome because of the connective tissue diseases. TEVAR can be used during an open procedure if something goes wrong and the surgeons need to pivot to another option or to place a graft over an implanted prostheses previously placed in an open surgical procedure.

The CDC recommends that an evaluation be made by both a cardiologist and a cardiothoracic surgeon annually in order to monitor the dilation of the aortic valve [1]. It's also generally recommended to have imaging done annually of the aortic valve to monitor its function and size and to possibly treat a dangerously dilated valve [7]. Even with annual checks of the aortic root diameter, it's still possible for a patient to experience extreme dilation and dissection before the next routine evaluation and imaging. If one imaging shows that the patient is approaching the threshold for surgical intervention, then more frequent imaging will be scheduled by the physician [8]. This can be very frustrating for the patient as they slowly wait for their aorta to dilate enough that something can be done about it.

Right now there is no option for the patient to test their aortic root dilation at home so in order to determine how close to surgical intervention they have become, they must be evaluated by a physician. This creates a lot of anxiety while they wait for the next evaluation by their physician to determine if they need open surgery or if they can continue living their normal life.

Innovation for the care of Marfan syndrome:

As of right now It's standard for patients with Marfan syndrome to be checked regularly for aortic root dilation in a medical facility. The standard time between evaluations is one year but as the aortic root continues to dilate, evaluations become more frequent in order to catch the dilation before dissection occurs [8]. The only way to do this at the moment is in a medical facility through echocardiography and, in cases where precision is key, CT angiography and MRI [9]. One solution to this issue is to install an interior aortic root pressure monitoring device that rests inside the aortic root and is able to measure pressure changes, wall strain, and deformation in the aorta.

The device would need to be made of a biocompatible and flexible material like a medical-grade silicone or a polymer-based composite in order to match the flexibility of the aorta and reduce mechanical mismatch with the aortic wall. The device would also have to have some sort of power source. This could be in the form of an internal battery or possibly even an outside source that can wirelessly power the device.

The device would be inserted through a minimally invasive procedure, most likely catheterization through a blood vessel in the groin area. The device would wirelessly send signals to a smart device nearby that would log the data and analyze the pressure, strain, and deformation to check for dilation. If the dilation reaches a critical threshold, the patient and their physician will be automatically alerted to allow for immediate surgical intervention before dissection can occur. This device reduces the need for frequent doctor's visits and allows the patient more freedom in their life without having to worry about the aortic root dilation. They can constantly monitor the dilation rate and size giving them peace of mind about their own health journey.

Long-term implanted pressure sensors have been previously implanted in human arteries successfully [10]. In a study of twenty patients, nineteen of the implants successfully and accurately read the data consistently when compared to the standardly measured datasets. This shows that the implant itself is entirely possible in the aortic root. The pressure data can be used in addition to other data collected by the implant such as aortic wall stiffness and deformation to calculate the dilation of the aortic root and in turn the need for surgical intervention.

The device could either be powered by a small long-lasting battery or wirelessly through radio frequency magnetic telemetry from an external power source like in the Swedish study performed by Henrik Casimir Ahn1, Baz Delshad1, and Jacek Baranowski [10]. The external power source would provide a virtually unlimited supply of power without need for another surgery to present the device with additional power.

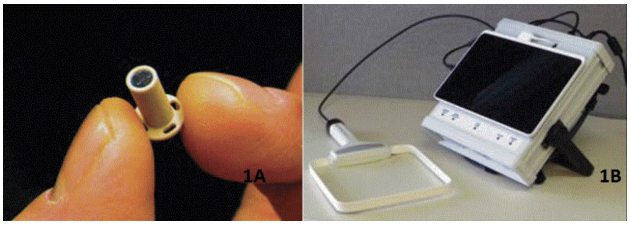

Figure 1: a) An 18 mm implant. The sensor is at the distal end, and the proximal part has a flange with 4 holes for fixation sutures. **b)** shows an antenna and a tablet pc on a read-out unit. With the permission of ISS Inc [10].

Figure 1 is the device used in the Swedish clinical trial. Figure 1a is the implanted device that went into the aorta and Figure 1b is the external device that powers the device and reads the data exported by the implant. Not having an internal battery would also decrease the size that the device needed to be because it would not have to have a storage compartment or converter for the battery. This device could increase the quality of life for people with Marfan syndrome and make it easier to catch and treat aortic dilation before aortic dissection occurs.

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