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Review article

Exploring the biology of valvular heart disease: Time to move into the twenty-first century

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INTRODUCTION

Valvular heart disease (VHD), when severe and prolonged, creates a hemodynamic overload, the consequences of which damage the myocardium - leading to heart failure and death if left uncorrected by mechanical intervention. In 1906 Sir William Osler wrote in the sixth edition of his famous textbook "The Principles and Practice of Medicine", that the prognosis of valvular heart disease (VHD) depended upon the severity of disease, the presence or absence of symptoms, and upon heart size.[1] Remarkably, 100 years later, the ACC/AHA Guidelines for the treatment of VHD essentially rely upon the same criteria,[2] albeit heart size is measured more accurately than in Osler's day and the outcome of VHD has been changed dramatically by valve surgery. And, because man has also been fascinated by the heart's motion, quantification of this motion (today usually by ejection fraction (EF)) has been added to evaluate cardiac performance. Still, timing of mechanical therapy is largely based on disease severity, symptoms, heart size and heart motion . . . not much of an advance in over a century, especially considering the leaps of progress made in other fields of medicine.

If these criteria produced a perfect outcome wherein patients treated optimally lived a normal functional lifespan there would be no need for a different approach. And arguably there are reports of normal life span following mitral valve repair and following aortic valve replacement with a pulmonary autograft.[3,4] Unfortunately these outcomes are an exception and life span is shortened by as much as 15 years following standard practice for valve replacement today (Figure 1).[5] Obviously many factors may play a role in this shortened life expectancy. Complications inherent to valve prostheses may reduce life span by causing thromboembolism, anticoagulant-related hemorrhage, or by requiring additional surgery to replace failed prostheses. On the other hand, it may be that patients are being operated too late in the course of their disease to gain full benefit from valve replacement, even when current guidelines are followed. It is likely that our Oslerian vintage tools are not giving us enough insight into the disease processes of VHD in order to intervene in the most timely fashion.

CURRENT INDICATORS USED FOR THE TIMING OF VALVE SURGERY

Symptom onset

In every valve lesion the onset of symptoms represents an adverse demarcation in the natural history of the disease.[6–14] In the case of aortic stenosis the inflection point is most dramatic with death occurring at the rate of 25%/ year for symptomatic patients versus $<1\%$ per year for asymptomatic patients.[7,15] Although symptoms are a subjective and less-than-perfect measure of cardiac status, they indicate pathophysiology in a way that no other convenient objective index can. Symptoms are an amalgam of left and right ventricular systolic function, diastolic function, filling pressures, vascular resistance, coronary blood flow and cardiac output. Thus symptom analysis is key in evaluating any patient with VHD.

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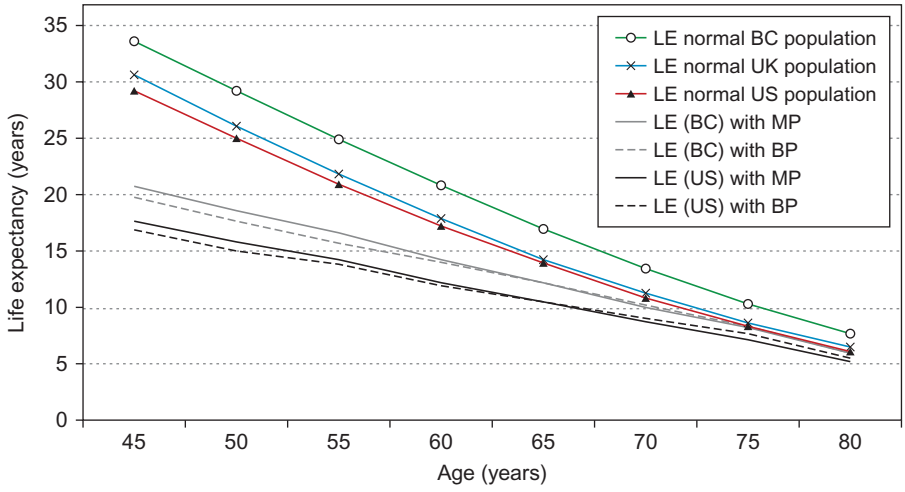

Figure 1. Life expectancy (LE) is plotted against age for normal subjects in British Columbia (BC), the United Kingdom (UK) and the United States (US) and for patients treated with an aortic bioprosthesis (BP) or mechanical prosthesis (MP). At age 45, life expectancy is up to 15 years shorter than normal for patients receiving a prosthetic aortic valve. Taken from reference 5 with permission.

