**The Role of Endocarditis in Sudden Cardiac Death: Highlighting the value of the autopsy, pathological features and cardiac complications**

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**ABSTRACT:**

**Objective:** Endocarditis is increasing in incidence due to growing numbers of cardiac interventions, valve replacements and immunosuppressants. It can be difficult to diagnose clinically, has high mortality and can present as sudden cardiac death (SCD) with few/subtle preceding symptoms. True incidence of SCD related to endocarditis is unknown.

**Methods:** Retrospective analysis of UK national database of 6000 cases of SCD, 1994-2020, for “endocarditis” as cause of death.

**Results:** Of 30 cases (0.50%), 19(63%) were male and mean age was 36.2 ± 20.1 years. Post-mortem examination showed the aortic valve (AV) was solely affected in 13(43%), mitral in 9(30%), tricuspid in 2(6.7%) and pulmonary in 1(3.3%). Three cases (10%) had more than one valve affected and 2(6.7%) were non-valvular affecting the ascending aorta. Vegetations ranged from small easily-missed irregularities to large fungating masses. Ten (33%) patients developed aortic abscesses, 2 of which had aneurysms, 13 (43%) had coronary artery septic emboli with micro-abscesses and myocardial infarction, and 2 (6.7%) were healed endocarditis with perforation and regurgitation. Thirteen (43%) had an identifiable underlying valve abnormality or replacement, most common being a bicuspid aortic valve (7;54%).

**Conclusions:** This study highlights that although rare, endocarditis is an important cause of SCD in those with normal valves, valvular disease and valve replacement surgery. Absence of a pre-mortem diagnosis in 70% of our cohort highlights the need for detailed analysis of the heart and cardiac valves at autopsy. Gross appearance of vegetations varies widely and can be missed. Awareness of associated cardiac complications is required for elucidation of the cause of death and will provide valuable lessons for clinicians.

**KEYWORDS**

Endocarditis, Valvular Disease, Sudden cardiac death

**1. INTRODUCTION:**

Infective endocarditis (IE) is defined as an infection within the inner surface of the heart and most commonly affects the aortic or mitral valves, with infection of the tricuspid and pulmonary valves reported to account for less than 10% of cases.1 Infection by staphylococcal and streptococcal bacteria accounts for 80% of endocarditis cases with *Staphylococcus aureus (S. aureus)* the most frequent causative organism.1 IE predominantly affects individuals with structural heart disease and is increased in those with valve replacements, intravascular prosthetic material, transvascular valve insertions and intracardiac devices. 2,3 These interventions are increasing in number and subsequently the overall incidence of endocarditis is rising with it becoming a disease of the elderly as well as the immunosuppressed. The increase in IE incidence in the UK has also been correlated with a reduction in routine antibiotic prophylaxis prescription.4 The increase in endocarditis incidence seen in the UK is also reflected in other European countries predominantly secondary to increases in healthcare-related IE, organ failure and valve surgery as reported in Italy and France.4–6

The clinical diagnosis of endocarditis is based on the modified Duke criteria which relies on the detection of infecting microorganisms in addition to echocardiographic and clinical findings.1 The introduction of these criteria as a diagnostic tool has improved early recognition of endocarditis, however, there remains a high risk of severe morbidity and mortality.7IE can cause sudden death in both the infant and adult populations, however the majority of the literature consists of single case reports with no reported large autopsy series.8,9 In a recent cohort of 847 IE hospital patients in France, 94 deaths were reported, with 71(76%) said to be directly related to IE.10 Ten of the 94 deaths (11%) occurred suddenly, however none of the patients underwent an autopsy examination to determine the exact cause of death.10

Here we present our experience of endocarditis in a large UK-based series of sudden cardiac death (SCD), along with the autopsy findings associated with each case. This paper highlights the importance of thorough post-mortem examination and detailed pathological examination of the cardiac valves in all cases of SCD with referral to a cardiac pathology specialist recommended in selected cases.

**2. METHOD:**

**2.1 Study Population**

The CRY Centre for Cardiovascular Pathology is a specialist referral centre for cases of suspected SCD across the UK, receiving ~800 cases per year and with a database of over 6000 cases. SCD was defined as a natural death occurring from a presumed cardiac cause with death occurring within 1 hour of symptom onset or within 24 hours of the individual last being seen alive and well.

