**TABLE OF CONTENTS**

- **Introduction**
  By Jean-Pierre Després, PhD, FAHA, Editor-in-Chief  page 2

- **Editorial**
  By Philippe Pibarot, DVM, PhD, FACC, FAHA, Guest Editor  pages 3-4

- **Molecular mechanisms of insulin resistance in obesity**
  By André Marette, PhD  pages 5-9

- **The visceral adipocyte and cardiometabolic risk factors**
  By André Tchernof, PhD  pages 10-13

- **Serum insulin and inflammatory markers in overweight people with and without dyslipidemia**
  By Philip Barter, MBBS, FRACP, PhD  pages 14-16

- **Cardiometabolic risk: the surgeon’s perspective**
  By Patrick Mathieu, MD
  Philippe Pibarot, DVM, PhD, FACC, FAHA
  Jean-Pierre Després, PhD, FAHA  pages 17-20

- **“Valvulo-metabolic” risk in aortic stenosis**
  By Philippe Pibarot, DVM, PhD, FACC, FAHA  pages 21-25
Welcome to the first edition of the CMReJournal, the official online journal of the International Chair on Cardiometabolic Risk. The Chair created this journal to complement its website and its many other projects, which include conferences and presentations, educational symposia, and publications in peer-reviewed, indexed scientific/medical journals.

The CMReJournal will feature short, straightforward papers on issues relevant to abdominal obesity and cardiometabolic risk. These papers will include a number of appealing, downloadable figures and will focus on key findings and messages. The CMReJournal can be viewed onscreen or printed for your later enjoyment. Registered website users should expect to receive three to four thematic issues per year. Depending on the topics to be covered, we will also regularly invite Guest Editors to share their specific expertise with us. For this first issue of the CMReJournal, we are delighted that Dr. Philippe Pibarot of the Quebec Heart Institute at Hôpital Laval Research Centre (Université Laval) has agreed to serve as Guest Editor.

We hope the CMReJournal will become a popular forum for us to share ideas, findings, and concepts surrounding abdominal obesity and cardiometabolic risk. We also welcome your suggestions regarding themes or topics you would like covered. Please feel free to contact us with feedback and/or suggestions. The CMReJournal belongs to you!
EDITORIAL

By Philippe Pibarot, DVM, PhD, FACC, FAHA
Guest Editor philippe.pibarot@med.ulaval.ca

It is a great pleasure and privilege to serve as the Guest Editor of this first issue of the CMReJournal. This issue includes five articles that provide important new insights into the assessment and management of cardiometabolic risk (CMR).

New methods for the prediction and treatment of obesity-related insulin resistance
In his article, Dr. André Marette, a scientist at Hôpital Laval Research Centre, Quebec City, Canada, provides new insights into the potential mechanisms involved in the promotion of obesity-related insulin resistance. This review emphasizes the need to speed up the discovery of new diagnostic tools to predict the development of insulin resistance in obese individuals and to find novel therapeutic targets to improve the pharmacotherapy of obese diabetic subjects when lifestyle modifications fail to achieve the therapeutic goals.

The visceral adipocyte: does it contribute to CMR?
In this issue of the journal, Dr. André Tchernof, a scientist at Centre Hospitalier Universitaire de l'Université Laval (CHUL) Research Centre, Quebec City, Canada, presents an overview of his research efforts to establish the potential mechanisms relating the visceral adipocyte to cardiometabolic risk factors. Dr. Tchernof concludes that the pathogenesis of the metabolic syndrome and its associated CMR involves several mechanisms, including visceral adipose tissue, fatty acid release, reduced peripheral lipid storage, and secreted cytokines.

