Spontaneous Calcific Embolization Associated with Calcific Aortic Stenosis

By Keith E. Holley, M.D., Robert C. Bahn, M.D., Dwight C. McGoon, M.D., and Harold T. Mankin, M.D.

Spontaneous calcific embolization associated with calcific aortic stenosis is considered by some authors to be an uncommon occurrence. The current investigation was undertaken to determine the incidence and to document the nature, localization, and consequences of calcific embolization occurring spontaneously in patients with calcific aortic stenosis. Calcific embolization following operations on the aortic valve has also been investigated and will be reported in a separate communication.

Material and Methods

The material for this study consisted of 122 adult male and 43 adult female patients with calcific aortic stenosis examined at the Mayo Clinic between January 1940 and August 1961, inclusive, in whom necropsy had established the presence of aortic valvular stenosis.

Some patients were excluded from final consideration for the following reasons: (1) the gross specimen of the heart was either unavailable or unsuitable for complete re-examination; (2) the left atrium, left ventricle, or first portion of the ascending aorta was the site of calcified thrombi; (3) the ascending aorta was the site of extensive atherosclerotic calcification; (4) a mitral valvotomy had been carried out prior to death; or (5) the aortic valve was stenotic but not calcified.

The original description of each heart was reviewed. Each heart was re-examined, and the presence of aortic stenosis accompanied by gross nodular calcification was confirmed. Almost 85 per cent of the patients of this series exhibited moderate to severe calcification of the aortic valve. No attempt was made to determine the etiology of the aortic stenosis. Cross sections of the entire length of the subpericardial portion of each coronary artery were grossly examined at intervals of 1 to 3 mm. The most distal portions of the coronary arteries were examined at intervals of 1 mm. in an attempt to effect a complete examination of the arterial lumen. Each artery was carefully searched for focal constrictions, and portions of each focally narrowed segment were removed for histologic examination. Coronary sclerosis was graded on the basis of a maximal narrowing of a main coronary artery as follows: grade 1 (0 to 25 per cent obstruction); grade 2 (26 to 50 per cent obstruction); grade 3 (51 to 75 per cent obstruction); and grade 4 (76 to 100 per cent occlusion).

Ten “random” samples of myocardium were obtained from the left ventricle and ventricular septum. The base of the myocardial sample measured approximately 2.0 by 1.5 cm., and each sample measured about 0.4 cm. in thickness. Two paraffin sections 10 μ in thickness were cut in a plane parallel to the base of the sample.

The arterial supply to either old or recent infarcts of the brain, heart, and kidneys were examined when gross specimens were available, and additional histologic sections were taken when necessary. The organs of patients in whom necropsy was performed during the time the study was in preparation received the most extensive examination.

All tissue was stained with hematoxylin and eosin. Calcified coronary, cerebral, and renal arteries and the sections of calcified aortic valves were decalcified in ethylenediaminetetra-acetic acid. Sections of aortic valves and all arteries containing calcific emboli were stained with Verhoeff’s elastic-tissue stain and counterstained with van Gieson’s stain. Further examination of some aortic valves and embolic material was carried out with the use of the following stains: Mallory-Heidenhain, Gomori’s silver stain for reticulum, azure-eosin at pH 4.5 and 3.0; periodic acid-Schiff (PAS), PAS counterstained with alcian blue, Hale’s colloidal iron, luxol fast blue counterstained with cresyl violet, methyl violet, Mallory phosphotungstic acid, and Gram stain (Brown); alizarin red S stain for calcium was used to confirm the presence of calcium.

A calcific particle was considered to be embolic when both of the following criteria were fulfilled: (1) the presence of calcific material, sometimes accompanied by collagen or elastic fibers in the lumen of an artery or arteriole; and (2) the absence of intimal or medial atheromatous plaques or calcification in the segment of artery containing the emboli.
Patients in whom the calcific emboli were considered to have occurred spontaneously exhibited the following characteristics: (1) there was no antecedent aortic valve surgery or (2) aortic valve surgery was performed and death occurred within the first 72 hours after operation, and the intimal fibroblastic proliferation and collagenous deposits in the region of the embolus were of such a degree as to exclude it from having occurred at operation or during the early postoperative period.

