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Notice:

ValveXchange, Inc. products have not been approved by the U.S. FDA or any other Regulatory Agencies. This newsletter contains forward looking statements which represent management's best judgment, but are speculative and may not occur as projected or not at all.

NEWS RELEASE

January / February 2010



From the Desk of Ivan Vesely, Ph.D.

Dear Colleagues

It has been a year since we began large animal studies implanting our exchangeable leaflet heart valve. Over that 12 month period we did 18 implants, 7 exchanges and still have 2 sheep alive with exchanged leaflets. **THE VALVE JUST WORKS.....!** To date, we have had no valve failures, no perivalvular leakage, and no valve performance problems at all. 2010 promises to be a great year for VXi.

We have also recently been awarded a \$250,000 grant from the State of Colorado under their Bioscience Discovery Evaluation Program (BDEGP) to support local emerging companies that have licensed technology from a Colorado University. In our [November Newsletter](#), we reported on licensing a novel modeling technology from [Dr. John Carroll, Cardiology, University of Colorado Health Sciences Center](#). This technology enables the creation of patient-specific 3-D plastic models of the heart and its chambers, and will be useful for training physicians in the implant and the exchange of the VXi valves.

Our [web site](#) continues to evolve and expand. We now have an expanded [Physicians](#) page that explores the many options for selecting a prosthetic valve, supported by an extensive bibliography. Also on the web site is a short video that summarizes the VXi product portfolio. This video can be viewed on the VXi web site by clicking [here](#).

We are also happy to report that VXi has received yet another patent on its exchangeable valve technology. With the addition of European Patent 1,049,425 "System for Minimally Invasive Insertion of Bioprosthetic Heart Valve", we now have 7 issued patents and an additional 11 applications pending. The USPTO has also recently accepted "VALVEXCHANGE" as a U.S. Trademark No. 2.897,597.

For those new to this Newsletter, ValveXchange is an emerging technology company based in Colorado. We call ourselves "The Lifetime Tissue Valve Company" and are developing the first-of-its-kind "serviceable" bioprosthetic valve. By offering periodic, minimally invasive exchange of the worn-out leaflet set, young and physically active patients can avoid the use of a mechanical valve and the associated Coumadin® anticoagulation therapy. By adhering to the time-proven design tenets of conventional bovine pericardial valves, we believe that the ValveXchange system will offer the best combination of least-invasive techniques and greatest valve longevity and durability.

Press Release

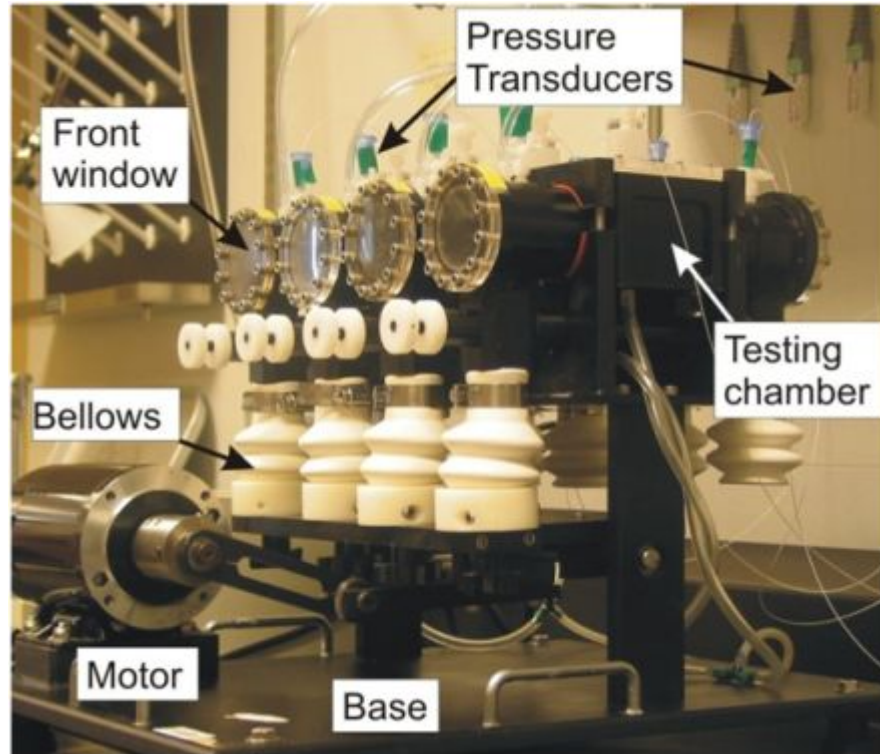
ValveXchange Receives \$250,000 Grant from the State of Colorado

