Epidemiology of arrhythmias in India: how do we obtain reliable data?

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Ventricular tachyarrhythmias represent an important cause of preventable death in the developing world. The vast majority of these arrhythmias occur secondary to underlying coronary artery disease. Sudden death due to malignant ventricular tachyarrhythmias can be the initial manifestation of coronary artery disease in many patients. Inadequate recognition and management of coronary artery disease and its risk factors in developing countries adversely impacts on their prevalence. Strategies to improve documentation of such events in the community are discussed.

Keywords: Atrial and ventricular arrhythmias, coronary artery disease, epidemiology, sudden death.

Introduction

CARDIAC arrhythmias, especially ventricular tachyarrhythmias are an important public health problem. It is estimated that serious ventricular tachyarrhythmias are responsible for death in nearly 50% of patients with coronary artery disease (CAD). Most of these patients succumb to these tachyarrhythmias before receiving medical aid[1]. In fact, ventricular arrhythmias may be the initial manifestation of CAD in these patients. As these arrhythmias leave little clues of their presence, it is a challenging task for the clinician, epidemiologist as well as the pathologist to accurately ascribe a cause to these deaths in such patients. Reasons for uncertainty arise from lack of medical contact before death, absence of an organized emergency medical response during the episode, lack of autopsy data, lack of interaction with family to ascertain circumstances of death, incomplete data collection and reporting on death certificates from civic authorities and hospitals, etc. Even when performed, autopsies may not always accurately pinpoint the cause of death in patients with cardiac disease – for instance, the autopsy may reveal nothing in sudden death victims in whom the tachyarrhythmia results from an ion channelopathy. The cause of death in such patients may remain conjectural unless exhaustive batteries of appropriate genetic tests are conducted. Reliable data are even sparser from developing nations on the proportion of sudden death events. This is relevant as cardiovascular diseases are the new epidemic in these nations. It was estimated[2] that nearly 30 million Indians had cardiovascular disease in 2003, which represented a prevalence of 8–10% among urban Indians. This has a huge public health impact with a significant loss in potentially useful life-years due to premature, unexpected cardiovascular deaths. This was estimated to be 9.2 million years in 2000 and expected, to rise[3] to nearly 18 million years by 2030. Whether ethnicity can affect incidence of sudden death is also not well documented in these populations[4].

While ventricular tachyarrhythmias represent an increasing clinical concern, atrial tachyarrhythmias also remain an important cause of morbidity and occasionally mortality. Atrial arrhythmias such as atrioventricular nodal tachycardias and atrioventrciular reciprocating tachycardias are an important cause of paroxysmal arrhythmias that are relatively benign though sudden death is a rare complication in patients with manifest bypass tracts and atrial fibrillation. However, both these tachycardias are readily amenable to medical and interventional therapy. Atrial fibrillation, on the other hand, has been an important cause of morbidity and mortality. This is especially true in patients with valvular heart disease, which is the dominant form of heart disease in children and young adults in developing countries. Atrial flutter and fibrillation have been associated with embolism, stroke, heart failure, frequent hospitalizations, etc. in these patients. In an older population, atrial fibrillation is frequently associated with hypertension, CAD as well as heart failure. Reliable strategies, therefore, need to be designed and implemented to improve reporting of these arrhythmias in developing nations.

Prevalence of arrhythmias in the developing world – impact of health dynamics

Ventricular arrhythmias, theoretically, can be a greater public health concern in India than in the developed world. These differences can be directly attributed to an inadequate recognition and management of CAD. Patients with acute myocardial infarction (MI) are far less likely to receive thrombolytic therapy, especially in rural areas due to economic and logistic constraints. Even in urban areas, timely thrombolysis is less likely due to numerous reasons. As first-generation thrombolytic agents

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(largely streptokinase) are used in India, which are far less effective than third-generation thrombolytics, infarct sizes are likely to be larger, contributing to greater ventricular dysfunction. It has been shown that utility of thrombolytic agents declines as a function of time, with streptokinase having little benefit on enzymatic infarct size even as early as 3 h after infarction in some studies[5]. This can lead to a poorer left ventricular function, and in the long term, could translate into a higher incidence of late ventricular arrhythmias, which have a direct bearing on overall cardiovascular mortality.

