Calcification of the Aortic Valve in the Dialyzed Patient

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Cardiovascular disease is the leading cause of mortality in patients with end-stage renal disease (ESRD), with cardiac disease alone accounting for 40% of all deaths. Ischemic heart disease, heart failure, and cardiomyopathy are the most frequent causes of cardiac death (1), but valvular abnormalities are also common in these patients and may cause significant morbidity and mortality (2–9). In principle, the origin of valvular alterations can be congenital, infectious, or dystrophic (10). The majority of valvular lesions observed in ESRD patients are acquired, mostly secondary to dystrophic calcification of the valvular annulus and the leaflets. The mitral and aortic valves are the preferential sites for dystrophic valvular calcification in ESRD. For a long time, the calcification of the aortic valve and annulus was considered an age-associated degenerative lesion with little functional importance. Recent studies of elderly subjects in the general population have shown, however, that aortic-valve sclerosis carries an increased risk of death from cardiovascular disease and myocardial infarction (11). In ESRD patients, aortic-valve sclerosis and calcification may progress rapidly and calcific aortic stenosis (AS) develops frequently (7,9,12). With the age of patients treated by dialysis increasing constantly, the prevalence of aortic valve calcification and its complications will increase in parallel.

Etiology and Pathophysiology

Acquired calcification and/or stenosis in ESRD is usually infectious or degenerative in origin (7). In the early stages, the anatomy of these two conditions is rather specific, but the specificity is lost when progressive calcification supervenes. Valvular disease of infectious origin has decreased in frequency, and today the majority of calcific aortic valve disease in the general population is degenerative (senile) in origin. In degenerative aortic calcification, the lesions are first seen at the site of valve insertion. They extend in the direction of the cusps. Commisural fusion is present only in advanced stages when calcium deposits protrude and fuse the valve leaflets (10). Aortic calcification in ESRD patients is almost constantly associated with widespread calcification of the myocardium, mitral valves, aorta, and large- or medium-sized arteries, including coronary arteries (6).

The degenerative (wear and tear) etiology appears to underlie the dystrophic calcification of aortic valves (10). Aortic valves are submitted to cyclic mechanical stress. The stress is related to pressure gradients and turbulent blood flow resulting from the high acceleration rate and peak velocity when blood flows through the aortic valve. Apart from cyclic opening and closure of the valves, high frequency vibration of the leaflets is produced by turbulent flow. Over the lifespan, the repetitive mechanical stress causes fatigue and rearrangement of bioelastomers, leading to microfractures in the biomaterials ultimately resulting in fibrosis and calcification. Calcification further increases peak ejection velocity and causes turbulent blood flow, thus creating a vicious cycle. Renal failure and dialysis superimpose further pathomechanisms. This conclusion is supported by the observation that a correlation is found between...
duration of hemodialysis treatment and presence of heart valve calcification (4,5) (Table 1).

ESRD promotes valvular disease by hemodynamic and biochemical mechanisms. The blood flow velocity and the degree of turbulence across the aortic valve are determined by aortic valve area and blood flow rate (stroke volume). As a result of anemia, arteriovenous (AV) shunts, and overhydration, cardiac output is increased in patients on hemodialysis. Even in patients with normal valve area, these conditions can increase peak flow velocity and generate flow turbulence. Moreover, the heart rate is increased. This causes an increased number of opening/closure cycles and a higher rate of repetitive stress. The role of systemic hypertension in the pathogenesis of aortic-valve calcification is uncertain, although a significant correlation was found in some (8) but not all studies (9,16). The number of years on hemodialysis treatment is significantly correlated with the presence of aortic calcification. This observation is presumably explained by the progressively longer time during which the patients are exposed to the above hemodynamic and biochemical risk factors. As mentioned above, calcification of the aortic valves is usually associated with extensive atherosclerosis involving the coronary arteries and the major central elastic arteries, for instance, the aorta. The two pathologies presumably share common atherogenic factors in their pathogenesis (6). In the general population, both diabetes mellitus and hypercholesterolemia are risk factors for development of the valvular lesion (10,17).