Overweight people are not all equal in terms of CMR
Because not all overweight individuals are at increased risk of diabetes and cardiovascular disease, the challenge for the clinician is to identify the subgroup of individuals who have “at risk” obesity. Dr. Philip Barter of the Heart Research Institute, Sydney, Australia, presents the key findings of a large epidemiological study that stresses the importance of simple measures such as plasma triglycerides and HDL-C in identifying those overweight people who have the metabolic syndrome and are at high cardiovascular risk.
**CMR in cardiac surgery**

Dr. Patrick Mathieu, a heart surgeon and clinical scientist at Hôpital Laval, Quebec City, Canada, presents the cardiac surgeon’s perspective on CMR. Specifically, he demonstrates based on his recent findings that the metabolic syndrome negatively affects the patient’s postoperative outcome following coronary artery bypass graft surgery and aortic valve replacement.

**Valvulo-metabolic risk**

Finally, I introduce the concept of “valvulo-metabolic risk,” which can be defined as the risk of valvular heart disease resulting from the metabolic abnormalities associated with visceral obesity and metabolic syndrome. This is a new emerging field of research that may have important clinical implications given that valvular heart diseases are among the most frequent cardiovascular diseases and are associated with a high risk of morbidity and mortality.

We hope that you will enjoy this first issue of the CMReJournal, and we welcome your comments about the content and format of this issue as well as your suggestions for future issues.
Insulin resistance is defined as reduced insulin action in metabolic and vascular target tissues. Whereas it is widely recognized that insulin resistance is a key pathogenic factor in the development of diabetes and cardiovascular disease (CVD), its etiology remains elusive. In this short report, we will summarize our research efforts toward establishing the potential mechanisms responsible for promoting insulin resistance in key metabolic tissues.

**Inflammation as a cause of insulin resistance**

While obesity-linked diabetes and CVD are known to be chronic inflammatory disorders, the underlying mechanisms by which inflammation promotes these metabolic diseases remain poorly understood. Studies in my laboratory identified inducible nitric oxide synthase (iNOS) as a key inflammatory mediator in obesity, causing insulin resistance in skeletal muscle [1-4] (Figure 1) and impairing insulin action in the liver through inhibition of adiponectin secretion by adipose tissue [5] (Figure 1). Studies by other groups have confirmed the role of iNOS in obesity-linked insulin resistance [6-8] and further indicated that iNOS induction in blood vessels is also involved in mediating vascular dysfunction in obesity [8]. The underlying cause of inflammation in obesity remains poorly understood, but one theory is that it lies within the origin of fat cells. Indeed, metabolic and immune pathways have evolved to be closely linked and interdependent. The finding that obesity is characterized by macrophage accumulation in adipose tissue [9, 10] and that macrophages and fat cells share the expression of multiple genes has added another dimension to our understanding of the development of adipose tissue inflammation in obesity. The role of immune cells in promoting inflammation in obesity has also recently been confirmed in humans [11-13]. What remains to be determined is how obesity promotes an inflammatory process not only in adipose tissue, but also in skeletal/cardiac muscles and liver. In this regard, recent studies point toward hypoxia as a key triggering event in the development of an inflammatory state in obesity [14-16]. However, this remains to be confirmed and better characterized, especially in human obesity.
Nutrient sensing through the mTOR pathway promotes insulin resistance

Recent studies by our group and others suggest that nutrient satiation promotes insulin resistance by activating the protein kinase mTOR pathway, a sensing complex that integrates nutrient and hormonal signals [17-21]. We first proposed that mTOR operates a negative feedback loop by phosphorylating the first substrate of the insulin receptor, IRS-1, on multiple serine residues, uncoupling IRS-1 from the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, two effectors of insulin’s metabolic actions [20] (Figure 1). This metabolic feedback loop has been found in myocytes [20, 22], adipocytes and hepatocytes [17, 23] as well as in liver and muscle tissues of rats [17], suggesting that the mTOR pathway plays a major role in the regulation of glucose homeostasis. Importantly, we and others have shown that mTOR and its effector S6K1 are “overactivated” in skeletal muscle, liver and adipose tissue of both genetic and dietary animal models of obesity-linked insulin resistance [17, 24]. We have further shown that the mTOR pathway negatively modulates insulin’s metabolic actions in skeletal muscle and adipocytes of healthy subjects [17, 22]. We have also recently identified that serine 1101 in the IRS-1 protein is a molecular target of S6K1 in the liver of obese animals and in skeletal muscle during infusion of human subjects with amino acids [25]. Whether increased activation of S6K1 is a common feature of human obesity and insulin...
resistance is currently unknown, but IRS-1 (Ser-1101) and S6K1 (Thr-389) may represent future diagnostic tools in order to predict and design therapeutic treatments.