**2.2 Pathological Examination**

Pathological examination of all cases was conducted with the permission of Her Majesty’s Coroner and next-of-kin according to specific guidelines, and all relevant information regarding the deceased is provided by the referring pathologist/coroner.11

**2.3 Endocarditis Pathological Diagnosis**

Pathological diagnosis of endocarditis was based on both macroscopic and microscopic criteria. Macroscopically, diagnosis required the presence of vegetations on the valves and/or an abscess. Microscopically, the presence of inflammation and bacterial colonies were required. For diagnosis of healed endocarditis we recorded the presence of valve perforation and/or thickening macroscopically, and this was confirmed microscopically by the presence of fibrosis and a cellular infiltrate composed of macrophages and/or giants cells.

**2.4 Subjects**

An extraction of the UK national SCD database filtering for “endocarditis”as the cause of death was undertaken on all prospectively collected cases between 1994 and 2020. The resulting cases were analysed for epidemiological information, available clinical history and pathological findings. Data is presented as number (%) with averages as mean (± standard deviation).

**3. RESULTS:**

From over 6000 cases present in the CRY Database of SCD, there were 30 cases with a recorded cause of death of “endocarditis”. The data from these cases were extracted and initially assessed on the basis of patient demographics and available clinical information. Sex breakdown identified a higher ratio of male (19 cases) to female (11 cases) patients with a mean age of 36.2 (± 20.1) years. Clinical history identified that 16 individuals (53%) had reported prior symptoms which included fever, lethargy, chest pain and shortness of breath. Five of these individuals had a previous diagnosis of endocarditis whereas 4 had a premortem clinical diagnosis of endocarditis and died in hospital shortly following. However, cause of death was not provided by the doctors in these instances and the cases were referred for post-mortem and subsequent specialist cardiac review.

The cohort was divided into two groups based on the nature of the valve; group 1 were cases with native valves (24, 80%), and group 2 those with a documented history of valve replacement (6, 20%) (Table 1). Upon specialist pathological examination, 7 (29%) of individuals within the native valve group were found to have a bicuspid aortic valve. The most common procedure within group 2 was replacement of the aortic valve (4/6) with two of these patients also having an aorta root replacement with a Dacron graft. All aortic replacements were performed due to aortic stenosis of the native valve. Group 2 also contained 2 cases of non-aortic replacement; 1 tricuspid valve replacement (due to previous intravenous drug abuse) and 1 pulmonary valve replacement (secondary to complex cyanotic heart disease with pulmonary atresia, pulmonary artery hypoplasia, ventricular septal defect (VSD) and major aortopulmonary collateral arteries (MAPCAs)). One individual with a bioprosthetic aortic valve displayed healed endocarditis with perforations of the mitral valve, though all other individuals with a valvular history had endocarditis of that affected valve i.e. the focus of infection at post-mortem examination corresponded with the site of their intervention or abnormality.

Table 1. Breakdown of the cohort. Group 1 with no history of cardiac intervention and group 2 with documented valvular replacement.

|  |  |  |
| --- | --- | --- |
| Group 1- Native Valve | No Cardiac History | 17 |
| Bicuspid Aortic Valve | 7 |
| Group 2- Prosthetic Valve | Aortic Valve Replacement | 2 |
| Aortic Valve Replacement + Dacron Aorta | 2 |
| Tricuspid Valve Replacement | 1 |
| Pulmonary Valve Replacement | 1 |

Overall, the most common single affected site of IE across the cohort was the aortic valve (13, 43%) (Table 2). Ten (77%) of these cases also showed post-mortem evidence of an associated abscess of the ascending aorta, with 2 cases in this group additionally developing an aneurysm (Table 2). The second most common individual site was the mitral valve (9, 30%), and interestingly, all except one of these cases (a bioprosthetic AV) came from group 1. In 2 cases, the aortic, mitral and tricuspid valves were all affected by endocarditis and again, these individuals had no known history of valve disease. The aortic and mitral valves were affected by endocarditis in a single case with a bicuspid aortic valve. There were additionally 2 (6.7%) cases of non-valvular endocarditis; one abscess and rupture of an ascending aorta Dacron graft resulting in infarct due to thrombus in the left main stem, and one pseudoaneurysm of sinus of Valsalva.

Table 2. Breakdown of the cohort into site of infection affected by endocarditis.

|  |  |
| --- | --- |
| Aortic Valve | 13 |
| Aortic + Mitral Valves | 1 |
| Aortic, Mitral + Tricuspid Valves | 2 |
| Mitral Valve | 9 |
| Tricuspid Valve | 2 |
| Pulmonary Valve | 1 |
| Non-valvular | 2 |

Macroscopic examination of each case illustrated that the gross appearance of vegetations varied significantly both on native valves (Figure 1A) and replacement valves (Figure 1B). Vegetations appeared in some cases as a slight rough patch of granularity on the valvular cusp whilst in other cases were present as gross vegetative protrusions. The extreme end of the spectrum showed complete destruction of the entire valve. In every case of non-healed IE, microscopic examination revealed the expected features of the infective vegetations with dark pink fibrin on the surface and bacteria within, along with aggregates of neutrophils destroying the valve tissue (Figure 1C).