Changes in ventricular function

Ejection fraction

It is generally accepted that left and or right ventricular (LV/RV) function is a major determinant of outcome in cardiac disease in general and in VHD specifically. The property of contractility is the innate ability of the myocardium to generate force independent of preload and it is this property (contractility) that is thought most important in determining prognosis in VHD. Prior to the molecular biology era, a great many investigations attempted to derive the perfect index of contractility in the belief that, if such a measure were found, it could better forecast outcome in heart disease in general and lead to better timing of surgery for VHD.[16,17] An early fall in contractility detected by this proposed index would signal that waiting further would lead to irreversible myocardial damage and a poor outcome following surgery. The ideal index of contractility would be independent of preload, afterload and ventricular volume and mass, reproducible, sensitive to changes in contractility and easy to apply. No index meeting these criteria was ever devised. Unfortunately the cardiology world has settled on ejection fraction as its chosen measure of cardiac function. Ejection fraction is easy to apply but unfortunately is load sensitive, a major problem in VHD where load may be extremely abnormal. Thus the high afterload in aortic stenosis may decrease EF while contractility is relatively well preserved, potentially misleading the clinician into believing the patient is at too high a risk for surgery.[18–20] Conversely, the increased preload of MR might buoy EF even when contractility is depressed, potentially leading to unwise delay in valve repair or replacement.[21–23] As such, current methods for judging contractility are crude at best. In response we interpolate, lowering the EF value of concern in aortic stenosis and raising it in mitral regurgitation.

End systolic dimension (or volume)

Ejection fraction is dependent on preload, afterload and contractility. However end systolic dimension (or end systolic volume), while dependent upon contractility, afterload and eccentric hypertrophy (LVH), is independent of preload.[24–26] Accordingly, in volume overloading lesions such as aortic and mitral regurgitation, lesions that increase preload, a preload-independent measure of function should be useful. Indeed end systolic dimension and end systolic volume have been predictive of outcome in valvular regurgitation and are incorporated into the modern guidelines for the timing of valve surgery for those lesions.[2,23,27–29]

Strain and strain rate imaging

Myocardial strain is the change in length of a myocardial segment in relation to a reference length and is similar in concept to ejection fraction for the whole ventricle. Strain rate is the change in strain over time. It is similar to the whole ventricle's mean velocity on contractile element shortening (V_{cf}), defined

as ejection fraction/ejection time.[30] Both strain rate and V_{cf} are relatively preload independent but afterload dependent. Strain rate imaging, especially of the LV's long axis has been shown to be more sensitive to impaired myocardial function than is EF.[31]

Size and mass

It is generally held that development of hypertrophy in response to the hemodynamic load of valvular heart disease is both adaptive and maladaptive.[32–34] Concentric hypertrophy in pressure overload normalizes systolic wall stress (afterload) helping to maintain normal ejection performance. Eccentric hypertrophy in volume overload increases chamber volume allowing the ventricle to compensate for the volume lost to regurgitation. However when excessive, concentric LVH causes reduced coronary blood flow, impaired contractility and reduced diastolic compliance all leading to heart failure and death. Excessive eccentric LVH also increases systolic wall stress (afterload) and impairs myocardial efficiency.[34] Thus both concentric and eccentric hypertrophy, beyond the limit of compensation, is associated with worsened outcomes.

CURRENT STATE OF THE ART

We have tools for the evaluation of VHD at our disposal. However using these tools has produced outcomes that are still suboptimal in many cases. These tools show us the results of disturbed biology that has been present for months or years before they are manifest as obvious cardiac pathology. Prior to evidence of reduced cardiac performance or of excessive size and mass, a host of biologic processes must take place that initiate these changes. It seems reasonable to think that detection of these biologic changes could predict outcome and thus initiate intervention before the far-downstream changes in size and function have taken place.