January, 2010. Denver - ValveXchange Inc. is pleased to announce that it has received a \$250,000 grant from the State of Colorado under the [Bioscience Discovery Evaluation Grant Program \(BDEGP\)](#). This program is designed to spur economic development and help companies succeed in developing new technologies, business structures, and product development. Grants up to \$250,000 were awarded in 2009 to support the commercialization of therapeutic or diagnostic products, devices, or instruments to improve human health; bioscience technologies that improve agriculture, or biofuels.

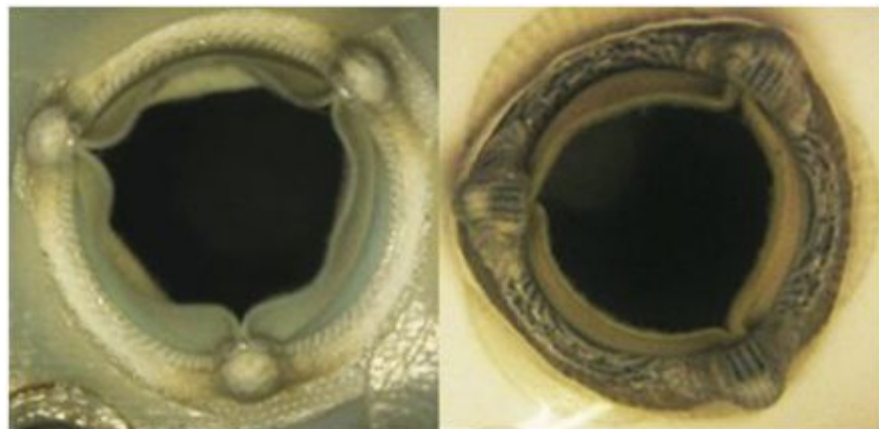
Technology Report

Pulse Tank Testing Reveals Good Leaflet Function

Our hydrodynamic durability tester (shown below) consists of 4 individual chambers isolated from each other, so that different types of valves can be used in different chambers simultaneously. In initial testing, our valves accumulated over 15 million cycles without incident.



In a recent side-by-side comparison, we took low speed and high speed (1000 frames per second) videos of the VXI Vitality™ and the Edwards Perimount™ valves in the hydrodynamic tester. The low speed videos were obtained in our lab and the high speed video in the lab of [Dr. Lakshmi Prasad Dasi](#), a new faculty member at Colorado State University, formerly a member of [Dr. Yoganathan's team at Georgia Tech](#). We were very pleased to see wide leaflet opening patterns, and smooth leaflet curvatures of the VXi Vitality™. In the images below, the Edwards valve is shown at left and the VXi Vitality is at right.



Other News



As can be seen from this historical review of mechanical valves, the overall trend in their evolution has been away from the bulky, obstructive ball-in-cage, and single leaflet design, to the more fluid dynamically efficient bileaflet designs.

The evolutionary history of tissue valves has been equally rich, but visually less apparent. In the early days, many mistakes were made and valves failed early. [The Ionescu-Shiley valve](#) is a good example of that. Put stitches in the wrong spot and you get stress concentrations and early failure. Both stented and stentless valve designs have come and gone - I only wish that I had a similarly impressive poster of tissue valves.

With transcatheter valves, it is still too early to tell which designs will make it and which will not. Much of the "weeding out", however, has already started - not because of clinical failures, but because of economic hard times. For example, [Hansen Medical, who acquired the AortTx transcatheter valve](#), has recently stopped its development because of financial pressures.