According to recent studies, atherogenesis and presumably also degenerative disease of the aortic valves involve accumulation of lipids; oxidized LDL in particular is associated with a chronic inflammatory process with accumulation of macrophages and T lymphocytes and culminates in calcium deposits (18–20). A similar chronic proinflammatory state and increased concentrations of oxidized LDL are also observed in hemodialyzed patients. Dystrophic calcifications are most consistently associated with disorders of phosphorus and calcium metabolism, particularly an elevated calcium-phosphorus product (Ca × P) (2,4,6,9). Poor phosphorus control and hyperphosphatemia are the principal culprits (8,9) (Table 1), while hypercalcemia and parathyroid hormone excess play an ancillary role (4–6). Undoubtedly, in ESRD patients secondary hyperparathyroidism can cause hyperphosphatemia, hypercalcemia, and high a Ca × P product, conditions favorable for the development and progression of calcification. Nevertheless, valvular calcification may occur in ESRD patients even in the absence of secondary hyperparathyroidism. Indeed, in the study of Ureña et al. (9), in 62% of the patients with AS it was shown that hyperphosphatemia was associated with signs of adynamic bone disease and not with hyperparathyroidism. In the general population, the presence of dystrophic calcifications of the cardiovascular system are correlated with low bone mass and the presence of osteoporosis (21). In ESRD patients, adynamic bone disease is associated with an increased frequency of hyperphosphatemia, hypercalcemic episodes, and extraskeletal calcifications. In the study of Braun et al. (6) on dialyzed patients, the presence of calcifications of the aortic valves was associated with a higher frequency and severity of coronary calcifications. The coronary calcium score was inversely related to bone mass.

Increasing use of calcitriol and calcium-containing phosphate binders increases the enteral calcium absorption and may favor the development of hypercalcemia, increased Ca × P product, adynamic bone disease, and secondary hyperphosphatemia. All of these conditions also favor the development of valvular calcifications. In the study by Ureña et al. (9), plasma 25(OH) vitamin D3 concentrations were higher in dialysis patients with AS.

The functional and structural consequences of aortic valve calcification depend on the degree of LV outflow obstruction. When aortic valve calcification progresses so that hemodynamically significant obstruction occurs, the LV is submitted to an increasing pressure load and develops compensatory hypertrophy (10). Elevated systolic wall stress from LV pressure overload promotes an adaptive process, characterized by parallel addition of sarcomeres resulting in a disproportionate increase of LV wall thickness in the presence of a normal chamber radius, i.e., concentric hypertrophy (22). LV hypertrophy is both beneficial and detrimental. The benefit is linked to the fact that the number of sarcomeres, the wall thickness, and the working capacity of the LV are increased while at the same time parietal tensile stress is kept stable, so that energy is spared. These beneficial effects permit maintenance of normal systolic function during the phase of compensated adaptive hypertrophy. Nevertheless, even during this phase of compensated hypertrophy, LV relaxation and diastolic filling are already impaired (10).

In patients with severe AS, LV diastolic pressure is elevated. A further increase occurs during atrial systole, secondary to enhanced contraction of the hypertrophied left atrium. Atrial contraction plays an important role in filling the noncompliant left ventricle. Loss of an appropriately timed atrial contraction as occurs in atrial fibrillation may result in dramatic clinical deterioration in patients with AS (10). While the beneficial effects of LV hypertrophy dominate in the initial phase of adaptation to overload, later in the course of the disease sustained overload leads to the development of cardiomyopathy, so-called “cardiomyopathy of overload.” This phase is characterized by the depression of the contractile state and dilation of the LV with abnormal elevation of systolic wall stress, decline in ejection fraction, and reduction of cardiac output. In this maladaptive phase, the oxygen consumption and energy expenditure of the overloaded myocardial cells are increased.

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<td>Age (yr)</td>
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a Response: aortic calcification (2-yes/1-no). Regression done on population of 130 ESRD patients. Proportion of patients with aortic calcification: 46.2% (personal data). ($r^2 = 0.360$; model $\chi^2 = 60.1$; model $P = 0.00001$).
leading to a chronic energy deficit. When oxygen consumption is increased, the LV ejection time is prolonged, the diastolic time is shortened, and wall stress is increased (23).