The histologic diagnosis of calcific embolization to the coronary arteries was not difficult. The calcific particles were distinctive, resembling the calcium seen on the calcified aortic valve. Histological and histochemical studies of both emboli and nodular aortic valves demonstrated the following two common characteristics: (1) both gave positive reactions for calcium with the alizarin red S stain and (2) decalcified valves and emboli contained a similar PAS-positive matrix with focal basophilia that was best demonstrated with the azure-eosin stain (pH 4.5). Unlike calcified atheroma or atheromatous emboli, the calcific emboli contained no deposits of cholesterol and were not associated with the presence of lipid-laden macrophages. Unlike bland or septic thromboemboli, the calcific emboli contained no fibrin, no remnants of erythrocytes or leukocytes, and no colonies of microorganisms.

Results

Forty-five instances of spontaneous calcific embolization were found in 31 of 165 patients. There were 28 patients in whom emboli were observed in the major or minor coronary vessels, or both, and nine patients in whom emboli were present in the arterial supply of other organs (kidney seven, brain one, eye one) (table 1). The ages of patients exhibiting spontaneous emboli ranged from 39 to 89 years.

Major Coronary Emboli

The left coronary artery was the site of emboli in three cases (left anterior descending one, circumflex two) and the right coronary artery was the site in seven cases (main two, posterior descending five). The size of the emboli varied from 1 to 3 mm. in greatest dimension. The lumen of the vessels involved was reduced from 50 to 95 per cent of the original internal diameter. In all patients the intimal reaction to the calcific particle was complete, that is, elastic and collagenous fibers completely surrounded the particle and the endothelial lining of the vessel was completely restored (figs. 1 and 2). Coronary sclerosis was graded as 1 in four cases, 2 in two cases, and 3 in four cases. In three patients an old myocardial infarct was observed distal to the obstructed vessel.

Minor Coronary Branches

Eighteen patients of the 165 studied exhibited 22 emboli to minor coronary branches. The average size of the emboli was 0.3 mm. in greatest dimension (range 0.1 to 0.6 mm.); on the average, the embolus occluded 75 per cent of the lumen of the vessel (figs. 3 and 4). Endothelial reaction to the calcific particle was complete in 10 instances, partial in eight, and minimal or absent in six. Coronary sclerosis was graded as 1 in 10 cases, 2 in six cases, and 3 in two cases. Microscopic foci of myocardial injury in the area supplied by the obstructed vessel was observed in only three instances, but in none of these patients was there any clinical evidence of an acute episode of myocardial ischemia.

Eye

In one patient a calcific embolus was identified in the central retinal artery of the right eye. The calcific particle measured 0.1 mm. in its greatest diameter and was enclosed by fibroblasts and collagenous fibers (fig. 5). No major changes could be identified in the
CALCIFIC EMBOLIZATION WITH AORTIC STENOSIS

Table 1

<table>
<thead>
<tr>
<th>Site</th>
<th>Arteries affected</th>
<th>Number of patients</th>
<th>Total number of emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Major coronary (subepicardial)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Minor coronary (intranmyocardial)</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Kidney</td>
<td>Large (main renal interlobular)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Small (arcuate interlobular afferent)</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Brain</td>
<td>Large (right middle cerebral)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye</td>
<td>Central retinal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>37*</td>
<td>45</td>
</tr>
</tbody>
</table>

*Six patients had emboli in two or more sites.

Histologic sections of retina examined. Embolization had apparently occurred approximately 2 years prior to death, at which time the patient experienced sudden transient loss of vision in the right eye.

Brain

In one patient, embolization had occurred to the right middle cerebral artery. The embolus obstructed approximately 30 per cent of the lumen of the vessel and was completely enclosed by fibroblasts and collagenous fibers (fig. 6). Although the internal elastic membrane of the middle cerebral artery was distorted, it was not broken. No old infarct could be identified distal to the embolus, and no chronic functional deficits were described on the report of the patient's history or physical examination.

Kidney

Emboli were found to involve smaller renal vessels in seven (arcuate three, interlobular four) of the 165 cases studied. A single embolus was found in four cases, two emboli in two cases, and three emboli in one case (fig. 7). The size of the emboli varied from 0.1 to 1.0 mm., the lumen of the artery being totally occluded in only one case. This was the only instance in which old renal cortical infarction was demonstrated distal to the site of embolization. Intimal fibroblastic proliferation had enclosed the embolus completely or nearly completely in all instances. No evidence of

Figure 2

a. Left circumflex coronary artery, 8 cm. from its origin, in a 45-year-old man who died 48 hours after aortic valvotomy for severe calcific aortic stenosis. White calcified embolus is seen occluding nearly half of arterial lumen. Myocardial scarring is also present. Coronary sclerosis was grade 1. b. Section of coronary artery demonstrates complete enclosure of embolus by intimal fibrous proliferation (Verhoeff's elastic-van Gieson; × 16). c. Left ventricular myocardium distal to embolus, showing old healed myocardial infarct (hematoxylin and eosin; reduced from × 32).
Left ventricular myocardium of a 49-year-old woman with severe calcific aortic stenosis. Calcific embolus is seen nearly occluding a nutrient coronary arteriole. Minimal reaction of vessel wall to embolus is present (hematoxylin and eosin; reduced from $\times 50$).