Even in patients with diagnosed CAD, pharmacologic therapy is inadequate, especially in non-metropolitan cities in India. This can have an adverse effect on ventricular remodelling and predispose for greater ventricular dysfunction. For example, several large trials have demonstrated the anti-arrhythmic benefits of beta-blockers, angiotensin converting enzyme inhibitors (ACEI) and statins. In the BHAT trial, propranolol reduced sudden death by 47% in patients with heart failure[6]. It also reduced overall mortality by 27% in patients with congestive heart failure. Similarly, ACEI have been shown to reduce arrhythmic and overall mortality. Statins have also been demonstrated to reduce ventricular arrhythmias in ICD recipients. Therapeutic benefit of beta-blockers, angiotensin-converting enzyme inhibitors and statins is not extended to most patients with overt CAD in India. This pattern of under prescription of potentially useful drugs known to extend survival in patient populations eligible to receive it, has been well documented in other countries as well. In a national survey on prescription patterns of beta-blockers after myocardial infarction, it was demonstrated that beta-blockers were not prescribed to nearly two-thirds of patients eligible to receive them in some regions in the US[7]. Under usage was more likely if the physician was a general practitioner or family practice physician. These inadequacies expose the patient to a higher overall mortality as well as arrhythmic risk. In a study that analysed the potential health and economic benefits of improved beta-blocker use amongst all potential recipients, it was projected that there would be approximately 72,000 fewer deaths if nearly 400,000 post MI patients received beta-blockers over 20 years[8]. This assumed a decrease in sudden death by 32% and a decrease in recurrent MI and revascularization by 27%.

Similar concerns exist with prevalence, awareness and treatment of atrial fibrillation. As opposed to the developed countries, a sizeable burden of atrial fibrillation still occurs in patients with rheumatic valvular heart disease in India. There is a dearth of detailed data on epidemiologic outcomes of rheumatic atrial fibrillation in India. Inconsistent practice patterns with regard to anticoagulation especially expose patients to a high risk of thromboembolism. Inappropriate initiation of chronic amiodarone therapy results in long-term toxicity due to amiodarone. Moreover, its pharmacological interaction with warfarin (the effect of warfarin is potentiated) requires close supervision of the patient's international normalized ratio. Due to sustained improvements in life expectancy, India is also exposed to the burden of atrial fibrillation in the elderly.

Pathophysiology of sudden cardiac death – public health impact

Most sudden death events in the community are due to cardiac causes, most commonly secondary to CAD. Other cardiac disorders such as dilated and hypertrophic cardiomyopathies, valvular heart disease, congenital heart disease, ion channel abnormalities, etc. together account for approximately 5% of sudden deaths. Vascular diseases such as aortic aneurysms, haemorrhagic stroke, pulmonary embolism, etc. may present with a sudden death event. Non-cardiovascular diseases such as epilepsy, acute asthma, and poisoning are also well described to result in sudden death.

However, majority of sudden cardiac death (SCD) events in the community are due to ventricular tachyarrhythmias – either ventricular tachycardia or ventricular fibrillation. Bradyarrhythmias contribute only to a small minority of events terminating in SCD. Most of these arrhythmias represent direct consequences of underlying cardiovascular disease. Only 5–10% of SCD events occur in the absence of CAD or congestive heart failure. Autopsies performed on sudden death victims demonstrate that most have evidence of significant obstructive CAD in two or three coronary arteries[9]. Contrary to popular perception, only small minorities of sudden death victims have a MI. Despite succumbing to these ventricular tachyarrhythmias, paradoxically, the vast majority of resuscitated victims of sudden death do not have documented symptomatic ventricular arrhythmias before the SCD event. Although the incidence of sudden death is higher in patients with CAD who have frequent ventricular ectopy along with ventricular dysfunction (left ventricular ejection fraction less than 30%), population studies have demonstrated that majority of serious ventricular tachyarrhythmias actually occur in patients who lack both of the above markers. It is thus extremely important to assess the burden of CAD in the community to accurately ascertain the population at risk for future ventricular tachyarrhythmias. Mere assessment of the prevalence of ambient ventricular ectopy alone as a marker for future serious ventricular arrhythmias in patients with CAD grossly underestimates the impact of ventricular arrhythmias.

Strategies that target control of CAD risk factors in the community will thus help in reigning in ventricular arrhythmias. Factors responsible for SCD in the community are therefore the same risk factors that lead to CAD. Therefore, hypertension, diabetes, dyslipidemia, smoking, physical activity, dietary patterns, left ventricular hypertrophy, etc. all affect community burden of CAD and

therefore SCD[10–12]. Several studies have attempted to identify risk factors that specifically predict risk of SCD rather than CAD. Amongst these at least two markers, increased resting heart rate and heavy alcohol consumption, have been identified that indicate a high-risk group[13,14].