**AMPK: turning on metabolism while turning off insulin resistance**

AMPK is a member of a metabolite-sensing protein kinase family that acts as a fuel gauge monitoring cellular energy levels [26, 27]. When AMP kinase “senses” decreased energy stores, it acts to switch off ATP-consuming pathways and switch on alternative pathways for ATP regeneration. AMPK is activated by exercise/muscle contraction [28] but also by several classes of drugs that are currently used for treatment of diabetes and CVD, including thiazolidinedione (TZD), and that activate proliferator-activated receptor gamma (PPARg). We have recently reported that PPARg agonists inhibit iNOS induction in macrophages, myocytes and adipocytes through activation of AMPK [29] (Figure 1). These studies indicate that AMPK is a master switch that turns on metabolic pathways while turning off inflammation in insulin target tissues and macrophages. Interestingly, AMPK may also improve insulin sensitivity by blunting the activation of the mTOR/S6K1 pathway (Figure 1). Indeed, activation of AMPK by the pharmacological activator AICAR or by the anti-diabetic drug metformin inhibits mTOR/S6K1 in various cell types [30, 31]. AMPK may therefore represent a key therapeutic target since its activation can blunt both inflammation and nutrient sensing signals believed to play a key role in promoting insulin resistance in obesity.

**SHP-1: a new target for the treatment of insulin resistance?**

Because tyrosine phosphorylation is key to insulin signal transduction, protein tyrosine phosphatases (PTPs) are prominent candidates to negatively regulate insulin action. Previous studies have shown that the PTPs PTP1B and LAR (leukocyte related-antigen) are negative regulators of the insulin receptor kinase in liver and peripheral insulin target tissues [32-34]. PTP1B-deficient mice are leaner, exhibit increased energy expenditure and are protected from insulin resistance in the liver and skeletal muscle [35, 36]. Neuron-specific PTP1B KO also increased leptin sensitivity and improved glucose homeostasis, suggesting that PTP1B regulates body mass and adiposity primarily through actions in the brain [37].

We have recently identified the PTP SHP-1 as a novel inhibitor of insulin receptor signalling in liver and skeletal muscle [38]. We found that mouse models with a functionally deficient SHP-1 protein are remarkably glucose tolerant and insulin sensitive for glucose metabolism as a result of increased insulin signalling to the IRS/PI3K/Akt pathway in both liver and muscle tissues. These findings indicate that SHP-1 plays an important role in the regulation of insulin signalling in liver and muscle. Preliminary data also demonstrates that SHP-1 is expressed in adipose tissue and modulates lipid metabolism and adiposity (A. Marette, unpublished data) but the mechanisms involved remain poorly understood. It will be important in the near future to clarify the role of SHP-1 in controlling insulin sensitivity in insulin-resistant states and investigate whether this PTP is a potential target for anti-diabetic drugs.

**Concluding remarks**

Given the prevalence of obesity worldwide and the increase in associated health complications such as diabetes and CVD, the need for a mechanistic understanding of obesity-related insulin resistance remains a major research priority. We also need to speed up the discovery of new biological markers and diagnosis tools to assess insulin resistance and predict its development in populations at risk.
Finally, it is critical to find novel therapeutic targets to improve the pharmacotherapy of obese diabetic subjects, which is a crucial measure when lifestyle modifications (e.g., physical activity, diets) fail to achieve the therapeutic goals.

References


Numerous studies have shown the strong and independent association between fat accumulation on anatomical structures such as the mesentery and greater omentum (i.e., visceral fat accumulation) and risk factors for type 2 diabetes and cardiovascular disease [1]. This strong association suggests a close physiological link between fat cells located within the visceral fat compartments, the visceral adipocytes, and metabolic abnormalities. This brief review will discuss potential mechanisms relating the visceral adipocyte to cardiometabolic risk factors.