Review of the cohort identified four key cardiac complications associated with IE; aneurysm formation (Figure 2A), septic emboli with micro-abscesses and myocardial infarction (Figure 2B), damage to the membranous septum (Figure 2C) and healed endocarditis (Figure 2D).

While abscess within the ascending aorta was identified in 10 (33%) cases, formation of an aneurysm was present in 3 cases (10%). Aneurysm occurred exclusively in cases with infection of the aortic valve and ascending aorta. One of these cases had a previous history of bioprosthetic aortic valve replacement and ascending aorta Dacron graft whereas the other 2 had no underlying valve abnormalities or replacements.

The presence of septic emboli and subsequent micro-abscesses and myocardial infarction was identified in 13 cases (43%) with the original focus of infection being solely aortic valve (6), solely mitral valve (5) aortic, mitral and tricuspid valves (1), and non-valvular with ascending aorta ruptured aneurysm occurring at the level of the coronary ostia (1). All cases with this complication involved infection of the left-side of the heart, predominantly the aortic valve. Furthermore, 10 (77%) of the cases with septic emboli and resulting micro-abscess and infarct were in group 1 having had no previous known valvular history.

The spread of infection into the membranous septum was noted in 5 cases (17%) all of which included infection of the aortic valve. Two of these cases additionally had involvement of the mitral and tricuspid valves where the vegetations had perforated through the membranous septum to involve the right side of the heart. The 2 cases involving the aortic, mitral and tricuspid valves both had native valves with no abnormalities whereas the other cases affecting solely the aortic valve included 2 bicuspid aortic valves and one case of left ventricular outflow tract (LVOT) reconstruction due to congenital heart disease related aortic stenosis. Upon histological analysis, the atrioventricular node tissue was seen to be destroyed and replaced by neutrophils.

The final complication, that of healed endocarditis with valvular perforations, was identified in 2 cases (6.7%). One case of healed endocarditis involved the tricuspid valve with no previous valvular pathology. The other involved an individual with a history of a tissue bioprosthetic aortic valve replacement, however the healed infection was found to affect the native mitral valve and not the bioprosthesis. The identified valvular incompetence resulted in ventricular decompensation; however cardiac failure had not been identified in either of these individuals.

**4. DISCUSSION:**

Although retrospective and descriptive in nature, this study is the largest autopsy series of IE-related SCD and highlights the importance of autopsy in this difficult to diagnose condition. Most of our cases were male and young with underlying congenital valve disease (+/- replacement) accounting for 43% of cases. IE may be missed in an older age group where granularity on a valve may be mistaken for valve ageing and sclerosis.

**4.1 Site of Infection**

Analysis of this cohort of endocarditis-related SCD contradicts the notion that an individual with underlying structural valve abnormality or following an intervention, such as a valve replacement, is more likely to develop endocarditis. Prosthetic valves have been said to account for 16-34% of all IE cases, in agreement with our study which highlighted that 20% of cases occurred following valve replacement.12 Despite improvements in diagnosis and therapy, endocarditis associated with prosthetic valves has a high rate of mortality, as supported by our case series.13 Separate from valve interventions, changes in the geometry of a native valve can also alter the flow of blood leading to thrombus formation and microorganism adhesion, making underlying valve disease with deformed leaflets, such as bicuspid aortic valve (BAV), the main risk factor of IE.14 Again this is in agreement with the data presented here where 54% of a “valvular history” group had BAV. Analysis of the site of infection within this cohort also identified that 83% of cases were solely left-sided, when taking into account the additional two cases involving the aortic, mitral, and tricuspid valves, this is consistent with previous studies demonstrating that right-sided IE is rare and accounts for only 5-10% of all cases.15 This differs from the classical picture of tricuspid valve endocarditis resulting from an IV drug user injecting into their peripheral veins. The move to a left-sided disease is potentially due to the increased number of interventions occurring on the left side of the heart. Additionally, our data series identified that 57% of cases came from individuals with normal native valves and no previous valvular history, contradicting studies that have reported IE developing on a normal valve in up to 30% of cases.14 These cases within the cohort that identified with no cardiac history that may predispose to endocarditis could be a result of the changing affected population.