The pathogenesis of the chronic energy deficit is complex and involves an impairment of coronary circulation and decreased coronary reserve. In the genesis of the coronary malfunction, several factors play a role: (1) medial hypertrophy of small coronary vessels with raised coronary resistance and reduced maximal dilation; (2) increased resistance to coronary flow caused by higher extravascular compressive forces exerted by the hypertrophic myocardium; (3) upward shift of the plateau of autoregulated coronary flow (absolute coronary flow is increased but flow per gram of tissue is decreased); (4) shift of the autoregulatory range to higher perfusion pressures; (5) diminished relative myocardial capillary density; and (6) decrease in the duration of the diastole due to increased LV ejection time. Because in the subendocardium the resistance to flow is higher and the metabolic demand is greater, the subendocardial layers are more susceptible to ischemia than the subepicardial layers. The increase in extracellular matrix and collagen content permits the maintenance of the mechanical efficiency of the contracting heart at the expense of impaired diastolic filling. Another factor that accounts for abnormal diastolic function of hypertrophied myocardium is lusitropic abnormalities, i.e., delayed relaxation as a result of the slower reuptake of calcium by the sarcoplasmic reticulum. The prolongation of cytosolic calcium transients increases the duration of the action potential. Delayed afterdepolarization contributes to arrhythmias, which are further favored by conduction abnormalities linked to the fibrosis and enlargement of hypertrophied hearts (23). In patients with ESRD and LV outflow obstruction, the pressure overload is accompanied by flow/volume overload caused by anemia, AV shunts, and sodium and water retention. In some cases, aortic regurgitation resulting from dystrophic calcification further augments flow/volume overload of the LV (24). Superposition of flow to pressure overload in ESRD accelerates the development of LV enlargement and LV hypertrophy (25).

Clinical Manifestations

Natural History

The natural history of nonstenotic aortic valve calcification in ESRD patients has not been systematically analyzed in longitudinal studies. In nonuremic patients, aortic valve sclerosis is associated with a 50% increase in the risk of death from cardiovascular causes, and this is true even in the absence of hemodynamically significant obstruction of the LV outflow (11). Simple calcifications are clinically asymptomatic, but are frequently associated with: restricted motion of the leaflets, hindered aortic valve opening, and decreased area of the valvular orifice. The aortic valve area is highly dependent on body surface area and age. The effect of age on aortic valve opening and orifice is particularly pronounced in ESRD patients (Figure 1). The natural history of aortic calcification in ESRD patients is frequently characterized by rapid evolution from the stage of asymptomatic calcification to the stage of severe valvular stenosis (2,7,9). In a study of Ureña et al. (9), the mean time interval was 16.8 ± 1.9 mo. The mean annual decrease in aortic valve area in those patients who developed AS was 0.23 cm²/yr (0.3 cm²/m²) compared with 0.05 to 0.1 cm²/yr in nonuremic patients. Progression toward AS was significantly more frequent in men. Such rapid progression of AS was associated with a significant decrease in survival. In the study of Ureña et al. (9), mean survival after the onset of symptomatic AS was 23 ± 9.4 mo. In the study of Baglin et al. (7), patients who underwent surgery for calcific valvulopathy and AS had a median survival of 36 mo. Among patients who did not undergo surgery, median survival was 13 mo.

In ESRD patients, the signs and symptoms of AS are similar to those in nonuremic patients, i.e., angina pectoris, syncope, and heart failure (10). The most common causes of death are heart failure and sudden death. Even in patients without coronary artery disease, angina may occur because of the combination of increased oxygen demand and reduction of oxygen supply. But in ESRD patients, generalized atherosclerosis also involving coronary arteries is frequently associated with aortic calcification and stenosis and must be excluded in all patients with AS who develop angina. Syncope may occur in ESRD

![Figure 1. Correlation between age and aortic valve area in the general population (left panel) and end-stage renal disease (ESRD) patients (right panel). The figure illustrates a more pronounced age dependency of valve area in ESRD patients.](image-url)
patients with AS as a consequence of exertional vasodilation or a vasodepressor response. Syncope at rest may be induced by atrial fibrillation, which is the most frequent dialysis-induced arrhythmia. Loss of synchronized atrial contraction leads to a precipitous decline of cardiac output. Heart failure is common in ESRD patients with AS and it is usually precipitated by volume overload.