The hypertriglyceridemic state of visceral obesity is primarily due to VLDL overproduction [2, 3]. Availability of fatty acids in the liver is recognized as the primary determinant of this overproduction [3], which has led to the hypothesis that an increased fatty acid flux from adipose tissue located within the abdominal cavity through the portal vein to the liver could potentially explain visceral obesity-related hypertriglyceridemia [4]. Visceral adipose cells are believed to be hyperlipolytic and poorly responsive to insulin inhibition [4-6]. A recent study by our group is the largest to date to be performed in women on this issue [7]. We found that although lipolytic rates were higher in subcutaneous adipocytes when values were expressed on an absolute basis (per cell) (Figure 1), the responsiveness of omental adipocytes to positive lipolytic stimuli was much higher than that of subcutaneous adipocytes (Figure 2). We also reported in the study that omental vs. subcutaneous differences in lipolysis were relatively constant throughout the spectrum of adiposity values (Figure 3). Conversely, in men, no
difference was observed in the size of omental vs. subcutaneous fat cells. Accordingly, basal lipolysis and lipolytic responses to positive stimuli expressed either as a function of cell number or as fold response over basal levels were not significantly different in omental vs. subcutaneous fat cells [8]. We suggest that regional differences in adipocyte size (or lack thereof) are important determinants of regional differences in adipose tissue metabolism.

Other mechanisms could also explain the close association between excess visceral fat accumulation and cardiometabolic risk factors. Results on ectopic fat accumulation have led to the suggestion that insulin resistance may be due to increased lipid burden on skeletal muscle and liver from a reduced capacity for excess fat storage in the presence of excess energy intake [9-11]. According to this hypothesis, insulin resistance could be due not only to lipids released from fat, but also to a reduced capacity for excess lipid handling and storage in peripheral fat depots [11, 12].

More recently, the endocrine and paracrine nature of the adipose organ (Figure 4) has emerged as a new line of investigation, and adipose tissue-secreted cytokines (adipokines) are believed to mediate part of the link between visceral fat accumulation and cardiometabolic risk. Studies in humans and rodents have shown that the various cell types found in visceral adipose tissue (adipocytes, stromal or vascular cells, macrophages, etc.) release cytokines such as resistin, adiponectin, TNF-α, and IL-6, which may contribute to obesity-related insulin resistance [13-15].
Adiponectin, a cytokine produced in adipose tissue, has been shown to be decreased in obesity, type 2 diabetes, and atherosclerosis [16, 17]. Recent data indirectly suggest that adiponectin is reduced primarily in omental fat of obese subjects, which would indicate yet another possible preferential link between visceral fat accumulation and cardiometabolic risk factors.

Taken together, visceral adipose tissue fatty acid release, reduced peripheral lipid storage, and secreted cytokines may all be involved in the etiology of insulin resistance, the metabolic syndrome, and related global cardiometabolic risk.

References

Overweight and obesity are increasing worldwide at an alarming rate and are setting the scene for a major epidemic of type 2 diabetes and premature cardiovascular disease (CVD). Overweight people frequently have a cluster of abnormalities that includes impaired fasting glucose, hyperinsulinemia, elevated blood pressure, a dyslipidemia characterized by a low level of high density lipoprotein cholesterol (HDL-C) and high plasma triglyceride, and an increased level of inflammatory markers in their blood. A commonly used term for the clustering of abnormalities associated with being overweight is the metabolic syndrome.

The question arises: do overweight people whose plasma lipids are normal differ from their dyslipidemic counterparts in terms of the presence of the other components of the metabolic syndrome?

This question has been addressed by comparing two distinct groups of overweight people: one of people with low HDL-C cholesterol and high triglyceride (dyslipidemic group) and the other of people with a higher than average HDL-C cholesterol and a lower than average plasma triglyceride (normolipidemic group). These subjects were a subset of the GEMS Study.