Taking cognizance of the large volume of data documenting earlier and more aggressive CAD in Indians, the Government of India has recently launched a comprehensive programme to prevent premature CAD and diabetes. Several factors such as demographic shifts, changes in nutrition (nutrition transition), industrialization and urbanization have led to the emergence of several new risk factors in Indians. These include, among others, increasing prevalence of hypertension, diabetes, smoking, obesity, increased consumption of processed foods and sedentary lifestyles[15,16]. Due to this economic boom, CAD risk factors are increasingly more prevalent among the lower socio-economic groups. Lack of health awareness along with inadequate preventive health infrastructure is worrisome as the CAD epidemic can possibly be nipped in the bud by appropriate public education campaigns.

Assessing ventricular arrhythmias in the general population

The simplest method of assessing ventricular arrhythmias in the general population is by conducting a cross-sectional study. This provides crude data on the burden of disease in the population. However, such a study requires screening of a large population, is cumbersome to perform and is of limited use for the clinician. What is of more relevance for the physician is to assess the clinical circumstances in which the arrhythmia occurs. Thus arrhythmias occurring in patients with CAD, cardiomyopathies, ventricular dysfunction and bundle branch block would be of more clinical importance, as they are more likely to have a SCD event. Myerburg[17] demonstrated that although patients with ventricular dysfunction with or without ventricular arrhythmias are at high risk for a SCD event, this population subset constitutes only 20–30% of the patients who eventually die of sudden death in the community. The bulk of SCD occurs in patients who have risk factors for CAD and have near-normal ventricular function. Thus, it is paradoxical that the bulk of SCD due to ventricular arrhythmias in the community occurs in patients who have never had a documented ventricular arrhythmia till their SCD event. This is amply borne out by the Oregon Sudden Unexpected Death Study, where nearly 50% of patients who had SCD had normal ventricular function[18]. Most of these patients did not have recognized CAD. It is likely that these deaths are due to myocardial ischaemia in patients with unrecognized CAD. In an initial publication by the same authors[19], CAD ($>50\%$ coronary artery stenosis on autopsy) was the most common pathological abnormality seen in adult SCD victims who underwent an autopsy.

Classifying sudden cardiac death events

Numerous methods have been used to reliably assess the probability of a sudden, unexpected death to be due to cardiac causes. The Hinkle and Thaler classification is the most widely accepted method used to classify an event as a SCD event[20]. The authors classified events in which the subject collapsed suddenly without any prior clinical signs of circulatory collapse as arrhythmic sudden death. More than 90% of illnesses that lasted less than 1 h ended in arrhythmic death. Deaths that occurred up to a day or later after the onset of the index event were due to circulatory failure. These included deaths due to acute respiratory obstruction, haemorrhage, infection, stroke or other non-cardiac events. Thus, using a 1 h time definition helped in segregating cardiac from non-cardiac deaths. The World Health Organization criteria for SCD also incorporate a 24 h period cut-off in including deaths due to presumed cardiac causes when the event is un-witnessed and the victim had been noted to be alive and symptom-free before the presumed SCD event. However, there will always be limitations to the accuracy with which a death event can be classified as a SCD event. In fact, even in ICD recipients, some of the sudden death events have been actually demonstrated on autopsy to be due to massive pulmonary embolism or due to a vascular event, even though the clinical circumstances suggested sudden arrhythmic death[21]. Despite these limitations, clinical information obtained from bystanders and emergency responders who are witnesses to the terminal event is the most reliable source of information, short of a post mortem in classifying SCD.

Retrospective vs prospective data collection on SCD events

As most SCD events occur out-of-hospital before any contact with health professionals, it is difficult to accurately ascribe a cause for death in these victims. Although an autopsy is the ideal method for most reliably assessing the cause of death, autopsy rates are very low in most communities. Physicians, medical examiners or coroners therefore classify deaths according to available clinical data. Death occurring within minutes in an otherwise healthy individual is most typically classified as an arrhythmic death, although death due to pulmonary embolism or a ruptured aortic aneurysm is equally instantaneous. However, data on time to death are generally not available to the physician for out-of-hospital deaths. Therefore, retrospective review of death records has been reported to grossly over estimate SCD incidence in communities. In a study comparing a strategy of multiple

source surveillance vs retrospective death certificate-based review of SCD events in a large community in the US, Chugh *et al.*[19] reported a threefold over estimation of SCD events using retrospective review of death records. These limitations of retrospective data analysis could conceivably be even greater in developing countries. Therefore, the best estimate of SCD burden in the community in such regions would be by prospective data collection on SCD events.