Same patient as in figure 2. Sudden transient blindness occurred 2 years prior to death. Site of embolism is central retinal artery of right eye. Calcific particle is enclosed by intimal reaction (hematoxylin and eosin; reduced from $\times 32$).

Wenger and Bauer (1958) added two cases of coronary embolism of calcific material; however, calcific left atrial thrombi were thought to be the probable source. Wigle's (1957) study, which included seven cases of aortic stenosis, revealed three instances of calcific embolism in nonoperated hearts. Vessels of 2 mm. and 1.5 mm. in diameter and a nutrient arteriole had contained calcific emboli. Edwards (1961) presented examples of spontaneous and postsurgical emboli in his discussion of the complications in aortic stenosis.

Hollenhorst (1961) recently reported the finding of an "irregular, white body" on funduscopic examination in three patients with roentgenologic evidence of aortic valvular calcification. He noted that the calcific nature of these particles had not been proved. One patient in our present series had a calcific embolus to the central retinal artery. The embolus had lodged in the artery where the vessel coursed through the optic nerve and was not seen on funduscopic examination. That such a "white body" is in fact a calcareous embolus had been demonstrated more clearly by Edwards in the case of a patient 11 days after aortic valvotomy for calcareous disease.

In the present study, evidence of sponta-
neous calcific embolization was found in almost one fifth of the 165 cases of calcific aortic stenosis. Ten patients (6 per cent) were shown to have embolization of the major coronary arteries, while 18 patients (11 per cent) had embolization of minor coronary arteries. Old silent infarction of the myocardium was noted in three instances of occlusion of the major coronary arteries and three of occlusion of minor coronary arteries by spontaneous calcific emboli. No myocardial injury could be ascribed to the other coronary emboli, although in some cases nearly the entire lumen was obstructed.

Organized inspection of the entire parenchyma of the other highly vascularized organs such as the kidneys, brain, and retina was not possible. In the light of the observed incidence of embolization to the heart, the kidney, the brain, and the eye, one might conclude that general spontaneous calcific embolization is not a rare event among patients with calcific aortic stenosis but that few of these events in themselves lead to extensive infarction or to clinically obvious disorders.

Summary

The problem of spontaneous calcific embolization was investigated at necropsy in 165 patients with calcific aortic stenosis. Minor coronary arteries contained calcific emboli in 18 patients (11 per cent), and major coronary arteries contained calcific emboli in 10 (6 per cent). Examination of the brain, kidney, and eye also disclosed spontaneous calcific emboli. In three instances of major coronary artery embolization, there was evidence of old silent infarction but no associated clinical disorder. Calcific embolization is apparently not rare in cases of calcific aortic stenosis, but this phenomenon does not appear to lead very often to extensive infarction or to clinically obvious disorders.

References

4. Holley, K. E., Bahn, R. C., McGoon, D. C.,


Chaucer's Doctor

With us ther was a Doctor of Phisik:
In all this world ne was ther noon hym lik.
To speke of phisik and of surgerye:
For he was grounded in astronoyme.
He kepte his pacient a ful greet deel
In houres, by his magyk natureel.
Wel koude he fortunen the ascendent
Of his ymages for his pacient.
He knew the cause of everich maladye,
Were it of hoot, or cold, or moyste, or drye,
And where they engendred and of what humour:
He was a verray purrfit praktisour.
The cause y-knowe and of his harm the roote,
Anon he yaf the sike man his boote.
Ful redy hadde he his apothecaries
To sende him drogges and his letanaries.
For ech of hem made oother for to wynne.
Hir friendshipe was nat newe to bigynne.
Wel knew he the olde Esculapius
And Deyscorides, and eek Rufus,
Olde Ypoeas, Haly and Galyen,
Serapion, Razis and Avyeen,
Averrois, Damascien and Constantyn,
Bernard and Gatesden and Gilbertyn.
Of his diete mesurable was he,
For it was of no superfluitee,
But of greet norissyng and digestible.
His studie was but litel on the Bible.
In sangwyn and in pers he elad was al.
Lyned with taffata and with sendal.
And yet he was but esy of dispence,
He kepte that he wan in pestilence.
For gold in phisik is a cordial.
Therefore he lovede gold in special.—
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