Figure 1: Characteristics of the study population
Subjects were recruited from two centres in Europe (Oulu, Finland and Lausanne, Switzerland), one centre in the USA (Dallas, Texas), one centre in Canada (Ottawa), and one in Australia (Adelaide) [1].

The study included 715 (57% male) cases and 1073 (54% male) unrelated controls (Figure 1). The mean body mass index (BMI) in the cases and controls was 28.7 and 28.2 kg/m², respectively. The waist circumference of the cases was substantially and significantly greater than in controls. The difference in waist circumference remained statistically significant (p<0.001) when adjusted for BMI (Figure 2). Plasma hs-CRP was significantly higher in cases than controls, whereas adiponectin was significantly lower in the cases (Figure 3).

The plasma lipids in the cases and controls differed in several respects, most of which were predictable. Apart from the pre-specified differences in levels of HDL cholesterol and plasma triglyceride, cases had significantly higher levels of plasma total cholesterol, apo B, and non-HDL cholesterol than controls. Cases also had smaller LDL particles than controls. The concentration of plasma glucose was significantly higher in cases than controls. Fasting insulin and homa-IR were also significantly higher in cases than controls (Figure 4).

The results of this study may be of major clinical importance in the face of the worldwide epidemic of overweight and obesity and the associated increased risk of type 2 diabetes and CVD. This analysis of the GEMS study clearly indicates that not all overweight people are at the same risk, with a much higher risk group being identified by the simple measurement of plasma...
triglyceride and HDL-C cholesterol. The finding that overweight people who are normolipidemic tend to have normal glucose and insulin metabolism, low levels of inflammatory markers, and normal blood pressure suggests that such people may be at relatively low risk of developing diabetes and CVD despite being overweight.

Thus, identification of people solely on the basis of an elevated plasma triglyceride and a low HDL-C cholesterol uncovers an overweight group of people who have a generalized metabolic disorder.

In contrast, overweight people with normal plasma lipids have normal glucose and insulin metabolism, low levels of inflammatory markers, and normal blood pressure. Such people may thus be at relatively low risk of developing diabetes and CVD despite being overweight.

This study emphasizes the importance of simple measures such as plasma triglyceride and HDL-C cholesterol in identifying those overweight people who have the metabolic syndrome and are at high cardiovascular risk.

References

Visceral obesity has been recognized in recent years as a strong determinant of metabolic abnormalities and cardiovascular risk [1]. In the last decade, we have also seen an increasing number of individuals with visceral obesity, insulin resistance and the atherogenic lipoprotein phenotype [2]. More and more studies have highlighted the fact that excess abdominal fat is the strongest determinant of metabolic disorders [3]. These studies have helped to single out important components associated with visceral obesity, such as low HDL concentrations, high triglyceride levels, insulin resistance and a low-grade inflammatory state [4]. While these metabolic disorders have been established as important determinants of coronary events, it is only recently that these abnormalities associated with visceral obesity have been evaluated as potential risk factors following heart surgery [5]. In addition to playing a role in atherosclerosis, at-risk abdominal obesity is also thought to play a role in the degeneration of implanted valve bioprostheses (BPs) [6]. Hence, it now appears that visceral obesity is a global cardiovascular risk that also encompasses surgical risk and heart valve diseases.

Figure 1: Mechanisms whereby the metabolic syndrome could confer a higher operative morbidity and mortality
The metabolic syndrome: a risk factor in cardiac surgery

In previous studies, diabetes has been associated with increased morbidity following a cardiac surgery [7]. However, whether diabetes increases perioperative mortality is contentious [8, 9]. Furthermore, while obesity, as defined by body mass index (BMI), has been associated with increased morbidity following a coronary artery bypass grafting (CABG) surgery, it has not been associated with a higher mortality rate [10]. In light of the pro-inflammatory condition associated with abdominal obesity, we have recently hypothesized that individuals characterized by the metabolic syndrome (MS) would be at greater risk. In 5,304 patients undergoing a CABG, we documented that a substantial proportion of patients (46%) were characterized by the MS.