Technical challenges, however, remain. For example, the complex intertwined Nitinol mesh of the [Sadra Medical](#) valve makes it at [risk of fretting at cross-over points](#) from the cyclic deformations in vivo. There have also been reports of [fracture of the Nitinol cage of the Medtronic Melody](#) valve, although this was not significant enough to prevent the FDA from granting market approval for treating pediatric patients with congenital heart defects - a patient group that has few other options.

With clinical experience accumulating, some of the complications associated with transcatheter valves have been reduced, while others have become more certain. For example, the reason why patients undergoing TAVI occasionally die from renal problems has been clarified by [Bagur in a recent paper published in the European Heart Journal](#). An important issue reportedly associated with TAVI patients is that almost half of them already have chronic renal disease. The administration of contrast agent and the manipulation of large catheters in the aorta can dislodge atherosclerotic plaque particles that can contribute to renal injury. However, when these patients are managed better, such as reducing blood transfusions and minimizing the use of contrast agent, they do well. Indeed, renal injury following transfemoral TAVI appears to be lower than following surgical aortic valve replacement, when all other patient factors are accounted for, most likely because of the avoidance of cardiopulmonary bypass.

Other reports, however, show a perplexing increase in kidney injury, even in the absence of contrast and cardiopulmonary bypass - this during transapical implantation of transcatheter valves. A recent paper by Strauch from Cologne reported that [TransAPical Aortic Valve Implantation \(TAP-AVI\) led to acute kidney injury \(AKI\) in 57% of their patients](#). Both the [Bagur](#) and the [Strauch](#) papers reported no correlation between the amount of contrast used, but in both studies the amount of contrast was comparable between those patients who developed AKI and those that did not. Interestingly, the Bagur paper has relatively low incidence of AKI (12%) whereas the Strauch paper had a high incidence of AKI (57%). The only

major difference between the two papers was that Strauch used about 115 ml of contrast, whereas Bagur used less than 100 - not a huge reduction. Both papers, however, noted that the major single predictor of developing AKI was bad kidneys before the procedure. Strauch also noted that congestive heart failure was also a predictor. It should also be noted that transapical patients typically have a higher risk profile than transfemoral patients.

My opinion as to who develops AKI - well that all depends on how sick you are prior to the procedure and how well you can take the various periods of low cardiac output, hypoxia and contrast agent administered, as the valve is being delivered. As experience with delivery improves and less contrast is used, it is likely that incidence of AKI will continue to go down.

Strokes, however, continue to be a point of concern with TAVI. While the incidence of [symptomatic stroke can be lower than 5%](#), the incidence of "Silent Strokes" is remarkably high. A Silent Stroke is defined as one that [does not cause any noticeable symptoms, but does cause brain damage](#). The [on-line literature is rich with reports](#) of silent strokes leading to [persistent memory problems, dementia, and accelerated loss of mental skills](#). Silent stroke has also been linked to a [40% increase in depression](#). So how serious is Silent Stroke following TAVI? According to a recent report, at least [80% of patients treated with either the Sapien or the CoreValve device had new lesions visible through MRI scans](#). On the other hand, 48% of those undergoing conventional open heart surgery had the same lesions.

Undergoing TAVI thus roughly doubles the risk of Silent Stroke, yet reduces the risk of renal injury, when compared to traditional, open heart, on-pump valve replacement surgery. Clearly, there are many other complications associated with either procedure, and compromises and difficult choices thus need to be made. For now, TAVI is reserved for the old, really sick, inoperable patient - at least in the US. In Europe, however, TAVI is beginning to penetrate into the younger, less sick, more operable patients. One particularly interesting recent paper from Germany notes that "[*Patients with a good functional status are likely to benefit more from TAVI than... high risk patients*](#)" and a similar comment with regard to [treating severely symptomatic patients](#) also suggests that TAVI works better in healthier patients.

Excuse me!? Are we now promoting that TAVI be used on healthier patients instead? What about that additional 30% of patients with heart valve disease that go untreated - the original population for whom TAVI was developed? Are these patients now a "bad risk for TAVI technologies"? Are we now going to promote TAVI for younger patients because they do better after TAVI than the original, old, frail, inoperable patient?