Verbal autopsy

Lack of reliable national civil data on deaths in many low and middle-income developing countries has led to adoption of verbal autopsy as an alternative source of data on deaths[22–24]. This is a retrospective method that utilizes the services of non-medical persons to ascertain the cause of death by an interview, frequently reformed many months after the victims death. Probability of cause of death is based on algorithms designed for different diseases. Physicians review the data collected from the interview and classify the cause of death. This form of death ascertainment has been useful in cancer-related deaths. However, the sensitivity and specificity of this method is limited for many other causes of death[25,26]. It should be noted that the discrepancy between the treating clinicians and pathologists in ascribing the cause of death[26] may be to the tune of 10–30%. Even though the role of verbal autopsy in improving the percentage of classifiable death in developing countries is undeniable, its ability to accurately classify the cause of death may be low. Therefore, though this method has been used in India before, its utility for gathering accurate disease-specific mortality may be limited.

Strategies to improve data collection

Some of the most exhaustive and reliable data on community burden of SCD have been from Rochester and Olmsted County, Minnesota[27]. The significant factor central to obtaining reliable data from this area has been its geographical location that has permitted its residents to have their health-care needs be addressed by a handful of providers. With the Mayo Clinic, Olmsted Medical Group and its affiliates providing all health needs for the community, comprehensive data maintenance provides a unique epidemiological opportunity to assess public health. As majority of the residents in Olmsted are of middle-class background and have graduate-level education, it is easier to conduct epidemiological studies. The Rochester Epidemiological Project has population data due to a unique medical record linkage system that accurately documents medical and surgical care provided to its residents.

Similar opportunities need to be explored in India to permit accurate data collection. Such studies permit population-based analytical studies due to accurate documentation and cross verification. Participation of allied agencies such as emergency medical responders, police departments, fire services and civic agencies registering births and deaths aids in resource-building. Such opportunities in India will lie in large industrial townships that are relatively isolated from other urban centres. Such townships generally have middle-class families with an educated locale who may be more receptive to an epidemiological survey. Closer cooperation from medical care providers and community resources is also possible in such instances. Even a prospective study designed to follow events closely for 1 year will be able to generate valuable data.

Emergency response service providers are frequently the first point of contact for SCD victims. Although most patients do not survive to hospital discharge due to delays in emergency response team requisition by bystanders and their arrival, such organized responses have helped improve survival rates. From an epidemiological point of view, these teams help in more accurate ascertainment of circumstances of the terminal events. Similar services from a local provider have been initiated in some cities in India. Database sharing with such service providers is essential in planning any epidemiological study.

Despite efforts to accurately ascribe the cause of death as arrhythmic vs non-arrhythmic, many deaths will remain to be classified inaccurately. Not all arrhythmic deaths are sudden and not all sudden deaths are secondary to arrhythmias. Therefore, using SCD as a surrogate marker for arrhythmic events can miss arrhythmic events in populations. Assessing total cardiac mortality is therefore as important as assessing SCD[28].

Conclusion

Ventricular arrhythmic events in populations are a crude reflection of the CAD burden in the community. Accurate assessment of this disease burden is necessary to understand the epidemiology of CAD in different ethnic groups. For example, in a study on Asian ethnic minorities in the United Kingdom, the prevalence of SCD amongst Indo-Asians and Afro-Caribbean groups was substantially lower than in Caucasians. This lower than expected SCD rate is surprising as CAD has been clearly documented to be far more aggressive in South Asians[4]. Whether these are chance observations or represent a confounding ethnic variable needs to be validated.

Usefulness of national programmes also lies in realistic assessment of domestic needs. Such programmes are extremely essential for appropriate allocation of scarce fiscal resources. Epidemiologic data from individual countries are extremely useful in recognizing disease pat-

terns within the country and appropriately utilizing the knowledge to promote disease control measures. For example, most epidemiologic studies have documented that majority of SCD events occur in domestic locations or under hospice care[29]. A much smaller proportion occurs in public places. This information is useful as a programme to install automatic external defibrillators would not be cost-effective for states with limited financial resources. Instead, primary prevention programmes that improve knowledge about CAD and SCD along with an emergency responder programme may be more cost-effective.

National data are also useful to extricate appropriate budgetary allocation for health care. It is well recognized that the burden of chronic non-communicable diseases is under estimated by most developing nations[30]. It is still widely believed that cardiovascular and other such non-communicable disease control programmes should be delayed till national programmes on infectious diseases attain their targets. It is important that local and national governments, health agencies, voluntary organizations and professional bodies actively pursue prevention programmes that target this global epidemic. Robust scientific data that document this alarming trend would bolster the claims of the medical community in increasing efforts for disease prevention and control.

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