POTENTIAL NEW TARGETS FOR DETECTING MYOCARDIAL PATHOLOGY

Elevated catecholamines

Catecholamines are intrinsic to normal cardiovascular function, maintaining cardiac output and blood pressure at rest and helping to adjust the circulation to changes in cardiac output demand.

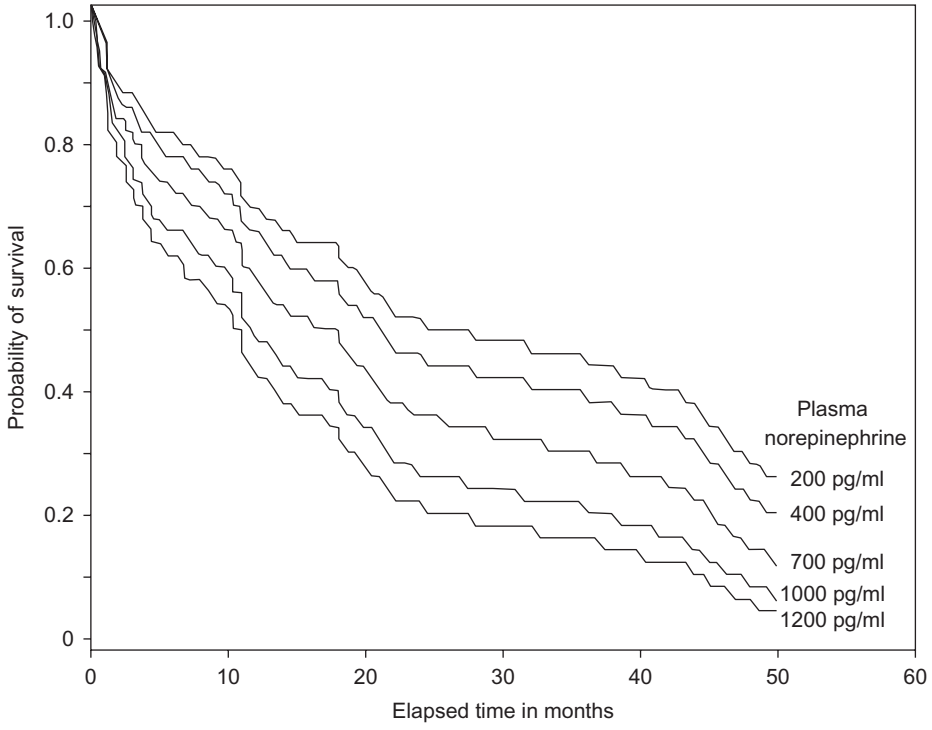

Figure 2. Probability of survival is plotted against serum norepinephrine levels for patients with heart failure. The higher the level of circulating catecholamines the shorter the life span. Taken from reference 36 with permission.