**4.2 Vegetations**

Vegetations are universally recognised as the key morphological feature of IE and are assessed using echocardiography for clinical diagnosis as well as pathologically for determination of cause of death. Histological examination of valve tissue shows a variety of patterns and degrees of inflammation according to the infecting organism.1 With regard to size, Luaces *et al.* have shown that the size of vegetation is determined by anatomical factors and that increased size is not associated with an increased risk of death, in keeping with our study where the size of vegetations varied greatly.16 Cardiologists, cardiac surgeons and pathologists need to be aware of this variation to ensure improved detection of IE during echo, valve replacements and autopsy. Surgeons and pathologists should sample any suspicious lesion on a valve if in doubt about the possibility of IE. IE may be missed in an older group where granularity on a valve may be mistaken for valve ageing and sclerosis.

Microscopic analysis of our cohort showed aggregates of neutrophils and bacteria destroying the valve tissue with the vegetations themselves filled with organisms and outlined with fibrin. Given the heterogeneity of the macroscopic appearances, if granularity is seen on the valve surface at the time of autopsy, the authors would recommend a low threshold for histological sampling to confirm an IE diagnosis, as well as adequate sampling for microbiological correlation. As highlighted by this study, the appearance of vegetations can vary significantly between cases and thrombus can be easily mistaken for vegetation, stressing the vital role of histology in the diagnosis of valvulitis, especially in scenarios when a pathogen cannot be identified.3

**4.3 Cardiac Complications**

Mortality of IE is high and is associated with pathologies affecting the conduction system, the coronary arteries and the valve itself. Pathological examination of this cohort of patients identified four important cardiac complications of IE; aneurysm formation, septic emboli with subsequent myocardial infarction, damage to the membranous septum and healed endocarditis. These complications can be associated with direct damage to cardiac structures as well as disturbance of the electrical conduction of the heart, leading to SCD. In previous work, specific pathogens have been found to be associated with characteristic clinical presentations of IE, for example the high rate of septic emboli seen with *S. aureus* or the association of enterococcal infection with annular abscesses, however due to our lack of microbiological correlation we are unable to comment on these findings.17

The formation of aneurysms at any site requires the presence of high intravascular pressure, and as a result they rarely occur in the right side of the heart, as in our cohort where all aneurysm cases resulted following infection of the aortic valve.15 Consequences of aneurysm formation are significant, and in our population include a dilated aortic root and perforation of the aortic wall.

While systemic embolization is a well-known complication of IE, myocardial infarction due to embolism in a coronary artery is rare and has been reported to occur in 1.5% of cases.9 This cohort however, identified 13 cases (43%) of septic emboli with subsequent micro-abscesses and myocardial infarction, a significant increase compared to previous reported literature. Due to the anatomical location of the coronary ostia, this complication most commonly arises when the left side of the heart is involved by IE. However, the mitral valve is stated to have a higher incidence of coronary emboli compared to the aortic valve, which is contrary to our findings where the involvement of the aortic and mitral valves were roughly equal.19 This difference could however be due to the cohort being predominantly aortic valve focussed with respect to interventions/abnormalities with no mitral valve interventions noted. Regardless of the site of origin, the resulting coronary embolus causes a decrease in blood flow to an already inflamed myocardium and can cause septic myocardial infarct which may prove fatal. We believe that discrepancies between the reported rates of coronary emboli in the literature and the findings presented here, could simply be due to a failure to take histological samples once the diagnosis of IE has been made on macroscopic visualisation of vegetations. Histological examination of cardiac tissue and coronary arteries is essential in all cases of IE if this complication is to be detected and its true incidence realised.

Damage to the membranous septum and thus the conduction system, and the atrioventricular node in particular, can be a fatal result of the spread of endocarditis. This complication leads to (fatal) arrythmias as infection spreads and interferes with the electrical rhythm of the heart ultimately leading to heart block and sudden death.15 AV node damage can also occur as an added complication of a ruptured aneurysm of the aortic vessel wall as infection spreads towards the conduction bundle.15

The macroscopic effect of healed infection on a valve is likely to be more obvious in a previously normal valve, in comparison to a damaged or stenotic valve, as it is not thickened and thus is an easy target for leaflet perforation.20 This is illustrated by our results where both cases involved a so-called normal valve. Macroscopically in these cases, perforation was seen in the leaflets which lead to regurgitation and valvular incompetence. This incompetence and subsequent left ventricular decompensation along with congestive heart failure is reported to be the most common complication of valve leaflet damage.14 Microscopically, healed endocarditis in this cohort revealed non-specific inflammation with a cellular infiltrate comprising lymphocytes, plasma cells and giant cells. The presence of giant cells, absence of neutrophils, and a relative or complete lack of microorganisms, is thought to be indicative of a subacute-chronic phase of the infection which can be associated with calcification of vegetations and the formation of hard, nodular deposits.14 The calcification of the valvular leaflets in turn leads to stenosis thus reducing blood flow through the heart. Without previous clinical diagnosis, histological examination is the only way to prove the presence of healed infection, once again highlighting the importance of thorough histological cardiac examination during post-mortem.