We also found that the MS conferred a three-fold risk of in-hospital mortality and was independently associated with postoperative complications such as renal failure and atrial fibrillation (AF) [5, 11]. Significantly, subjects with diabetes and without the MS were not at higher risk. Although the mechanisms underpinning these processes are complex and not yet fully understood, it is tempting to speculate that low grade inflammation associated with visceral obesity could increase in the postoperative period, contributing to the development of complications.

Postoperative AF, a common complication following cardiac surgery with incidence varying between 30-50%, is associated with a substantial increase in morbidity and cost for the healthcare system [12]. The mechanisms that contribute to this arrhythmia in the postoperative period are multifaceted and may involve oxidative stress as well as activation of the autonomic system [13]. In addition, obese individuals have a higher prevalence of ventricular diastolic dysfunction and elevated plasma volume, which may contribute to atrial remodelling [14]. Atrial remodelling and enlargement may therefore provide an anatomical substrate by which triggering factors in the postoperative period can cause electrical inhomogeneity and arrhythmia.

Given the high prevalence of the MS in the surgical population referred to CABG, the large number of procedures performed each year worldwide and the three-fold risk of operative mortality conferred by the MS, reducing the prevalence of this condition would certainly lead to better outcomes. However, the question remains as to whether the operative risk associated with the MS could be modified in the context of emergent non-elective procedures. In order to resolve this issue, further research is needed to identify the mechanisms associated with the MS and surgical mortality/morbidity and thereby fuel the development of novel therapeutic strategies to acutely reduce this risk.

Figure 2: Incidence of postoperative atrial fibrillation (POAF) in patients with or without the metabolic syndrome (MS)
Is structural degeneration of bioprostheses an atherosclerotic process?

Patients with advanced heart valve diseases often require valve replacement with prostheses. Currently, some 275,000 valve replacements are performed each year worldwide. It is estimated that bioprostheses (BPs) are used in half of these procedures. The use of a BP has the major advantage of obviating the need for anticoagulation in individuals for whom there is no other clinical indication of such treatment. However, the long-term longevity of BPs is impeded by structural valve degeneration (SVD), a process related to calcification and destruction of the extra-cellular matrix [15]. For years, SVD of BPs has been thought of as a passive process in which chemical fixation of tissues before implantation was responsible for calcification and subsequent degeneration, leading to clinical failure years after implantation. In recent years, different studies have identified that hypercholesterolemia, diabetes and absence of statin therapy were independent risk factors for the occurrence of BP dysfunction [6]. More recently, Briand et al. [6] have documented that diabetes, renal insufficiency and the MS were independent risk factors for the development of hemodynamic dysfunction of BPs. These studies have helped to highlight that SVD could be an active process that is influenced by atherosclerotic risk factors in the postoperative period.

Examination of explanted BPs has revealed that many prostheses have significant amounts of accumulated lipids. We recently demonstrated that most of these lipids were oxidized-LDLs (oxLDLs) and were located in areas of low shear stress. Moreover, oxLDLs were colocalized with dense cellular infiltrates composed of macrophages. Of particular significance is the fact that foam cells were identified along with macrophages expressing scavenger receptors. Furthermore, activated macrophages expressed a high level of metalloproteinase-9 (MMP-9) and could thus play a role in matrix degradation. These studies strengthened the hypothesis that a lipid-driven process, which could be influenced by metabolic factors, participates in the SVD process. Hence, recent clinical and pathological studies have underlined that modifiable risk factors contribute to SVD and may thus represent new, near-term therapeutic avenues in order to promote the longevity of implanted BPs.

Conclusion

Recent studies have identified that the MS is a frequent condition in those who undergo heart surgery and that it is independently associated with a substantial operative risk. Furthermore, metabolic risk factors have been shown to influence the development of heart valve diseases, including SVD of BPs. Emerging evidence indicates that visceral obesity must be considered a global cardiovascular risk that acts at multiple levels, from the development of coronary artery disease and heart valve pathology to
the operative risk associated with CABG. It is thus of crucial importance to reduce the prevalence of at-risk obesity and develop efficient therapeutic strategies for individuals with this risk factor.