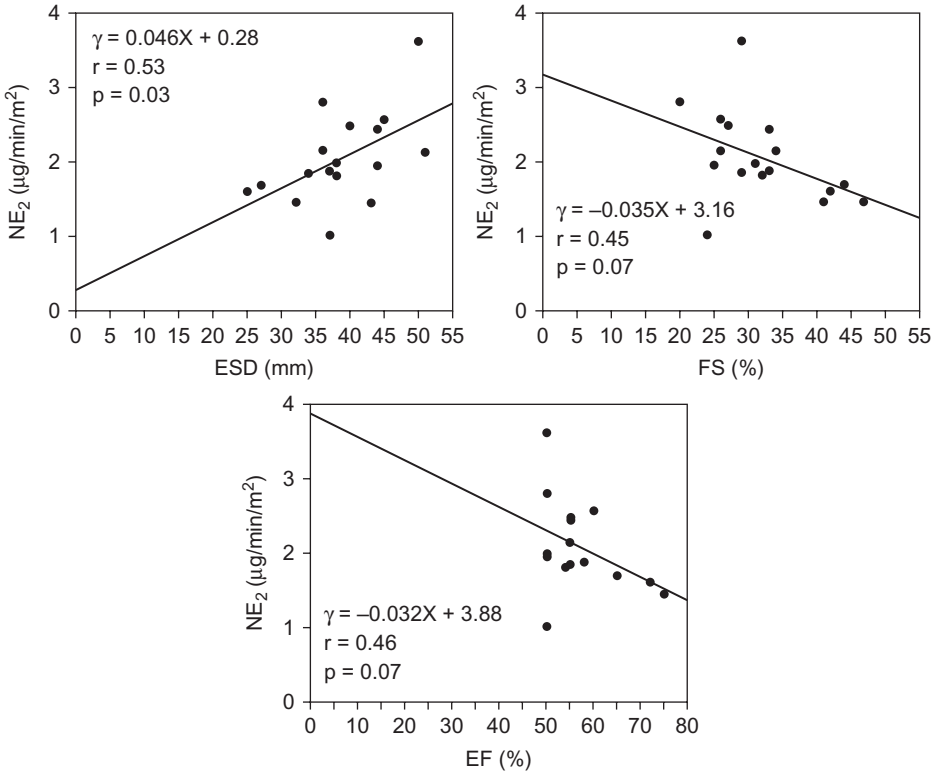

Figure 3. **Norepinephrine (NE) levels in patients with mitral regurgitation are plotted against end systolic dimension (ESD), LV fractional shortening (FS) and LV ejection fraction (EF). Higher NE levels are associated with poorer LV performance. Taken from reference 40 with permission.**

Thus normal levels of catecholamines are both safe and beneficial. However persistent elevations in catecholamines may obscure intrinsic myocardial dysfunction by increasing inotropic state.[35] Further, chronic persistently increased catecholamines are cardiotoxic, leading to heart failure and death (Figure 2).[36] While the data in Figure 2 could be interpreted to indicate that sicker patients require greater endogenous inotropic support than those less severely affected, it is more probable that higher

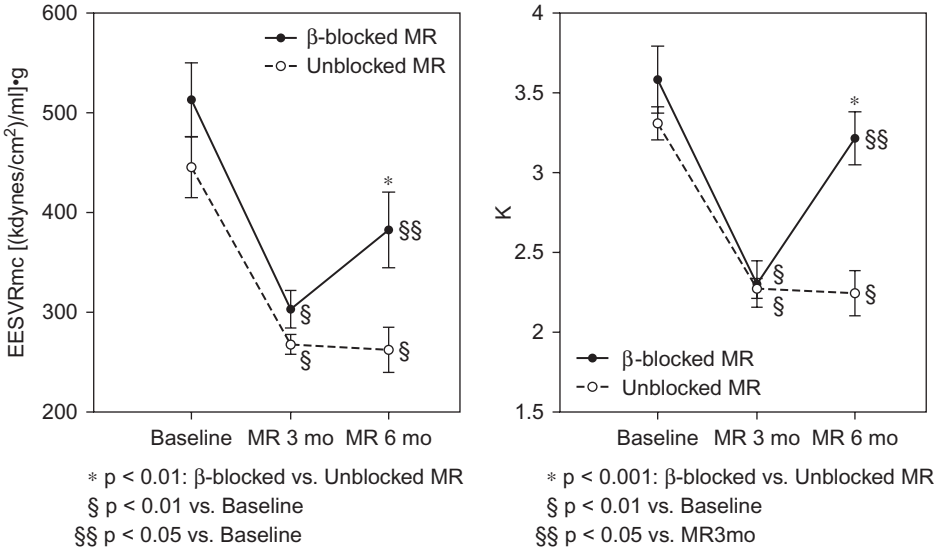

Figure 4. **The slope of the end ejection stress-volume relationship (left panel) and end systolic elastance (K, right panel) for dogs at baseline, after 3 months of mitral regurgitation (MR 3mo) and after 6 months of MR (MR 6 mo) are shown. Animals receiving beta blocker (solid line, closed circle) showed improved contractility while those receiving placebo (dotted line, open circle) showed no improvement. Taken from reference 37 with permission.**