**Diagnosis**

**Physical Examination**

Auscultation reveals the typical ejection murmur, which is maximally audible at the level of the right third intercostal space, is usually diamond-shaped with maximal intensity during meso-systole, is reinforced after a long diastole interval (for instance, after a premature beat), and is transmitted to the carotid area. Nevertheless, heart murmurs are frequently noted in ESRD patients without valvular abnormalities, probably as the result of a hyperkinetic circulation with flow and pressure overload from AV fistula, anemia, and hypertension.

**Laboratory Examination**

The electrocardiogram shows the signs of pressure overload, i.e., an abnormally high Sokolow–Lyons index associated with repolarization abnormalities in the left side precordial leads. The x-ray is of limited diagnostic value. It may show aortic valve calcification and a high cardiothoracic index. Doppler echocardiography is the best tool for diagnosis and follow-up. One can easily calculate the transaortic pressure gradient (in mmHg), based on the simplified Bernoulli’s law, and the valve area, based on the continuity equation. One assumes that for a given flow within a tube, the product of aortic-valve section area (AVa) and aortic velocity (AoV) is equal to the product of LV outflow area (LVOa) and LV outflow velocity (LVOV) according to the formula: \( AVa \times AoV = LVOa \times LVOV \).

Assuming a circular section area, LVOa is quantified by measurement of the diameter of the outflow tract using bi-dimensional echocardiography. LV outflow velocity is measured by pulsed Doppler and transvalvular velocity by continuous Doppler. The intra-observer reproducibility of aortic valve area measurements is very good, particularly with respect to the Doppler flow measurement. In contrast, the measurement of the diameter of the LV outflow tract is far less accurate. The coefficient of variation for the latter measurement between two echocardiography laboratories is 12.4 ± 10.9% (0 to 37%) (26).

For follow-up, one can use a simplified continuity equation, assuming a constant value for the LV outflow tract (usually a diameter of 2 cm corresponding to an area of 3.14 cm\(^2\) is assumed). The coefficient of variation for these Doppler velocity measurements reaches 0.01 ± 0.009% (26). Similar to the approach used for invasive measurements (for which the Gorlin formula is used), the transvalvular volume flow rate enters into the Doppler echocardiographic continuity equation (27,28). Therefore, one must pay particular attention to the timing of the measurement relative to the dialysis session. The timing of examination must be constant, and preferably the patient should be examined on an interdialytic day. Doubling or halving the flow rate could increase or decrease the estimated or the calculated area by +30% or −20%, respectively. The absolute variation is no more than 0.14 cm\(^2\) (27). A potential decrease in LV contractile function when the disease progresses also has to be taken into account and may cause serious errors in the assessment of the severity of AS.

The importance of Doppler examination is twofold: It is noninvasive and can be easily repeated. It evaluates the “effective” orifice area. No controlled information is available to assess the clinical relevance of the procedure in terms of assessment of morbidity and selection of the time for surgery. In the absence of such information in ESRD compared to nonuremic patients, the same criteria are used to select the time of surgery, i.e., a mean pressure gradient equal to or higher than 50 mmHg, and a valvular area lower than 0.70 cm\(^2\). Because one can never exclude coronary artery disease (which may be asymptomatic), it is wise to perform preoperatively invasive measurement of the severity of AS and to combine this with a coronary angiogram, since potentially both valvular and coronary diseases necessitate surgical correction. When comparing noninvasive and invasive measurements, one should be aware of the fact that, using the measurement of AS based on the Gorlin formulas, the anatomical area estimate may differ from that obtained by noninvasive measurements. Promising new approaches to the determination of the area of the valvular orifice are currently under evaluation: two-dimensional measurement during transesophageal echocardiography, three-dimensional computerized transesophageal echocardiography, and nuclear magnetic resonance imaging.