**5. STUDY LIMITATIONS:**

This study is limited by the absence of provisional microbiological results and correlation. Due to the nature of the referred specimens, specifically the fact that cases are referred formalin fixed and as part of coronial investigation, we were unable to determine the pathogen responsible for infection in each patient. Furthermore, we do not receive *every* case of sudden cardiac death across the UK. However, we believe that our results are a valuable representation of SCD due to IE in the UK population and highlight fundamental pathological findings which should be of interest to pathologists, cardiologists and cardiac surgeons who encounter such cases and their complications in their practice.

**6. CONCLUSION:**

Infective endocarditis is evolving in terms of disease demographics, predominantly due to changes in the affected population and increases in medical intervention.3 Whilst our cohort comprised many individuals with a native valve abnormality or previous valve replacement, the majority involved cases with no underlying valvular history, and the use of immunosuppressants and an ageing population is likely to further alter the population at risk of IE in the future. In agreement with current literature, analysis of our cohort identifies that IE usually affects the left sided heart valves, however it is important for pathologists to thoroughly assess the heart and valves in their entirety due to the greatly varied appearance of vegetations which can be subtle and easily missed. Vegetation variation is also important for cardiologists using echocardiography for clinical diagnosis and surgeons performing valvular intervention surgeries. Awareness of the cardiac complications associated with IE, specifically aneurysm formation, septic emboli with myocardial infarction, membranous septum damage and healed endocarditis, is also key knowledge for practicing autopsy pathologists. Histological assessment of the vegetations themselves along with affected valvular tissue, coronary arteries and myocardium is crucial for the direct visualisation of infection (past or present) and the elucidation of resultant damage. Ultimately, this study highlights the importance of thorough pathological examination in determining the cause of sudden death in individuals affected by endocarditis.

**DECLARATION OF CONFLICTING INTERESTS:**

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

**FUNDING:**

Cardiac Risk in the Young (CRY) funds the Cardiovascular Pathology Laboratory. KG is an NIHR-funded clinical lecturer.

**ETHICS:**

The Research Ethics Committee Number for the CRY Cardiovascular Pathology Department is 10/h0724/38 approved by NRES Committee London. This study is a retrospective analysis of the database which is covered by the existing ethics approval and therefore did not require further ethical consideration.

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**FIGURE LEGENDS:**

All figures for colour online only.

**Figure 1. Demonstration of the varying gross appearance of vegetations in both native and replacement valves along with histological appearance**.

**A** shows the gradient of vegetations on a native valve. These can vary from subtle rough patches on the ventricular surface of the valve cusp, to small vegetations protruding from a bicuspid aortic valve in the non-coronary leaflet, to clustered vegetations attached to the mural leaflet of the mitral valve and finally to large fungating vegetations that destroy the entire atrial surface of the aortic valve.

**B** demonstrates the appearance of vegetations on valve replacements including vegetations covering a bioprosthetic tricuspid valve replacement and a homograft aortic valve destroyed by vegetations.

**C** indicates the microscopic appearance of vegetations highlighting the dark pink fibrin surrounding the surface of the vegetation with bacteria within. Aggregates of neutrophils destroying the valve tissue can be noted.

**Figure 2. Pathological complications associated with endocarditis**

**A** shows an aneurysm in the aortic root where a hole in the aortic wall has developed behind where a vegetation attaches to the valve. Slicing through this hole reveals a bulging aneurysm in the aortic root.

**B** shows septic emboli with micro-abscess and myocardial infarction as a result of friable vegetation. Bacteria becomes embed within the coronary branches after embolising into the coronary ostia and can be seen as a dark cluster of bacteria surrounded by neutrophils embed within the myocardium.

**C** shows the involvement of the membranous septum in the spread of infection. Vegetations have perforated the aortic valve and spread through the membranous septum and conduction system to infect and perforate the tricuspid valve.

**D** shows evidence of healed endocarditis. Perforations in the valve cusp due to previous infection can be seen with microscopy indicating a non-specific image with a few lymphocytes, plasma cells and a giant cell in the valve tissue.