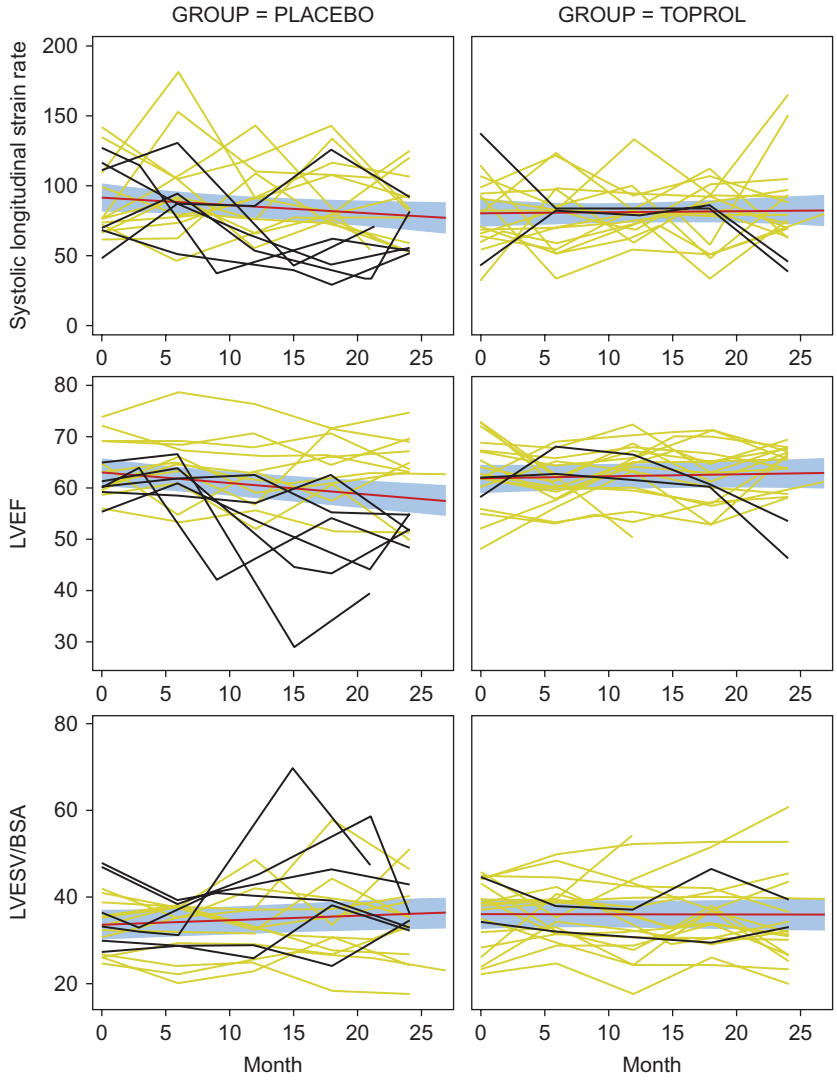

Figure 5. Patients with mitral regurgitation randomized to receive placebo (left panel) demonstrated increased end systolic volume index (LVESV/BSA) and decreased longitudinal systolic strain over 2 years while patients randomized to receive the beta blocker Toprol (right panel) demonstrated no deterioration in LV function. Taken from reference 39 with permission.

levels of catecholamines cause an earlier demise. Indeed the concept that beta blockade protects the myocardium from the deleterious effects of catecholamines is now a mainstay in the treatment of heart failure with systolic dysfunction. Accordingly, beta blockade has been shown as an effective therapy in the treatment of experimental mitral regurgitation and may also have benefit in clinical mitral regurgitation (Figures 3–5).[37–40]

These data lead to the hypothesis that an early increase in circulating catecholamines in VHD might be the first indication of myocardial dysfunction, obscuring impairment that cannot be detected by conventional tests,[35] while simultaneously contributing to further damage and a poor outcome. If so, serial measurement of catecholamines might be used to detect early LV failure, leading to earlier and more beneficial mechanical intervention in VHD.