A recent publication on a large, [multi-center Canadian trial of severely symptomatic patients](#) reports a 10.4% 30-day mortality after TAVI - this for patients with a 9.8% predicted surgical mortality, according to their STS score. These patients are thus not being served any better than they would have been, had they had aortic valve surgery by the "average" surgeon that

reports data to the STS ([STS registry has nearly 800 participants and over 3 million patient records](#)). Indeed, had they been seen by an above average surgeon that frequently operates on elderly, frail patients, they would have had better operative and 30 day mortality, than what happened to them after TAVI - that, in the hands of perhaps the most experienced interventional cardiologists doing TAVI.

Surviving the procedure, however, is not the end of the story. Few people now believe that transcatheter valves are going to last any longer than 5-7 years. So even if the patient does well after TAVI and is spared the painful recovery after valve surgery, what happens when the transcatheter valve wears out in a few years? Do we then implant a proper valve, or do we implant another transcatheter valve inside the other? Interestingly, there has been one example of a [failed transcatheter valve patient being "rescued" by an open implant of a surgical valve](#) - this on a patient that was presumably too high risk for surgery to begin with.

A valve-in-a-valve might be considered if there are no other options. But when better options exist, the compromises and trade-offs for each need to be explored. In the application of TAVI, we must not forget the long-standing issue of Patient Prosthesis Mismatch (PPM). The May 2009 issue of the Journal of Heart Valve Disease includes an interesting paper by [Urso from Spain about the quality of life after PPM](#). That paper is accompanied by an [Editorial on the topic by Pibarot and Dumesnil](#) from Quebec, Canada, both of whom are well known for studying the effects of PPM. What becomes clear from reading these two articles is that PPM was, is, and will

continue to be a serious issue. While PPM may not impact survival of the elderly, it nevertheless does impact their "quality of life", as measured by the Physical Component of the [SF-12 test](#), which grades responses to questions like "Are you limited in activities such as pushing a vacuum cleaner or playing golf". For the elderly, presence of PPM and thus a diminished valve area leads to a diminished quality of life, resulting primarily from reduction in the ability to do exercise and other desirable activities. In the younger population, there was not only a reduction in quality of life, but also in patient survival. This is likely due to the greater expected life span of younger patients. In these patients, the negative hemodynamic effects of PPM had more time to take their toll on the cardiovascular system. So while younger patients do better with TAVI than do older patients, the diminished Effective Orifice Area (EOA) will lead to PPM, reduced quality of life and even early death. Unfortunately, many individuals will opt for this fate, as humans often select against "short term pain for long term gain", and instead choose a way of life that postpones the tough decisions.

So why will TAVI lead to PPM and long-term health issues if applied to younger patients? Quite simply it is the ongoing presence of the large, calcified native aortic valve cusps. Since these large nodular leaflets remain in the aortic root, it is difficult to imagine how one can obtain an effective orifice area as large as if the leaflets were not there. Prior to insertion of surgical valves, these bulky, nodular leaflets are cut out. With TAVI, they are not - they are simply pushed aside into the Sinuses of Valsalva (see image right). Had these leaflets been cut out, a greater opening would have likely been available for the implantation of a conventional surgical valve, and hence a greater EOA.



Circling back to the evolution of transcatheter valves, it should also be pointed out that there are additional compromises that are made with these devices, relative to surgical valves. Some of these transcatheter valves have fewer compromises, others have more. Universally, however, the trade off is a non-surgical implant in exchange for diminished longevity and other potential risks during implantation. In the table below, I have summarized the key design features of many of the transcatheter and minimally invasive valves currently in development and/or in clinical trials (Click www.valvexchange.com/products/images/table.jpg) for larger image.