References

“VALVULO-METABOLIC” RISK IN AORTIC STENOSIS

By Philippe Pibarot, DVM, PhD, FACC, FAHA
Groupe de Recherche en Valvulopathies (GRV),
Hôpital Laval Research Centre / Quebec Heart Institute
Université Laval, Quebec, Canada
philippe.pibarot@med.ulaval.ca

Valvulo-metabolic risk can be defined as the risk of valvular heart disease resulting from the metabolic abnormalities associated with visceral obesity and the metabolic syndrome (MS). It is therefore the cardiometabolic risk that specifically relates to valvular heart disease.

Burden of aortic valve stenosis
Calcific aortic valve disease starts with a thickening and calcification of the aortic valve cusps, named aortic valve sclerosis, which subsequently progresses toward aortic valve stenosis (AS) causing significant hemodynamic obstruction of the left ventricular (LV) outflow tract. Calcific AS is the most frequent cardiovascular disease after coronary artery disease (CAD) and hypertension in developed countries. The prevalence of AS in the USA is 0.3-0.5%, which translates to approximately 600,000 to 1 million people. The prevalence of AS also increases markedly with age: from 0.02% in 18–44 year olds to 3.0% in the 75 years and older group. It is projected that 40% of people over age 65 are expected to survive to age 90 in the year 2050 compared to 25% in 2000. This major increase in life expectancy during the next several decades will increase the burden of valvular heart diseases. The only efficient treatment for symptomatic severe AS is aortic valve replacement surgery or transcatheter valve implantation. It is estimated that AS is directly responsible for approximately 15,000 deaths and 80,000 valve procedures per year in North America. This disease is therefore associated with a major health and socio-economic burden.

Aortic valve stenosis: an atherosclerotic disease?
For a long time, calcific AS has been considered a “degenerative” disease because it was thought to be the result of aging and “wear and tear” of the aortic valve. This perception has changed over the years with the publication of several studies showing that AS shares many cellular similarities with vascular atherosclerosis. Furthermore, AS has been linked to several traditional risk factors for CAD including age, male gender, hypercholesterolemia, diabetes, hypertension, smoking, and obesity. There is now a growing body of evidence supporting the concept that AS is an active disease involving atherosclerotic pathways. This, in turn, raises the possibility that AS might be a modifiable disease. However, we cannot directly transpose what we have learned about CAD or peripheral arterial disease to aortic valve disease because there are important anatomical and biomechanical distinctions between the aortic valve and the arteries. Moreover, the occurrence of clinical events is essentially determined by plaque vulnerability (inflammation, large lipid core, thin fibrous cap) in CAD versus volume and
stiffness of aortic valve cups in AS. Hence, calcification is a predominant factor in aortic valve disease, whereas its role in CAD remains unclear.

**Valvulo-metabolic risk in aortic stenosis**

The team of Drs. Couet and Arsenault at Hôpital Laval Research Centre induced visceral obesity and some typical features of the MS by feeding a wild-type mouse strain with a high carbohydrate/high fat diet [1]. Interestingly, these animals developed a mild aortic valve stenosis over a period of four months. These experimental data prompted us to examine the association between the MS and progression of aortic valve disease in patients with at least moderate AS [2]. In this population, 40% of the patients had the NCEP-ATP III clinical criteria of the MS. The patients with the MS had a much faster stenosis progression as documented by Doppler-echocardiography and a four-fold increase in the risk of adverse events defined as aortic valve replacement or death (Figure 1) [2].