Myocardial fibrosis

As noted above, the hemodynamic overloads of VHD lead to myocardial hypertrophy that is initially thought to be a compensatory mechanism that helps to bear the overload. In pressure overload, new sarcomeres are laid down in parallel, increasing wall thickness and ventricular stiffness.[41] However the increase in contractile elements of the myocardium is accompanied by increased collagen and other

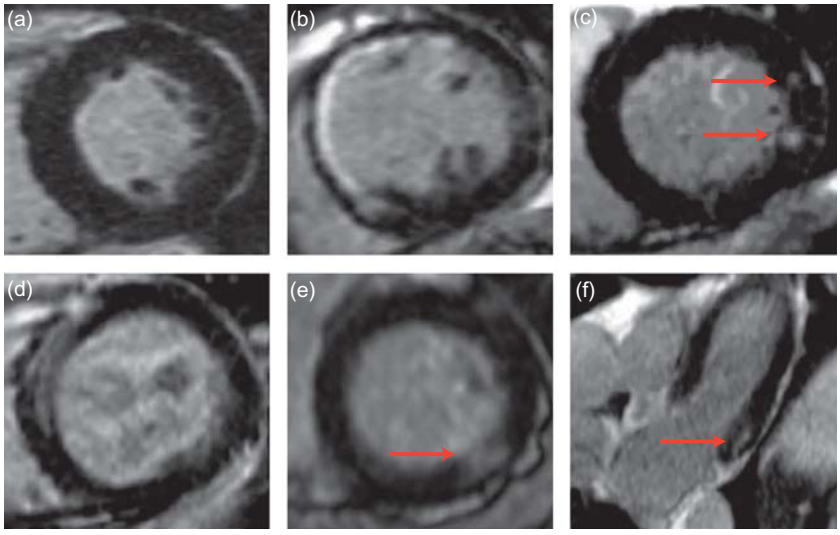

Figure 6. Patterns late gadolinium enhancement (LGE) observed in patients with aortic stenosis. (A) No LGE. (B) Infarct LGE with a subendocardial pattern observed in the septum and anterior wall. (C) Two focal areas of midwall LGE in the lateral wall of the left ventricle (red arrows); (D) Midwall LGE in a more linear pattern affecting the septum. (E) Short- and (F) long-axis views of midwall LGE (red arrows) of the inferolateral wall in the same patient. Taken from reference 43 with permission.

components of the extracellular matrix. These non-contractile elements further increase myocardial stiffness, leading to diastolic dysfunction,[41,42] while replacement of contractile elements with extracellular elements leads to systolic dysfunction. In both cases fibrosis and increased in extracellular matrix contribute to heart failure and reduced prognosis even after successful valve replacement (Figure 6).[43] Therefore the early detection of myocardial fibrosis in VHD might represent an opportune time to intervene before still more damaging fibrosis develops. The imaging capabilities of the twenty-first century enhance our ability to detect fibrosis as another marker that myocardial health is declining, in turn signaling the need for valve intervention.

BNP

Despite the amazing breadth of biologic pathways involved in myocardial signaling, when confronted with an overload the myocardium has only 3 basic mechanisms for compensation: increasing its mass (hypertrophy), increasing preload, and activation of neurohumoral mechanisms such as the adrenergic nervous system noted above. B-type natriuretic hormone (BNP) is released during sarcomere stretch (increased preload) and is also increased in LVH. Decades ago, Ross introduced the concept of afterload mismatch and preload reserve.[44] In this paradigm, increased afterload presented by the stenotic aortic valve or aortic regurgitation[45] requires increased force for chamber emptying. This need is met by increased sarcomere stretch (preload). In turn increased fiber stretch results in increased release of BNP. Pure volume overload as encountered in mitral regurgitation also engenders increased preload and BNP. Thus increased BNP may be a surrogate for excessive load, LVH or heart failure. Many studies of BNP in VHD already exist that suggest that BNP levels are predictive of outcome (Figures 7, 8).[46–52] However each study has arrived at a different value of BNP (or Pro n-t-BNP) indicative of danger, thus making it difficult to use in clinical decision making. This variance is probably attributable to differences in age, sex, LV mass and potentially unknown factors that affect BNP besides preload that confound its usage. However it reasonable to conclude that persistently increasing BNP in patients with VHD portends worsened LV function and thus increasing natriuretic peptide levels may be an early warning of decompensation and for the need for definitive therapy.