		Approach	Coronary overlap	Reposition-able	Exchange-able	Flexible Stent Posts	Precise Central Gap	Stent circularity	120 deg leaflet symmetry	Expected longevity
Edwards Perimount		Surgical	NO	NO	NO	YES	YES	YES	YES	HIGH
ValveXchange Vitality		Surgical	NO	NO	YES	YES	YES	YES	YES	HIGH
ValveXchange Vanguard		Transapical	NO	YES	YES	YES	YES	YES	YES	HIGH
Arbor Trilogy		Surgical	NO	NO	NO	YES	YES	YES	YES	HIGH
ATS 3F		Surgical	NO	NO	NO	YES	UNCERTAIN	YES	UNCERTAIN	UNCERTAIN
Sorin Perceval		Surgical	YES	NO	NO	YES	UNCERTAIN	YES	YES	UNCERTAIN
Edwards Sapien		Trans-femoral Transapical	NO	NO	NO	NO	NO	NO	NO	LOW
Medtronic CoreValve		Trans-femoral	YES	NO	NO	NO	NO	NO	NO	LOW
Medtronic Ventor		Transapical	UNCERTAIN	NO	NO	UNCERTAIN	NO	NO	NO	LOW
Direct Flow		Trans-femoral	UNCERTAIN	YES	NO	NO	NO	NO	NO	LOW
Sadra		Trans-femoral	UNCERTAIN	YES	NO	NO	NO	NO	NO	LOW
AorTx		Trans-femoral Transapical	NO	YES	NO	UNCERTAIN	UNCERTAIN	UNCERTAIN	UNCERTAIN	LOW
Jena Valve		Trans-femoral Transapical	NO	NO	NO	YES	NO	NO	NO	LOW
Lutter		Trans-femoral	UNCERTAIN	NO	NO	NO	NO	NO	NO	LOW
LPI		Trans-femoral	UNCERTAIN	NO	NO	NO	NO	NO	NO	LOW
Heart Leaflet Technologies		Trans-femoral	UNCERTAIN	NO	NO	YES	NO	NO	NO	LOW
Endolaminal Technologies		Trans-femoral	UNCERTAIN	NO	NO	NO	NO	NO	NO	LOW

The left two columns denote the company, the valve name and a picture of the valve that I managed to get off the web. The third column denotes whether it is surgical (open, on-pump) or off-pump transfemoral or transapical. Often these are the main distinguishing features of a new valve technology. However, it is the subsequent columns which really point to the engineering features that are likely to provide benefit or produce complications. For example "Coronary Overlap" - the presence of valve components inside the Sinuses of Valsalva, or covering the coronary ostia

- is an important feature. In the case of the CoreValve, blood has to flow through the Nitinol mesh in order to feed the coronaries. Whether this will grow over with pannus in a few years is unclear, but certainly a reasonable question. At the one-year time point, [pannus apparently does not cover the Nitinol mesh where it overlaps the coronary ostia](#). Similarly, the Sorin Perceval relies on metallic components inside the Sinus of Valsalva for positioning. Although designed to avoid the coronary ostia in perfectly symmetrical aortic roots, diseased native valves are rarely symmetrical. There is thus the risk that one of the vertical posts may overlap a coronary ostium. An ongoing concern with valves employing a large amount of bare Nitinol is the risk of emboli from the thrombus that apparently accumulates in the various crevices. The image at right, taken from the paper by [Bonan et al.](#) shows the outflow view of a CoreValve that had been in the patient for 350 days who died of renal disease and respiratory distress. The amount of adherent thrombus to the Nitinol cage should give some pause for concern.



The last 5 columns, however, are the most important. In previous editions of this newsletter, I introduced the three tenets of good valve design - those features which are common to highly successful, long-lived tissue valves - (i) flexible stent posts, (ii) precise central gap between leaflets, and (iii) absolute 120 degree symmetry in leaflet position. No valve constructed from an expandable mesh can assure leaflet symmetry and precision of the central gap, and few have incorporated flexible stent posts. None of the valves constructed from such a mesh can thus be expected to have the same durability as surgical valves - like the Edwards Perimount. The Arbor Trilogy, being a sutureless surgical valve, may have the features of a long-lived valve but without the exchangeability of the VXi products, or the off-pump delivery of the VXi Vanguard. Only the VXi Vitality and the Vanguard incorporate these important design features into a transapical access valve.