**Treatment**

**Medical**

Once present, the calcifications of the aortic annulus and the aortic valve are not readily reversible. Therefore, one of the primary goals in the management of patients with ESRD is to prevent calcifications, and when they are present to prevent their progression and the development of AS. Long-term control of phosphatemia and avoidance of excessive calcium intake are the principal therapeutic strategies. Because increased phosphate concentration is the principal cause of a high Ca × P product, aggressive treatment of hyperphosphatemia is of utmost importance. Because the use of calcium-containing binders and the resulting excessive calcium intake frequently cause hypercalcemia, the use of calcium-free binders such as Sevelamer and a cautious lowering of dialysate calcium concentration could be an alternative approach. The role of parenteral calcitriol in the pathogenesis of calcium overload and development of calcifications could be potentially important. In the study of Ureña et al. (9), progressive and rapid evolution of aortic stenosis was mainly observed in patients with relatively high plasma vitamin D3 levels. The treatment of ESRD patients with AS is basically similar to that recommended for patients without chronic renal disease.

Nevertheless, because of the potentially rapid progression of stenosis, echocardiographic examinations should be repeated frequently, e.g., every 6 mo, even in asymptomatic patients with little obstruction. An effort should be made to prevent
hemodynamic overload and hyperkinetic circulation with high cardiac output and a high transvalvular blood flow rate, because these factors could contribute to a progressive increase in calcification and reduction of valvular orifice area. This is particularly true for sodium and water overload, which must be controlled by ultrafiltration. Ultrafiltration is problematic, however, because patients with AS and LV hypertrophy have noncompliant left ventricles. Excessive reduction of end-diastolic filling pressure can abruptly lower cardiac output and provoke hypotension and syncope. The same dramatic sequelae may be produced by atrial fibrillation, i.e., when the boosting effect of atrial contraction on LV filling is lost. The use of controlled ultrafiltration and a dialysate potassium concentration of 3 mMol/L are advised. Prompt treatment of arrhythmia and its causes is also mandatory. Endocarditis prophylaxis according to general principles is also a necessity in ESRD patients with valvular disease. The risk of bacterial endocarditis is relatively high in patients with AS and intermediate in cases with degenerative valvular disease.

Surgical

The evolution of AS in ESRD patients is frequently rapid and is associated with a poor outcome. Consequently, cardiac valve replacement should be considered in all patients with tight stenosis (<0.5 cm²/m²) in whom signs such as angina, syncope, or dyspnea develop. Surgery should be performed before contractility of the LV has decreased and cardiac failure has developed. The operative risk in ESRD patients is difficult to assess because the number of large studies is limited. This is particularly true for the results of combined procedures with concomitant coronary bypass grafting or mitral valve surgery. According to more recent reports, surgery has an acceptable operative mortality and achieves reasonable cardiac rehabilitation (7,29). In the study by Baglin et al. (7), the median survival of hemodialyzed ESRD patients after replacement of calcified AS was 36 ± 1.2 mo. Median survival was <1 yr in patients in whom AS was related to endocarditis and in whom AS was combined with other vascular lesions. Nevertheless, the long-term survival of ESRD patients with AS is limited compared to nonuremic patients in whom the 5-yr actuarial survival rate is approximately 85% (10). Even though the global early mortality was as low as 7% in the 13 patients reported by Deleuze et al. (29), early mortality may be up to 50% in patients requiring more complex procedures. Morbidity is also considerable and mainly the result of low cardiac output. The efficiency of balloon aortic valvuloplasty was not studied in ESRD patients. From our limited personal experience, the major disadvantage of this technique was rapid restenosis occurring in less than 6 mo. Because of the high risk of calcification, bioprosthesis are contraindicated in ESRD patients, and the choice of prosthetic material is limited to mechanical valves. Unfortunately, there is no information on the functional duration of such material in ESRD patients, and frequent evaluation of prosthetic valve function is of particular importance. Doppler echocardiographic examination should be performed at least once a year. As before surgery, the annual evaluation of the dental status is required for prevention of endocarditis. Mechanical valves make oral anticoagulant therapy mandatory, and the international normalized ratio must be strictly maintained in the correct range.

In conclusion, calcifications of the aortic valve and annulus are frequent in patients with ESRD. These lesions often evolve rapidly to the stage of hemodynamically significant aortic valve stenosis. Aortic stenosis has a very poor prognosis and surgery should be considered early on. Age, duration of dialysis treatment, and hyperphosphatemia are the most important risk factors.

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