These results are also consistent with those of the large epidemiological study Multi-Ethnic Study of Atherosclerosis (MESA), where the prevalence of aortic valve sclerosis was markedly higher in the subjects with the MS and/or diabetes [3]. This association was observed in both men and women. We also found that valvulo-metabolic risk may persist beyond aortic valve replacement. The diseased native valve is often replaced by a bioprosthetic valve made of bovine
or porcine tissues fixed with glutaraldehyde. The “Achilles heel” of these bioprostheses is their limited durability. The bioprosthetic tissue may indeed undergo degenerative processes leading to valve stenosis or regurgitation; these processes are more frequent and faster in younger patients. We recently reported that the MS and diabetes are powerful independent predictors of the degeneration of bioprosthetic valves (Figure 2) [4]. These provocative results suggest that, in contrast to previous beliefs, some active mechanisms potentially related to atherosclerotic pathways may contribute to the structural deterioration of bioprosthetic valves.

Figure 3 presents the factors that may explain the association between the MS and calcific aortic valve disease of both native and bioprosthetic valves. Visceral obesity, which is by far the most prevalent form of the MS, is associated with enhanced production of small dense LDL particles; reduced plasma levels of HDL; increased production of inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and C-reactive protein; and reduced production of the “good” adipokine, adiponectin, which has several anti-atherogenic properties. These factors may enhance production of oxidized LDL and may stimulate inflammation and osteoblastic differentiation of myofibroblasts within the aortic valve cusps. When analyzed collectively, these findings suggest that the metabolic abnormalities associated with visceral obesity and the metabolic syndrome may be involved in the development and progression of native aortic valve disease and with the structural deterioration of the bioprosthetic valve following aortic valve replacement.

Implications with regard to prevention and treatment of aortic stenosis

In light of these findings, patients diagnosed with aortic valve sclerosis or stenosis or who underwent bioprosthetic valve implantation should be systematically screened for the presence of the MS (using the hypertriglyceridemic waist, NCEP-ATP III, or IDF algorithms). If the MS is present, these patients should probably be followed more closely so as to track the evolution of their valve function and the appearance of symptoms. Aggressive changes in lifestyle habits, such as increasing physical activity and implementing dietary changes to reduce waist circumference, should also be applied in these high-risk patients. However, targeting the features of the MS with some specific pharmacological approach should be withheld until the benefit of such medications is established in clinical trials.
The two pharmacological agents that are currently under the most scrutiny for potentially delaying AS progression are statins and ACE inhibitors. The two first clinical trials published until now have provided conflicting results [5, 6]. The SLATIRE trial showed no significant difference between the statin and the placebo with regard to stenosis progression [5], whereas the open-label RAAVE trial reported a slower stenosis progression in patients with elevated LDL treated with statin compared to those with normal LDL left untreated [6]. When analyzed collectively, these studies suggest that AS patients with hypercholesterolemia may benefit from statin therapy and that these drugs may be more efficient in the early stages (i.e., aortic valve sclerosis or mild/moderate AS) than in the late stages (i.e., severe AS) of the disease. However, it is well known that statins and ACE inhibitors have little or no effect on the metabolic perturbations associated with the MS. As a matter of fact, in our recent study, we found that patients with the MS had a fast stenosis progression and a high risk of adverse events, regardless of the presence of statin therapy (Figure 4).

These findings further support the concept that statins may be necessary but not sufficient in a substantial proportion of patients, those with the MS in particular, and that other targets of therapy should be considered in these patients. The findings presented in this article suggest that visceral obesity may be a promising therapeutic target in those with calcific aortic valve disease. To this end, we need properly designed mechanistic and interventional studies to determine the most appropriate behavioural or pharmacological approaches to efficiently reduce and manage valvulo-metabolic risk.

References


For more information:

www.cardiometabolic-risk.org

Contact us

Jean-Claude Coubard
Executive Director

Office:  + (33) 1 47 09 91 74
Cellular:  + (33) 6 33 34 78 13

Mailing address and secretariat:

International Chair on Cardiometabolic Risk
Hôpital Laval Research Centre
Pavilion Marguerite-D’Youville, 4th Floor
2725 chemin Ste-Foy
Québec QC G1V 4G5
CANADA

Tel.: 1 (418) 656-8711, extension 3183
E-mail: chair.cardiometabolic-risk@crhl.ulaval.ca
Fax: 1 (418) 656-4953