Procedural complications are certainly expected to decrease as experience with transcatheter valves accumulates. However, technology needs to help. For example, it would be advantageous if valves and delivery systems were designed to avoid long periods of fluoroscopy and high doses of contrast. A trend away from fluoroscopy, towards ultrasound imaging, is therefore desirable. Where technology must be the absolute leader, however, is in the design of devices that do not subject the patient to undue

risk of complications during and after delivery - including early failure through structural deterioration. At ValveXchange, we believe we are addressing these requirements with valve designs that are inherently durable, yet at the same time minimizing invasiveness.

Summary:

One of the objectives of this newsletter, as well as the content on our web site, is to educate. We wish to educate not only patients who face heart valve replacement procedures, but also those organizations who are considering ValveXchange Inc. as a potential partner. My Reality Check articles, in particular, encourage healthy skepticism in transcatheter valves - an emerging technology that has taken the valve world by storm. Having said that, VXi is also developing transcatheter valve technology to be competitive to existing transapical valve implantation (TAP-AVI). It should be appreciated, however, that all valve technologies and valve implant approaches have their own set of pros and cons, their advantages and shortcomings. No single technology is best for everyone. Patients, in particular, should examine the segment of our web site where we discuss the [compromises that transcatheter valves require](#) - be they technologies from other companies or from VXi. With the Vitality and the Vanguard, now in development, we believe we have a suite of technologies that best meets the broadest patient requirements.

I look forward to sharing details of our progress with you in the coming months.

Sincerely,

Ivan Vesely, Ph.D.
Founder and Chief Scientific Officer
ValveXchange Inc.
vesely@valveXchange.com

Recent News Releases

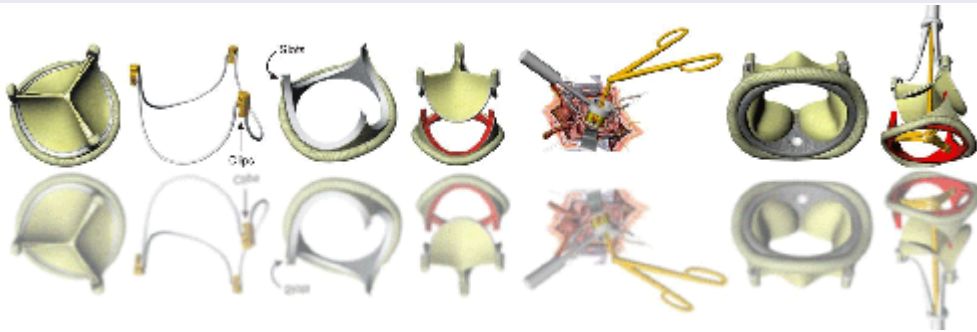
November 19, 2009. Aurora, CO - ValveXchange Inc. recently executed a license agreement with the University of Colorado for a process to transform cardiac imaging data into high-quality three-dimensional models used for heart valve product development, clinician training, and pre-procedure planning. [Read More.](#)

October, 2009. Denver - ValveXchange Inc. is pleased to announce that Dr. Antonio Calafiore has joined the VXi Medical Advisory Board. Dr. Calafiore is recognized internationally for pioneering off-pump coronary artery bypass grafting and the "Calafiore technique" of myocardial preservation. Dr. Calafiore has recently moved from Italy to Riyadh, Saudi

Arabia as the director of the Prince Sultan Cardiac Center. [Read More.](#)

September, 2009. Denver - ValveXchange Inc. is pleased to announce that Michael J. Mack, M.D., has joined the VXi Medical Advisory Board. Dr. Mack is Director of Cardiovascular Research and Cardiovascular Medicine of the Heart Hospital Baylor Plano and Director of Cardiovascular Surgery for the Baylor Healthcare System. He is considered to be the most noted authority on the emerging field of transcatheter valves. [Read More.](#)

June, 2009. Denver - ValveXchange Inc. announces that Walter Randolph "Randy" Chitwood, Jr., M.D., FACS, FRCS has joined the VXi Medical Advisory Board. Dr. Chitwood was the principal investigator of the FDA robotic mitral valve trials that led to approval for this use in the United States. Today, he is the world's leader in robotic mitral valve surgery. [Read More.](#)



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