Troponin

Troponin release is now the gold standard for myocardial damage accrued from myocardial ischemia, usually in the context of coronary artery disease. However in VHD, especially in aortic stenosis where coronary blood flow is abnormal, the myocardium is often subjected to ischemic

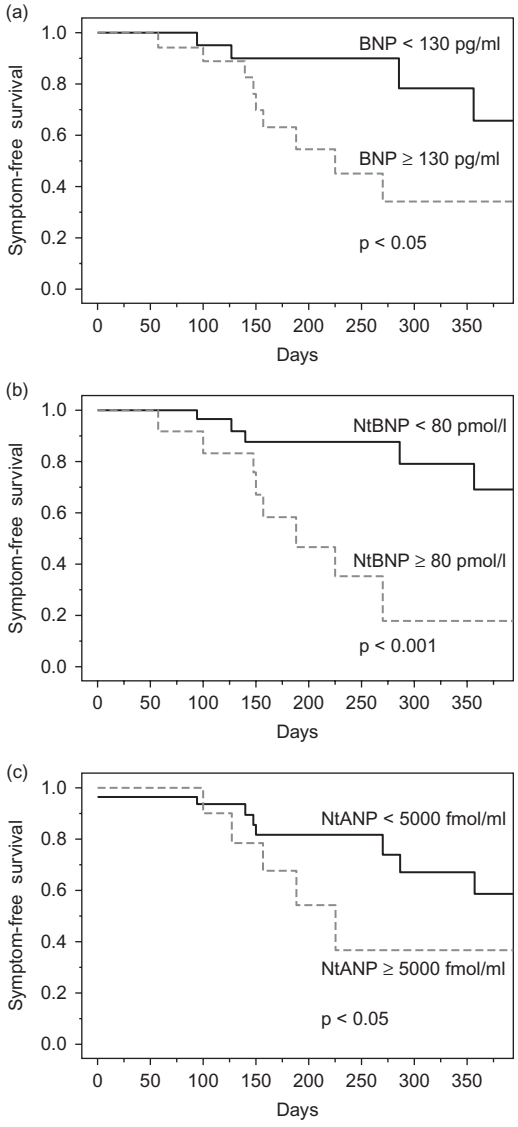

Figure 7. Symptom-free survival is plotted against initial levels of B type natriuretic peptide (BNP, upper panel) n-terminal BNP, NtBNP, middle panel) and n terminal atrial natriuretic peptide (NtANP, lower panel). Patients with higher levels of natriuretic peptides had a worse prognosis despite similar disease severity. Taken from reference 47 with permission.

conditions during exercise even when the epicardial coronaries are normal.[53–55] Such episodes might be expected to result in troponin release and indeed increased troponin is found in patients with severe AS (Figure 9).[56] It might be that persistent troponin elevation is associated with progressive deterioration of myocardial function, leading to heart failure and death. As such elevated troponin levels in the patient with aortic stenosis and perhaps other VHD might signal the need for early intervention.

MMP

Matrix metalloproteinases comprise a large group of zinc-containing endopeptidases that control the integrity of the extracellular myocardial matrix. Remodeling of the heart, especially in response to a volume overload but also in pressure overload, results in MMP activation. Early detection of persistent MMP activation might signal a cascade of events leading to ventricular dysfunction.[57,58] In turn persistently elevated MMP levels also suggest persistent LV remodeling that might herald decompensation.

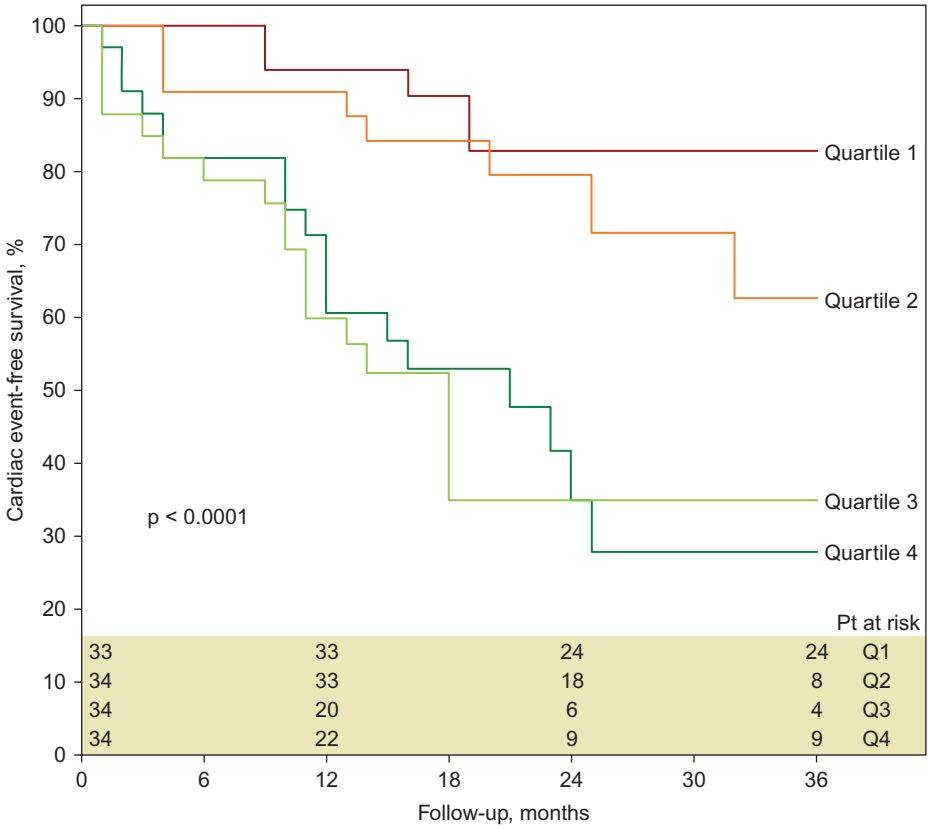

Figure 8. Cardiac event-free survival for asymptomatic patients with severe mitral regurgitation is plotted against quartiles of entry level BNP. Higher BNP portended a worse prognosis. Taken from reference 52 with permission.

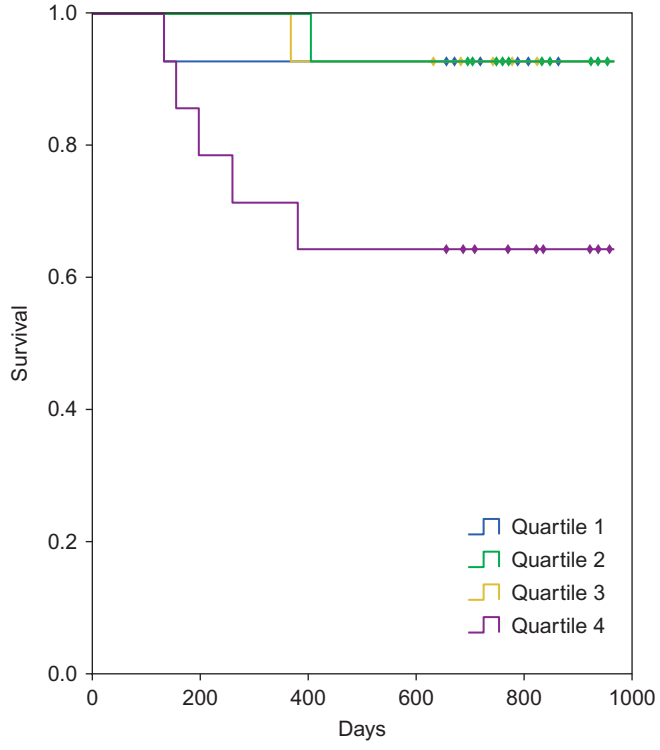

Figure 9. Survival for patients with aortic stenosis is plotted according to quartile of troponin. Elevated troponin was associated with a worse prognosis. Taken from reference 56 with permission.

CONCLUSION

The hemodynamic overloads of valvular heart disease are accompanied by a host of biologic changes eventually resulting in myocardial damage, ventricular dysfunction, heart failure and death. Currently, we detect the ensuing consequences of these biologic abnormalities far downstream, when they have caused abnormalities in cardiac size, mass and ventricular emptying. If early detection of abnormal biology were found to inevitably result in these myocardial changes, such detection could lead to earlier, safer intervention, improving post-intervention outcomes. Most of these perturbations are simple to detect requiring only a blood test that can be repeated serially, easily, and inexpensively. Pursuing this biologic approach should move us ahead from the century old markers of heat size and symptoms as the triggers of operative intervention for valvular heart disease to a more mechanistic approach to the patient with valvular heart disease.

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